INDUCTION OF LABOUR: FACILITATION OF LABOUR ONSET, PREDICTION OF SUCCESS AND IMPROVING THE INDUCTION PROCESS

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (BY PRIOR PUBLICATION)

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Abstract

Labour is induced in about 25% of pregnancies demonstrating its importance in contemporary obstetric practice. The papers forming the thesis are grouped as follows surrounding the central theme of inducing labour:

1) Coitus as a home remedy and membrane sweeping as an office procedure to facilitate onset of labour

The works on coitus provide important lessons about human studies. The initial promise from an observational study demonstrating an association of coitus with earlier labour onset was not supported by the findings of two subsequent clinical trials on coitus as an intervention. The secondary data analysis of the first trial also provide evidence that coitus at term does not facilitate labour onset. The paper on serial weekly membrane sweeping to facilitate labour onset in women desiring vaginal birth after Caesarean did not demonstrate statistically significant results but the observed effect is smaller than assumed.

2) Evaluation of sonographic predictors of successful induction of labour resulting in vaginal delivery

The works on ultrasound parameters as predictors of successful labour induction contributed to the developing literature. We confirmed that transvaginal ultrasound is better tolerated than digital assessment for the Bishop Score. This can be important for

maternal satisfaction in obstetric care. Transvaginal ultrasound measurement of cervical length is probably a better predictor of labour inducibility than Bishop Score but additional equipment and skill acquisition are needed. Our original study linking membrane sweeping and cervical length changes as assessed by transvaginal ultrasound demonstrate a positive association between postsweep cervical shortening and subsequent vaginal delivery. Postsweep cervical shortening may be a marker of cervical pliability leading to labour success.

3) Novel refinements of currently used labour induction regimens to improve efficiency in high, mixed and low risk populations.

The work on membrane sweeping as an immediate adjunct to formal labour induction is important as it confirms that adjunctive membrane sweeping reduces operative delivery. Concurrent titrated oxytocin infusion and dinoprostone pessary in nulliparas with intact membranes and unfavourable cervixes is a viable option based on our largely positive findings. The few past trials on concurrent regimens all used quite different regimens; any meta-analysis would be difficult to constitute and interpret. On the other hand in nulliparas with unfavourable cervixes after term prelabour rupture of membranes, labour induction with titrated oxytocin infusion is possibly better leaving little rationale for a future concurrent regimen trial. The case for immediate titrated oxytocin infusion following amniotomy for labour induction in parous women with favourable cervixes is more balanced. Immediate oxytocin is quicker at achieving vaginal delivery but minor abnormality in fetal heart rate tracing is also more common.

Abstrak

Induksi bersalin perlu dilakukan dalam 25% kehamilan, menunjujjkan kepentingannya dalam rawatan obstetrik waktu sekarang. Penyelidikan-penyelidikan dikumpulkan seperti berikut mengiringi tema permulaan bersalin:

1) Persetubuhan sebagai remedi di rumah dan pelekangan membran sebagai prosedur klinik bagi memudahkan permulaan proses bersalin.

Penyelidikan mengenai persetubuhan memberi pengajaran penting tentang kajian keatas manusia. Walaupun penemuan awal didapati dari kajian pemerhatian, kedua-dua kajian klinikal asal dan analisis data sekunder selanjutnya memberi bukti komtemporari bahawa persetubuhan yang di jangka, tidak memudahkan permulaan bersalin. Kertas original pada siri pelekangan membran setiap minggu dikalangan wanita yang berhasrat kelahiran normal selepas pembedahan Cesarean mungkin kurang cukup bilangan kes dikaji kerana kesan yang didapati adalah lebih kecil dari andaian..

2) Penilaian sonografi sebagai prediktor induksi bagi kejayaan kelahiran vagina.

Penyelidikan terhadap parameter ultrasound sebagai peramal kejayaan induksi bersalin menyumbang kepada pembangunan penerbitan ini. Kami mengesahkan bahawa ultrasound melalui vagina adalah lebih disenangi daripada penilaian digital bagi penentuan Skor Bishop. Ini adalah faktor penting bagi kepuasan ibu dalam penjagaan obstetrik. Pengukuran panjang serviks menggunakan ultrasound melalui vagina

mungkin boleh meramal induksi bersalin dengan lebih baik daripada Skor Bishop tetapi ia memerlukan peralatan tambahan dan pemerolehan kemahiran. Kajian asal kami menghubungkait pelekangan membran dan perubahan panjang serviks yang dinilai secara ultrasound transvaginal menunjukkan kaitan yang positif antara pemendekkan serviks selepas pelekangan dan kelahiran vagina. Pemendekkan serviks selepas pelekangan sebagai penanda kesesuaian serviks membawa kepada kejayaan bersalin membuka pintu.

3) Penghalusan novel bagi rejim induksi bersalin untuk meningkatkan kecekapan dalam populasi yang berisiko tinggi, rendah dan kedua-duanya.

Empat kajian klinikal dapat membantu amalan dalam kerja klinikal. Kertas kerja mengenai pelekangan membran sebagai adjunk segera kepada induksi bersalin secara formal adalah penting kerana ia mengesahkan bahawa hasil dari penambahan pelekangan membran dapat mengurangkan bersalin secara pembedahan. Titrasi infusi oxytocin serentak dengan pesari dinoprostone bagi nulliparas yang membran masih utuh dan servik yang belum sesuai adalah pilihan yang berdaya maju berdasarkan penemuan positif yang kami dapati. Beberapa kajian yang dijalankan bagi rejim serentak, semua menggunakan rejimen agak berbeza; apa-apa meta –analisis akan sukar dibentuk dan ditafsir. Sebaliknya bagi nulliparas dengan serviks yang matang; pemecahan air ketuban secara spontan diperingkat ‘term’ bersalin dengan titrasi infusi oxytocin adalah mungkin lebih baik; mengakibatkan sedikit sahaja rasional untuk kajian regimen serentak dimasa depan. Kes bagi titrasi oxytocin dengan lebih cepat berikutan pemecahan ketuban bagi induksi kelahiran untuk multipara dengan serviks

yang matang adalah lebih seimbang. Infusi oxytocin dengan segera membolehkan kelahiran vagina dengan lebih pantas tetapi sedikit perubahan pada degupan jantung janin juga lebih biasa dijejaki.

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Name of Degree: PhD (Prior Publication)

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Induction of Labour: Facilitation of Labour Onset, Prediction of Success and Improving the Induction Process

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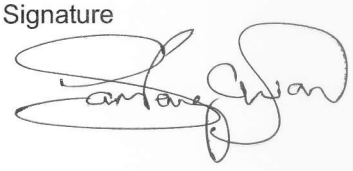
Candidate's Signature  Date 5 MARCH 2014

Subscribed and solemnly declared before,

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(6) Saya sedar sepenuhnya sekiranya dalam masa penghasilan Hasil Kerja ini saya telah melanggar suatu hakcipta hasil kerja yang lain sama ada dengan niat atau sebaliknya, saya boleh dikenakan tindakan undang-undang atau apa-apa tindakan lain sebagaimana yang diputuskan oleh UM.

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The twelve publications serving as the basis for this PhD (Prior Publication) thesis of the candidate Tan Peng Chiong are all collaborative works with co-authors. Co-authors have contributed to various extents on the concept, design, execution, data analysis and interpretation, critique of manuscript drafts prior to journal submission and approval of the final submitted manuscript. The candidate fully acknowledges the contribution of all co-authors, including many who had spent longer hours on the ground in the conduct of the studies.

The following are co-authors in order of number of publication co-authorships and then in publication chronology: Professor Siti Zawiah Omar (8), Associate Professor Vallikkannu Narayan (3), Professor Jamiyah Hassan (2), Dr Suguna Subramaniam (2), Dr Yow Choon Ming (2), Dr Nada Sabir (2), Dr Sofiah Sulaiman (2), Dr Reena Jacob, Dr Andi Anggerik, Associate Professor Noor Azmi Mat Adenan, Associate Professor Noraihan M Nordin, Associate Professor Quek Kia Fatt, Dr Sumithra Devi Valiapan, Associate Professor Paul Tay Yee Siang, Dr Siti Aishah Daud, Dr Mukhri Hamdan, Dr Kiren Sidhu, Dr Khine Pwint Phyu, Ms Halimanja Sabdin, Dr Noorkardiffa Syawalina Omar, Dr Ezra Yusop and Dr May Zaw Soe.

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The financial supports for the studies are acknowledged where applicable within the original publications: they are generally from the personal resources of the investigators and internally from University of Malaya Medical Centre and University of Malaya.

Candidate's Declaration

The twelve papers submitted for the thesis were all peer reviewed journal articles (published from 2006 to 2013). The studies are not the products of a conventional PhD program. All the studies are collaborations involving different groups of co-investigators who are acknowledged by individual article co-authorships with the candidate's specific role and all co-authors investigators' were fully spelt out in the synopses of the individual papers in the appendix.

The candidate was a prime contributor to the concept and design of most of the studies, performed the primary data analysis and interpretation for all the papers, drafted all the manuscripts then coordinated co-authors contributions for the final draft and was the corresponding author for all the publications. The candidate is also the first author for 10 of the 12 papers, second author in one and senior author in another. The candidate asserts a major intellectual input in all 12 publications.

List of Abbreviations

95% CI	95% confidence interval
AOR	Adjusted odds ratio
ARM	Artificial rupture of membranes/ Amniotomy
CS	Caesarean section
ERC	Elective repeat Caesarean
IOL	Induction of labour
OR	Odds ratio
P	P-value
PG	Prostaglandin
PROM	Prelabour rupture of membranes at term
ROC curve	Receiver operator characteristic curve
RR	Relative risk
TOLAC	Trial of labour after Caesarean
VBAC	Vaginal birth after Caesarean

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A. List of Publications, Journal Information, Citations, Candidate Author Role

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1. Synopsis and Theme

These twelve selected papers [listed in Appendix A](Hamdan, Sidhu, Sabir, Omar, & Tan, 2009; Omar, Tan, Sabir, Yusop, & Omar, 2013; Tan, Andi, Azmi, & Noraihan, 2006; Tan, Daud, & Omar, 2009; Tan, Jacob, & Omar, 2006; Tan, Khine, Sabdin, Vallikkannu, & Sulaiman, 2011; Tan, Soe, Sulaiman, & Omar, 2013; Tan, Suguna, Vallikkannu, & Hassan, 2006; Tan, Valiapan, Tay, & Omar, 2007; Tan, Vallikkannu, Suguna, Quek, & Hassan, 2007; Tan, Yow, & Omar, 2007, 2009) put forward for the thesis are collaborative efforts with other investigators who are co-authors. Authors' roles are more extensively defined in Appendix B. The full original publications are in Appendix C. Studies underlying these papers overlap in time in their execution reflecting practical consideration of opportunity when ideas, funds and willing collaborators coalesced. The papers arising from reports of these studies demonstrate a logical, consistent, progressive and coherent research program to investigate issues surrounding labour induction over recent years by the candidate and fully comply with University of Malaya PhD by Prior Publication regulations (Appendix D).

In keeping with the thesis title "Induction of Labour: Facilitation of Labour Onset, Prediction of Success and Improving the Induction Process", the publications are grouped as follows to demonstrate the candidate's research program:

1) Research focused on coitus as a home remedy and membrane sweeping as an office procedure to facilitate onset of labour

2) Research focused on evaluating sonographic predictors of successful induction of labour resulting in vaginal delivery

3) Research focused on novel refinements of currently used labour induction method or regimen in order to improve efficiency in high, mixed and also low risk populations.

1.1. Research focused on coitus as a home remedy or membrane sweeping as an office procedure to facilitate onset of labour

This paper(Tan, Andi, et al., 2006) reported on an original prospective observational study based on diary keeping of coital activity from 36 weeks gestation until birth in 200 healthy women. The main aim of the study was to study coitus in late pregnancy and its correlation with the onset of labour.

Major findings

Reported sexual intercourse at term was influenced by a woman's perception of coital safety, her ethnicity, and her partner's age. After multivariable logistic regression analysis controlling for the women's ethnicity, education, occupation, perception of coital safety, and partner's age, coitus at term remained independently associated with reductions in postdate pregnancy (adjusted odds ratio [AOR] 0.28, 95% confidence interval [CI] 0.13– 0.58, P = .001), gestational length of at least 41 weeks (AOR 0.10, 95% CI 0.04 – 0.28, P < .001), and requirement for labour induction at 41 weeks of gestation (AOR 0.08, 95% CI

0.03– 0.26, P < .001). At 39 weeks of gestation, 5 (95% CI 3.3–10.3) couples needed to have intercourse to avoid one woman having to undergo labour induction at 41 weeks of gestation. Coitus at term had no significant effect on operative delivery (adjusted P = .15).

These original findings were promising as they point to a potential role for vaginal intercourse as a home remedy to facilitate labour, reduce the incidence of prolonged pregnancy and lessen the need for labour induction.

A randomised "advise-coitus" trial(Tan, Yow, et al., 2007) followed directly motivated by the findings of our previous observational study on coitus(Tan, Andi, et al., 2006). The trial report was on 215 women scheduled for non-urgent induction of labour. The trial intervention was physician advice to apply coitus as a safe and effective mean to facilitate labour onset and hence avoid the need for the scheduled induction. Control women were also told coitus was safe and asked to keep a coital diary. The aim of the study was to demonstrate that women at term with planned labour induction the following week would heed medical advice to apply coitus which in turn would facilitate labour thus reduced the need for formal labour induction.

Major findings

Women assigned to the advised-coitus group were more likely to report coitus before delivery (60.2% compared with 39.6%, relative risk [RR] 1.5, 95% confidence interval 1.1–2.0; P.004), but the spontaneous labour rate was not

different (55.6% compared with 52.0%, relative risk 1.1, 95% confidence interval 0.8 –1.4; P.68). Caesarean delivery rate, neonatal and other secondary outcomes were also not different.

These findings did not support our hypothesis that the intervention would facilitate labour. However, the participants were substantially different in their characteristics and circumstance from the women in our previous observational study(Tan, Andi, et al., 2006) which held out the possibility that recommending coitus might still be an effective intervention if applied earlier from 36 weeks gestation to healthy women.

We performed a secondary data analysis(Tan, Yow, et al., 2009) of our earlier "advise coitus" trial(Tan, Yow, et al., 2007) to explore the association of reported coitus and orgasm at term with pregnancy outcome irrespective of original assignment of intervention. The analysis was designed to evaluate the effect of actual coitus rather than the intervention of "advising coitus".

Major findings

On univariate analysis, the inverse association of coitus with spontaneous labour was borderline negative (odds ratio [OR] 0.6; 95% confidence interval [CI] 0.3–1.0; p-value is 0.052). Orgasm was not associated with spontaneous labour (p = 0.33). After adjustment for potential confounders, coitus (AOR 0.4; 95% CI 0.2–0.8; p = 0.009) had a significant inverse association with spontaneous labour.

Coitus and orgasm were not associated with any evaluated adverse pregnancy outcome.

The finding that coitus had an inverse association with spontaneous labour was counter-intuitive. Neither reported coitus nor reported orgasm was associated with any other adverse pregnancy outcome. This indicated that coitus at term was safe. Although this was a post hoc secondary analysis, the finding of an inverse association is important nevertheless when read with the negative result of the original trial as it reinforced the notion that coitus might be ineffective in facilitating labour. However there were plausible reasons for the inverse relationship such as lack of opportunity for coitus brought on by the rapid onset of spontaneous labour and prelabour symptoms or signs inhibiting coitus. Hence the inverse association might be due to imminent labour inhibiting coitus rather than coitus actually prolonging a pregnancy.

Another “advise-coitus” trial(Omar et al., 2013) was also conceived as a direct response to the findings of our earlier observational study(Tan, Andi, et al., 2006). This randomised trial was conceived in anticipation that our first advise-coitus trial(Tan, Yow, et al., 2007) in women scheduled for labour induction would demonstrate positive findings. This latter trial’s planned recruitment was of 1600 healthy women who were coitally abstinent in the preceding four weeks when recruited at 36-38 weeks gestation. We selected abstinent participants to maximise the ability of the intervention to promote coitus and show an effect on downstream outcomes. The intervention was otherwise identical to the earlier

trial(Tan, Yow, et al., 2007) i.e. medical advice to apply coitus as a safe and effective means of facilitating labour thus avoiding the need for labour induction. The healthy participants and their gestation at recruitment closely matched the conditions of our observational study(Tan, Andi, et al., 2006), and the perception was that recommending coitus is most likely to be effective in this population. Trial accrual was slow; an interim analysis was performed after 1200 women had been recruited.

Major Findings

The intervention to delivery interval (mean ± SD) was 3.2 ± 1.4 versus 3.3 ± 1.3 weeks (P = 0.417), gestational age at delivery 39.4 ± 1.2 versus 39.5 ± 1.2 weeks (P = 0.112), and labour induction rate 126/574 (22.0%) versus 120/576 (20.8%) (P = 0.666) for the advise-coitus and control arms, respectively and were similar. Coitus prior to delivery was more often reported in the advise-coitus arm compared with the control arm: 481/574 (85.3%) versus 458/576 (79.9%) (RR 1.5, 95% CI 1.1–2.0, P = 0.019). The median (interquartile range) reported number of coital acts of 3 (2–5) versus 2 (1–4) (P = 0.006) was higher for the advise-coitus arm. Other pregnancy and neonatal outcomes did not differ between the groups.

Interim analysis after 1200 had been recruited indicated it would be futile to continue the trial to the target of 1600 participants. Post hoc analysis showed that in women reporting coitus compared to abstinent women, their intervention to delivery interval and labour induction rate were no different, consistent with the

data from our first trial. These two trials show that women heeded medical advice to use coitus but such advice did not have the desired effect of facilitating earlier labour probably because coitus was not efficacious in that respect.

We also instituted a randomised trial(Hamdan et al., 2009) to evaluate serial weekly membrane sweeping compared to serial weekly vaginal examination for Bishop Score determination from 36 weeks gestation in 211 women who planned vaginal birth after one previous transverse lower segment Caesarean delivery (with and without prior vaginal birth) on facilitating labour. Labour induction and prolonged pregnancy after prior Caesarean are associated with poor outcome hence the importance of facilitating labour onset for them. Participants and care providers were blinded to the intervention.

Major findings

The spontaneous labour rate was 78.5% compared with 72.1% (relative risk [RR] 1.1, 95% confidence interval [CI] 0.9 – 1.3; *P*=.34), the induction of labour rate was 12.1% compared with 9.6% (RR 1.3, 95% CI 0.6 –2.8; *P*=.66), and the all-cause caesarean delivery rate was 40.2% compared with 44.2% (RR 0.9, 95% CI 0.7–1.2; *P*=.58) for the membrane sweeping and control groups respectively. We considered PROM to be spontaneous labour. Gestational age at delivery (mean ± standard deviation) of 39.6 ± 1.0 weeks for the membrane sweeping group compared with 39.6 ± 0.9 weeks for the control group (*P*=.84) was not different.

We calculated that a randomised trial predicated on reducing all-cause Caesarean delivery in the particularly high risk subgroup of women who wanted vaginal birth after one previous Caesarean delivery but without any prior vaginal birth will require 574 such women in each arm with alpha set at 0.05 and beta at 0.2 based on all cause Caesarean delivery rates of 52.1% vs. 60.3%.

1.2. Research focused on assessing sonographic predictors of successful induction of labour resulting in vaginal delivery

A prospective study(Tan, Suguna, et al., 2006) was performed in 152 term women just prior to their labour induction. Transabdominal sonography was performed to obtain fetal biometry for fetal weight estimation and amniotic fluid index; and transvaginal sonography to obtain cervical length and to detect funnelling at the internal cervical os. The receiver operator characteristic curve was used to determine the best cut-off for cervical length as a predictor of Caesarean delivery. In addition clinical characteristics of Bishop Score, parity status, short stature, age, ethnicity, gestational age, and medical history of diabetes and hypertension were considered in the analysis. Multivariable logistic regression analysis was performed incorporating potential confounders to identify independent predictors.

Major findings

On univariate analysis using Fisher's exact test, parity, cervical length and Bishop Score were associated with Caesarean delivery. Following multivariable logistic regression analysis, only nulliparity (adjusted odds ratio (AOR) 5.2 (95% CI 2.2 –

12.2): P < 0.001) and transvaginal ultrasound-determined cervical length > 20 mm (AOR 2.8 (95% CI 1.0 –7.4): P = 0.04) were independently predictive of Caesarean delivery in labour induction. Maternal age, maternal height, gestational age, indication for labour induction, amniotic fluid index, cervical funnelling and ultrasound-estimated fetal weight did not predict Caesarean delivery.

Our study controlled for a number of potential confounders before establishing scan determined long cervix as an independent predictor of CS following labour induction. This study identified independent predictors of induction failure after appropriate adjustment of potential confounders. It showed that sonographic estimated fetal weight and amniotic fluid index were not predictive of Caesarean delivery at labour induction.

At about the same time, we also evaluated the tolerability of transvaginal ultrasound of the cervix compared to Bishop Score assessment in a larger population of 249 women immediately prior to their labour induction.(Tan, Vallikkannu, et al., 2007) All women were exposed to both techniques. Transvaginal ultrasound was found to be better tolerated than Bishop Score assessment – the mean visual analog scale pain score was significantly and substantially lower with transvaginal ultrasound.

Major findings

Transvaginal sonography was significantly less painful than digital examination for Bishop Score (mean difference in the 11-point VAS score of 3.46; P < 0.001).

Comparing transvaginal scan and Bishop Score assessments, 86.3% found transvaginal assessment to be less painful, 6.4% found both procedures to be equally painful and only 7.2% felt that transvaginal assessment was more painful. Analyses of the ROC curves for cervical length and Bishop Score indicated that both were predictors of Caesarean delivery (area under the curve 0.611 vs. 0.607; P = 0.012 vs. P = 0.015, respectively) with optimal cut-offs for predicting Caesarean delivery of > 20 mm for cervical length and Bishop Score ≤ 5. Cervical length had superior sensitivity (80% vs. 64%) and marginally better positive (30% vs. 27%) and negative (89% vs. 83%) predictive values. Multivariate logistic regression analysis revealed that only nulliparity (adjusted odds ratio (AOR) 4.1; 95% CI, 2.1 – 8.1; P < 0.001) and transvaginal sonographic cervical length > 20 mm (AOR 3.4; 95% CI, 1.4 – 8.1; P = 0.006) were independent predictors of Caesarean delivery.

This study's stronger originality was in establishing in a large study population as a primary study aim that transvaginal ultrasound is better tolerated than Bishop Score assessment. A previous study that looked at a subset of only 40 of their study women and another study of 50 women that looked at tolerability as a secondary outcome(Chandra, Crane, Hutchens, & Young, 2001; Paterson-Brown, Fisk, Edmonds, & Rodeck, 1991) also found transvaginal scan to be less painful. Our study with a sample size of 249 was one of the largest studies at publication that investigated transvaginal ultrasound in predicting labour inducibility.

With our previous research experience on membrane sweeping and transvaginal ultrasound(Hamdan et al., 2009; Tan, Jacob, et al., 2006; Tan, Vallikkannu, et al., 2007; Tan, Vallikkannu, Suguna, Quek, & Hassan, 2009), we constituted an original study(Tan et al., 2011) evaluating the immediate effect of membrane sweeping on cervical length by transvaginal ultrasound in 160 women at 40 weeks gestation that underwent membrane sweeping to facilitate labour. The women were all scheduled for labour induction at 41 weeks for prolonged pregnancy. Membrane sweeping is an established method for facilitating labour.(Boulvain, Stan, & Irion, 2005) Our study also investigated cervical shortening in response to membrane sweeping on the subsequent need for labour induction and Caesarean delivery.

Major findings

The mean presweep cervical length ± SD was 21.0 ± 10.0 mm; the postsweep length was 23.8 ± 10.9 mm, an average increase of 2.8 ± 0.6 mm ($P < .001$). Cervical shortening after membrane sweeping was noted in 53 of 160 cases (33%). Cervical shortening was associated with a reduction in subsequent all-cause caesarean delivery but not labour induction on bivariate analysis. After adjustment for maternal age, parity, presweep Bishop score, postsweep cervical length, oxytocin augmentation, epidural analgesia, and meconium-stained fluid, cervical shortening post membrane sweeping was independently predictive of a reduction in Caesarean deliveries (adjusted odds ratio, 0.24; 95% confidence interval, 0.06–0.90; $P = .034$).

We postulated that cervical shortening post membrane sweeping might be a measure of cervical pliability predicting easier cervical dilatation once in labour but shortening was not indicative of the initiation of the cascade of biological mechanisms leading to onset of labour.

1.3. Research focused on novel refining of currently used labour induction method or regimen to improve efficiency and acceptability in high, mixed and also low risk populations.

We performed a trial to evaluate a single adjunctive membrane sweep at commencement of formal labour induction in 264 women of mixed parity and cervical favourability with various indications for labour induction on improving the induction process. Post-intervention, standard labour induction management and labour care was extended to all participants.

Major findings

Women randomised to membrane sweeping compared to controls had higher spontaneous vaginal delivery rate (69% compared with 56%, $P = .041$), shorter induction to delivery interval (mean 14 compared with 19 hours, $P = .003$), fewer that required oxytocin use (46% compared with 59%, $P = .037$), shorter duration of oxytocin infusion (mean 2.6 compared with 4.3 hours, $P = .001$) and improved visual analog score (VAS) for birth process satisfaction (mean 4.0 compared with 4.7, $P = .015$). The reduction in dinoprostone dose used (mean 1.2

compared with 1.3, $P = .082$) was not significant. Post sweeping VAS for pain (mean 4.7 compared with 3.5, $P < .001$) was significantly increased.

We recommended that adjunctive membrane sweeping at initiation of formal labour induction at term should be performed as there was significant benefit.

Following on the positive result of our adjunctive membrane sweeping study, we switched our attention to improving the labour induction process in the high risk of labour induction failure women: nulliparas with unfavourable cervixes and intact membranes. We performed a randomised controlled trial(Tan, Valiapan, et al., 2007) that compared titrated oxytocin infusion concurrently with dinoprostone pessary compared with titrated placebo saline infusion concurrently with dinoprostone pessary for the first 6 hours of labour induction in 208 women. After the 6 hours, standard open label induction and labour care was applied.

Major findings

Concurrent oxytocin infusion with dinoprostone pessary did not significantly increase vaginal delivery rate within 24 hours (48.6 versus 35.9%; P = 0.07, RR 1.4 [95% CI 1.0–1.9]). It reduced the requirement for repeat dinoprostone (37.1 versus 61.2%; P = 0.001, RR 0.61 [95% CI 0.45–0.81]) and improved maternal satisfaction with the birth process (median score of 3 versus 5 on a 10-point visual analogue scale, P = 0.007). Caesarean rates were not different (41.9 versus 44.7%, P = 0.52). Uterine hyperstimulation syndrome was uncommon and not

different. Induction to delivery interval although shorter (after excluding 2 extreme outliers) 24.2 ± 16.3 versus 26.2 ± 14.2 hours (P = 0.36) was not significantly different.

At the time of publication, our trial was the largest that dealt with concurrent use of dinoprostone and oxytocin for labour induction. Although the trial did not demonstrate an increase in vaginal delivery within 24 hours (P = 0.07), the result was borderline and given the positive data from earlier trials(Bolnick et al., 2004; Christensen et al., 2002; Hennessey, Rayburn, Stewart, & Liles, 1998; Stewart et al., 1998), our study might still be underpowered as the observed effect was smaller than the pilot data from earlier trials we used in our sample size calculation. This intervention should be tested in larger studies. Meaningful meta-analysis is difficult as the earlier trials used very diverse concurrent regimens.

Having produced favourable original data on concurrent oxytocin-PG labour induction regimen in nulliparas with intact membranes and unfavourable cervixes(Tan, Valiapan, et al., 2007), we extended our effort to evaluating concurrent PG-oxytocin in nulliparas with ruptured membranes and unfavourable cervixes. This original randomised double blind controlled trial(Tan, Daud, et al., 2009) compared concurrent dinoprostone pessary and titrated oxytocin infusion to placebo pessary and titrated oxytocin infusion in 114 women who underwent labour induction indicated by PROM.

Major Findings

Vaginal delivery rates within 12 hours were 25/57 (43.9%) versus 27/57 (47.4%), median maternal satisfaction VAS was 8 [interquartile range 2] versus 8 [IQR 2] P = 0.38, uterine hyperstimulation was 14% vs. 5.3% P = 0.20, overall vaginal delivery rates 59.6% vs. 64.9% P = 0.70 and induction to vaginal delivery interval 9.7 vs. 9.4 hours P = 0.75 for concurrent treatment versus oxytocin. There was no significant difference for any other outcome.

Our original findings were that concurrent vaginal dinoprostone and intravenous oxytocin for labour induction of term PROM did not expedite delivery or improve patient satisfaction. Although not significant, the concurrent use arm generally has less favourable outcomes. This inverse trend indicates that in women with PROM, the addition of dinoprostone to the "gold standard" titrated oxytocin infusion(Hannah et al., 1996) is unlikely to be beneficial and there seems little basis for pursuing similar trials.

Having performed two trials(Tan, Daud, et al., 2009; Tan, Valiapan, et al., 2007) with concurrent oxytocin-PG labour induction régimen in high risk nulliparas with unfavourable cevixes, we switched our attention to parous women with favourable cervixes following ARM to induce labour where instead of intensifying the labour induction régimen, we sought to minimise interventions as these women are easily induced into labour. We compared immediate titrated oxytocin infusion to titrated placebo saline infusion after amniotomy for labour induction in 206 women.(Tan et al., 2013) After four hours, blinded trial infusions were stopped and open label standard obstetric management was instituted.

Major Findings

Vagina delivery rates at 12 hours were 91/96 (94.8%) vs. 91/94 (96.8%) RR 0.98 95% CI 0.92-1.04) P = 0.72 and satisfaction VNRS (median [interquartile range]) 3 [3-4] vs. 3 [3-5] P = 0.36 for immediate vs. delayed arms respectively and were similar. Caesarean delivery, maternal fever, postpartum haemorrhage, uterine hyperactivity and adverse neonatal outcome rates were similar. The immediate oxytocin arm had a shorter amniotomy to delivery interval of 5.3 ± 3.1 vs. 6.9 ± 2.9 hours P < 0.001 and lower epidural analgesia rate of 2.9% vs. 9.9% RR 0.3 95% CI 0.1-1.0 P = 0.046 but fetal heart rate abnormalities on cardiotocogram was higher, 28.6% vs.16.8% RR 1.7 95% CI 1.0-2.9 P = 0.048. In the delay arm, oxytocin infusion was avoided by 35.6%.

We concluded that immediate or delayed oxytocin infusions were reasonable options after amniotomy for labour induction in parous women with favorable cervixes. The choice should take into account care provision locally and the woman's wish.

These publications(Hamdan et al., 2009; Omar et al., 2013; Tan, Andi, et al., 2006; Tan, Daud, et al., 2009; Tan, Jacob, et al., 2006; Tan et al., 2011; Tan et al., 2013; Tan, Suguna, et al., 2006; Tan, Valiapan, et al., 2007; Tan, Vallikkannu, et al., 2007; Tan, Yow, et al., 2007, 2009) show the focus and depth of the candidate's research into core issues around labour facilitation and induction; an

important area of pregnancy care which directly affects about a quarter of all maternities in advanced economies that required labour induction. (WHO, 2011)

The majority (7/12) of the studies were randomised “blinded” clinical trials(Hamdan et al., 2009; Omar et al., 2013; Tan, Daud, et al., 2009; Tan, Jacob, et al., 2006; Tan et al., 2013; Tan, Valiapan, et al., 2007; Tan, Yow, et al., 2007), recognised as the most robust methodology for providing quality scientific evidence to guide clinical practice. All the research presented is thematically linked to labour initiation and induction, culminating in study reports being published for the most part in the most influential journals in the field of obstetrics and gynaecology.

The contribution of the papers to the wider literature will be further explored in the introduction and conclusion chapters of this thesis.

2. Introduction

2.1. Description of the research problems investigated

Labour induction is induced in 25% of maternities in developed economies. (WHO, 2011) The research issues are grouped as follows to demonstrate a coherent cross sectional and longitudinal framework of the candidate's work with a brief link to the literature:

2.1.1. Coitus as a home remedy and membrane sweeping as an office procedure to facilitate onset of labour

Much of the previous research on coitus in pregnancy was focused on studying its potential adverse effect on preterm labour and PROM. The general consensus arising from these studies is that coitus in pregnancy is not associated with adverse pregnancy outcomes.(NICE-UK, 2008a) On the other hand, basic research was rarely done on the widely held folk belief(Schaffir, 2002) that coitus may facilitate labour at term.

Meta-analysis of 22 clinical trials has established the utility of outpatient membrane sweeping in facilitating labour onset, allowing 1 in 8 women to avoid formal labour induction but there is no significant impact on the Caesarean delivery rate.(Boulvain et al., 2005) Membrane sweeping is recommended by NICE UK guideline as a proven method that should be offered to women faced

with the prospect of labour induction for prolonged pregnancy.(NICE-UK, 2008b) Membrane sweeping's utility in facilitating labour in VBAC had not been studied. This high risk pregnancy subgroup is especially likely to benefit from expedited labour onset as their labour induction would involve significant risk of potentially catastrophic scar rupture and high risk of failed labour induction coupled with further concerns that a prolonged pregnancy after a prior Caesarean may be associated with intrauterine death.(Hamdan et al., 2009)

2.1.2. Sonographic and other predictors of successful induction of labour resulting in vaginal delivery

The Bishop score since its inception in 1964(Bishop, 1964) has remained the premier method for assessing favourability for labour induction. The score is obtained by a digital vaginal assessment which can be discomfiting.(Chandra et al., 2001; Paterson-Brown et al., 1991) Transvaginal ultrasound assessment of cervical length as a predictor of labour induction success has been studied in the early 2000s at our study inception but its tolerability and comparability versus the Bishop score was uncertain at the time.(Chandra et al., 2001; Novakov-Mikic, Ivanovic, & Dukanac, 2000; Paterson-Brown et al., 1991). By the early 2000s, oligohydramnios in late pregnancy was known to be associated with poorer pregnancy outcome.(Casey et al., 2000; Garzetti, Ciavattini, La Marca, & De Cristofaro, 1997) However, the utility of ultrasound estimation of fetal weight and amniotic fluid volume to predict labour induction outcome was unknown. Using

transvaginal ultrasound to assess cervical length changes after membrane sweeping to facilitate labour onset was original and unique.(Tan et al., 2011)

2.1.3. Novel refinement of currently used labour induction methods to improve efficiency

Membrane sweeping's utility as an immediate adjunct to formal labour induction with PGs or amniotomy and oxytocin infusion had only been reported once within a trial setting(Foong, Vanaja, Tan, & Chua, 2000) with promising results. Nulliparas with an unfavourable cervix undergoing labour induction is a still major challenge(Grobman, 2012) as their Caesarean delivery rate is high and the process is often prolonged even when successful. PGs and oxytocin are effective induction agents typically use sequentially during labour induction.(Swamy, 2012) Concurrent use of these agents are infrequently studied with only a few smaller scale trials done which have shown shortening of the induction to delivery interval without compromising safety.(Bolnick et al., 2004; Christensen et al., 2002; Hennessey et al., 1998; Stewart et al., 1998) On the other hand, in parous women with prior vaginal birth and a favourable cervix, a simple amniotomy alone may effectively induce labour and early oxytocin augmentation can be unnecessary.(Howarth & Botha, 2001) Previous trials from 1970s and 1990s(Moldin & Sundell, 1996; Patterson, 1971) have been of mixed populations of nulliparous and parous women and compared delaying oxytocin augmentation for 24 hours after amniotomy, an approach that is no longer contemporarily relevant as the evidence clearly shows that amniotomy alone is less

efficient(Bricker & Luckas, 2000). Current debate is focused on a much shorter latency of up to four hours before commencing oxytocin. A single trial has provided data that in nulliparas, a 4-hour delay compared to immediate titrated oxytocin infusion is less efficient and acceptable to women.(Selo-Ojeme et al., 2009) No trial data of a 4-hour delay versus immediate oxytocin following amniotomy for labour induction in exclusively parous women with favourable cervixes existed prior to our trial.

2.2. Research progress linking the research papers

2.2.1. Coitus as a home remedy or membrane sweeping as a clinic procedure to facilitate onset of labour

The four papers on coitus(Omar et al., 2013; Tan, Andi, et al., 2006; Tan, Yow, et al., 2007, 2009) provide salutary lessons about human studies. Observational studies are inherently weaker in producing robust scientific evidence and should be confirmed by randomised trials. Interesting initial data might not be reproducible, demonstrating the fallibility of statistics, confounding and happenstance. The longitudinal works on term coitus as whole showed scientific rigor and thoroughness and provided strong evidence that coitus's perceived value to facilitate labour is probably a folklore rather than factual. The original clinical trials(Omar et al., 2013; Tan, Yow, et al., 2007) and the secondary data analysis(Tan, Yow, et al., 2009) of the earlier trial(Tan, Yow, et al., 2007) are likely to provide the contemporary evidence base on term coitus and labour onset.

The original paper on serial membrane sweeping on women desiring VBAC(Hamdan et al., 2009) although the finding was not significant provides pilot data for estimating the benefit of weekly membrane sweeping in these high risk women to help plan powered studies to safely improve vaginal birth rates.

2.2.2. Sonographic predictors of successful induction of labour resulting in vaginal delivery

The two publications(Tan, Suguna, et al., 2006; Tan, Vallikkannu, et al., 2007) on ultrasound parameters as predictors of successful labour induction contributed to the still developing literature in this area. We provided quality evidences that transvaginal ultrasound is better tolerated than digital assessment for the Bishop Score. This is an important consideration as maternal satisfaction is assuming greater prominence in obstetric care. Transvaginal ultrasound measurement of cervical length is at least as good a predictor of labour inducibility as the Bishop Score but additional equipment and skill acquisition are needed; on a practical level extension of its use faced resource and training issues. Our original study coupling membrane sweeping with assessment of cervical shortening by transvaginal ultrasound(Tan et al., 2011) which demonstrated a positive association of shortening with subsequent vaginal delivery opens the door for further research in this area. We postulated the concept of post sweep cervical shortening as a marker of cervical pliability during a forthcoming labour leading to vaginal delivery.

2.2.3. Novel refinement of currently used labour induction method or regimen to improve efficiency and acceptability in high and low risk women

The four clinical trials(Tan, Daud, et al., 2009; Tan, Jacob, et al., 2006; Tan et al., 2013; Tan, Valiapan, et al., 2007) inform clinical practice. The paper on membrane sweeping as an immediate adjunct to formal labour induction has the potential for clinical impact – it confirms the finding of a solitary previous trial(Foong et al., 2000) and strengthens the evidence for adjunctive membrane sweeping as a simple and minimal cost intervention to reduce operative delivery. Concurrent titrated oxytocin and dinoprostone pessary infusion in nulliparas with intact membranes and unfavourable cervixes is a viable option(Tan, Valiapan, et al., 2007) based on our trial data which showed safety but mixed beneficial findings. The current standard labour induction regimen with vaginal PG(Kelly, Malik, Smith, Kavanagh, & Thomas, 2009) is relatively inefficient in these women at high risk of induction failure. A meaningful meta-analysis of the few trials evaluating concurrent regimens is difficult as the regimens used in the other trials were diverse as discussed in our trial report and further powered study is warranted.(Tan, Valiapan, et al., 2007) On the other hand in nulliparas with unfavourable cervixes after PROM, labour induction with titrated oxytocin infusion alone (Hannah et al., 1996) is possibly better with many outcomes showing a positive trend in its favour, leaving little logic to pursue further studies of a concurrent approach in PROM.(Tan, Daud, et al., 2009) The case for

immediate titrated oxytocin infusion following amniotomy for labour induction in parous women with favourable cervixes is more nuanced. Immediate oxytocin is quicker at achieving vaginal delivery and may even reduce need for epidural anaesthesia but minor abnormality in fetal heart rate tracing was also more common but without any increase in the operative delivery rate.(Tan et al., 2013) In a busy delivery suite with constant pressure on bed availability or where the woman is focused on a faster process, immediate oxytocin is a tempting first option.

3. Literature Review

3.1. Brief Overview

In the United States of America, the rate of labour induction has risen from 9.5% to approximately 23% from 1990 to 2009.(Swamy, 2012) The latest population based data indicate that labour is induced in 22.9% of maternities nationally in the USA in 2012 (Martin, Hamilton, Osterman, Curtin, & Mathews, 2012) and in 23.3% of maternities in National Health Service facilities in England in 2012-13(NHS_Information_Centre., 2014).

3.2. Indications for labour induction

Ideally labour should be induced when there is evidence that the fetal or maternal risk of continuing a pregnancy is outweighed by an attempt at expedited vaginal delivery, induction is acceptable to the mother and is cost effective.(Chauhan & Ananth, 2012) There are as many as 21 recognised indications for labour induction according to a review of three current national practice guidelines (United States [ACOG](Obstetrics, 2009), Canada [SOGC](SOG-Canada, 2001) and United Kingdom(NICE-UK, 2008b) but these guidelines are often incongruent on their recommendations with unanimous agreement for only three indications (fetal death, distance from hospital and PROM) of the 21 listed indications.(Chauhan & Ananth, 2012) World Health Organisation (2011) guideline for induction of labour is sparser still with labour induction clearly recommended only for prolonged pregnancy (at or after 41 weeks gestation) and term PROM.(WHO, 2011) The implication is that many accepted indications for

induction of labour are “soft” and a delay may be feasible if induction failure seemed likely. However findings from randomised trials suggest that an expectant approach is not more likely to result in vaginal delivery when labour induction is indicted by prolonged pregnancy [≥ 41 weeks gestation](Hannah et al., 1992), diabetes [≥ 38 weeks gestation](Kjos, Henry, Montoro, Buchanan, & Mestman, 1993), term PROM [≥ 37 weeks gestation](Hannah et al., 1996) or hypertension [≥ 36 weeks gestation](Koopmans et al., 2009).

The most common contemporary indications for labour induction include prolonged pregnancy(Hannah et al., 1992), premature rupture of the membranes(Hannah et al., 1996), diabetes(Tan, Ling, & Omar, 2009; Witkop, Neale, Wilson, Bass, & Nicholson, 2009) , hypertension(Hutcheon et al.) and non-reassuring fetal status(Spong et al., 2011). Elective induction of labour on maternal request is also not infrequently encountered in contemporary practice.(NICE-UK, 2008b) Our centre’s data showed that induction of labour is not more frequently needed in pregnancies previously affected by hyperemesis gravidarum, a common early pregnancy complication.(Tan, Jacob, Quek, & Omar, 2007)

3.3. Clinical implications of labour induction

Induction of labour has potential adverse clinical consequences apart from the direct expense. Compared to spontaneous labour, an induced labour is more likely to result in Caesarean delivery (even in parous women)(Battista, Chung, Lagrew, & Wing, 2007; Glantz, 2005; Hoffman, Vahratian, Sciscione, Troendle, & Zhang,

2006; Jonsson, Cnattingius, & Wikstrom, 2013; Xenakis, Piper, Conway, & Langer, 1997) with almost a doubling in risk for nulliparas(Dublin, Lydon-Rochelle, Kaplan, Watts, & Critchlow, 2000; Johnson, Davis, & Brown, 2003; Luthy, Malmgren, & Zingheim, 2004; Maslow & Sweeny, 2000; Seyb, Berka, Socol, & Dooley, 1999; Vahratian, Zhang, Troendle, Sciscione, & Hoffman, 2005; Yeast, Jones, & Poskin, 1999). Nulliparous women requiring caesarean delivery after labour induction were more likely to have fetal acidaemia, admission to the neonatal intensive care unit, chorioamnionitis, and endometritis.(Blackwell, Refuerzo, Chadha, & Samson, 2008) Labour induction may also be associated with non-reassuring fetal heart rate patterns(Glantz, 2005), instrumental delivery and neonatal admission.(Cammu, Martens, Ruyssinck, & Amy, 2002) However other studies show that labour induction per se is not predictive of Caesarean delivery after adjusting for nulliparity and the unfavourable cervix.(Alexander, DD, & Leveno, 2001; Prysak & Castronova, 1998) It is noteworthy that studies cited above(Battista et al., 2007; Blackwell et al., 2008; Cammu et al., 2002; Dublin et al., 2000; Glantz, 2005; Hoffman et al., 2006; Johnson et al., 2003; Jonsson et al., 2013; Luthy et al., 2004; Maslow & Sweeny, 2000; Seyb et al., 1999; Vahratian et al., 2005; Xenakis et al., 1997; Yeast et al., 1999) have generally compared outcome of induced labour to spontaneous labour, when more appropriately the analysis should be on an "intention to treat basis" as onset of spontaneous labour cannot be guaranteed and the impact of advancing gestational age arising from expectant management also need to be accounted for.

3.4. Risk factors for failed labour induction

Nulliparity and an unripe cervix are the two major risk factors for a failed labour induction resulting in an unplanned Caesarean delivery.(Grobman, 2012; Talaulikar & Arulkumaran, 2011) When both are present, a Caesarean delivery rate of 35%-45%(Tan, Daud, et al., 2009; Tan, Valiapan, et al., 2007) has been reported in trial settings and the induction to delivery can be prolonged with vaginal delivery rate at 24 hours of only 36%-49%.(Tan, Valiapan, et al., 2007) Induction of labour in nulliparas with unfavourable cervixes remains a major clinical challenge.

3.4.1. The unripe cervix: *Bishop Score vs. cervical length by transvaginal ultrasound*

Predictive information on the likelihood of successful induction and of other adverse pregnancy outcomes after a failed induction is of use in the counselling of women faced with the prospect of having their labour induced, not least to manage expectations. This information may allow women to make an informed choice of going ahead with labour induction, opting for elective Caesarean delivery if immediate delivery is essential or await further cervical maturation or even spontaneous labour in cases where the indication for labour induction is "soft".

Since its introduction originally to predict onset of spontaneous labour in 1964, the Bishop Score(Bishop, 1964) and its modifications have become the established predictor of cervical favourability for the speedy and successful

induction of labour(Baacke & Edwards, 2006). The Bishop Score is a summation score derived from per-vaginal digital assessment of various parameters concerning the cervix uteri and of the position of the fetal head. Obtaining the Bishop Score is a more discomfiting exercise compared to transvaginal sonography for cervical length as found in a study of 50 women(Paterson-Brown et al., 1991) and a secondary analysis of a subset of 40 women from a larger study.(Chandra et al., 2001) We confirmed in a large study of 249 participants that transvaginal ultrasound assessment of cervical length was better tolerated than the Bishop Score assessment.(Tan, Vallikkannu, et al., 2007) A better tolerated assessment method is an important consideration in quality care from the women's perspective.

Since the 1990's, cervical length derived from transvaginal ultrasound has emerged as a viable alternative to the Bishop Score in predicting successful labour induction. A shorter cervix on transvaginal ultrasound is better predictive of faster(Boozarjomehri, Timor-Tritsch, Chao, & Fox, 1994) or of successful labour induction(Gabriel et al., 2002; Gabriel, Darnaud, Gonzalez, Leymarie, & Quereux, 2001; Pandis, Papageorghiou, Ramanathan, Thompson, & Nicolaides, 2001; Rane, Guirgis, Higgins, & Nicolaides, 2003, 2004; Ware & Raynor, 2000; Yang, Roh, & Kim, 2004) compared to the Bishop Score but this finding of superiority is not consistently demonstrated(Chandra et al., 2001; Gonen, Degani, & Ron, 1998; Reis et al., 2003; Rozenberg, Chevret, Chastang, & Ville, 2005). In the early 2000s, the value and role of transvaginal ultrasound derived cervical length in pre-labour induction assessment was unresolved and remains so today.

3.4.2. Sonographic fetal and cervical parameters as integrated predictors of successful labour induction

Up to the mid 2000's the predictive value for labour induction success of estimated fetal weight by ultrasound(Morgan & Thurnau, 1988), amniotic fluid volume(Alchalabi, Obeidat, Jallad, & Khader, 2006; Venturini, Contu, Mazza, & Facchinetti, 2005) and cervical length by transvaginal ultrasound(Bartha, Romero-Carmona, Martinez-Del-Fresno, & Comino-Delgado, 2005; Chandra et al., 2001; Novakov-Mikic et al., 2000; Paterson-Brown et al., 1991; Reis et al., 2003) have been evaluated but usually not in an integrated manner(Peregrine, O'Brien, Omar, & Jauniaux, 2006) and results are often inconsistent across studies. We undertook a prospective study in women who underwent labour induction assessing these ultrasound parameters in conjunction with other relevant clinical characteristics and established after multivariable logistic regression analysis that only a long cervix (> 20 mm) by transvaginal ultrasound and nulliparity were independently predictive of Caesarean delivery following labour induction. Estimated fetal weight, amniotic fluid index and other clinical characteristics were not predictive of Caesarean delivery.(Tan, Suguna, et al., 2006)

3.5. Optimal gestation for elective labour induction

Interestingly, a 2006 paper using a decision analytic model using retrospective data from a single institution finds that after controlling for potential confounders, there was a higher rate of Caesarean delivery risk among women with expectant

management beyond 38 weeks (adjusted odds ratio [AOR] 1.80; 95% CI 1.29-2.53), 39 weeks (1.39; 95% CI 1.08-1.80), and 40 weeks (AOR 1.27; 95% CI 1.00-1.62)(Caughey, Nicholson, Cheng, Lyell, & Washington, 2006).

A 2009 systematic review also applying a decision analytic model finds that in each of the models, women who were electively induced had better overall outcomes among both mothers and neonates as estimated by total quality-adjusted life years as well as by reductions in specific perinatal outcomes such as shoulder dystocia, meconium aspiration syndrome, and preeclampsia. However, the findings of cost-effectiveness at 40 and 39 weeks of gestation were not robust to the ranges of the assumptions made.(Caughey et al., 2009)

Subsequently (2010) a multicentre perinatal database analysis also shows that babies born with elective induction are associated with better neonatal outcomes compared to spontaneous labour but elective induction may be associated with an increased hysterectomy risk.(Bailit et al., 2010)

Another analysis (2011) using data from the Danish Birth registry finds that from gestational week 39 and thereafter, there was no difference with regard to CS rates in labour among nulliparous and parous women when comparing women with induced labour and those women who waited for a later labour, either induced or spontaneous.(Rasmussen & Rasmussen, 2011)

A 2013 Californian birth registry study also indicates with elective induction at 37-40 weeks the odds of caesarean delivery were lower among women with elective induction compared with expectant management across all gestational ages and parity (37 weeks [odds ratio (OR) 0.44, 95% confidence interval (CI) 0.34-0.57], 38 weeks [OR 0.43, 95% CI 0.38-0.50], 39 weeks [OR 0.46, 95% CI 0.41-0.52], 40 weeks [OR 0.57, CI 0.50-0.65] without increased odds of severe lacerations, operative vaginal delivery, perinatal death, neonatal intensive care unit admission, respiratory distress, shoulder dystocia, or macrosomia.(Darney et al., 2013)

A 2013 meta-analysis of labour induction trials in women with intact membranes at term has also reported that "Meta-analysis of 31 trials determined that a policy of induction was associated with a reduction in the risk of CS compared with expectant management (OR 0.83, 95% CI 0.76-0.92)" but cautions that "additional trials are needed".(Wood, Cooper, & Ross, 2013)

In contrast, analysis using data from a New York State birth-certificate database shows that term labour induction compared with expectant management is associated with increased caesarean risk whether using a week-to-week comparison group or an expectant group that includes women the same week or beyond that of the index induction: the finding is still robust after adjustment for parity, high-risk factors, and demographic variables.(Glantz, 2010)

There is also indirect evidence from the meta-analysis of secondary data of a few randomised trials that elective labour induction at 37-40 weeks gestation may be associated with a lower Caesarean delivery rate compared to expectant management but has a higher instrumental vaginal rate(NICE-UK, 2008b) but the finding of reduced Caesarean delivery with labour induction at early term gestation is not consistently demonstrated(Dunne, Da Silva, Schmidt, & Natale, 2009).

In contrast, from the perspective of neonatal outcome there is increasing evidence that early term (37 to 38 weeks compared to 39 to 41 weeks) delivery is associated with adverse childhood outcome.(Boyle et al., 2012; Dong, Chen, & Yu, 2012)

Race can be a crucial factor to consider in determining the ideal timing for delivery: UK data indicate that black and South Asian women compared to white European women tended to go into spontaneous labour earlier and correspondingly their babies' respiratory system appeared to mature at an earlier gestation. In full term South Asian babies, the late gestation rise in antepartum stillbirth occurs one week earlier than in white Europeans.(Balchin & Steer, 2007; Balchin, Whittaker, Lamont, & Steer, 2008) Earlier delivery in late term by labour induction may be the better approach in some non-white Europeans to safeguard neonatal outcome.

The question of an ideal gestation for delivery by elective labour induction in late term as opposed to awaiting spontaneous labour onset can only be settled by large

scale powered controlled trials as to its benefit and cost effectiveness. If labour induction becomes indicated by 39 or 40 weeks gestation, the implication for obstetric care is profound as by the end of 38 weeks or 39 weeks, probably up to 80% and 50% of pregnancies at these respective gestations would not have spontaneously laboured yet leaving a majority to need elective labour induction.

3.5.1. Facilitating spontaneous labour and preventing a prolonged pregnancy

There is epidemiological evidence pointing to an increased risk for mother and baby as a pregnancy continues beyond 40 weeks but the data included both induced labours and spontaneous labours; the absolute risk of perinatal death associated with prolonged pregnancy is low at 2-3 per 1000.(NICE-UK, 2008b) A policy of induction of labour at 41 weeks gestation compared to expectant management is associated with fewer perinatal deaths without increasing the Caesarean delivery rate.(Gulmezoglu, Crowther, & Middleton, 2006) Amongst women who had spontaneous onset of labour, 22.4% started labour only at or after 41 weeks gestation.(NHS_Information_Centre, 2011) Many of these women will need labour induction for prolonged pregnancy with a policy of elective labour induction from 41^{+0} weeks gestation as recommended by NICE UK guideline(NICE-UK, 2008b). Simple measures particularly home remedies (e.g. coitus) that effectively facilitate labour in late term before 41 or 42 weeks gestation may be an economic way to reduce the need for labour induction indicated by prolonged pregnancy.

3.5.2. Coitus to Facilitate Onset of Labour

Coitus is widely believed by women to hasten the onset of labour.(Schaffir, 2002) Coitus during pregnancy is safe with no effect on perinatal mortality.(Klebanoff, Nugent, & Rhoads, 1984) Coitus during pregnancy is also not associated with preterm labour (Berghella et al., 2002; Kurki & Ylikorkala, 1993; Sayle, Savitz, Thorp, Hertz-Picciotto, & Wilcox, 2001) [even in the context of a twin pregnancy(Neilson & Mutambira, 1989)] or with PROM(Ekwo, Gosselink, Woolson, Moawad, & Long, 1993).

Coitus can increase uterine activity in women at higher risk of preterm labour compared to controls(Brustman, Raptoulis, Langer, Anyaegbunam, & Merkatz, 1989) suggesting that in women on the cusp of labour, coitus may tip such women into labour but would otherwise have little effect in women distant from their natural onset of labour. This rationale opens the potential for coitus to facilitate labour in women at term.

Despite widespread folk belief in the ability of coitus to expedite onset of labour(Schaffir, 2002), there were very few studies on the effect of coitus in initiating labour at term.(Tan, Andi, et al., 2006) Antenatal care guideline advice from the National Institute for Health and Clinical Excellence, UK (2008) states that “Pregnant woman should be informed that sexual intercourse in pregnancy is not known to be associated with any adverse outcomes” indicating it is safe. (NICE-UK, 2008a) We performed an original prospective study on the effect of coitus on onset of labour at term gestation with strongly positive findings.(Tan,

Andi, et al., 2006) There was no data from randomised trials on recommending/advising coitus as an intervention to facilitate labour at term until we undertook two such clinical intervention trials(Tan, Yow, et al., 2007) (Omar et al., 2013) with negative findings. In addition a secondary analysis of the earlier trial's data(Tan, Yow, et al., 2009) was also performed as a sensitivity as well as a hypothesis generating exercise with somewhat surprising and counterintuitive findings of an inverse correlation between coitus and earlier onset of labour.(Tan, Yow, et al., 2009)

3.6. Labour induction in VBAC

Induction of labour following a previous Caesarean is highly controversial as it is associated with increased risk of uterine rupture and a lower rate of vaginal delivery but is permitted by national guidelines with caution on the use of PGs.(American College of & Gynecologists, 2010; RCOG-UK, 2007; Sentilhes et al., 2013; SOG-Canada, 2005)

Uterine rupture rates were found to be 0.52% for spontaneous labour, 0.77% for labour induced without PGs, and 2.24% for PG induced labour.(Lydon-Rochelle, Holt, Easterling, & Martin, 2001) Induction of labour is also associated with increased risk of a failed TOLAC compared to spontaneous labour (Delaney & Young, 2003; Rageth, Juzi, & Grossenbacher, 1999; Shatz et al., 2013), an association which remains significant after adjustment for confounders(Landon et al., 2005) (Eden et al., 2010).

A 2012 Cochrane review failed to identify a single trial that compared labour induction for a TOLAC compared to ERC.(Dodd & Crowther, 2012) In 2012, an Australian multicentre trial of 2345 women reported that "Among women with one prior caesarean, planned ERC compared with planned VBAC was associated with a lower risk of fetal and infant death or serious infant outcome"(Hayter et al., 2010) which could be extrapolated to imply that with induced TOLAC, the advantage for planned ERC should be more evident.

Despite higher morbidity, two 2013 analyses rather controversially suggest that planned VBAC can still be cost effective "when the probability of TOLAC success was at the base value, 68.5%, TOLAC was preferred if the probability of uterine rupture was 4.2% or less. When the probability of uterine rupture was at the base value, 0.8%, the TOLAC strategy was preferred as long as the probability of success was 42.6% or more"(Gilbert et al., 2013) and "maternal morbidities emerged in twice as many cases in the TOLAC group than the ERCD group. However, a TOLAC was found to be the most-effective method of delivery because it was substantially less expensive than ERCD (€ 1,835.06 versus € 4,039.87 per women, respectively), and QALYs were modestly higher (0.84 versus 0.70). Our findings were supported by probabilistic sensitivity analysis." (Fawsitt et al., 2013)

Prior vaginal delivery is a strong predictor for successful labour after a previous Caesarean.(Eden et al., 2010) The Bishop score is also independently predictive of successful labour induction in women with a previous Caesarean.(Bujold et al.,

2004) A study from our centre have also demonstrated that labour induction and no prior vaginal births were independent risk factors for unplanned Caesarean delivery after a TOLAC delivery.(Tan, Subramaniam, & Omar, 2008) In women having their labour induced for a TOLAC without prior vaginal delivery, 49% were delivered by CS.(Grobman et al., 2007)

Membrane sweeping is of proven effectiveness in expediting labour (Boulvain et al., 2005). In women desiring TOLAC, we found serial weekly membrane sweeping was not effective in facilitating labour or reducing CS but this conclusion could represent a Type 2 statistical error as the observed effect was smaller than envisaged in our sample size calculation.(Hamdan et al., 2009)

3.7. Induction of labour versus planned Caesarean delivery

The practical alternative to induction of labour is a planned Caesarean delivery. There is no controlled trial comparing these alternatives. These are reasonable choices in a well-resourced setting where a Caesarean delivery is easily accessible and can be safely performed and a small family size is the desired norm. Indeed, delivery by Caesarean is already the stated choice of a substantial minority of 15.6% of pregnant women from middle to high income countries(Mazzoni et al.) but as is obvious even in this population, a large majority still prefers a vaginal birth .

Caesarean delivery compared to spontaneous vaginal delivery is associated with increased severe maternal outcomes.(Liu et al., 2007; Souza et al.) Elective Caesarean delivery although at lower risk than emergency Caesarean delivery,

still has increased maternal(Liu et al., 2007) and neonatal risks compared to delivery outcome following spontaneous labour(Dunne et al., 2009). Even intention to treat analysis of planned Caesarean delivery compared with planned vaginal delivery show a higher severe maternal morbidity rate but the absolute risk is low (27.3 and 9.0 respectively per 1000 deliveries) and maternal mortality rate is no different.(Liu et al., 2007)

Planned Caesarean delivery is associated with a stepwise increase in early neonatal respiratory morbidity from 36-40 weeks.(Stutchfield, Whitaker, Russell, & Antenatal Steroids for Term Elective Caesarean Section Research, 2005) Caesarean delivery is associated with a fetal injury rate of 1.1% (e.g. skin laceration, cephalohaematoma, clavicular fracture, brachial plexus, skull fracture and facial nerve palsy) and even elective Caesarean delivery is associated with a 0.5% fetal injury rate.(Alexander et al., 2006) In women desiring a larger family it should be factored in that maternal morbidity increases in tandem with the number of prior Caesareans: placenta accreta was present in 0.24%, 0.31%, 0.57%, 2.13%, 2.33% and 6.74% of women undergoing their first, second, third, fourth, fifth, and sixth or more caesarean deliveries, respectively. Hysterectomy was required in 0.65% of the first, 0.42% of the second, 0.90% of the third, 2.41% of the fourth, 3.49% of the fifth, and 8.99% of the sixth or more caesarean deliveries. In the 723 women with previa, the risk for placenta accreta was 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more caesarean deliveries, respectively.(Silver et al., 2006)

On the other hand, induction of labour has a 23% general risk of "failure" resulting in an unplanned Caesarean delivery.(NHS_Information_Centre, 2011) Labour induction is associated with lower maternal satisfaction compared to spontaneous labour but surprisingly, the induction to delivery interval is perceived to be the single most important factor contributing to patient satisfaction with the mode of administration of the inducing agent, more vaginal examinations and the increase in caesarean deliveries being considered as secondary issues when viewed from the women's perspective.(Shetty, Burt, Rice, & Templeton, 2005)

However, a review in 2012 on predictors of Caesarean delivery following induction of labour finds many limitations on the practicality and applicability of this knowledge of predictors in reducing Caesarean births: the author advocates patience during the induction process as a means of reducing Caesarean delivery.(Grobman, 2012) Studies that integrated predictors of failed induction in the management decision process on whether to proceed with labour induction when indications are "soft" have been very sparse.

3.8. Methods of induction of labour

Induction of labour of a viable pregnancy is currently initiated and effected by four principal methods:

i) amniotomy(Bricker & Luckas, 2000; Howarth & Botha, 2001),

ii) intravenous oxytocin infusion(Alfirevic, Kelly, & Dowswell, 2009; Howarth & Botha, 2001),

iii) prostaglandins typically PGE 1 or 2 (e.g. dinoprostone(Hughes, Kelly, & Kavanagh, 2001; Kelly, Kavanagh, & Thomas, 2003) or misoprostol(Bartusevicius, Barcaite, & Nadisauskiene, 2005; Kundodyiwa, Alfirevic, & Weeks, 2009); the latter originally developed as an anti-peptic ulcer agent is cheap, temperature stable and widely used but is not currently licensed for labour induction in Malaysia) administered either trans-vaginally(Boulvain, Kelly, & Irion, 2008; Kelly et al., 2009) or orally(Alfirevic & Weeks, 2006; Muzonzini & Hofmeyr, 2004) and

iv) mechanical methods(Boulvain, Kelly, Lohse, Stan, & Irion, 2001; Gelber & Sciscione, 2006) [e.g. membrane sweeping(Boulvain et al., 2005), transcervical balloon catheters(Vaknin, Kurzweil, & Sherman)].

A review article published in 2012 titled "Current Methods of Labor Induction" discussed fully the above methods(Swamy, 2012); it is clear that there has not been a paradigm shift in labour induction methods or agents since the introduction of prostaglandins more than 4 decades ago(Embrey, 1970; Karim, Trussell, Patel, & Hillier, 1968) and of oxytocin more 6 decades ago(Donnelly, 1949; Schneider, Ferguson, & Miller, 1951) although modes of administration and dosage regimens have been refined.

Current labour induction regimens are typically variations of the above methods with differences in sequence, combination, timing, dose, intensity and the route or vehicle of drug administration. These operational parameters can be adjusted to achieve higher effectiveness depending on clinical settings(NICE-UK, 2008b),

lending opportunities for clinical trials to evaluate the most efficient regimens particularly in settings where current labour induction failure rates are high or safety is in question (e.g. in nulliparas with unfavourable cervixes or VBAC attempts).

In contrast, in multiparous women with favourable cervixes whose labour are easily induced, it is a reasonable supposition whether a less aggressive regimen e.g. amniotomy alone followed by a short latency period (say of four hours) before augmenting with titrated oxytocin infusion could be a sufficient approach. Trial data on these commonly applied alternatives of immediate versus a 4-hour delayed titrated oxytocin infusion following amniotomy in favourable parous women was not available. We undertook four original randomised trials on various induction regimens in different populations to obtain quality data to help guide practice.(Tan, Daud, et al., 2009; Tan, Jacob, et al., 2006; Tan et al., 2013; Tan, Valiapan, et al., 2007)

3.8.1. Membrane Sweeping to Expedite and Induce Labour

Membrane sweeping involves digitally separating through the cervix membranes from the lower uterine pole as a means of initiating the cascade of events ultimately culminating in the onset of labour. The procedure has been described as "inserting the examining finger as high as possible past the internal cervical os, and the membranes were swept off the lower pole of the uterus by a complete circular sweep of the finger, once clockwise and once counter-clockwise. In the

event of a closed internal or external cervical os, the cervical canal or external cervix was swept with 2 circular motions".(Tan, Jacob, et al., 2006)

Membrane sweeping is an interesting method of facilitating labour as it is highly economical, can be performed without any additional equipment or drug (requiring only a gloved hand) in an office setting, fairly easy and quick to perform and has a short learning curve in order to master. However, it is an discomfiting procedure which may also cause mild vaginal bleeding.(Boulvain et al., 2005)

In a Cochrane review of 22 trials comprising 2797 women, membrane sweeping is demonstrated to be effective in expediting onset of labour with eight women needing to undergo membrane sweeping for one woman to avoid formal labour induction. However, the overall Caesarean delivery rate is not reduced by membrane sweeping.(Boulvain et al., 2005) Despite these limitations, UK National Institute of Health and Clinical Excellence 2008 guideline on induction of labour recommends that prior to formal induction of labour, women should be offered a vaginal examination for membrane sweeping.(NICE-UK, 2008b)

Membrane sweeping performed at the initiation of labour as an immediate adjunct to either amniotomy (with or without oxytocin infusion) or vaginal dinoprostone has been shown to shorten the induction to labour interval and increase spontaneous vaginal delivery rates in nulliparas with unfavourable cervixes according to a solitary randomised controlled trial report evaluating this more

novel application.(Foong et al., 2000) We conducted a similar clinical trial and corroborated the theory that adjunctive membrane sweeping at formal labour induction improved labour and delivery outcomes.(Tan, Jacob, et al., 2006) This corroboration demonstrates reproducibility, a critical component of the scientific process leading to a robust evidence base to guide practice.

Women with a previous lower segment Caesarean delivery who desire VBAC have a particular need to avoid induction of labour due to the high unplanned Caesarean delivery rate and higher risk of uterine rupture with induction. In women who did not have a prior vaginal delivery attempting a trial of VBAC by labour induction, only 51% achieved vaginal delivery.(Grobman et al., 2007) Published data from our centre also shows a similar vaginal delivery rate 52.1% after labour induction amongst women attempting VBAC.(Tan, Subramaniam, et al., 2008) In women attempting VBAC, uterine rupture rates were 1% versus 0.4% (OR 2.86, 95% CI 1.75-4.67) in induced and spontaneous labour respectively, a significantly higher rate with induced labour.(Landon et al., 2004) The risk of intrapartum uterine rupture was also higher among women who had not previously given birth vaginally (adjusted OR 2.5, 95% CI 1.6 to 3.9) and amongst those whose labour was induced with PG (OR 2.9, 95% CI 2.0 to 4.3).(Smith, Pell, Pasupathy, & Dobbie, 2004) Gestational age after 40 weeks is also an independent risk factor for uterine rupture at a trial of VBAC.(Kiran, Chui, Bethel, & Bhal, 2006). Risk of unexplained stillbirth associated with previous caesarean delivery was apparent from 34 weeks. The absolute risk of unexplained stillbirth at or after 39 weeks' gestation was 1.1 per 1000 women who had had a

previous CS and 0.5 per 1000 in those who had not due mostly to an excess of unexplained stillbirths.(Smith, Pell, & Dobbie, 2003)

Membrane sweeping which is a proven non-pharmacologic outpatient method of initiating labour in low or average risk women(Boulvain et al., 2005) have a potentially unique role in women desiring VBAC to help them avoid a prolonged pregnancy and formal labour induction with its attendant high adverse outcome risks. We evaluated weekly serial membrane sweeping at term in high risk women desiring VBAC but did not succeed in demonstrating benefit.(Hamdan et al., 2009)

We postulated that membrane sweeping might cause a small immediate change in cervical dilatation based on a post hoc analysis of our adjunctive membrane sweeping trial.(Tan, Jacob, et al., 2006) The immediate mechanical effect of membrane sweeping on cervical length on transvaginal ultrasound and the impact cervical shortening may have on predicting downstream obstetric outcomes have not previously been evaluated. We performed a novel study combining transvaginal ultrasound assessment of cervical length, membrane sweeping and pregnancy outcome.(Tan et al., 2011)

3.9. Failed induction of labour

The definition of a failed induction of labour is not universally agreed upon with many versions on offer.(Talaulikar & Arulkumaran, 2011) This lacuna is deeply problematic for practice as a “failed induction” is considered a legitimate indication for Caesarean delivery even though many indications for labour induction are “soft” lacking a strong evidence based justification.

In the University of Malaya Medical Centre, the standard labour induction regimen for women with unfavourable cervixes is bolus vaginal dinoprostone pessary (twice daily for up to 4 doses) with amniotomy and oxytocin infusion to follow sequentially after cervical ripening. A failed induction often resulting in Caesarean delivery is typically called if the cervix fails to ripen sufficiently to allow amniotomy after 4 doses of vaginal dinoprostone over two days or there is no progress after six hours of titrated oxytocin infusion following amniotomy. Cases may occasionally be managed more conservatively when membranes are still intact as illustrated in a trial report on labour induction from our centre where “one woman was allowed nine ‘rest’ days following initial failed induction and another had two rest days”(Tan, Jacob, et al., 2006) before a further attempt at induction. Not infrequently, up to six doses of dinoprostone may also be given over three days to ripen the cervix. Our centre does not use misoprostol for labour induction in any circumstance as a matter of hospital policy as misoprostol is not licensed for labour induction in Malaysia.

It is illuminating that the 2011 WHO guideline on induction of labour highlights in its executive summary that “Failed induction of labour does not necessarily indicate CS.”(WHO, 2011)

In the 2011 PROBAAT trial where transcervical Foley balloon is compared with vaginal dinoprostone for induction of labour, the protocol permitted “if the cervix was still unfavourable for amniotomy after 48 h of treatment, women were generally assigned a day of rest followed by another 48 h of induction. If after these 5 days the cervix was still unfavourable, induction was defined as failed and further management was decided by the treating obstetrician”, indicating a highly tolerant approach to a prolonged labour induction process.(Jozwiak et al., 2011) A 2012 review titled “Failed induction of labor: strategies to improve the success rates” also suggested in failed primary labour induction for prolonged pregnancy where the urgency for delivery is not paramount, a patient approach with assessment to establish reassuring fetal status followed by a 48 hours “rest period” before recommencing another induction regimen if that is acceptable to the woman as a reasonable measure to reduce Caesarean delivery rates.(Talaulikar & Arulkumaran, 2011) Whilst intellectually persuasive as being capable of reducing Caesarean delivery the acceptability, safety and cost effectiveness of a policy that tolerates a prolonged induction process has not been thoroughly evaluated.

3.10. Dynamics of induced labour

Electively induced nulliparous labour with cervical ripening had substantially slower latent and early active phases but elective induction without cervical

ripening, on the other hand, was associated with a faster labour progression from 4 to 10 cm compared to spontaneous labour.(Vahratian et al., 2005) Induced parous women compared to non-induced women also has a shorter active phase than those admitted in spontaneous labour whether or not cervical ripening by Foley's catheter is needed.(Hoffman et al., 2006) Among women who reach full dilation, labour proceeds similarly regardless of induction status but induced nulliparas may have an increased risk of haemorrhage and caesarean delivery.(Janakiraman, Ecker, & Kaimal, 2010)

A 2014 consensus statement developed jointly by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine on safe prevention of the primary caesarean delivery also suggest a more patient approach to labour progress stating "it may be necessary to revisit the definition of labor dystocia because recent data show that contemporary labor progresses at a rate substantially slower than what was historically taught".("Obstetric care consensus no. 1: safe prevention of the primary cesarean delivery," 2014)

Understanding and knowledge of these labour dynamics will help manage expectation during the intrapartum period for providers and women alike and may reduce inappropriate diagnosis of failed labour induction or labour dystocia.

3.11. Addressing selected research issues in the induction of labour

Current research issues regarding induction of labour include

1. Can the need of formal labour induction be reduced with simple (“home”) or office measures to facilitate labour onset?
2. Are there reliable and clinically usable pre-induction characteristics that can predict labour induction failure that will permit informative counselling for a maternal decision to either delay induction or opt for Caesarean delivery if the chance of induction failure is high?
3. What are the most effective, efficient, acceptable and safe methods for successful labour? In particular given the multiplicity of indications for labour induction, which induction regimen may be best for a given situation?

This candidate presents a body of published research works that contribute to answering the issues highlighted above with a “work in progress” label still applicable for many of these questions.

4. Conclusions

4.1. Thesis publications: Cumulative effect and significance

The twelve publications selected for the thesis comprised four original papers on coitus to expedite labour onset(Omar et al., 2013; Tan, Andi, et al., 2006; Tan, Yow, et al., 2007, 2009), three original studies of membrane sweeping to increase potency of labour induction regimen, expediting spontaneous labour in VBAC and understanding membrane sweeping's mechanism of effect using sonography(Hamdan et al., 2009; Tan, Jacob, et al., 2006; Tan et al., 2011), two original studies of sonographic assessment of cervical length and fetal parameters to predict successful labour induction(Tan, Suguna, et al., 2006; Tan, Vallikkannu, et al., 2007), three original studies on labour induction regimens: concurrent use of intravenous oxytocin infusion and vaginal dinoprostone to intensify the induction effort in women at high risk of labour induction failure(Tan, Daud, et al., 2009; Tan, Valiapan, et al., 2007) and in contrast a de-intensified regimen of delayed oxytocin after amniotomy in the induction of labour of parous women with favourable cervixes(Tan et al., 2013).

4.1.1. Coitus Papers

Coitus is an interesting avenue which we explored given its longstanding folk status as a facilitator of labour(Schaffir, 2002). Potentially, coitus is a natural and often orgasmic(Tan, Yow, et al., 2009) method that the couples could apply themselves for the purpose of getting labour started. We evaluated the effect of coitus on labour onset in a prospective diary based study with exciting positive

findings,(Tan, Andi, et al., 2006) We explored advising coitus to women scheduled for labour induction to establish whether such an intervention might expedite labour onset and reduce need for labour induction with somewhat disappointing finding that women will heed such advice but there was no impact on onset of labour.(Tan, Yow, et al., 2007) This report(Tan, Yow, et al., 2007) was abstracted by Obstetrical and Gyneological Survey with an editorial commentary shortly after publication (Obstet Gynecol Surv: Volume 63(3), March 2008, pp 127-128). We also studied the effectiveness of giving such advice as an intervention in low risk and coitally abstinent women at 36 weeks gestation, demonstrating again that advice was heeded but there was no significant impact of onset of labour.(Omar et al., 2013)

The diary based study of the effect of coital activity in late term on the onset of labour and its benefits was carried in 2002-3 with data from 200 women with uncomplicated pregnancies. We wrote then that ‘a literature search of PubMed was carried out on January 15, 2006, in all languages, using the search terms “coitus” or “sexual intercourse” and “labor induction,” “postdate” and “post term,” looking for articles published between January 1966 and January 2006. No relevant article was found, indicating a paucity of data on coitus at term on length of gestation and induction of labor’(Tan, Andi, et al., 2006). The article was subsequently published in July 2006. Our finding that “reported sexual intercourse at term was associated with earlier onset of labor and reduced requirement for labour induction at 41 weeks” was original and of importance as it was the first demonstration of coitus as a simple even enjoyable (orgasmic) means(Tan, Yow,

et al., 2009) of reducing the need for labour induction for prolonged pregnancy which is a major issue in contemporary obstetrics(Tan, Andi, et al., 2006).

As a direct impetus from the finding that coitus can trigger labour onset at term from our diary study(Tan, Andi, et al., 2006), a follow on randomised control trial of advising women to have coitus as a means of expediting labour to avoid their imminently scheduled labour induction was carried out from 2005-6 with 210 women available for analysis. The trial report published in 2007 shows that women assigned to the advised-coitus group were more likely to report coital activity but their spontaneous labour rate was no different.(Tan, Yow, et al., 2007)

The above finding(Tan, Yow, et al., 2007) was unexpected and a secondary analysis of the trial data using multivariable logistic regression analysis was subsequently published with the counter-intuitive finding that "women who reported coitus were less likely to go into spontaneous labour prior to their scheduled labour induction"(Tan, Yow, et al., 2009). We postulated that the rationale behind our finding of an inverse association between reported coitus and frequency of coitus to spontaneous labour onset may be because abstinence was a consequence of imminent labour (the time interval within the study was only 3-4 days on average before hospitalisation for birth) limiting the opportunity for coitus or of reduced libido due to preceding symptoms or signs of imminent labour, like increased uterine contractions and passage of a show(Tan, Yow, et al., 2009). Coitus is a complex activity during pregnancy that is difficult to influence

and can be affected by the libido and safety beliefs of the couple(Tan, Andi, et al., 2006). Speculatively, a woman on the short run up to an imminent spontaneous labour might have subtle symptoms causing her to be less inclined to have sex with her partner. The couple might also be fastidious in the presence of prelabour signs. This might have given rise to the counterintuitive observation we made that coitally active woman scheduled for imminent labour induction was likely to present in spontaneous labour later than those who did not report coitus.(Tan, Yow, et al., 2009)

A second intervention trial(Omar et al., 2013) was also instituted arising directly from the earlier observational study(Tan, Andi, et al., 2006). This trial recruited women at 36 weeks gestation who were recently abstinent of coitus. The intervention was identical to the earlier trial(Tan, Yow, et al., 2007); participants randomised to the advice arm were told that coitus is safe, can effectively expedite labour and will reduce the need for labour induction for prolonged pregnancy. 1200 women were recruited and randomised from March 28 2008 to June 15 2011. The trial report was published in 2013. Again, women assigned to the intervention were more likely to report coitus but labour onset and labour induction were not different. Post hoc, we compared also the pregnancy duration and labour induction rate of the coitally active versus abstinent participants regardless of trial intervention assignment. Intervention to delivery interval and labour induction rates were similar; women whose labour was induced reported fewer episodes of coitus. We proceeded to perform a post hoc multivariable logistic regression analysis to evaluate the risk factors for labour induction

incorporating frequency of reported coitus, recruitment to delivery interval, ethnicity, PROM and nulliparity into the model. After adjustment, frequency of reported coitus (as a continuous variable) was not independently associated with labour induction.(Omar et al., 2013)

These various trial and secondary analyses (Omar et al., 2013; Tan, Yow, et al., 2007, 2009) taken as a whole are not supportive of coitus as an effective facilitator of labour at term but coitus is safe.

A prospective study by Schaffir(Schaffir, 2006) published in the same issue of Obstetrics and Gynecology as our diary based study(Tan, Andi, et al., 2006) shows that 50.5% reported sexual intercourse at term. The gestational age at delivery of those women who were sexually active at term was greater than those who were not. After adjusting for the effect of time, those who were sexually active the previous week had Bishop Scores that were, on average, lower compared with those who abstained; the study report conclude that sexual intercourse at term is not associated with ripening of the cervix and does not hasten labour. It has to be said that the results and analysis from our intervention trials(Omar et al., 2013; Tan, Yow, et al., 2007, 2009) were generally in better keeping with Schaffir's than our diary based study's(Tan, Andi, et al., 2006) findings.

A PubMed search (accessible via http://www.ncbi.nlm.nih.gov/pubmed) on 2 February 2014 using search terms: coitus and onset of labour without limitations revealed no later publications following our series in this setting, indicating that our work is still providing the latest evidence base on this issue.

4.1.2. Membrane Sweeping Papers

Membrane sweeping has potential for significant benefit when used as adjunct in formal induction as shown by the findings from a solitary trial.(Foong et al., 2000). Our trial findings(Tan, Jacob, et al., 2006) were fully supportive of the previous findings of benefit. Our report(Tan, Jacob, et al., 2006) was swiftly followed by a commentary and meta-analysis where data from Foong et al(Foong et al., 2000) and ourselves(Tan, Jacob, et al., 2006) were combined with the conclusion that "pooling the data for the two studies resulted in a significant increase in spontaneous vaginal delivery rates for those undergoing sweeping of the membranes and overall vaginal delivery rates.(Sanchez-Ramos, 2006) Membrane sweeping is simple procedure requiring no additional equipment or drug which takes only seconds when deployed as an adjunct to current "gold standard" induction regimens. An absolute 12% increase in vaginal delivery rate and 7.2% reduction in Caesarean rate with adjunctive membrane sweeping as shown by Ramos-Sanchez's meta-analysis represents a significant advance.

A second randomised trial of membrane sweeping followed, focused on high risk women who desired a VBAC(Hamdan et al., 2009) where timely onset of spontaneous labour is especially important as labour induction is fraught with

significant risk of uterine rupture and high risk of unplanned Caesarean delivery.(Landon et al., 2004; Lydon-Rochelle et al., 2001; Shatz et al., 2013) Additionally there is evidence that intrauterine death rate may be especially high as pregnancy is prolonged in these women with prior Caesarean.(Smith et al., 2004) This trial involved weekly serial membrane sweeping against a control group that underwent weekly vaginal examination for Bishop Score only. The trial recruited 213 women from September 2007 to November 2008 and found that "serial membrane sweeping at term in women who planned VBAC has no significant effect on the onset of labour, pregnancy duration, induction of labour or repeat Cesarean delivery."(Hamdan et al., 2009)

In the earlier adjunctive membrane sweeping trial(Tan, Jacob, et al., 2006) we found that women randomised to sweeping had a decreased incidence of having a closed cervix at the initial Bishop Score assessment which was unlikely to be due to chance event as all other Bishop Score components and all other subject characteristics were similar. We postulated that clinicians had recorded the post sweep cervical dilatation assuming that sweeping caused the cervix to dilate and the mechanically dilated and disrupted cervix might offer less resistance to further dilation.(Tan, Jacob, et al., 2006) This hypothesis combined with the candidate's interest and expertise in transvaginal ultrasound assessment of cervical length(Tan, Suguna, et al., 2006; Tan, Vallikkannu, et al., 2007) precipitated a prospective study to evaluate the immediate effect of membrane sweeping on sonographic cervical length and to assess cervical shortening as a putative marker of cervical pliability leading to increased chance of later vaginal delivery.(Tan et

al., 2011) We found that a shortened cervix following membrane sweeping was independently predictive of a reduction in Caesarean delivery but sweeping on average actually resulted in a slight lengthening of the cervix. We posit that the cervical lengthening might be a consequence of the decompression of the cervix as the fetal head was pushed off the cervix during membrane sweeping. It is also plausible that sweeping "stretched" the cervix, lengthening it temporarily.

For women desiring VBAC where it is particularly important to avoid labour induction with its attendant high risk of repeat emergency caesarean delivery and scar rupture(Grobman et al., 2007; Landon et al., 2004), serial weekly membrane sweeping at term presents an excellent opportunity to expedite labour for these women to avoid prolonged pregnancy and labour induction, an avenue which we explored in a randomised clinical trial but found negative results.(Hamdan et al., 2009)

A PubMed search (accessible via http://www.ncbi.nlm.nih.gov/pubmed) on 2 February 2014 using search terms: membrane sweeping and induction of labour without limitations revealed no later publications following our series on adjunctive membrane sweeping, membrane sweeping targeted at women for VBAC or the use of transvaginal ultrasound of the cervix to evaluate the effect of membrane sweeping.

4.1.3. Sonography of cervical length and fetal parameters

A small number of research groups in the late 1990's and early 2000's were also attempting to derive predictive algorithms for successful labour induction using various ultrasound(Rane et al., 2004) and combined ultrasound and clinical parameters(Peregrine et al., 2006). Prior to 2003, at the inception of our study(Tan, Suguna, et al., 2006), to our knowledge at the time there was no study that integrated clinical and sonographic parameters to identify independent predictors of labour induction failure although transvaginal cervical length(Boozarjomehri et al., 1994; Chandra et al., 2001; Gabriel et al., 2001; Gonen et al., 1998; Novakov-Mikic et al., 2000; Pandis et al., 2001; Paterson-Brown et al., 1991; Ware & Raynor, 2000), amniotic fluid index(Saunders, Amis, & Marsh, 1992) and estimated fetal weight(Combs, Singh, & Khoury, 1993; Morgan & Thurnau, 1988) have been separately evaluated. Our study was published in Dec 2006. We found nulliparity and cervical length of more than 20 mm on transvaginal sonography were independent predictors of caesarean delivery.(Tan, Suguna, et al., 2006) In February 2006, Peregrine et al reported in Obstetrics and Gynecology on a cohort of 267 women that parity, body mass index, height, and ultrasonic transvaginal cervical length are the most accurate parameters in predicting the risk of caesarean delivery after induction of labour after also assessing amniotic fluid volume and estimated fetal weight by ultrasound.(Peregrine et al., 2006) Our study report(Tan, Suguna, et al., 2006) was abstracted by Obstetrical and Gyneological Survey with an editorial commentary shortly after publication (Obstet Gynecol Surv: Volume 62(3), March 2007, pp 170-171). Interestingly, a later secondary analysis of our data which we also reported showed that an unfavourable Bishop Score but not a long cervix on

transvaginal ultrasound was an independent predictor of neonatal admission after delivery following labour induction after adjustment.(Tan, Suguna, Vallikkannu, & Hassan, 2008).

Cervical length by transvaginal ultrasound as a predictor of successful labour induction compared to the Bishop Score was extensively researched since the early 1990's with conflicting findings.(Boozarjomehri et al., 1994; Chandra et al., 2001; Gabriel et al., 2002; Gabriel et al., 2001; Gonen et al., 1998; Pandis et al., 2001; Paterson-Brown et al., 1991; Rane et al., 2003, 2004; Reis et al., 2003; Rozenberg et al., 2005; Ware & Raynor, 2000; Yang et al., 2004)

Starting in 2003 and completing in 2005, 249 women were recruited by our team just prior to their labour induction for a prospective study comparing transvaginal ultrasound for cervical length and Bishop Score in assessing tolerability and predicting the outcome of the labour induction. The study report was published in May 2007.(Tan, Vallikkannu, et al., 2007) Prior to 2003 when recruitment for our study commenced, the studies were smaller in scale (the largest of which reported on 240 women)(Boozarjomehri et al., 1994; Chandra et al., 2001; Gabriel et al., 2002; Gabriel et al., 2001; Gonen et al., 1998; Novakov-Mikic et al., 2000; Pandis et al., 2001; Paterson-Brown et al., 1991; Ware & Raynor, 2000). We also provided strong and convincing data from our large study group of 249 women that transvaginal ultrasound was better tolerated: the two previous studies on tolerability of transvaginal ultrasound analysed the data from a subset of 40 women only in a pilot study(Chandra et al., 2001) and from 50 women in a

secondary data analysis(Paterson-Brown et al., 1991). Our data and other later publications contributed to the extensive literature on transvaginal ultrasound derived cervical length as a predictor of successful labour induction. (Daskalakis et al., 2006; Elghorori, Hassan, Dartey, Abdel-Aziz, & Bradley, 2006; Gomez-Laencina et al., 2012; Gomez Laencina et al., 2007; Keepanasseril, Suri, Bagga, & Aggarwal, 2007; Lyon, Kapoor, & Juneja, 2011; Maitra, Sharma, & Agarwal, 2009; Meijer-Hoogeveen, Roos, Arabin, Stoutenbeek, & Visser, 2009; Park, 2007; Park et al., 2011; Pitarello Pda, Tadashi Yoshizaki, Ruano, & Zugaib, 2013; Uyar, Erbay, Demir, & Baytur, 2009; Vankayalapati et al., 2008) Recent randomised clinical trial data have also suggest that transvaginal ultrasound may replace Bishop Score as a practical method for assessing cervical favourability for labour induction. (Bartha et al., 2005; Park et al., 2011)

In addition to contributing a significant volume of data to the ongoing debate about the relative roles of transvaginal ultrasound for cervical length versus Bishop Score for predicting successful labour induction, we confirmed transvaginal ultrasound is better tolerated than per-vaginal digital assessment to obtain the Bishop Score.(Tan, Vallikkannu, et al., 2007) A further secondary analysis of our data from this larger study showed that a long cervix on transvaginal ultrasound just prior to labour induction is a far better predictor of Caesarean delivery in nulliparous women than in parous women.(Tan, Vallikkannu, et al., 2009)

A 2011 publication concludes that “based on our findings and available information in the literature, it seems that cervical length measured by transvaginal ultrasonography has the potential to replace the traditional Bishop score, provided that such a facility is available when needed.”(Bastani, Hamdi, Abasalizadeh, Pourmousa, & Ghatrehsamani, 2011)

4.1.4. Labour induction regimens

In women who require labour induction but are at high risk for Caesarean delivery using conventional regimens [we studied such women who were nulliparous, had poor cervical favourability with intact membranes(Tan, Valiapan, et al., 2007) or following PROM(Tan, Daud, et al., 2009)], we hypothesise that a more aggressive regimen with concurrent use of dinoprostone and oxytocin infusion might hasten induction to delivery interval and improve the rate of vaginal delivery whilst being well tolerated and safe. Concurrent agent regimes are infrequently studied, heterogeneous and available studies then were typically underpowered and hypothesis generating rather than definitive.(Bolnick et al., 2004; Christensen et al., 2002; Hennessey et al., 1998; Stewart et al., 1998)

Labour occurs within 24 hours of amniotomy for labour induction in 90.1% of women.(Cooley et al., 2010) Previous trials have shown that in sub-analyses confined to parous women, immediate oxytocin following amniotomy was associated with a 93% and a 1 hour delay associated with a 95% delivery rate within 12 hours.(Moldin & Sundell, 1996; Patterson, 1971) In parous women with favourable cervixes after amniotomy for labour induction, it is unclear whether

oxytocin is required and if so, when it should be started as these women was usually inducible by amniotomy alone. We investigated immediate titrated oxytocin infusion compared with a 4-hour delay in oxytocin infusion in a double blind randomised trial following amniotomy for these women.(Tan et al., 2013)

Over 2005-6, we recruited 220 nulliparas with unfavourable Bishop Score and intact membranes into a double-blind randomised trial of concurrent vaginal dinoprostone and titrated intravenous oxytocin infusion compared against vaginal dinoprostone for labour induction. The recruitment of 220 women exceeded calculated sample size based on pilot data from an earlier study of 150 women.(Stewart et al., 1998) Our trial report was published in 2007.(Tan, Valiapan, et al., 2007) The primary outcome of vaginal delivery within 24 hours was not significantly higher with concurrent therapy but maternal satisfaction based was. Although our induction regime is different from previous smaller scale trials(Bolnick et al., 2004; Christensen et al., 2002; Hennessey et al., 1998; Stewart et al., 1998) of concurrent therapy with PG and oxytocin for labour induction, the positive results of these smaller trials and our own borderline positive result would suggest that as a strategy, concurrent therapy can be both effective and safe in nulliparas with an unfavourable cervix and intact membranes. We called for further study. Since then, a trial of 500 women of mixed parity and unfavourable cervix published in 2011 has shown contrasting finding of decreased vaginal delivery within 24 hour and increased Caesarean delivery rate with concurrent therapy.(Gungorduk, Yildirim, Gungorduk, Ark, & Tekirdag)

Following the promising data obtained with concurrent therapy labour induction with intact membranes(Tan, Valiapan, et al., 2007), from 2007-8 we undertook a double blind trial of concurrent titrated oxytocin infusion and single dose vaginal dinoprostone compared against titrated oxytocin infusion (current standard therapy in labour induction of PROM) and placebo pessary in nulliparous women with unfavourable cervixes but this time in women with PROM. At the inception of our randomised clinical trial, there was no other trial of concurrent therapy in the induction of labour for premature membrane rupture. We recruited 116 women as per sample size calculation. We reported in 2009 that the vaginal delivery within 12 hours, caesarean delivery, uterine hyperstimulation and maternal satisfaction with the birth process were similar across both arm of the trials. Compared to titrated oxytocin, the addition of vaginal dinoprostone concurrently to the induction regime appeared to offer no advantage as the trend for most beneficial outcomes favours titrated oxytocin infusion only.(Tan, Daud, et al., 2009) This finding would appear to limit the potential of concurrent agent labour induction in PROM.

Labour occurs within 24 hours of amniotomy for labour induction in 90.1% of women.(Cooley et al., 2010) However a Cochrane review concludes that data is lacking about the value of amniotomy alone for induction of labour.(Bricker & Luckas, 2000) Another Cochrane review states that amniotomy and oxytocin infusion can induce labour but the optimal timing of oxytocin infusion following amniotomy is not known.(Howarth & Botha, 2001) Only a small number of labour induction trials addressing the timing of starting oxytocin infusion after

amniotomy had been performed. In two earlier studies (from 1971 and 1996)(Chandra et al., 2001; Moldin & Sundell, 1996; Patterson, 1971) that comprised mixed populations of parous and nulliparous women who underwent labour induction, amniotomy in combination with early (immediate or one hour delay) oxytocin infusion shortens the latency to birth when compared with amniotomy followed by a delay of up to 24 hours before oxytocin infusion. A 2009 report of an open label trial in nulliparas demonstrates that immediate compared with delayed oxytocin (of four hours) is associated with the earlier establishment of active labour at 4 hours, a shorter amniotomy-delivery interval and greater maternal satisfaction.(Selo-Ojeme et al., 2009)

The twelve publications have contributed original and substantial data to the literature around core issues related to getting labour started. The body of work comes together appropriately as a PhD Thesis by Prior Publication of the University of Malaya.

Appendix A

List Of Publications, Journal Information, Citations And Candidate's Role

Publications In Print Date Order	Journal ISI-WOS Status (2012)			Candidate's Role in Research and Publication
	Specialty Rank*	Impact Factor*	Cites*	
I. Tan PC, Jacob R, Omar SZ. Membrane sweeping at initiation of formal labor induction: a randomized controlled trial. Obstet Gynecol. 2006 Mar;107(3):569-77.(Tan, Jacob, & Omar, 2006)	2/78 Tier 1 O&G	4.798	10	First and corresponding author for the publication. Candidate co-conceived the trial with RJ, assisted in the setting up and running of the trial, performed the primary data analysis and drafted and finalised the manuscript for publication.
II. Tan PC, Andi A, Azmi N, Noraihan MN. Effect of coitus at term on length of gestation, induction of labor, and mode of delivery. Obstet Gynecol. 2006 Jul;108(1):134-40.(Tan, Andi, Azmi, & Noraihan, 2006)	2/78 Tier 1 O&G	4.798	14	First and corresponding author. Candidate assisted in the study design, performed the primary data analysis and drafted and finalised the manuscript for publication.

List Of Publications, Journal Information, Citations And Candidate's Role

III. Tan PC, Suguna S, Vallikkannu N, Hassan J. Ultrasound and clinical predictors for Caesarean delivery after labour induction at term. Aust N Z J Obstet Gynaecol. 2006 Dec;46(6):505-9.(Tan, Suguna, Vallikkannu, & Hassan, 2006)	59/78 Tier 4 O&G	1.298	7	First and corresponding author. Candidate conceived and designed the study, performed or supervised the ultrasound assessments, did the primary data analysis and drafted and finalised the manuscript for publication.
IV. Tan PC, Vallikkannu N, Suguna S, Quek KF, Hassan J. Transvaginal sonographic measurement of cervical length vs. Bishop Score in labor induction at term: tolerability and prediction of Cesarean delivery. Ultrasound Obstet Gynecol. 2007 May;29(5):568-73.(Tan, Vallikkannu, Suguna, Quek, & Hassan, 2007)	2/31 Tier 1 Acoustics	3.557	20	First and corresponding author. Candidate conceived and designed the study, performed and supervised some of the ultrasound assessments, did the primary data analysis (assisted by KFQ) and drafted and finalised the manuscript for publication.

List Of Publications, Journal Information, Citations And Candidate's Role

V. Tan PC, Valiapan SD, Tay PY, Omar SZ. Concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction of nulliparas with an unfavourable cervix: a randomised placebo-controlled trial. BJOG. 2007 Jul;114(7):824-32.(Tan, Valiapan, Tay, & Omar, 2007)	7/78 Tier 1 O&G	3.760	8	First and corresponding author. Candidate conceived and designed the trial, assisted in the setting up and running of the trial performed the primary data analysis and drafted and finalised the manuscript for publication.
VI. Tan PC, Yow CM, Omar SZ. Effect of coital activity on onset of labor in women scheduled for labor induction: a randomized controlled trial. Obstet Gynecol. 2007 Oct;110(4):820-6.(Tan, Yow, & Omar, 2007)	2/78 Tier 1 O&G	4.798	8	First and corresponding author Candidate conceived and designed the trial, assisted in the setting up and running of the trial, performed the primary data analysis and drafted and finalised the manuscript for publication.

List Of Publications, Journal Information, Citations And Candidate's Role

VII. Tan PC, Yow CM, Omar SZ. Coitus and orgasm at term: effect on spontaneous labour and pregnancy outcome. Singapore Med J. 2009; 50(11) : 1062-7.(Tan, Yow, & Omar, 2009)	108/155 Tier 3 Int Med	0.630	1	First and corresponding author. Candidate conceived, designed, performed the primary analysis and drafted the original trial report (listed at VI above) that was the basis of this secondary report. Candidate conceived the study, performed the analysis and drafted and finalised the manuscript for publication.
VIII. Tan PC, Daud SA, Omar SZ. Concurrent dinoprostone and oxytocin for labor induction in term premature rupture of membranes. Obstet Gynecol. 2009 May;113(5):1059-65.(Tan, Daud, & Omar, 2009)	2/78 Tier 1 O&G	4.798	10	First and corresponding author. Candidate conceived and designed the trial, assisted in the setting up and running of the trial, performed the primary data analysis and drafted and finalised the manuscript for publication.

List Of Publications, Journal Information, Citations And Candidate's Role

IX. Hamdan M, Sidhu K, Omar SZ, Sabir N, Tan PC. Serial membrane sweeping at term in planned vaginal birth after Caesarean: A randomised controlled trial. Obstet Gynecol. 2009 Oct;114(4):745-51.(Hamdan, Sidhu, Sabir, Omar, & Tan, 2009)	2/78 Tier 1 O&G	4.798	5	Senior and Corresponding author. Candidate assisted in trial design, performed the primary data analysis and drafted and finalised the manuscript for publication.
X. Tan PC, Khine PP, Sabdin NH, Vallikkannu N, Sulaiman S. Effect of membrane sweeping on cervical length by transvaginal ultrasonography and impact of cervical shortening on cesarean delivery. J Ultrasound Med. 2011 Feb;30(2):227-33.(Tan, Khine, Sabdin, Vallikkannu, & Sulaiman, 2011)	13/31 Tier 2 Acoustics	1.402	3	First and corresponding author. Candidate conceived and designed the study, performed and supervised some of the ultrasound assessments, did the primary data analysis and drafted and finalised the manuscript for publication.

List Of Publications, Journal Information, Citations And Candidate's Role

XI. Omar NS, Tan PC, Sabir N, Yusop ES, Omar SZ. Coitus to expedite the onset of labour: a randomised trial. BJOG. 2013 Feb;120(3):338-45.(Omar, Tan, Sabir, Yusop, & Omar, 2013)	7/78 Tier 1 O&G	3.760	1	Corresponding and second author. Candidate conceived and designed the study with NS, assisted in the setting up of the trial, performed the primary data analysis and drafted and finalised the manuscript for publication.
XII. Tan PC, Soe MZ, Sulaiman S, Omar SZ. Immediate compared with delayed oxytocin after amniotomy labor induction in parous women: a randomized controlled trial. Obstet Gynecol. 2013 Feb;121(2 Pt 1):253-9.(Tan, Soe, Sulaiman, & Omar, 2013)	2/78 Tier 1 O&G	4.798	1	First and corresponding author. Candidate conceived and designed the trial, assisted in the setting up and running of the trial, performed the primary data analysis and drafted and finalised the manuscript for publication.

*Journal Ranking, Specialty and Impact Factor data taken from the latest available (2012) Journal Citation Reports® of ISI Web of Knowledge^{SM}. Citation data last accessed on 12 Feb 2014.

Appendix B

Publication Detail

Tan PC, Jacob R, Omar SZ. Membrane sweeping at initiation of formal labor induction: a randomized controlled trial. Obstet Gynecol. 2006 Mar;107(3):569-77.

Authors' Roles in Publication

Role	**Major Contribution**	**Other Contribution**
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Reena Jacob Tan Peng Chiong,	Siti Zawiah Omar
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Reena Jacob, Tan Peng Chiong	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Reena Jacob	
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	Reena Jacob
Manuscript Writing	Tan Peng Chiong	
Manuscript Critique	Siti Zawiah Omar Reena Jacob	
Journal Submission and Correspondence	Tan Peng Chiong	

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Tan PC, Andi A, Azmi N, Noraihan MN. Effect of coitus at term on length of gestation, induction of labor, and mode of delivery. Obstet Gynecol. 2006 Jul;108(1):134-40.

Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Andi Anggerik, Noor Azmi	Noraihan Nordin Tan Peng Chiong
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Andi Anggerik, Noor Azmi	Tan Peng Chiong
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Andi Anggerik	Noor Azmi
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	Andi Anggerik
Manuscript Writing	Tan Peng Chiong	
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Tan PC, Suguna S, Vallikkannu N, Hassan J. Ultrasound and clinical predictors for Caesarean delivery after labour induction at term. Aust N Z J Obstet Gynaecol. 2006 Dec;46(6):505-9.

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Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong Suguna Subramaniam	Jamiyah Hassan Vallikkannu Narayanan
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong Suguna Subramaniam	Vallikkannu Narayanan
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Vallikkannu Narayanan, Suguna Subramaniam,	Tan Peng Chiong
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	
Manuscript Writing	Tan Peng Chiong	
Manuscript Critique	Jamiyah Hassan	Suguna Subramaniam Vallikkannu Narayanan,
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Tan PC, Vallikkannu N, Suguna S, Quek KF, Hassan J. Transvaginal sonographic measurement of cervical length vs. Bishop score in labor induction at term: tolerability and prediction of Cesarean delivery. Ultrasound Obstet Gynecol. 2007 May;29(5):568-73.

Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong, Vallikkannu Narayanan	Suguna Subramaniam, Jamiyah Hassan
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong Vallikkannu Narayanan	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Vallikkannu Narayana, Suguna Subramaniam	Tan Peng Chiong
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong Quek Kia Fatt	
Manuscript Writing	Tan Peng Chiong	
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Tan PC, Valiapan SD, Tay PY, Omar SZ. Concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction of nulliparas with an unfavourable cervix: a randomised placebo-controlled trial. BJOG. 2007 Jul;114(7):824-32

Authors' Roles in Publication

Role	**Major Contribution**	**Other Contribution**
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong	Sumithra Valipan Siti Zawiah Omar Paul Tay Yee Siang
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong Sumithra Valiapan	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Sumithra Valiapan	
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Manuscript Writing	Tan Peng Chiong	
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Tan PC, Yow CM, Omar SZ. Effect of coital activity on onset of labor in women scheduled for labor induction: a randomized controlled trial. Obstet Gynecol. 2007 Oct;110(4):820-6.

Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong	Yow Choon Ming. Siti Zawiah Omar
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong,	Yow Choon Ming
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Yow Choon Ming	
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	
Manuscript Writing	Tan Peng Chiong	
Manuscript Critique	Siti Zawiah Omar	Yow Choon Ming
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Tan PC, Yow CM, Omar SZ. Sexual intercourse and orgasm at term: Effect on spontaneous labor. Singapore Med J. 2009; 50(11) : 1062-7

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Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong	Yow Choon Ming Siti Zawiah Omar
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Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong	Siti Aishah Daud, Siti Zawiah Omar
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Siti Aishah Daud, Tan Peng Chiong	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Siti Aishah Daud	
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	
Manuscript Writing	Tan Peng Chiong	
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Hamdan M, Sidhu K, Omar SZ, Sabir N, Tan PC. Serial membrane sweeping at term in planned vaginal birth after Cesarean: A randomised trial. Obstet Gynecol. 2009 Oct;114(4):745-51.

Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Kiren Sidhu Mukhri Hamdan	Nada Sabir Tan Peng Chiong
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Kiren Sidhu Mukhri Hamdan	Nada Sabir
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Mukhri Hamdan	Nada Sabir
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	Mukhri Hamdan
Manuscript Writing	Tan Peng Chiong	
Manuscript Critique	Mukhri Hamdan Siti Zawiah Omar Kiren Sidhu Nada Sabir	
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Authors' Roles in Publication

Role	**Major Contribution**	**Other Contribution**
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong Khine Pwint Phyu	Sofiah Sulaiman Vallikkannu Narayanan Halimanja Sabdin
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong Khine Pwint Phyu	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Halimanja Sabdin Khine Pwint Phyu Tan Peng Chiong	Vallikkannu Narayanan Sofiah Sulaiman
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	Khine Pwint Phyu
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Authors' Roles in Publication

Role	**Major Contribution**	**Other Contribution**
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong Nada Sabir	Siti Zawiah Omar
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Nada Sabir Tan Peng Chiong	
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	Noorkardiffa Omar Ezra Sophia Yusop	Nada Sabir
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong Noorkardiffa Omar	Nada Sabir Ezra Sophia Yusop Siti Zawiah Omar
Manuscript Writing	Tan Peng Chiong	
Manuscript Critique	Noorkardiffa Omar Nada Sabir Siti Zawiah Omar	Ezra Sophia Yusop
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Authors' Roles in Publication

Role	Major Contribution	Other Contribution
Concept of Study e.g. Framing of Hypothesis, Research Methodology, Literature Search	Tan Peng Chiong	Siti Zawiah Omar May Zaw Soe Sofiah Sulaiman
Preparation of Study Proposal e.g. Sample Size Calculation, Ethics Application, Funding Applications	Tan Peng Chiong	May Zaw Soe
Execution of Study e.g. Recruitment, Performing Intervention, Data Collection, Database Entry	May Zaw Soe	
Data Analysis and Interpretation e.g. Database Clean-up, Re-organisation, Analysis and Interpretation	Tan Peng Chiong	May Zaw Soe Siti Zawiah Omar
Manuscript Writing	Tan Peng Chiong	
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Appendix C

Membrane Sweeping at Initiation of Formal Labor Induction

A Randomized Controlled Trial

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OBJECTIVE: To determine the benefit of membrane sweeping at initiation of labor induction in conjunction with formal methods of labor induction.

METHODS: Two hundred seventy-four women at term with a singleton fetus in cephalic presentation and intact membranes were randomly assigned to receive membrane sweeping or no membrane sweeping at initiation of formal labor induction with either dinoprostone pessary or amniotomy. Outcome measures included mode of delivery, induction-to-delivery interval, dinosprostone dose, any oxytocin use and duration of oxytocin use in labor, visual analog score for pain associated with sweeping, and visual analog score for satisfaction with the birth process.

RESULTS: Two hundred sixty-four women (136 sweep and 128 no sweep) had their data analyzed. Ten women (4 sweep and 6 no sweep) were excluded because of exclusion criteria infringements. Swept women had higher spontaneous vaginal delivery rate (69% compared with 56%, $P = .041$), shorter induction to delivery interval (mean 14 compared with 19 hours, $P = .003$), fewer that required oxytocin use (46% compared with 59%, $P = .037$), shorter duration of oxytocin infusion (mean 2.6 compared with 4.3 hours, $P = .001$) and improved visual analog score for birth process satisfaction (mean 4.0 compared with 4.7, $P = .015$). The reduction in dinoprostone dose used (mean 1.2 compared with 1.3, $P = .082$) was not significant. Postsweeping visual analog score for pain (mean 4.7 compared with 3.5, $P < .001$) was significantly increased.

CONCLUSION: Membrane sweeping at initiation of labor induction increased the spontaneous vaginal delivery rate, reduced oxytocic drug use, shortened induction to delivery interval, and improved patient satisfaction.
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LEVEL OF EVIDENCE: I

Induction of labor occurs in about 20% of term pregnancies but is associated with a lower rate of spontaneous vaginal delivery in comparison with spontaneously occurring labor.[1]

The physiologic basis of membrane sweeping leading to labor is well established and has been shown to release endogenous prostaglandins,[2–4] phospholipase A[3] and oxytocin (Ferguson's reflex).[5] Uterine contraction frequency is also increased by membrane sweeping.[3] The release of prostaglandins can last at least 6 hours.[4]

Membrane sweeping alone is an effective but less efficient method of labor induction compared with more established methods such as vaginal prostaglandin or amniotomy with oxytocin infusion.[6–8] A recent Cochrane meta-analysis of membrane sweeping trials concluded that although it reduces the number of women progressing to postterm gestation and the need for formal labor induction, sweeping is not associated with a reduction in cesarean or instrumental delivery, and it can cause discomfort and vaginal bleeding.[8]

We did a literature search on PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) using search terms "membrane sweeping" or "membrane stripping" and "labor induction" on November 24, 2005, for studies in all languages published between January 1966 and November 2005 inclusive, looking for trials of membrane sweeping or membrane stripping and labor induction. Although many studies of membrane sweeping have been reported, these studies focus on attempts to reduce incidence of postdates and formal labor induction as identified in the Cochrane review.[6] We found only 1 study that dealt specifically with mem-

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brane sweeping in conjunction with formal labor induction.[9] That study demonstrated positive benefits of membrane sweeping only among nulliparas requiring prostaglandin for labor induction.

Because membrane sweeping is uncomfortable,[6] we were interested in determining whether 1 systematic membrane sweep done at initiation of formal labor induction had any beneficial effects.

MATERIALS AND METHODS

A randomized trial was done to compare the effect of membrane sweeping to no sweeping at initiation of labor induction at term. The study was approved by the local institutional review board, and written consent was obtained in all cases. This study was done at a tertiary referral university hospital with more than 5,000 deliveries per annum in Kuala Lumpur, Malaysia.

Based on an earlier study,[9] which reported a nonsignificant increase in the spontaneous vaginal delivery rate from 75% to 85% with sweeping, sample size calculation using an α of 0.05 and β of 0.8 indicated that 270 women were needed in each group for an appropriately powered randomized study on the effect of membrane sweeping in conjunction with formal labor induction. We analyzed our results after having recruited 274 women in total.

Women at term (37 to 42 weeks), with a singleton fetus, intact membranes, and cephalic presentation were recruited when they presented to the induction bay of the delivery suite for labor induction. Recruitment was carried out by the investigators or the staff of the induction bay. Women with a previous cesarean delivery, intrauterine fetal death, or known gross fetal anomalies were excluded. Recruitment took place from March 2004 to February 2005. All women who were approached agreed to participate (Fig. 1). Membrane sweeping for prior cervical ripening was not routinely offered in our institution.

Women who agreed to participate were first stratified into nulliparas and multiparas groups. Randomization was effected by the use of sealed opaque envelopes with a piece of paper inside bearing the legend "Sweep" or "No Sweep". Envelopes were prepared in blocks of 20 (10 sweep and 10 no sweep) for each stratified group. Envelopes were then shuffled and placed in boxes marked "Nulliparas" and "Multiparas." Boxes were refilled as required with blocks of 20 envelopes. For random assignment to treatment groups, an envelope was withdrawn from the appropriate box and allocated to the woman. Once allocated, an envelope was discarded if a woman chose to withdraw or recruitment was in error. The allocated envelope was opened by the clinician performing the initial vaginal examination just before that examination. A sticker bearing the identification of the randomized woman was affixed to the paper bearing the legend "Sweep" or "No Sweep," and the paper was placed in a sealed drop box until unblinding at the end of the study.

The treatment allocation was not revealed to the women, and only the clinician performing the initial vaginal examination at initiation of labor induction was aware of the allocation. The investigators were also blinded to the treatment allocation. The treatment allocation was not recorded in the women's charts. There was a potential weakness in the masking process because the clinician performing the sweep might have been involved in the continuing management of the woman. However, we had institutional guidelines on labor induction and labor, and there was no indication of systematic breach of the guidelines. Data were collected in a prospective manner.

The method of induction of labor was decided at the initial vaginal examination on the induction bay. Women assigned to "sweep" had their cervix swept by inserting the examining finger as high as possible past the internal cervical os, and the membranes were swept off the lower pole of the uterus by a complete circular sweep of the finger, once clockwise and once counterclockwise. In the event of a closed internal or external cervical os, the cervical canal or external cervix was swept with 2 circular motions. Dinoprostone (3 mg) pessary placement in the posterior fornix or amniotomy immediately followed. Bishop score was then recorded. Women assigned to "no sweep" had a straightforward cervical assessment for Bishop score followed immediately by either dinoprostone or amniotomy. We applied universal electronic fetal monitoring to our induced women.

Membrane sweeping was done only at the initiation of labor induction for sweep-assigned women. No subsequent sweeping was performed on the first day of labor induction for any women, even if the induction process was continuing. Women assigned to "no sweep" did not have any sweeping in conjunction with labor induction on the first day of induction. However, we did not prohibit sweeping in labor or sweeping if the woman had not gone into labor after the first 24 hours. All randomly assigned women received their allocated treatment.

A visual analog score (VAS) based on a scale of 0 to 10, with 0 representing no pain to 10 representing unbearably severe pain, was obtained from the women immediately after commencement of labor induction by a blinded investigator.

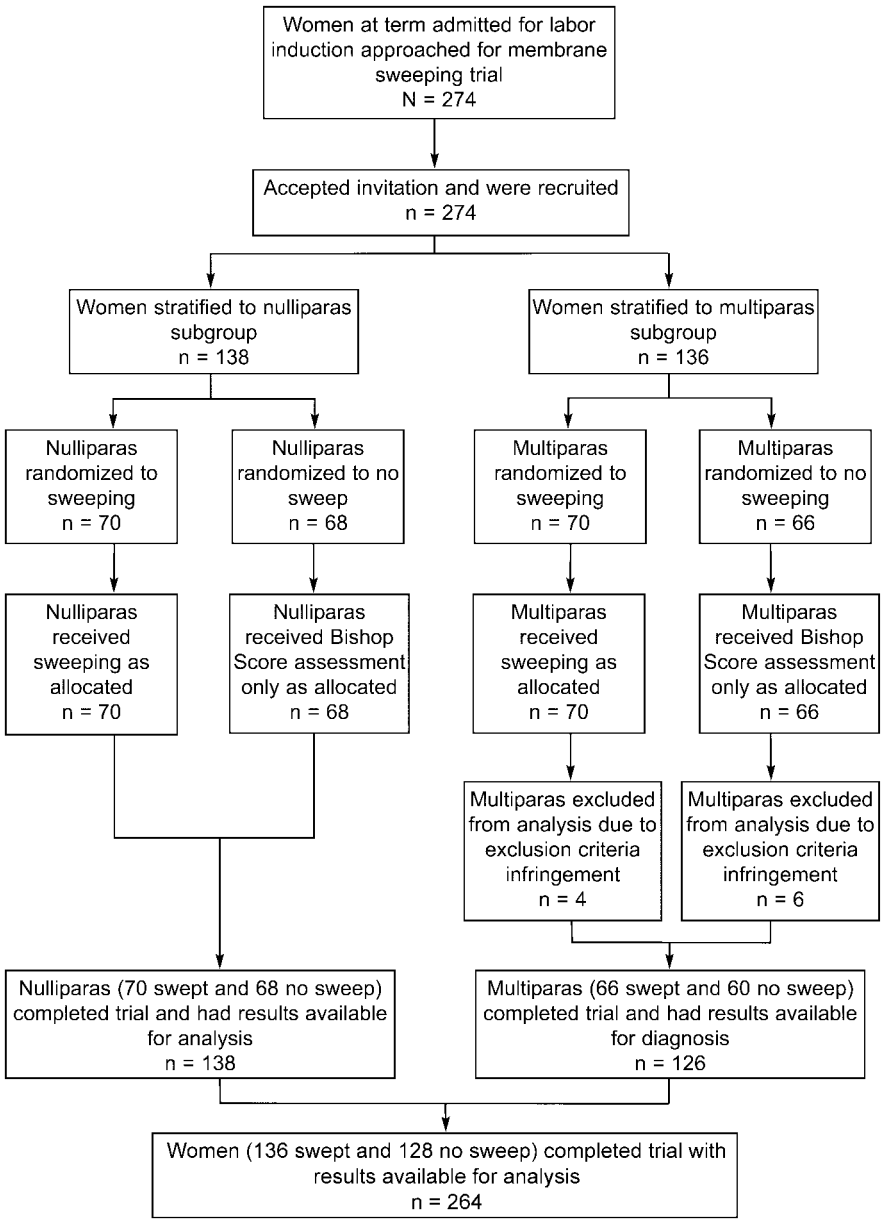

Fig. 1. Flow chart of trial recruitment and progression.
Tan. Membrane Sweeping at Labor Induction. Obstet Gynecol 2006.

In our institution, dinoprostone pessary was used for labor induction if the Bishop score was unfavorable (≤ 4), and amniotomy usually was performed when the cervix was 3 cm or more dilated and the presenting part was low. In unfavorable women, after dinoprostone pessary insertion, the woman was assessed 6 hours later, at which time depending on the cervical dilatation and presence of contractions a further dinosprostone pessary might be inserted or amniotomy performed. We allowed a maximum of 2 doses of dinoprostone per day. We reassessed routinely again 6 hours later, and if the cervix remained unfavorable, women with nonurgent indications were usually rested overnight and the process repeated the following morning. Following amniotomy for labor induction, oxytocin was usually started within 2 hours if contractions were inadequate. The start of labor induction was taken as time of insertion of the first dinoprostone pessary or of amniotomy, depending on the method of labor induction used.

Once in established labor (regular contractions and cervical dilatation ≥ 3 cm), vaginal assessment was usually done every 4 hours initially unless otherwise indicated. Oxytocin was started for labor augmentation when labor progress fell below the action line in the partogram. Our intravenous oxytocin

infusion regime started at 2 mU/min. A doubling in dosage was made every 30 minutes until contractions of 4 to 5 every 10 minutes were achieved or there was cardiotocograph abnormality. The maximum oxytocin dose was 32 mU/min. Once started, oxytocin infusion was continued to delivery unless otherwise indicated.

As soon as possible after delivery, another VAS was obtained by the investigator from the women to gauge their perception of the birth process before their hospital discharges. The scale ranged from 0 to 10, with 0 representing very satisfied to 10 representing very dissatisfied.

Outcome measures collected included mode of delivery, induction to delivery interval, any use of oxytocin in labor, duration of oxytocin infusion in labor, dose of dinoprostone used, and VAS results. Secondary outcomes recorded included meconium staining of liquor, Apgar score at 5 minutes, umbilical cord blood pH value at delivery, admission for neonatal care, indications for neonatal care admissions, indications for operative delivery, induction to delivery interval 12 hours or less, and induction delivery interval of 24 hours or less. Secondary analysis based on parity was also planned.

Data were entered into a statistical software package SPSS 11 (SPSS Inc., Chicago, IL), and GraphPad Instat and QuickCalcs software (GraphPad Software Inc., San Diego CA) were also used for data analysis. The SISA software (Uitenbroek, DG; http://home.clara.net/sisa/fiveby2.htm, accessed November 12, 2005) was used to perform Fisher exact tests with data sets larger than 2×2. The Kolmogorov-Smirnov test was used to check for normal distribution. The *t* test was used to analyze means and distributions with the Mann-Whitney *U* test used to check for consistency in the event that a *t* test was applied on nonnormal data and ordinal data, the Fisher exact test was used for categorical data sets (up to 2×5), χ^2 for larger categorical data sets, and relative risk (RR) and its 95% confidence interval (CI) calculated using GraphPad Instat program. Numbers needed to treat and its 95% CI were generated with GraphPad QuickSeal. $P < .05$ in any test was considered statistically significant, and all tests used 2-tailed results.

RESULTS

We recruited a total of 274 women (138 nulliparas and 136 multiparas). Ten multiparas were excluded from the analysis (4 sweep and 6 no sweep) because of exclusion criteria infringement (6 with previous cesarean section scars, 3 prelabor rupture of membranes, and 1 with known gross fetal anomaly). This left 264 women for analysis; 138 nulliparas (70 sweep and 68 no sweep) and 126 multiparas (66 sweep and 60 no sweep). Two hundred twenty-eight (86.4%) women underwent dinoprostone induction and, only 36 (13.6%) had primary amniotomy for labor induction. There was no significant difference between the groups in any characteristic listed (Table 1 and Table 2).

Distributions of duration of oxytocin use, induction to delivery interval, dose of dinoprostone use, and VAS were found to be nonnormal. Because our sample sizes were large, we used the *t* test for primary analysis and presented our finding as mean ± standard deviation. The Mann-Whitney *U* test was also used for analysis on these outcomes. No significant inconsistency was found between *t* test and Mann-Whitney *U* test *P* values.

Swept women had higher spontaneous vaginal delivery rate (69% compared with 56%, $P = .041$), shorter induction to delivery interval (mean 14 hours compared with 19 hours, $P = .003$), fewer that required oxytocin use (46% compared with 59%, $P = .037$), shorter duration of oxytocin infusion (mean 2.6 hours compared with 4.3 hours, $P = .001$) and improved VAS for birth process satisfaction (mean 4.0 compared with 4.7, $P = .015$). The reduction in dinoprostone dose used (mean 1.2 compared with 1.3, $P = .082$) was not significant. Postsweeping VAS for pain (mean 4.7 compared with 3.5, $P < .001$) was significantly increased (Table 3).

The number needed to treat to achieve an additional spontaneous vaginal delivery was 8 (95% CI 4–78). The RR for operative delivery was 0.71 (95% CI 0.51–0.97). The number needed to treat to avoid the use of oxytocin in labor was also 8 (95% CI 4–90). The RR for any oxytocin use was 0.78 (95% CI 0.62–0.98). Even if we analyzed women (n = 139; 63 swept 76 no sweep) who only required oxytocin in labor, the mean ± standard deviation duration of use was still significantly shorter among swept women (5.6 ± 3.5 hours compared with 7.2 ± 3.5 hours, $P = .007$).

Secondary outcomes of induction delivery interval 12 hours or less (57% sweep compared with 48% no sweep, $P = .175$) and induction delivery interval 24 hours or less (86% sweep compared with 77% no sweep, $P = .057$) did not show any significant differences.

Planned secondary analysis based on subgroups of nulliparas and multiparas (Table 3) showed significant beneficial results among swept nulliparas in any oxytocin use, duration of oxytocin use, induction to delivery interval, and VAS satisfaction score. Swept multiparas had significant beneficial results in induc-

Table 1. Characteristics of Subjects Undergoing Membrane Sweeping or No Sweeping During Initiation of Labor Induction

Characteristic	Sweep (n = 136)	No Sweep (n = 128)	2-Tailed *P*
Age (y)	30.0 ± 5.3	29.2 ± 5.6	.28
Body mass index	29.4 ± 5.5	29.5 ± 5.2	.79
Ethnicity			
Malay	89 (65)	94 (73)	
Chinese	21 (15)	17 (13)	.47
Indian	24 (18)	15 (12)	
Others	2 (2)	2 (2)	
Gestation (wk)	39.9 ± 1.3	39.7 ± 1.3	.48
Parity	1.0 ± 1.5	1.0 ± 1.5	.78
Nulliparas	70 (51)	68 (53)	.81
Multiparas	66 (49)	60 (47)	
Indications for induction*			
Prolonged pregnancy	58 (35)†	46 (31)†	
Diabetes in pregnancy	48 (29)	40 (27)	
Hypertension in pregnancy	29 (18)	35 (23)	.3‡
Oligohydramnios	11 (7)	4 (3)	
Growth restriction	3 (2)	4 (3)	
Others	16 (10)	21 (14)	
Bishop Score			
Initial	5.1 ± 1.8	4.7 ± 2.0	.098
≤ 4	54 (40)	64 (50)	.108
≥ 5	82 (60)	64 (50)	
Method of induction			
Dinoprostone	116 (85)	112 (87)	.72
Amniotomy ± oxytocin	20 (15)	16 (13)	

Values are mean ± standard deviation or n (%). Statistical analysis of means by *t* test and categorical data by Fisher exact test (unless otherwise indicated).

* Forty-seven women had 2 indications for induction (27 swept and 20 no sweep), and 2 women had 3 indications (1 swept and 1 no sweep). Total indications were 315.

† Percentage added up to more than 100% due to rounding up to whole numbers in subgroups.

‡ Chi-square test.

tion to delivery interval and mean dose of dinosprostone use. However, if analysis of dinoprostone use in multiparas was based on multiparas who had undergone dinoprostone induction excluding those who had amniotomy induction, the result was no longer significant ($P = .078$). Swept nulliparas and multiparas had significantly higher VAS pain score. All the other main outcomes analyzed favored swept multiparas, even if statistical significance was not achieved. This study was not sufficiently powered to examine the effect of sweeping on subgroups.

Relative risks for operative delivery among a number of subgroups are shown on Figure 2. Statistically significant reductions in RR among swept women were obtained in the whole and Bishop score 5 or more groups only. All other groups also had RR less than 1, but 95% CI crossed 1.

Among swept women who had amniotomy induction, despite the small numbers (20 sweep, 16 no sweep), significant benefits, expressed as mean ± standard deviation (unless otherwise stated), were demonstrated in oxytocin infusion duration (3.5 ± 3.1 hours compared with 6.9 ± 3.7 hours, $P = .005$), induction to delivery interval (5.3 ± 2.4 hours compared with 7.7 ± 3.5 hours, $P = .019$), and birth process VAS (mean 2.4 ± 0.9 compared with 4.0 ± 2.2, $P = .005$). This result must be interpreted with caution because the numbers were small.

Labor complications and adverse neonatal outcomes were similar between sweep and no sweep groups (Table 2). However, our study was not powered to investigate the uncommon adverse neonatal events. Indications for operative delivery were also similar in both sweep and no sweep groups (Table 2).

Initial Bishop score was similar for both groups, 5.1 ± 1.8 compared with 4.7 ± 2.0 ($P = .098$). Further exploration of this possible trend indicated 1 component of Bishop score (cervical dilatation) showed a statistically significant difference (Fisher exact test, $P = .024$), with the swept group having fewer women with closed cervical os (Fig. 3). The other 4 components of Bishop score (cervical length, $P = .63$; cervical consistency, $P = .15$; station of the head, $P = .99$; and cervical position

Table 2. Indication for Operative Delivery and Neonatal Characteristic of Subjects Undergoing Membrane Sweeping or No Sweeping During Initiation of Labor Induction

	Sweep (n = 136)	No Sweep (n = 128)	2-Tailed *P*
Indications for operative delivery			
Cesarean delivery			
Fetal distress	12 (40)	20 (51)	
Poor progress	11 (37)	13 (33)	.47
Failed induction	3 (10)	5 (13)	
Others	4 (13)	1 (3)	
Instrumental delivery*			
Prolonged second stage	6 (50)	8 (47)	
Fetal distress	6 (50)	7 (41)	.72
Severe preeclampsia	0 (0)	2 (12)	
Birth weight (kg)	3.07 ± 0.43	3.16 ± 0.50	.132
Apgar scores at 5 minutes	9.9 ± 0.7	9.9 ± 0.7	.91
Apgar < 7 at 5 minutes	3 (2.2)	1 (0.8)	.62
Cord pH	7.30 ± 0.07	7.31 ± 0.07	.95
Cord pH ≤ 7.1	1 (1)	3 (2)	.36
Labor complications			
Meconium in liquor	9 (7)	3 (2)	.14
Admission to neonatal unit	8 (6)	4 (3)	.38
Indications for neonatal admission			
Meconium aspiration	2 (25)†	0 (0)	
Birth asphyxia	1 (13)	1 (50)	.55
Tachypnea	5 (63)	2 (50)	
Blood glucose monitoring	0 (0)	1 (0)	

Values are mean ± standard deviation or n (%). Statistical analysis of means by *t* test and categorical data by Fisher exact test.
* Forceps and vacuum vaginal delivery.
† Percentage added up to more than 100% due to rounding to nearest whole numbers in subgroups.

$P = .36$) did not show any difference between the sweep or no sweep groups.

DISCUSSION

Induction of labor involves starting a process which is probably self-sustaining once labor is established, and it is believed to involve a self-perpetuating cascade of endogenous release of prostaglandins.[10]

The results of this study indicated that membrane sweeping at initiation of formal labor induction in conjunction with established methods of labor induction had beneficial effects. The women recruited had their labor induced for a broad range of indications and represented the majority of women undergoing labor induction today.[1,11,12] Membrane sweeping is simple and quick, requires no equipment, and possibly needs only to be performed at the initiation of formal labor induction. Swept women expressed higher satisfaction with the birth process, even though sweeping was initially more painful. The finding that sweeping is painful has been shown.[13,14] Neonatal outcomes (Table 2) were similar, and this is in keeping with the findings from a recent meta-analysis.[6]

The additive beneficial effect of membrane sweeping with vaginal prostaglandin gel has been demonstrated by Doane and McCarty,[15] who show that compared with no intervention, sweeping alone, or prostaglandin gel alone, the combined approach reduces postterm pregnancies and antenatal visits. The combined treatment group has a median intervention-to-delivery interval of 1 day, indicating that it is an effective mode of labor induction. In our study, the median induction-to-delivery interval was 11 hours in the sweep group. Our study is consistent with the earlier finding that membrane sweeping with vaginal prostaglandin may have synergistic effects.

Foong et al[9] reported the only other randomized study of membrane sweeping in conjunction with formal labor induction and found reductions in cesarean delivery, induction labor interval, and total oxytocin dose used, but only in the subgroup of nulliparas who had required dinoprostone induction. In contrast, beneficial effects of sweeping were found across subgroups (Fig. 2) in our study. In our study, the number of women undergoing amniotomy induction was low, and further powered study is required. There are important differences between the study of Foong et al[9] and our study. Our study involved 1 sweep at initiation of labor induction compared with repeated sweeping until established labor. The earlier study had more patients amenable to amniotomy induction (33.5% compared with 13.6%) and lower overall

Table 3. Primary Outcomes of Membrane Sweep at Initiation of Labor Induction for Whole Group and Also Stratified According to Parity

	Sweep	No Sweep	2-Tailed *P*	Relative Risk (95% Confidence Interval)
Mode of delivery				
Whole group (N = 264)				
Spontaneous vaginal	94 (69)	72 (56)		
Instrumental vaginal	12 (9)	17 (13)	.094	
Cesarean	30 (22)	39 (31)		
Operative* compared with spontaneous vaginal	42/94	56/72	.041	0.71 (0.51–0.97)
Nulliparas (n = 138)				
Spontaneous vaginal	34 (49)	22 (32)		
Instrumental vaginal	12 (17)	14 (21)	.14	
Cesarean	24 (34)	32 (47)		
Operative* compared with spontaneous vaginal	36/34	46/22	.059	0.76 (0.57–1.01)
Multiparas (n = 126)				
Spontaneous vaginal	60 (91)	50 (83)		
Instrumental vaginal	0 (0)	3 (5)	.15	
Cesarean	6 (9)	7 (12)		
Operative* compared with spontaneous vaginal	6/60	10/50	.28	0.55 (0.21–1.41)
Duration of oxytocin infusion in labor (hr)				
Whole group	2.6 ± 3.7	4.3 ± 4.5	.001	
Nulliparas	3.7 ± 4.3	6.1 ± 4.6	.002	
Multiparas	1.4 ± 2.4	2.2 ± 3.3	.093	
Induction to delivery interval (hr)				
Whole group	14 ± 11	19 ± 15	.003	
Nulliparas	19 ± 12	26 ± 18	.011	
Multiparas	9 ± 6	11 ± 7	.024	
Oxytocin used during labor				
Whole group				
Yes	63 (46)	76 (59)	.037	0.78 (0.62–0.98)
No	73 (54)	52 (41)		
Nulliparas				
Yes	40 (57)	52 (76)	.019	0.74 (0.59–0.95)
No	30 (43)	16 (24)		
Multiparas				
Yes	23 (35)	24 (40)	.58	0.87 (0.55–1.37)
No	43 (65)	36 (60)		
Doses of dinoprostone used during labor induction				
Whole group	1.2 ± 0.7	1.3 ± 0.8	.082	
Nulliparas	1.4 ± 0.8	1.5 ± 0.9	.56	
Multiparas	0.9 ± .0.6	1.1 ± 0.6	.025	
Visual analog score† for pain at initiation of labor induction				
Whole group	4.7 ± 1.9	3.5 ± 2.2	< .001	
Nulliparas	4.8 ± 2.0	4.0 ± 2.2	.025	
Multiparas	4.5 ± 1.8	3.0 ± 2.1	< .001	
Visual analog score† for maternal satisfaction with birth process				
Whole group	4.0 ± 2.2	4.7 ± 2.5	.015	
Nulliparas	4.9 ± 2.2	6.0 ± 2.2	.006	
Multiparas	3.1 ± 1.8	3.4 ± 1.9	.44	

Values are mean ± standard deviation or n (%). Means were analyzed by *t* test and categorical data by Fisher exact test.
* Operative delivery includes cesarean and instrumental vaginal (vacuum and forceps) delivery.
† Score of 0 to 10. Low scores denote more favorable results.

operative delivery rate (19.4% compared with 37.1%) compared with this study. Because it was the standard protocol in both our institutions to perform amniotomy when the cervix was 3 cm or more dilated, higher cervical dilatation in their subjects may be the reason for less operative delivery, because initial cervical dilatation is the best predictor for operative delivery.[11,12] The RR for operative delivery in our

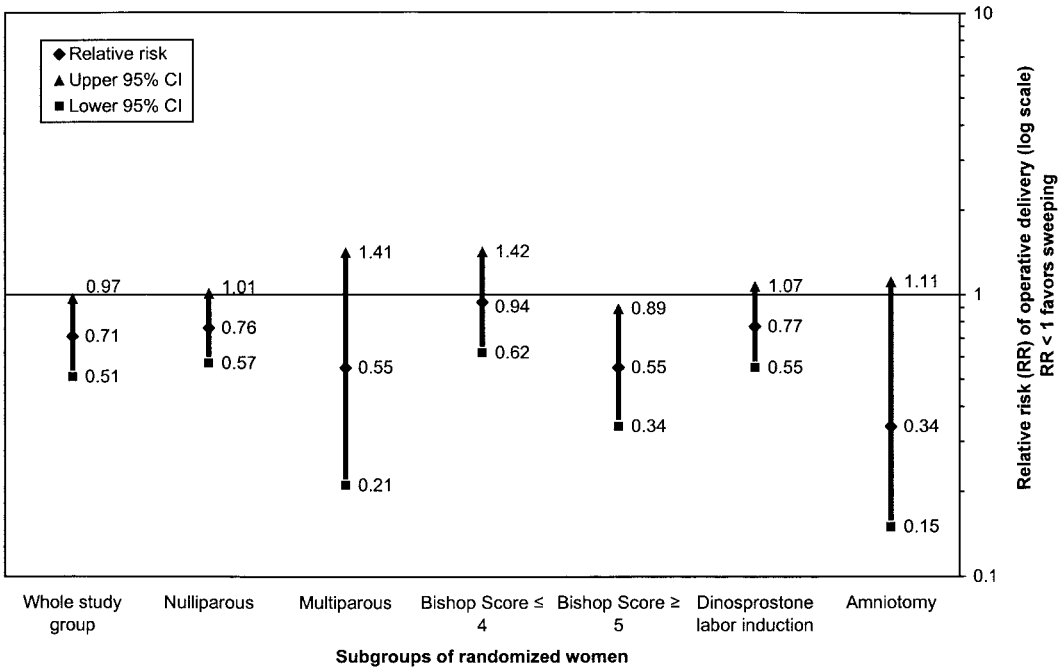

Fig. 2. Effect of membrane sweeping at initiation of labor induction on relative risk of operative delivery according to subgroups of randomly assigned women. CI, confidence interval.

Tan. Membrane Sweeping at Labor Induction. Obstet Gynecol 2006.

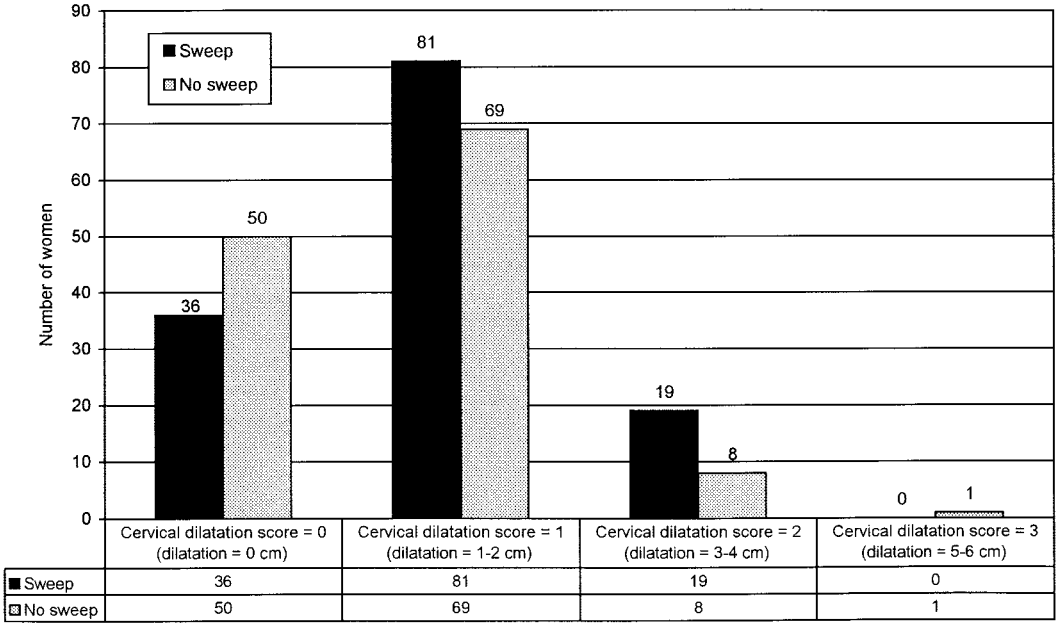

Fig. 3. Distribution of cervical dilatation component of Bishop score and treatment allocation (sweep compared with no sweep). Fisher exact test, $P = .024$.

Tan. Membrane Sweeping at Labor Induction. Obstet Gynecol 2006.

study was 0.71 (95% CI 0.51–0.97) compared with 0.60 (95% CI 0.35–1.02) for the earlier study.

The above indicated that membrane sweeping at initiation of formal induction was clearly beneficial but because our study did not prohibit subsequent sweeping after 24 hours nor formally assess subse-

quent sweeping, it was not possible to determine the precise effect of repeat sweeping. Further study is needed to clarify this issue. However, because 83% of our women delivered within 24 hours from commencement of labor induction and because we did not perform any additional sweeps in conjunction with labor induction within the first 24 hours in any study women, the positive effect of repeat sweeping was likely to be low. Because prostaglandin release after sweeping lasts for at least 6 hours,[6] repeat sweeping may not be necessary in formal labor induction where additional interventions are planned within 6 hours. Serial membrane sweeping during established nulliparous labor is not useful[16]

Women who were randomly assigned to sweeping in this study were found to have a decreased incidence of having a closed cervix at the initial Bishop score assessment (Fig. 3). This was unlikely to be due to a chance randomization event, because all other Bishop score components and all other subject characteristics were similar (Tables 1 and 2). Our study was pragmatically designed with only 1 vaginal examination at initiation of labor induction. Because Bishop score was routinely recorded after sweeping, some clinicians may thus have recorded the postsweep cervical dilatation for the Bishop score, assuming that sweeping caused the cervix to dilate. This may help explain sweeping's beneficial effect in our study, because the mechanically dilated and disrupted cervix might offer less resistance to further dilation. If membrane sweeping did cause cervical dilatation, more swept women might be expected to have undergone amniotomy induction. Amniotomy induction was 14.5% compared with 12.7% in sweep compared with no sweep women, respectively, in our study, which was not significant. This was expected, because our study women generally had closed or minimally dilated cervix (Fig. 3), and the limited upgrading probably did not permit significantly more amniotomy induction to be performed. Interestingly in the study of Foong et al,[9] where amniotomy induction was commoner, the ratio for amniotomy induction was 39.5% compared with 27.4% ($P = .059$) among sweep and no sweep women, respectively, despite prior matching for method of induction during randomization. Further study is required to see whether membrane sweeping has immediate effects on cervical dilation and resistance. Based on the results of our study, membrane sweeping had beneficial results, and sweeping at initiation of formal labor induction at term should be considered.

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Effect of Coitus at Term on Length of Gestation, Induction of Labor, and Mode of Delivery

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OBJECTIVE: To determine coital incidence at term and to estimate its effect on labor onset and mode of delivery.

METHODS: Healthy women with uncomplicated pregnancies and established gestational age were recruited to keep a diary of coital activity from 36 weeks of gestation until birth and to answer a short questionnaire. Two hundred women with complete coital diaries were available for analysis. Outcome measures include coitus, postdate pregnancy (defined as pregnancy beyond the estimated date of confinement), gestational length of at least 41 weeks, labor induction at 41 weeks of gestation, and mode of delivery

RESULTS: Reported sexual intercourse at term was influenced by a woman's perception of coital safety, her ethnicity, and her partner's age. After multivariable logistic regression analysis controlling for the women's ethnicity, education, occupation, perception of coital safety, and partner's age, coitus at term remained independently associated with reductions in postdate pregnancy (adjusted odds ratio [AOR] 0.28, 95% confidence interval [CI] 0.13–0.58, $P = .001$), gestational length of at least 41 weeks (AOR 0.10, 95% CI 0.04–0.28, $P < .001$), and requirement for labor induction at 41 weeks of gestation (AOR 0.08, 95% CI 0.03–0.26, $P < .001$). At 39 weeks of gestation, 5 (95% CI 3.3–10.3) couples needed to have intercourse to avoid one woman having to undergo labor induction at 41 weeks of gestation. Coitus at term had no significant effect on operative delivery (adjusted $P = .15$).

CONCLUSION: Reported sexual intercourse at term was associated with earlier onset of labor and reduced requirement for labor induction at 41 weeks.

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LEVEL OF EVIDENCE: II-2

Induction of labor occurs in approximately 20% of term pregnancies, and prolonged pregnancy (defined as a pregnancy of at least 41 weeks of gestation) accounted for 46% of these inductions in the United Kingdom.[1] In addition, 79% of prolonged pregnancies resulted in labor induction.[1] Sexual intercourse is commonly believed to hasten labor.[2] A Cochrane Review on sexual intercourse for cervical ripening and induction of labor could identify only a small trial with 28 women, from which no meaningful conclusions can be drawn.[3]

The effect of coitus on preterm labor is uncertain. A decreased risk of preterm birth has been reported to be associated with having intercourse in later pregnancy[4] and also with having orgasms.[5] On the contrary, increased risk of preterm births is also linked to having preterm intercourse.[6] Semen contains prostaglandin E,[7] breast stimulation has been shown to hasten the onset of labor,[8] and coitus and orgasm stimulates uterine activity,[9] thereby accounting for the expectation that sexual activity at term may promote labor.

A literature search of PubMed was carried out on January 15, 2006, in all languages, using the search terms "coitus" or "sexual intercourse" and "labor induction," "postdate" or "postterm," looking for articles published between January 1966 and January 2006. No relevant article was found, indicating a paucity of data on coitus at term on length of gestation and induction of labor. We undertook a prospective longitudinal study based on diary keeping to determine the incidence of coitus at term and to estimate its

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effect on important clinical issues like length of gestation, labor induction for prolonged pregnancy, and mode of delivery.

MATERIALS AND METHODS

A prospective longitudinal study based on diary keeping was done to investigate the effect of coitus from 36 weeks gestation until birth on length of gestation, postdate pregnancy (defined as pregnancy beyond the estimated date of confinement), labor induction for prolonged pregnancy (which we defined as pregnancy of at least 41 weeks gestation), and mode of delivery.

Women attending antenatal clinic between December 2002 and August 2003 had their antenatal charts scrutinized. A total of 344 healthy women were identified and approached to participate in the study; 241 were recruited, and following drop outs and exclusions, 200 women were left for final analysis (Fig. 1). We selected only healthy women with uncomplicated obstetric history and straightforward pregnancies close to 36 weeks of gestation to minimize the risk of medically indicated deliveries and also to ensure no medical impediment to coitus in late pregnancy. Women with a history of threatened miscarriage, antepartum hemorrhage, suspected fetal growth restriction, hypertension, gestational diabetes, multiple pregnancies, and in breech presentation in their present pregnancy were excluded. No study women had a previous preterm or postterm birth. We did not exclude women with a history of previous early miscarriage. Gestational age had been confirmed by a first-trimester ultrasound assessment in all recruited women.

Women who agreed to participate in the study answered a short questionnaire on their perception of coital safety in late pregnancy to provide details about their husbands and also some personal data. They were given a diary to chart coitus (defined as vaginal intercourse with penile penetration) from 36 weeks of gestation and to submit the diary on a weekly basis when they attend their routine antenatal clinic appointments. We did not ask the women to record orgasm, ejaculation into the vagina, or breast stimulation during intercourse. Any woman who failed to submit her diary for 2 consecutive weeks was contacted by telephone to obtain data.

Previous reports have shown that between 36% and 56% of healthy women are sexually active in late pregnancy.[4,10] According to a U.K. national report from 2002, 52.3% of women remained undelivered at 40 weeks of gestation.[11] Sample size calculation, using an α of 0.05 and β of 0.8, assuming a 50% abstinence

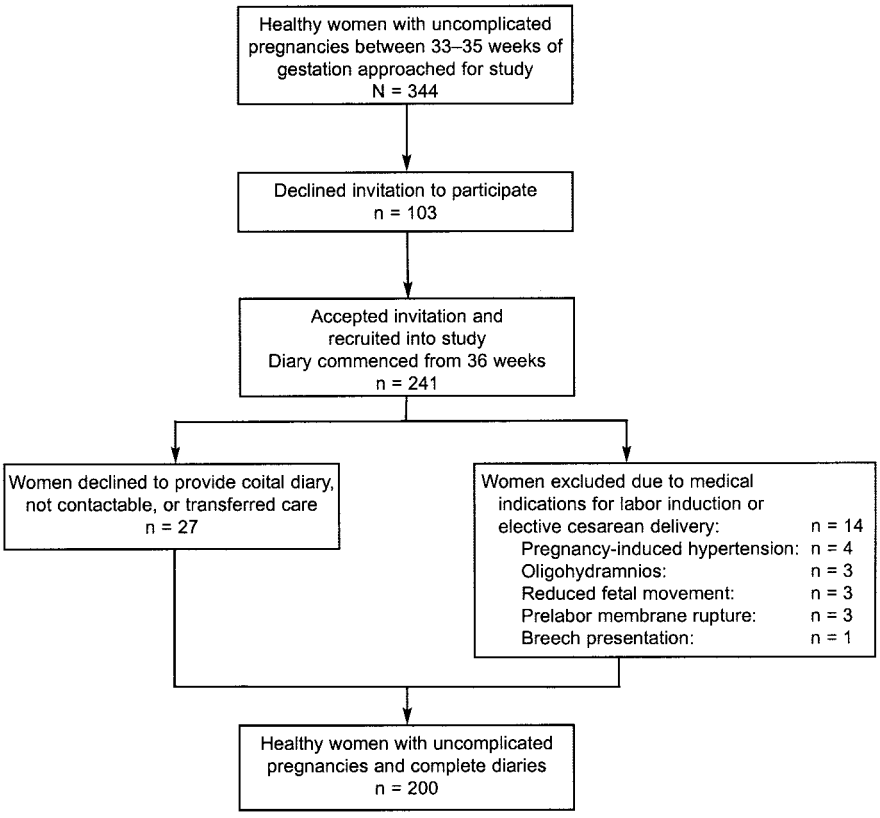

Fig. 1. Flow chart for the recruitment of women for coitus at term study.

Tan. Coitus and Labor Induction. Obstet Gynecol 2006.

rate in late pregnancy, and factoring in a risk ratio (RR) of 0.6 for being undelivered at 40 weeks of gestation among sexually active women compared with abstinent women, determined that 190 women were needed. Assuming a 20% dropout rate, 238 women needed to be recruited.

Women who reached 41 weeks of gestation at our center without contraindication for vaginal delivery were routinely offered labor induction for prolonged pregnancy. Labor induction was usually scheduled close to 41 weeks and 3 days of gestation. Induction was carried out with vaginal prostaglandin (dinoprostone 3 mg) when the cervix was unfavorable or amniotomy and oxytocin infusion if the cervical dilatation was 3 cm or more and the presenting part was low.

Each woman was contacted by telephone after delivery to ascertain her date of delivery, mode of delivery, and labor induction status and for us to answer any of her queries related to the study. The information obtained was checked with the delivery suite birth register and any discrepancy investigated and resolved.

Institutional approval for the study was obtained and institutional guidelines followed. All study women gave consent.

Data were entered into SPSS 13 software (SPSS Inc, Chicago, IL), and Fisher exact test for 2×2 data sets, *t* test for means, analysis of variance, and multivariable logistic regression analysis were performed using this software. In addition, GraphPad Instat and Quickcalcs software (GraphPad Inc, San Diego, CA) were also used for calculations of relative risk and number needed to treat with 95% confidence intervals (CIs).[12] Fisher exact test for categorical data sets greater than 2×2 was calculated using SISA software (Uitenbroek, DG; available at: http://home.clara.net/sisa/fiveby2.htm; retrieved April 21, 2006). $P < .05$ in any test was considered statistically significant, and all tests used two-sided results.

RESULTS

We approached 344 women for recruitment into the study. After taking into account decliners, dropouts, and exclusions, 200 healthy women with complete diaries were left for analysis (Fig. 1). All women in the study were married and living with their husbands. Of the 14 women who were excluded because of medical indications for expedited delivery, four were abstinent and ten had coitus at term, compared with 84 abstinent and 116 sexually active study women ($P = .41$). Of the 3 excluded women with prelabor rupture of membrane cases, two had coitus at term and one woman was abstinent.

Of the 116 (58%) women who had coital acts, the median number of coital acts was 4 (interquartile range 2). The characteristics of the study women are listed in Table 1. Women who had intercourse at term differed from abstinent women in ethnicity, educational attainment, occupation, partner's age, and their perception of coital safety in late pregnancy. After controlling for educational attainment and occupation, multivariable logistic regression analysis indicated that Malay ethnicity, younger husbands, and perception of coital safety remained independently associated with coitus.

The distributions of gestational age at delivery of women who had coitus at term and women who were abstinent are shown in Figure 2. Only 6.9% of sexually active study women remained undelivered at 41 weeks of gestation, compared with 29.8% of abstinent women (Fig. 2).

Women who had coitus at term had a mean reduction in gestational length of only 4.4 days (mean $\pm$ standard deviation gestational length 39.3 $\pm$ 1.1 weeks in sexually active versus 39.9 $\pm$ 1.2 weeks in abstinent women, $P < .001$), but this reduction meant that on univariable analysis they were less likely to go postdate (RR 0.59, 95% CI 0.42–0.85, $P = .001$), less likely to remain undelivered at 41 weeks of gestation (RR 0.37, 95% CI 0.20–0.69, $P < .001$), and less likely to require labor induction for prolonged pregnancy (RR 0.31, 95% CI 0.14–0.69, $P < .001$). After multivariable logistic regression analysis controlling for the women's ethnicity, education, occupation, perception of coital safety, and husband's age, coital activity remained associated with reductions in postdate pregnancy (adjusted odds ratio [AOR] 0.28, 95% CI 0.13–0.58, adjusted $P = .001$), being undelivered at 41 weeks of gestation (AOR 0.10, 95% CI 0.04–0.28, $P < .001$), and the requirement for labor induction indicated by prolonged pregnancy (AOR 0.08, 95% CI 0.03–0.26, $P < .001$). As coital frequency increased, mean length of gestation decreased and the RR of postdate pregnancies, of being undelivered at 41 weeks gestation, and of labor induction for prolonged pregnancy also decreased (Table 2).

After coitus, birth was most likely to happen within 2 days, with a probable continuing effect on delivery for up to 5 days (Fig. 3). The effect of coitus on promoting spontaneous labor and birth was fairly consistent across each week of term gestation period, with RR of 1.1–3.4 (Table 3). This finding suggested that, as onset of spontaneous labor peaks at 39–41 weeks,[1] less frequent intercourse would be required at these gestations per spontaneous labor stimulated compared with at 36–38 weeks of gestation. At 39

Table 1. Characteristics of Two Hundred Study Women According to Exposure to Coitus From 36 Weeks of Gestation to Delivery

	Coitus (n = 116)	No Coitus (n = 84)	*P*
Age (y)	27.7 ± 3.3	28.1 ± 3.8	.43
≤ 30	90 (78)	66 (79)	
> 30	26 (22)	18 (21)	1.0
Parity	0.77 ± 1.00	0.57 ± 0.73	.14
Nulliparas	60 (52)	41 (49)	
Multiparas	56 (48)	43 (51)	.78
Gravidity	1.9 ± 1.1	1.7 ± 0.83	.25
Ethnicity*			
Malay	92 (79)	35 (42)	< .001
Chinese	8 (7)	36 (43)	
Indian	16 (14)	13 (15)	
Education			
Tertiary/college	52 (45)	22 (26)	.008
School	64 (55)	62 (74)	
Occupation†			
Professional	41 (35)	18 (21)	< .001
Other	55 (47)	44 (52)	
Homemaker	20 (17)	22 (26)	
Body mass index	24.6 ± 4.3	24.3 ± 3.7	.70
Duration of marriage (y)	3.1 ± 3.2	2.6 ± 2.4	.22
Age at first coitus (y)	24.3 ± 3.0	24.3 ± 3.5	.97
Perception of coital safety in late pregnancy‡			
Safe	98 (84)§	42 (50)	< .001
Unsafe	7 (6)§	32 (38)	
Don't know	11 (9)§	10 (12)	
Planned pregnancy			
Yes	62 (53)	46 (55)	.89
No	54 (47)	38 (45)	
Previous miscarriage			
Yes	13 (11)	9 (11)	1.0
No	103 (89)	75 (89)	
Partner's age (y)	29.8 ± 4.0	31.5 ± 4.4	.004
≤ 30	79 (68)	39 (46)	.002
> 30	37 (32)	45 (54)	
Partner's education			
Tertiary/college	49 (42)	30 (36)	.38
School	67 (58)	54 (64)	
Occupation			
Professional	36 (31)	24 (29)	.76
Other	80 (69)	60 (71)	

Analysis performed using *t* test for mean and Fisher exact test. Data are expressed as mean ± standard deviation or n (%).

* Malays compared with non-Malays: $P < .001$.

† Professionals compared with nonprofessionals: $P = .041$.

‡ Coitus safe compared with don't know and coitus unsafe: $P < .001$.

§ Did not add up to 100% due to rounding to nearest whole number.

weeks of gestation, five couples would have to have intercourse for one women to avoid reaching 41 weeks of gestation still undelivered (number needed to treat[12] = 5, 95% CI 2.9–9.9). Similarly, at 39 weeks of gestation, five couples would need to have intercourse for one woman to avoid labor induction at 41 weeks of gestation for prolonged pregnancy (NNT = 5, 95% CI 3.3–10.3).

Among the 25 women who had labor induced at 41 weeks of gestation, the mean (± standard deviation) gestational age at birth was 41 weeks and 3 days ± 2 days. There was no perinatal mortality among the study women.

DISCUSSION

Coitus at term as a mode of initiating labor is a popular belief.[2] This prospective study of straightforward maternities with confirmed gestational age showed reductions in gestational length, postdate pregnancy, and labor induction at 41 weeks of gestation for prolonged pregnancy in women who continued to have intercourse at term. Biological plausibility for the effect of intercourse was enhanced by the observations that labor promotion was evident throughout term gestation (Table 3), the peak occurrence of birth was within 24–48 hours of intercourse (Fig. 3), and as the frequency of intercourse increased, its effect was more marked (Table 2).

At 39 weeks of gestation, 5 (95% CI 3.3–10.3) couples would need to have intercourse for one woman to avoid reaching 41 weeks of gestation. Similarly, 5 (95% CI 2.9–9.9) couples would need to have intercourse to avoid one labor induction for reaching 41 weeks of gestation. This finding has important clinical implications because labor induction at 41 weeks of gestation is a common practice.[1,13,14]

Our study shows that being non-Malay, and in particular, being a Chinese woman, was associated with coital abstinence at term. This finding is in agreement with Fok et al[15] who have shown that Chinese pregnant women had fewer sexual activities and less desire during pregnancy.

Eryilmaz et al,[16] in a recent study of Turkish women, has shown associations between sexual activities during pregnancy and duration of marriage, parity, gravidity, and education level. In our study, none of the above factors were independently associated with coitus at term. We found that having a husband aged 30 years or more was an independent risk factor for coital abstinence at term, and this male factor is consistent with the finding that men are the main initiators of sexual activity in pregnancy.[17]

In our study, as expected, women who felt that coitus was not safe were much more likely to abstain from intercourse. Coital safety in pregnancy is a universal issue, with 40% of Nigerian,[18] 45.4% of Pakistani,[17] 49% of Canadian,[19] and as many as 80% of Chinese[15] women expressing safety concerns.

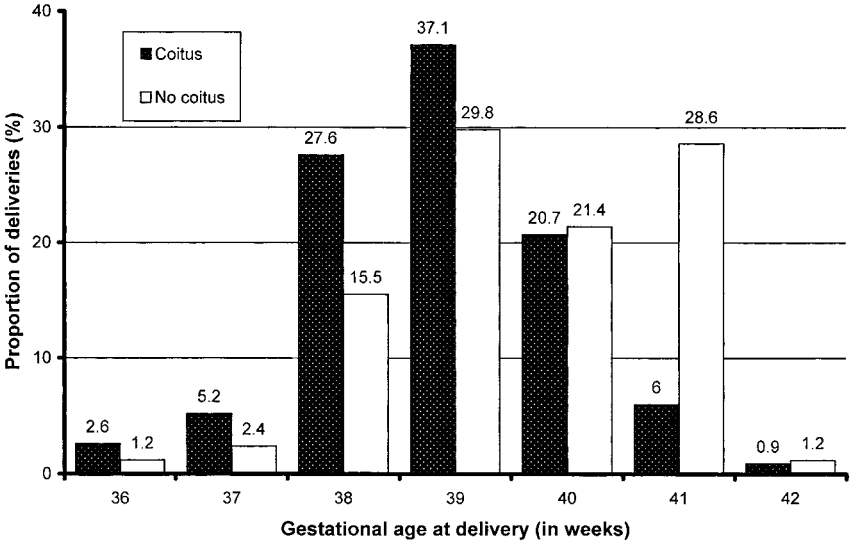

Fig. 2. Distribution of gestational age at delivery according to coital status at term in 200 study women.

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Table 2. Effect of Frequency of Coitus at Term on Postdate Pregnancy, Prolonged Pregnancy, Labor Induction for Prolonged Pregnancy, and Operative Delivery

	Outcome			
Coital Activity at Term	Mean ± SD	Yes	No	RR (95% CI)
Gestational length (wk)				
No coitus	39.9 ± 1.2 ($P < .001$*)			
Infrequent coitus†	39.7 ± 1.0			
Frequent coitus‡	39.1 ± 1.1			
Postdate pregnancy§				
No coitus		37	47	1
Infrequent coitus		11	30	0.61 (0.35–1.06)‖
Frequent coitus		13	42	0.39 (0.23–0.68)¶
Prolonged pregnancy#				
No coitus		25	59	1
Infrequent coitus		5	36	0.41 (0.17–0.99)**
Frequent coitus		3	72	0.13 (0.04–0.43)¶
Labor induction for prolonged pregnancy				
No coitus		20	64	1
Infrequent coitus		4	37	0.41 (0.15–1.12)‖
Frequent coitus		1	74	0.06 (0.01–0.41)¶
Operative delivery				
No coitus		8	76	1
Infrequent coitus		2	39	0.51 (0.11–2.3)‖
Frequent coitus		4	71	0.56 (0.18–1.8)‖

SD, standard deviation; RR, relative risk; CI, confidence interval.
Study women who were abstinent at term are taken as the reference group.
* Analysis of variance (ANOVA).
† *Infrequent coitus* is defined as coital frequency at term of no more than once per week. Coital frequency is calculated by dividing number of coitus from 36 weeks to birth by the interval (in weeks) from 36 weeks to birth.
‡ *Frequent coitus* is defined as coital frequency at term of more than once per week.
§ Postdate pregnancy is defined as pregnancy beyond the estimated date of confinement.
‖ $P \geq .05$.
¶ $P < .001$.
# *Prolonged pregnancy* is defined as pregnancy of at least 41 weeks of gestation.
** $P < .05$.

Among our study women, 60 (30%) did not feel that intercourse at term was safe–a lower percentage than in previous studies.

Because we have restricted our study to healthy women without pregnancy complications and because we excluded from our analysis a small number

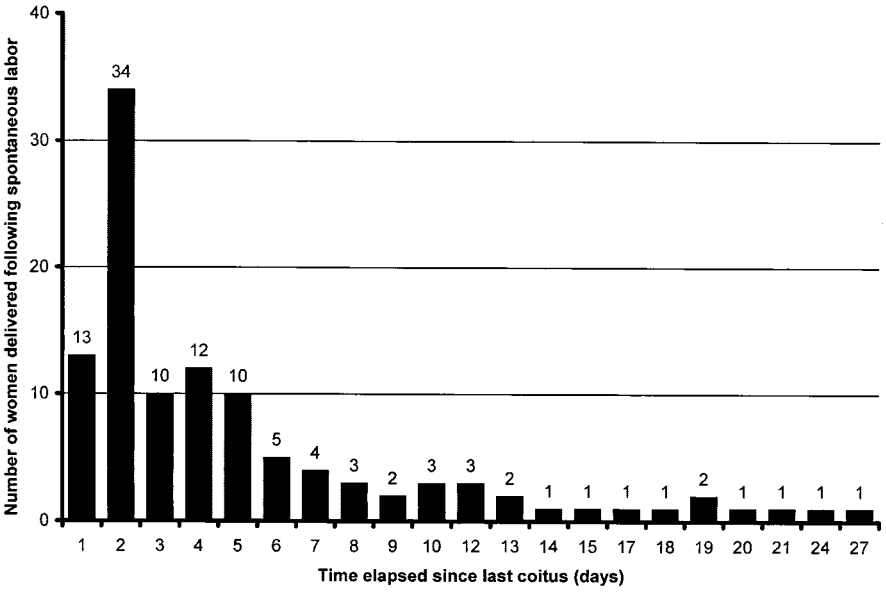

Fig. 3. Time elapsed since last coitus and delivery after spontaneous labor (111 women who had coitus at term).
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Table 3. Effect of Coitus From 36 Weeks of Gestation (at Each Gestational Week) on Spontaneous Labor and Delivery Within the Next Week

	Spontaneous Labor and Delivery Within Next Week			
Any coitus at	Yes	No	*P*	RR (95% CI)
36 weeks				
Yes	9 (10)	85 (90)	.07	3.4 (0.94–12.1)
No	3 (3)	103 (97)		
37 weeks				
Yes	31 (33)	62 (67)	.08	1.6 (0.98–2.50)
No	22 (21)	81 (79)		
38 weeks				
Yes	44 (65)	24 (35)	.36	1.1 (0.89–1.42)
No	69 (57.5)	51 (42.5)		
39 weeks				
Yes	44 (92)	4 (8)	.003	1.3 (1.12–1.55)
No	66 (69)	29 (31)		
40 weeks				
Yes	10 (83)	2 (17)*	.32	1.3 (0.96–1.80)
No	40 (63)	23 (37)†		
41 weeks				
Yes	0 (0)	0 (0)	No statistical analysis possible because no study woman had coitus at 41 weeks	
No	8 (24)	25 (76)‡		

RR, relative risk; CI, confidence interval.
Analysis is by Fisher exact test. Data are presented as n (%).
* Included one delivery after labor induction for prolonged pregnancy at 41 weeks.
† Included 22 deliveries after labor induction for prolonged pregnancy at 41 weeks.
‡ All 25 deliveries are labor inductions carried out at 41 weeks of gestation for prolonged pregnancy.

of women who developed minor complications, our study did not address the issue of safety, apart from ascertaining that all study women were discharged home with their infants. Previous studies of intercourse in pregnancy suggest that complications are uncommon and minor in nature.[15,19] However, in potentially compromised pregnancies, caution has to be applied because the effect of intercourse and orgasm has been described as being similar to an oxytocin contraction stress test.[9]

Our findings need to be confirmed by intervention studies. Any intervention based on such a com-

plex issue as sexual intercourse is likely to be challenging to implement effectively, and the widespread safety concern of women would have to be allayed before the suggested intervention could be widely adopted. Coitus at term can be an effective method for promoting spontaneous labor at term, thereby reducing the need for labor induction at 41 weeks of gestation.

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Original Article

Ultrasound and clinical predictors for Caesarean delivery after labour induction at term

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Abstract

Objective: To assess the relationship of ultrasound assessment for amniotic fluid, fetal weight, cervical length, cervical funneling and clinical factors on the risk of Caesarean delivery after labour induction at term.

Methods: On hundred and fifty-two women scheduled for labour induction at term agreed to participate. Sonography was performed to obtain fetal biometry, amniotic fluid index and cervical length and to detect funneling at the internal cervical os. The sonographic findings were concealed. Study women received standard care during labour induction.

Results: On univariate analysis using Fisher's exact test, parity, cervical length and Bishop score were associated with Caesarean delivery. Following multivariable logistic regression analysis, only nulliparity (adjusted odds ratio (AOR) 5.2 (95% CI 2.2–12.2): $P < 0.001$) and transvaginal ultrasound-determined cervical length of more than 20 mm (AOR 2.8 (95% CI 1.0–7.4): $P = 0.04$) were independent predictors of Caesarean delivery in labour induction. Maternal age, maternal height, gestational age, indication for labour induction, amniotic fluid index, cervical funneling and ultrasound-estimated fetal weight did not predict Caesarean delivery.

Conclusion: In women who had undergone labour induction at term with a singleton fetus, nulliparity and cervical length of more than 20 mm on transvaginal sonography were independent predictors of Caesarean delivery. This information is helpful for pre-induction counselling.

Key words: amniotic fluid index, Caesarean, cervical length, estimated fetal weight, induction of labour, ultrasound.

Introduction

Induction of labour occurs in about 20% of term pregnancies and is associated with a Caesarean delivery rate of about 20%.[1] Cervical length by transvaginal ultrasound[2] and amniotic fluid index (AFI)[3] have been shown to be predictors of Caesarean delivery in induced labour. Birthweight is also associated with Caesarean delivery,[4] but estimated fetal weight by ultrasound is not.[2] However, other authors have not found any association between low AFI at labour induction and Caesarean delivery.[5] Bishop score has been shown to be a better predictor of Caesarean delivery than cervical length on transvaginal ultrasound by some[6] but this finding is disputed by others.[7]

The predictive value of sonography prior to labour induction in predicting Caesarean delivery remained unsettled. A prospective study was therefore performed to assess the value of sonography for fetal biometry (to estimate fetal weight), AFI, cervical funneling and cervical length as well as patient characteristics on Caesarean delivery risk at labour induction as this information would be of use during pre-induction counselling to guide patient's choice.

Methods

This study was performed at a university hospital with about 5000 deliveries per annum. Women at term (37–42 weeks), with a singleton fetus, intact membranes and cephalic presentation were recruited when they presented to the induction bay of the delivery suite for labour induction. Recruitment was carried out by the investigators. Women with an intrauterine fetal death or known lethal fetal anomaly were excluded as the threshold for Caesarean delivery for these women would be very high and inclusion might skew results. Recruitment took place between January 2003 and August 2004. Of 153 women who were approached, only

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one woman declined transvaginal sonography, leaving 152 women for final analysis.

Following recruitment, women who participated in the study were asked to empty their bladder, and a transabdominal ultrasound examination was performed to obtain fetal biparietal diameter, head circumference, abdominal circumference and femur length. Estimated fetal weight was derived using the formula by Hadlock *et al.*[8] AFI was obtained by hypothetically dividing the pregnant uterus into four quadrants and measuring the deepest vertical liquor pool without any umbilical cord in each quadrant and summing the four measurements to obtain the AFI as previously described.[9] The amniotic fluid index was obtained three times in each woman. The mean of the three AFIs was taken as the representative AFI.

Immediately following the transabdominal examination, a transvaginal ultrasound was performed with the woman lying supine. The sagittal image of the entire cervical canal was acquired sonographically as previously described.[10] Measurement of cervical length was made from the internal os to external os in a straight line.[11] The cervical images were acquired three times in succession and the cervical length was measured for each image. The shortest length of the three measurements obtained was used for analysis.[12] Funneling was defined as funnel-shape appearance at the internal cervical os because of dilatation of the internal os. The sonographic findings were concealed from providers.

The ultrasound examination was performed by investigators with at least one year of experience in sonography with a 3.5-MHz curvilinear transabdominal probe and a 6-MHz endovaginal probe using either a Toshiba Eccocee (LET Medical Systems Corp., Miami Lakes, FL, USA) or a Capasee machine (Toshiba Medical Systems Corp., Tokyo, Japan).

The method of induction of labour was decided at the initial vaginal examination in the induction bay, at which time the Bishop Score was also obtained. Labour induction was commenced either with dinoprostone (3 mg) pessary placement in the posterior fornix or with amniotomy. We monitored all women who participated in the study with continuous electronic fetal monitoring in labour.

In our institution, dinoprostone pessary was used for labour induction if the Bishop score was unfavourable (less than five) and amniotomy usually performed when the cervix was at least 3 cm dilated and the presenting part was low. In women with unfavourable Bishop score, a further assessment was made after 6 h; depending on the cervical dilatation and the presence of contractions, a further dinosprostone pessary might be inserted or amniotomy performed. A maximum of two doses of dinoprostone per day were allowed. The women were then routinely assessed again after another 6 h, and if the cervix remained unfavourable, women with non-urgent indications were usually rested overnight and the process repeated the following morning. Following amniotomy for labour induction, oxytocin was usually started within 2 h if contractions were inadequate. The start of labour induction was taken as time of insertion of the first dinoprostone pessary or of amniotomy.

Once in established labour, vaginal assessment was usually performed every 4 h initially unless more frequent examination was indicated. Oxytocin was started for labour augmentation when labour progress fell below the action line in the partogram. Once started, oxytocin infusion was usually continued to delivery.

We defined low Bishop score as a score of less than five, low AFI as AFI of no more than five, short stature as a height of less than 1.5 m (this height was at least 1 standard deviation below the mean for our study population), normal estimated birthweight as between 2.5 and 4 kg and long cervix as cervical length on transvaginal sonography of more than 20 mm (after examination of the receiver operator characteristic curve for cervical length and Caesarean delivery).

Ethical approval for our study was obtained from the Medical Ethics Committee of University Malaya Medical Centre, University of Malaya. Our study followed the principles laid out in the Helsinki Declaration (revised Edinburgh 2000). Written informed consent was obtained from every participant.

Data were entered into a statistical software package SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Instat and QuickCalcs software (GraphPad Software Inc., San Diego, CA, USA) were also used for data analysis. SISA software (Quantitative Skills, Hilversum, Netherlands) was used to perform Fisher's exact test with larger than 2×2 datasets. The Kolmogorov–Smirnoff test was used to check for normal distribution. The *t*-test was used to analyse means, the Mann–Whitney *U*-test for non-parametric data, and the Fisher's exact test for categorical datasets. The relative risk and its 95% CI were calculated using GraphPad Instat program. A receiver operator characteristic curve was used to determine the appropriate cut-off of the cervical length for predicting Caesarean delivery. Multivariate logistic regression analysis was performed, utilising all variables with crude $P < 0.05$. $P < 0.05$ was taken as a significant level, and all tests used two-tailed results.

Results

The characteristics and outcome profiles of the 152 study women are listed in Tables 1 and 2. The overall Caesarean section rate was 23% (nulliparae's rate of 38.5% and multiparae's rate of 11.5%). A receiver operator characteristic curve indicated that the best cut-off for cervical length as a predictor for Caesarean delivery was 20 mm (sensitivity of 77%, specificity of 46%, positive predictive value of 30% and negative predictive value of 87%).

The gestational age was confirmed by ultrasound in 131 (87.5%) women, supported by compatible symphysis-fundal height before 24 weeks of gestation in 15 (9.9%) women, but four (2.6%) women attended late for antenatal care and gestational age was based on maternal menstrual dates.

Among women with Bishop score of ≤ 5, 84 of 86 (97.7%) had vaginal dinoprostone as the initial method of labour induction. Among women with cervical dilatation of ≥ 3 cm, 25 of 31 (80.6%) had amniotomy for labour induction and of the six remaining women who had vaginal dinoprostone

Table 1 Selected pregnancy outcomes of 152 study women undergoing labour induction

Outcome	Numbers (%), mean ± standard deviation or median [interquartile range: IQR]*
Mode of labour induction	
Vaginal dinoprostone	120 (78.9)
Amniotomy	32 (21.1)
Epidural analgesia in labour	38 (25)
Meconium stained liquor	7 (4.6)
Abnormal cardiotocograph in labour†	
Yes	22 (14.5)
No	130 (85.5)
Induction delivery interval (hours)	12.6 [IQR 17.2]
	17.7 ± 14.4
Induction to delivery interval > 12 h	78 (51.3)
Induction to delivery interval > 24 h	41 (27)
Mode of delivery	
Caesarean section	35 (23)
Instrumental vaginal	14 (9.2)
Spontaneous vaginal	103 (67.8)
Indication for Caesarean delivery	
Non-reassuring fetal status	17 (48.6)
Failure to progress	17 (48.6)
Intrapartum haemorrhage	1 (2.9)
Birthweight (kg)	3.20 ± 0.45
< 2.5	9 (5.9)
2.5–4	140 (92.1)
> 4	3 (2)
Apgar score at 5 min	10 [IQR 0]
	9.9 ± 0.5
Apgar < 7 at 5 min	1 (0.7)
Cord pH	7.32 [IQR 0.09]
	7.31 ± 0.08
Low cord pH < 7.1	2 (1.4)

*Median and interquartile range shown where data were non-parametric.
†Defined as abnormal if at least two of the following features – (i) absence of fetal heart rate accelerations, (ii) tachycardia (> 160 b.p.m.), (iii) reduced fetal heart rate baseline variability (< 5 b.p.m.) and (iv) late or variable decelerations, were present in the last hour prior to birth.

induction, five had a high presenting part with station of ≥ –2 cm. Two women had cervical dilation ≥ 3 cm and Bishop score of five. Among women with Bishop score of > 5 and cervical dilation of ≤ 2 cm, 32 of 37 (86.5%) had dinoprostone induction. Method of induction was not a significant predictor of Caesarean delivery in our study (12.5% Caesarean rate for amniotomy subgroup vs 25.8% for dinoprostone subgroup: $P = 0.16$).

The distribution for parity, gestational age, Bishop score and induction to delivery interval were found to be non-parametric. Data for these variables were displayed as median (interquartile range) and Mann–Whitney *U*-test was used to compare these variables.

Table 2 shows the interaction of sonographic findings and patient characteristics with Caesarean delivery. On univariate analysis, nulliparity, long cervix on transvaginal sonography and low Bishop score were significantly associated with Caesarean delivery. After adjustment, nulliparity (AOR 5.2 (95%CI 2.2–12.2): $P < 0.001$) and long cervix (AOR 2.8 (95%CI 1.0–7.4): $P = 0.04$) remained associated with Caesarean delivery. Low Bishop score, absence of cervical funneling, low AFI, ultrasound estimation of fetal weight outside the normal weight range and other studied patient characteristics did not predict Caesarean delivery in labour induction at term.

Discussion

The role of sonographic findings as a predictor for Caesarean delivery at labour induction at term remained unsettled. Low AFI has been found to be predictive of Caesarean delivery indicated by fetal distress[3] but others have not found such an association.[2,5] Our study did not show any association between low AFI and overall Caesarean delivery (Table 2: $P = 0.57$) nor low AFI and Caesarean delivery for fetal distress ($P = 0.22$).

Estimated fetal weight outside the normal range by sonography was also not associated with Caesarean delivery in our study. This finding is compatible with that of recent studies.[2,13,14] In addition, the mean birthweight of babies eventually delivered by Caesarean section was very similar to those delivered vaginally (Tables 2, $P = 0.87$). However, the number of fetuses estimated by ultrasound to be less than 2.5 kg ($n = 14$; 9.2%) or more than 4.0 kg ($n = 3$; 2.0%) were small in our study.

In our study, transvaginally assessed cervical length of more than 20 mm at labour induction was independently associated with Caesarean delivery. This finding is in keeping with recent studies[2,15,16] but others have not demonstrated such an association.[17]

The association between nulliparity and Caesarean delivery following labour induction was the strongest (AOR 5.2) in our study and this association has been consistently reported.[2,7]

Short stature has been reported to increase the risk of Caesarean delivery,[2,18] but in our study, the mean height of women who underwent Caesarean delivery was similar to those who had vaginal delivery; women with short stature (less than 1.5 m) were no more likely to have had Caesarean delivery (Table 2, $P = 0.59$) following labour induction at term.

Our study has some shortcomings – only 35 study women were delivered by Caesarean and the indication for induction of labour was heterogeneous. However, we had used multivariable logistic regression analysis to control for significant variables from univariate analysis.

Nulliparity and pre-induction sonographic cervical length of 20 mm were significant parameters in predicting the mode of delivery in our heterogenous group of study women. Including these parameters in a predictive model would assist in achieving better prediction and counselling of women for induction of labour of singleton pregnancy at term.

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Table 2 Pre-induction sonographic findings and patient characteristics stratified according to mode of delivery for 152 study women who had labour induction. Number (%), mean ± standard deviation or median [IQR: inter quartile range]*

	Caesarean delivery			
	Yes $n = 35$	No $n = 117$	*P*-value and relative risk: RR (95%CI†)	Adjusted *P*-value and AOR‡ (95%CI†)
Age (years)	30.7 ± 4.4	30.4 ± 5.0	$P = 0.80$	
≥ 35	5 (18.5)	22 (81.5)	$P = 0.62$	
< 35	30 (24)	95 (76)		
Parity	0 [1]	1 [2]	$P < 0.001$	
Nulliparae	25 (38.5)	40 (61.5)	$P < 0.001$	$P < 0.001$
Multiparae	10 (11.5)	77 (88.5)	RR 3.3 (1.7–6.5)	AOR 5.2 (2.2–12.2)
Ethnicity				
Malay	21 (21.9)	75 (78.1)	$P = 0.65$	
Chinese	4 (17.4)	19 (82.6)		
Indian	9 (29)	22 (71)		
Other	1 (50)	1 (50)		
Height (cm)	155 ± 5	157 ± 6	$P = 0.36$	
< 150	6 (27.3)	16 (72.7)	$P = 0.59$	
≥ 150	28 (21.7)	101 (78.3)		
Gestational age (weeks)	40 [3]	40 [3]	$P = 0.49$	
> 40	20 (27.4)	53 (72.6)	$P = 0.25$	
≤ 40	15 (19)	64 (81)		
Indication for induction¶				
≥ 41 weeks	17 (38.6)	48 (32.9)	$P = 0.74$	
Diabetes	10 (22.7)	40 (27.4)		
Hypertension	7 (15.9)	15 (10.2)		
Fetal status§	8 (18.2)	30 (20.5)		
Others	2 (4.5)	13 (8.9)		
Induction for diabetes				
Yes	10 (20)	40 (80)		
No	25 (24.5)	77 (75.5)	$P = 0.68$	
Bishop score	5 [3]	5 [3]	$P = 0.024$	
< 5	17 (34)	33 (66)	$P = 0.039$	$P = 0.27$
≥ 5	18 (17.6)	84 (82.4)	RR 1.9 (1.1–3.4)	AOR 1.6 (0.7–4.0)
Amniotic fluid index	9.7 ± 3.7	10.2 ± 4.7	$P = 0.57$	
≤ 5	1 (5.9)	16 (94.1)	$P = 0.122$	
> 5	34 (25.2)	101 (74.8)		
Transvaginal sonography				
Cervical length (mm)	24.5 ± 8.8	22.2 ± 9.5	$P = 0.20$	$P = 0.04$
> 20	27 (30.0)	63 (70.0)	$P = 0.018$	AOR 2.8 (1.0–7.4)
≤ 20	8 (12.9)	54 (87.1)	RR 2.3 (1.1–4.8)	
Funnelling				
Yes	5 (14.3)	30 (85.7)		
No	30 (25.6)	87 (74.4)	$P = 0.18$	
Estimated fetal weight (kg)	3.1 ± 0.5	3.1 ± 0.4		
< 2.5	4 (28.6)	10 (71.4)	$P = 0.87$	
2.5–4	30 (22.2)	105 (77.8)	$P = 0.96$	
> 4	1 (33.3)	2 (66.7)		

*Median and interquartile range shown for non-parametric data.
†95% confidence interval.
‡Adjusted *P*-value and adjusted odds ratio (AOR) shown where covariate was incorporated into the model for multivariate logistic regression analysis.
§Non-reassuring fetal status includes oligohydramnios, reduced fetal movement, small for gestational age, non-reassuring cardiotocograph and non-reassuring umbilical artery Doppler.
¶Indications total 190 as 37 women had two recorded indications for labour induction and one woman had three indications.

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Transvaginal sonographic measurement of cervical length vs. Bishop score in labor induction at term: tolerability and prediction of Cesarean delivery

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KEYWORDS: Bishop score; cervical length; Cesarean delivery; pain score; transvaginal ultrasound; visual analog scale

ABSTRACT

Objectives *To compare transvaginal sonography for cervical length measurement and digital examination for Bishop score assessment in women undergoing labor induction at term, to assess their tolerability (in terms of pain) and ability to predict need for Cesarean delivery.*

Methods *A prospective study was performed on 249 women admitted for labor induction. Cervical length was measured using transvaginal ultrasound examination. A 10-point visual analog scale (VAS) for procedure-related pain was obtained. Bishop score was determined just before labor induction and another pain score was obtained. Delivery outcome was recorded. Analyses were by t-test, Fisher's exact test, receiver–operating characteristics (ROC) curves and multivariate logistic regression.*

Results *Transvaginal sonography was significantly less painful than digital examination for Bishop score assessment (mean difference in VAS score 3.46;* $P < 0.001$*). Analyses of the ROC curves for cervical length and Bishop score indicated that both were predictors of Cesarean delivery (area under the curve 0.611 vs. 0.607;* $P = 0.012$ *vs.* $P = 0.015$*, respectively) with optimal cut-offs for predicting Cesarean delivery of* > 20 *mm for cervical length and Bishop score* ≤ 5*. Cervical length had superior sensitivity (80% vs. 64%) and marginally better positive (30% vs. 27%) and negative (89% vs. 83%) predictive values. Multivariate logistic regression analysis revealed that only nulliparity (adjusted odds ratio (AOR) 4.1; 95% CI, 2.1–8.1;* $P < 0.001$*) and transvaginal sonographic cervical length* > 20 *mm (AOR 3.4; 95% CI, 1.4–8.1;* $P = 0.006$*) were independent predictors of Cesarean delivery.*

Conclusions *Transvaginal sonography for cervical length measurement is better tolerated than digital examination for Bishop score assessment. Both cervical length and Bishop score are useful predictors of the need for Cesarean delivery following labor induction. A cervical length* > 20 *mm at labor induction at term is an independent predictor of Cesarean delivery.*

INTRODUCTION

Induction of labor occurs in about 20% of term pregnancies and is associated with a Cesarean delivery rate of about 20%[1]. The Bishop score[2], since its description in 1964, remains the gold standard for assessing favorability for induction of labor[3]. Transvaginal sonographic cervical length has been shown, by a number of studies[4–7], to be a better predictor of Cesarean delivery than Bishop score in women undergoing induction of labor, but this finding has not been reported consistently[8]. A recent meta-analysis concluded that transvaginal sonography has not been shown to be superior to Bishop score and calls for further research[3]. Previous studies[9,10] with limited numbers of women (40 and 50 women, respectively) have indicated that transvaginal sonography is less painful than digital examination for Bishop score.

The timing of labor induction for common indications such as diabetes in pregnancy[11], prolonged pregnancy[12] and hypertension in pregnancy[13] remains controversial. If a high risk of failed labor induction can be predicted reliably, the timing of labor induction can be reconsidered in many cases with soft indications. Therefore, a reliable and better tolerated method of preinduction assessment than the Bishop score would be a helpful tool in the

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assessment and counseling of women planned for labor induction.

The aim of this prospective study was to compare transvaginal sonography for cervical length measurement and digital examination for Bishop score assessment in women undergoing labor induction at term, to assess their tolerability (in terms of pain) and ability to predict the need for Cesarean delivery.

METHODS

Women at between 37 and 42 weeks' gestation with a singleton fetus, intact membranes and cephalic presentation were recruited when they presented to the induction bay of the delivery suite for labor induction. Recruitment was carried out by the investigators. Women with intrauterine fetal death or known gross fetal anomaly were excluded. This study was approved by our institutional review board and written consent was obtained in all cases.

We defined short stature as a height of < 150 cm, postdates as gestational age > 40 weeks, and categorized maternal age into < 35 years and ≥ 35 years to assess the effect of these parameters on Cesarean delivery.

Women were asked to empty the bladder before transvaginal ultrasound examination. Sonography was performed using a Toshiba Ecocee or a Toshiba Capasee (Tokyo/Otawara, Japan) machine equipped with a 6-MHz transvaginal probe, in a specially equipped room separate from the induction bay by operators who had at least 1 year's ultrasound experience. The sagittal image of the entire cervical canal was acquired sonographically as described previously[14]. Measurement of cervical length was made from the internal os to the external os in a straight line[15]. The cervical images were acquired three times in succession and cervical length measured for each image. The shortest length of the three obtained was used for analysis[16]. Funneling was defined as funnel shape appearance at the internal cervical os due to dilatation of the internal os, with the dilatation measuring at least 5 mm. The sonographic findings were concealed from the women and also from providers managing their labor induction. Following sonography, each woman was asked to indicate on a 10-point visual analog scale (VAS) her perception of pain during the procedure, with a score of 0 representing no pain and a score of 10 denoting unbearable pain.

Women were then moved back to the induction bay for pelvic assessment to obtain the Bishop score. The Bishop score was obtained by induction bay providers who were blinded to the sonographic findings. Another VAS pain score was obtained after pelvic assessment.

The method of induction of labor was decided after the initial vaginal examination in the induction bay. There was universal electronic fetal monitoring for women undergoing labor induction. Induction of labor was by dinoprostone (3 mg) pessary placed in the posterior fornix or amniotomy. In our institution, dinoprostone pessary was used for labor induction if the Bishop score was unfavorable (< 5) and amniotomy was usually performed when the cervix was ≥ 3 cm dilated and the presenting part was low. Following dinoprostone pessary insertion, further assessment was made after 6 h and, depending on the cervical dilatation and presence of contractions, a further dinosprostone pessary might be inserted or amniotomy performed. A maximum of two doses of dinoprostone per day was allowed. The women were then assessed routinely again after another 6 h and, if the cervix remained unfavorable, those with non-urgent indications were usually rested overnight and the process repeated the following morning. Following amniotomy for labor induction, oxytocin was usually given within 2 h if contractions were inadequate. Once in established labor, vaginal assessment was usually done every 4 h initially unless otherwise indicated.

A previous study[7] has reported Cesarean rates of 18.9% and 36.6% in women with sonographically short and long cervical lengths, respectively, who had undergone labor induction. Using an alpha of 0.05 and a power of 0.8, and assuming a ratio of 3 : 2 for long to short cervical lengths among study women, we calculated that 225 women needed to be recruited for an adequately powered study on transvaginal ultrasound examination of the cervix for predicting Cesarean delivery.

Data were entered into the statistical software package SPSS version 13.0 (SPSS Inc., Chicago, IL, USA), and GraphPad Instat and QuickCalcs software (GraphPad Software Inc., San Diego, CA, USA) were also used for data analysis. The *t*-test was used to analyze means, Fisher's exact test was used for categorical datasets, and relative risk with 95% CI was calculated using the GraphPad Instat program. Sensitivity, specificity, positive predictive value and negative predictive value (with 95% CI) and likelihood ratio of a test were also obtained using GraphPad Instat software. A receiver–operating characteristics (ROC) curve was used to determine the best cut-off for cervical length and Bishop score on risk of Cesarean delivery and the area under the curve (AUC) was derived. Multivariate logistic regression analysis was performed utilizing all variables with crude $P < 0.1$. $P < 0.05$ was taken as a significant level and all test results were two tailed.

RESULTS

Recruitment took place from January 2003 to October 2005. Two hundred and fifty-three women were approached. One woman declined transvaginal sonography. Another woman with a Cesarean section scar opted for elective Cesarean delivery after transvaginal ultrasound examination but before commencement of labor induction. Two other women at preterm gestation (35 weeks and 36 weeks) were recruited in error. These four women were excluded, leaving 249 women in the final analysis.

The characteristics, including the indications for labor induction and outcomes of the 249 study women stratified according to mode of delivery, are listed in Table 1. The

Table 1 Characteristics and outcomes of 249 women stratified according to mode of delivery

Variable	*Cesarean delivery* (n = *55*)	*Vaginal delivery* (n = *194*)	P	*Multivariate analysis* AOR (95% CI)*	P
Age (years, mean ± SD)	30.8 ± 4.5	30.1 ± 4.8	0.32		
Aged ≥ 35 years	9 (16.4)	33 (17.0)	1.0		
Parity (median (IQR))	0 (1)	1 (2)	< 0.001		
Nulliparous	38 (69.1)	70 (36.1)	< 0.001	4.1 (2.1–8.1)	< 0.001
Ethnicity					
Malay	34 (61.8)	127 (65.5)	0.16		
Chinese	6 (10.9)	36 (18.6)			
Indian	14 (25.5)	27 (13.9)			
Other	1 (1.8)	4 (2.1)			
Height (cm, mean ± SD)	156 ± 8	156 ± 6	0.54		
Height < 150 cm	8 (14.5)	23 (11.9)	0.64		
Gestational age (weeks, mean ± SD)	39.8 ± 1.5	39.9 ± 1.3	0.40		
Gestation > 40 weeks	30 (54.5)	91 (46.9)	0.36		
Indications for induction of labor†					
Diabetes mellitus	18 (29.0)	72 (32.4)	0.83		
Prolonged pregnancy	18 (29.0)	69 (31.1)			
Non-reassuring fetal status‡	9 (14.5)	34 (15.3)			
Hypertension	11 (17.7)	27 (12.2)			
Other	6 (9.7)	20 (9.0)			
Cervical length (mm, mean ± SD)	24.7 ± 7.9	21.7 ± 8.9	0.024		
Cervical length > 20 mm	44 (80.0)	102 (52.6)	< 0.001	3.4 (1.4–8.1)	0.006
No funneling at internal cervical os	50 (90.9)	149 (76.8)	0.022	1.3 (0.4–4.1)	0.65
Bishop score (mean ± SD)	5.1 ± 1.8	5.8 ± 1.8	0.021		
Bishop score ≤ 5	35 (63.6)	95 (49.0)	0.066	0.9 (0.4–2.0)	0.83
Pain score on VAS (mean ± SD)§					
Sonography	2.9 ± 2.0	2.3 ± 1.9	0.056		
Bishop score	6.2 ± 2.5	5.8 ± 2.3	0.27		
Mode of labor induction					
Vaginal dinoprostone	50 (90.9)	140 (72.2)	0.004	1.6 (0.5–5.2)	0.40
Amniotomy	5 (9.1)	54 (27.8)			
Birth weight (kg, mean ± SD)	3.2 ± 0.5	3.2 ± 0.4	0.71		
Apgar score at 5 min (mean ± SD)	9.9 ± 0.4	9.9 ± 0.4	0.57		
Apgar score < 7 at 5 min	0 (0)	1 (0.5)	1.0		
Umbilical cord pH (mean ± SD)	7.27 ± 0.07	7.31 ± 0.07	0.001		
Cord pH < 7.1	1 (1.8)	1 (0.5)	0.38		

Values are expressed as *n* (%) unless stated otherwise. Analysis was by *t*-test for means, Mann–Whitney *U*-test for parity (as distribution was non-parametric) and Fisher's exact test for categorical data. *Multivariate logistic regression analysis was used to identify independent predictors for Cesarean delivery using all variables with crude $P < 0.1$. Adjusted odds ratio (AOR) is shown for all variables used in the model. †Total of 284 indications as 33 women had two indications and one had three indications listed for induction of labor. ‡Non-reassuring fetal status included oligohydramnios, suspected intrauterine growth restriction, reduced fetal movement and suboptimal umbilical artery on Doppler examination or cardiotocography. §Score on visual analog scale (VAS) from 0 (no pain) to 10 (unbearable pain). IQR, interquartile range.

overall Cesarean section rate was 22.1% (55/249), 35.2% for nulliparas and 12.1% for parous women. Emergency Cesarean delivery following labor induction was indicated by fetal distress in 45.5% (25/55) and failure to progress in 54.5% (30/55).

The gestational age of the study women was confirmed by ultrasound examination in 214 (85.9%) women, supported by compatible symphysis–fundal height before 24 weeks' gestation in 29 (11.6%), and in six (2.4%) women who attended late for antenatal care, gestational age was based on maternal menstrual dates alone.

Transvaginal sonography was better tolerated than Bishop score assessment (mean ± SD score on VAS 2.4 ± 1.9 vs. 5.9 ± 2.4, respectively; mean difference 3.5 ± 2.9, $P < 0.001$, paired *t*-test). Two hundred and fifteen women (86.3%) found transvaginal assessment to be less uncomfortable, 16 (6.4%) found both procedures to be equally tolerated and only 18 (7.2%) women felt that transvaginal assessment was more uncomfortable than digital assessment for Bishop score.

ROC curves indicated that the best cut-off of cervical length for predicting Cesarean delivery was > 20 mm (sensitivity 80%, specificity 47%, positive predictive value 30%, negative predictive value 89% and accuracy 55%) and for Bishop score it was a score of ≤ 5 (sensitivity 64%, specificity 51%, positive predictive value 27%, negative predictive value 83% and accuracy 54%). Comparisons between transvaginal sonography and Bishop score in predicting Cesarean delivery are shown in Table 2.

The AUCs indicated that both cervical length and Bishop score were useful predictors of Cesarean delivery in labor induction (Figure 1). AUC, sensitivity, positive

Table 2 Comparison of transvaginal sonography for cervical length and Bishop score for predicting risk of overall Cesarean delivery and Cesarean delivery indicated by failure to progress following induction of labor

	Prediction of overall Cesarean delivery		*Prediction of Cesarean indicated by failure to progress**	
Parameter	*Cervical length > 20 mm vs. ≤ 20 mm*	*Bishop score ≤ 5 vs. > 5*	*Cervical length > 20 mm vs. ≤ 20 mm*	*Bishop score > 5 vs. ≤ 5*
Relative risk	2.8 (1.5–5.2)	1.6 (1.0–2.7)	3.1 (1.3–7.3)	1.5 (0.7–2.9)
P	< 0.001	0.067	0.005	0.33
Sensitivity (%)	80 (67–90)	64 (50–76)	80 (61–92)	60 (41–77)
Specificity (%)	47 (40–55)	51 (44–58)	47 (40–55)	51 (44–58)
Positive predictive value (%)	30 (23–38)	27 (20–35)	19 (13–27)	16 (10–24)
Negative predictive value (%)	89 (82–95)	83 (75–89)	94 (87–98)	89 (82–94)
Likelihood ratio	1.5	1.3	1.5	1.2
Area under receiver–operating characteristics curve	0.611 (0.53–0.69)	0.607 (0.52–0.69)	0.59 (0.50–0.69)	0.60 (0.51–0.70)

Values in parentheses are 95% CI. *Cesarean delivery indicated by fetal distress excluded from analysis as this outcome was considered to have an indeterminate association with failed induction.

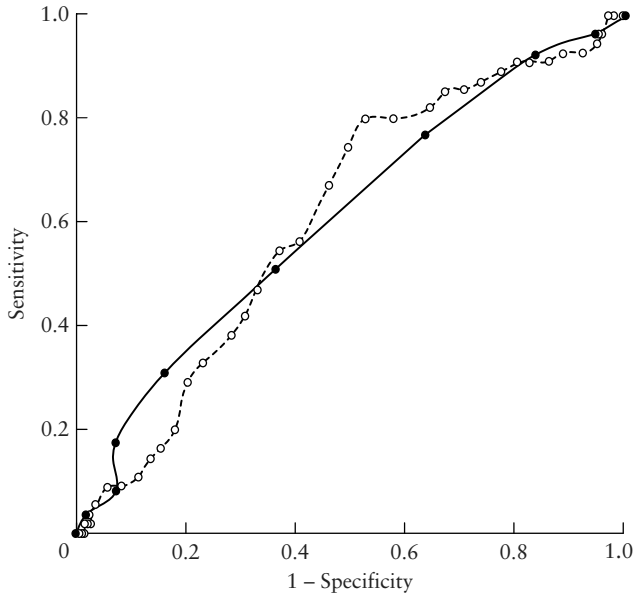

Figure 1 Receiver–operating characteristics curve for cervical length measured by transvaginal sonography (○) and Bishop score (●) in predicting Cesarean delivery.

and negative predictive values as well as accuracy were marginally better with transvaginal sonography than Bishop score in predicting global Cesarean delivery risk, but 95% CI values overlapped.

In the sub-analysis of cases in which Cesarean section was performed due to failure to progress (as opposed to because of fetal distress), cervical length > 20 mm remained significantly associated with Cesarean delivery ($P = 0.005$) whereas Bishop score ≤ 5 was not ($P = 0.33$) on categorical analysis with Fisher's exact test (Table 2).

On univariate analysis (Table 1) nulliparity, cervical length > 20 mm, absence of funneling at the internal cervical os and dinoprostone induction were all associated with Cesarean delivery. Bishop score ≤ 5 had a borderline result ($P = 0.066$). After multivariate logistic regression analysis controlling for the above variables, only nulliparity (adjusted odds ratio (AOR) 4.1; 95% CI, 2.1–8.1; $P < 0.001$) and sonographic cervical length > 20 mm (AOR 3.4, 95% CI, 1.4–8.1; $P = 0.006$) remained independently associated with Cesarean delivery.

A secondary analysis according to parity (Table 3) showed that transvaginal ultrasound examination of cervical length was marginally better in predicting Cesarean delivery than was Bishop score in both nulliparous and parous women. In nulliparas, the positive predictive value of a cervical length > 20 mm in predicting Cesarean delivery was 46% (95% CI, 33–59%) and the negative predictive value in parous women was 97% (95% CI, 88–100%).

When cervical length > 20 mm and Bishop score ≤ 5 were used to predict an induction-to-delivery interval exceeding 24 h, Bishop score ≤ 5 had a sensitivity of 71% (95% CI, 59–82%), specificity of 54% (95% CI, 47–62%), positive predictive value of 35% (95% CI, 27–43%), negative predictive value of 85% (95% CI, 77–91%) and likelihood ratio of 1.56. Sonographic cervical length > 20 mm had a sensitivity of 79% (95% CI, 67–89%), specificity of 48% (95% CI, 41–56%), positive predictive value of 34% (95% CI, 27–43%), negative predictive value of 87% (95% CI, 79–93%) and likelihood ratio of 1.54. The performance of Bishop score ≤ 5 and transvaginal cervical length > 20 mm as predictors of a prolonged induction-to-delivery interval was thus very similar.

DISCUSSION

Our finding has added to the available evidence[4–7,17–19] that transvaginal sonography is at least as good as the Bishop score in predicting Cesarean delivery in women undergoing induction of labor. In addition, we have confirmed the findings of other smaller studies[9,10] that transvaginal sonography is significantly less painful than digital examination for Bishop score assessment (3.5 fewer pain points on a 10-point VAS). Furthermore, our study showed that Bishop score was no longer significantly associated with Cesarean delivery once parity

Table 3 Comparison of transvaginal sonography for cervical length and Bishop score for predicting risk of Cesarean delivery in labor induction at term stratified according to parity

	Prediction of Cesarean delivery: nullipara		*Prediction of Cesarean delivery: para*	
Parameter	*Cervical length > 20 mm vs. ≤ 20 mm*	*Bishop score ≤ 5 vs. > 5*	*Cervical length > 20 mm vs. ≤ 20 mm*	*Bishop score > 5 vs. ≤ 5*
Relative risk	2.3 (1.2–4.4)	1.4 (0.8–2.4)	5.2 (1.2–22)	1.8 (0.7–4.6)
P	0.008	0.23	0.009	0.30
Sensitivity (%)	76 (60–89)	63 (46–78)	88 (64–99)	64 (38–86)
Specificity (%)	51 (39–64)	50 (38–62)	45 (36–54)	52 (43–61)
Positive predictive value (%)	46 (33–59)	40 (28–54)	18 (10–28)	15 (8–26)
Negative predictive value (%)	80 (65–90)	71 (57–83)	97 (88–100)	91 (82–97)
Likelihood ratio	1.6	1.3	1.6	1.3
Area under receiver–operating characteristics curve	0.617 (0.51–0.73)	0.567 (0.45–0.68)	0.650 (0.53–0.77)	0.645 (0.51–0.78)

Values in parentheses are 95% CI.

and cervical length were taken into account in a logistic regression model, as shown previously[5]. Funneling at the internal cervical os on sonographic assessment was not an independent predictor of Cesarean delivery either. In 44/50 cases (88%) in which funneling was noted, the cervical length was ≤ 20 mm, indicating a very strong association between funneling and a short cervix ($P < 0.001$). The above findings suggest that a scoring system using a combination of transvaginal assessment and Bishop score or funneling will not be useful as a predictor of Cesarean delivery as these variables were not independent predictors.

We performed a sub-analysis of Cesarean delivery indicated by failure to progress after excluding women in whom a Cesarean was performed because of fetal distress as the latter could not be considered a successful induction nor could it properly be considered a failed induction as the underlying cause was possibly predetermined and presumably 'uteroplacental insufficiency'. Arguably, a Cesarean delivery for failure to progress might be a closer indicator of failed induction as failure to reach established labor and failure to progress in labor might be attributed to current methods of labor induction failing to overcome a very unfavorable cervix. Transvaginal sonographic measurement of cervical length > 20 mm remained a better predictor than Bishop score ≤ 5 for this outcome.

Nulliparity, as anticipated, was a significant predictor for Cesarean delivery following induction of labor even after adjusted analysis[5,19]. Among nulliparas with a transvaginal sonographic cervical length > 20 mm, the predictive value for Cesarean delivery was 46%; a 46% Cesarean rate should be a cause for reflection if indications for labor induction were soft and the threshold for induction of labor might consequently be raised. Amongst parous women, the opposite effect might apply: with a cervical length ≤ 20 mm, the predictive value for vaginal delivery was 97%. This very high predictive value for vaginal delivery in parous women might lower the threshold for labor induction in borderline cases.

A particular problem with using transvaginal ultrasound measurement of cervical length as a predictor for Cesarean delivery at labor induction is the inconsistent cut-off values suggested by different studies, ranging from 18–20 mm[18], 26 mm[7], 27 mm[4] or even 30 mm[17]. Our study suggested a cut-off at a cervical length of 20 mm, similar to that in a large study by Rane *et al.*[18].

Digital vaginal assessment is an integral part of labor induction; it is required to place induction agents in the vagina or cervix, and to perform amniotomy or membrane sweeping, and the Bishop score is usually obtained within this context. It would be unfair to attribute all the discomfort of a vaginal assessment to Bishop score assessment as some of the discomfort is unavoidable with current methods of labor induction. Therefore, our finding of transvaginal ultrasound examination being better tolerated has to be interpreted within the context of vaginal examination being an integral part of the labor induction process in most cases, regardless of Bishop score assessment.

Interestingly, a recent randomized study comparing use of transvaginal sonographic assessment and Bishop score to guide preinduction cervical ripening with prostaglandins has shown a reduction in prostaglandin use without affecting successful labor induction with transvaginal ultrasonography[20].

Our study had some shortcomings. About 14% of study women did not have ultrasound confirmation of gestational age. However, there is no indication that the value of cervical scoring in determining favorability for induction of labor is confined to term gestation only[6]. In addition, we did not take into account maternal body weight. Body mass index is a recognized predictor of Cesarean delivery at labor induction[5]. The method of labor induction was not standardized in this study, but multivariate logistic regression analysis was used to control for this variable.

If oral agents are used for labor induction or the Bishop score is being gathered in the office for assessing favorability before deciding whether to induce labor, then transvaginal sonographic assessment of cervical length may be a better alternative for women than the Bishop score provided that the appropriate expertise and ultrasound equipment are available.

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Concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction of nulliparas with an unfavourable cervix: a randomised placebo-controlled trial

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Objective To compare concurrent oxytocin with dinoprostone pessary versus dinoprostone pessary in labour induction for nulliparas with an unfavourable cervix.

Design A randomised double-blind study.

Setting University Malaya Medical Centre, Malaysia.

Population Nulliparas at term with intact membranes, Bishop score ≤ 6 and admitted for labour induction.

Methods All women received 3 mg dinoprostone pessary for labour induction. Those randomised to the oxytocin arm received oxytocin infusion started at 1 mu/minute and doubled every 30 minutes to a maximum 16 mu/minute. Women assigned to placebo received identical volume of saline infusion. After 6 hours, infusion was stopped and vaginal reassessment performed to guide further management.

Main outcome measures Primary outcome was vaginal delivery within 24 hours.

Results Concurrent oxytocin infusion with dinoprostone pessary did not significantly increase vaginal delivery rate within 24 hours (48.6 versus 35.9%; $P = 0.07$, relative risk [RR] 1.4 [95% CI 1.0–1.9]). It reduced the requirement for repeat dinoprostone (37.1 versus 61.2%; $P = 0.001$, RR 0.61 [95% CI 0.45–0.81]) and improved maternal satisfaction with the birth process (median score of 3 versus 5 on a 10-point visual analogue scale, $P = 0.007$). Caesarean rates were not different (41.9 versus 44.7%, $P = 0.52$).

Conclusions Labour induction with concurrent oxytocin infusion and vaginal dinoprostone could be considered for nulliparas with an unfavourable cervix. Larger studies are needed.

Keywords Dinoprostone, induction of labour, oxytocin, prostaglandin, trial.

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Introduction

Contemporary labour induction rate is about 20% of term pregnancies[1,2] and has been increasing since the early 1990s.[1,2] Induction of labour is associated with a doubling in the caesarean section delivery rate compared with spontaneous labour.[3]

In nulliparas with an unfavourable cervix undergoing labour induction, caesarean delivery rate is reported to be more than 30%.[4] In a recent study on labour induction performed at our centre among nulliparas at term, the overall caesarean section delivery rate was 40.6%.[5] In a Cochrane meta-analysis of prostaglandins use in labour induction,[6] there is only one randomised controlled study of prostaglandin versus placebo of nulliparas with an unfavourable cervix, and this study[7] shows that 78.9% did not deliver vaginally within 24 hours of induction with prostaglandins.

Dinoprostone vaginal tablet or pessary is an effective method of cervical ripening and labour induction.[6] Oxytocin infusion is also effective in cervical ripening and labour induction, but a Cochrane meta-analysis has concluded that 'prostaglandin agents probably overall have more benefits than oxytocin alone'.[8] Dinoprostone pessary is as effective as gel or long-acting preparations and is also cheaper.[6]

There are few studies looking at concurrent oxytocin infusion with prostaglandin administration for cervical ripening and labour induction. We performed a PubMed search in all languages on 6 September 2006 using the terms

'prostaglandins and oxytocin and labor induction and trial' and found 408 entries, but only four entries related to concurrent use of oxytocin infusion with a prostaglandin for labour induction with intact membranes.[9–12] Three of these studies[10–12] have shown shorter induction-to-delivery interval with concurrent infusion of oxytocin with a prostaglandin agent at initiation of labour induction, but the largest of the four trials with 151 women did not demonstrate a significantly shorter induction-to-delivery interval with concurrent oxytocin infusion.[9]

Our study aim was to determine whether a concurrent 6-hour infusion of oxytocin at initiation of labour induction in conjunction with a commercially available 3-mg dinoprostone pessary would be of benefit to a group of nulliparas with an unfavourable cervix.

Methods

A double-blind randomised control study was performed to compare 6 hours of concurrent oxytocin infusion with vaginal dinoprostone 3-mg tablet with placebo saline infusion and vaginal dinoprostone 3-mg tablet at initiation of labour induction at term. The study was approved by the Medical Ethics Committee of University of Malaya Medical Centre, and written consent was obtained from all women. About 5000 women per year deliver at our centre.

Based on an earlier study[12] that showed a 76 versus 56% vaginal delivery rate within 24 hours of commencement of labour induction with the use of concurrent oxytocin infusion and prostaglandin gel versus a sustained-release prostaglandin vaginal insert, taking alpha of 0.05, power of 0.8 and a recruitment ratio of one to one, 97 women were needed in each arm for a suitably powered study with vaginal delivery within 24 hours as a primary outcome. Assuming a 10% drop out, a total of 216 women would need to be recruited.

Primary outcome was vaginal delivery within 24 hours. We collected a number of secondary outcome measures including change in Bishop score over the 6 hours of infusion, analgesic requirement during the 6 hours of infusion, total number of doses of dinoprostone pessary used, visual analogue scale (VAS) pain score after the 6-hour infusion period (using a 10-point score, with 0 representing no pain to 10 representing unbearable pain), meconium-stained liquor, intrapartum epidural analgesia use, oxytocin augmentation, duration of oxytocin augmentation (if needed), vaginal delivery within 12 hours of induction, postpartum haemorrhage of ≥500 ml, maternal blood transfusion, maternal fever, labour induction-to-delivery interval and delivery-to-discharge interval. Neonatal outcomes collected included neonatal admission, Apgar score at 5 minutes, umbilical cord blood pH and neonatal jaundice. As soon as possible after delivery, women were asked to provide a birth process satisfaction score using a 10-point VAS (with 0 representing complete satisfaction to 10 representing total dissatisfaction).

Nulliparous women at term (>36 weeks) with a singleton fetus, intact membranes, cephalic presentation and an unfavourable cervix (defined as a Bishop score ≤ 6)[9,10,12] were recruited after they presented to the induction bay of the delivery suite for scheduled labour induction. Recruitment was carried out by one of the investigators or the staff of the induction bay. Women with an intrauterine fetal death or known gross fetal anomaly were excluded. Recruitment was from August 2005 to July 2006.

Randomisation sequence was generated by an investigator (P.C.T.) not involved in recruitment using a computer random number generator. Three different block sizes of 8, 10 and 12 were used. The sequence of the block size to be used was also similarly determined. The master list for the randomised treatment allocation sequence was kept by the same investigator. The treatment allocation was placed into numbered, sealed, opaque envelopes each of which contained a piece of paper bearing the legend 'Oxytocin infusion' or 'Placebo saline infusion'.

After an eligible woman had consented to participate, the next available randomisation number was assigned to that woman, and the numbered treatment allocation envelope was then given to a study nurse not otherwise involved with the woman's management to be opened in an isolated area of the delivery suite. The nurse then prepared the allocated infusion solution according to written instructions. The prepared solution was then labelled with a pre-prepared sticker bearing the individualised randomisation number, the woman's name and the legend 'Trial Medication—Oxytocin or Saline Placebo'. Treatment allocation was not revealed to study women or providers.

For women assigned to the oxytocin arm, 10 units of oxytocin was added to 500 ml of commercially available 0.9% saline in a translucent plastic container, the container labelled as mentioned above and then shaken to distribute the drug evenly. This preparation contained oxytocin at a concentration of 20 mu/ml. For women assigned to placebo, an identical container of 0.9% saline only was labelled.

Prior to trial entry, a mandatory cardiotocography (CTG) was performed, and all study women had a reassuring CTG according to Royal College of Obstetricians and Gynaecologist, UK, criteria.[13]

Sterile vaginal examination was performed in the usual fashion, and the Bishop score was recorded. The 3-mg dinoprostone pessary was placed digitally as high as possible in the posterior fornix.

As soon as possible after the insertion of the dinoprostone pessary, intravenous infusion was started at a rate of 3 ml/hour (equivalent to 1 mu/minute of oxytocin if assigned to oxytocin), and the infusion rate was double every 30 minutes to a defined maximum of 48 ml/hour

(16 mu/minute of oxytocin)—this infusion rate would normally be achieved after 2 hours unless the uterine contraction frequency was more than five per 10 minutes An electric infusion pump was used in all cases. Trial protocol dictated that the infusion rate would be increased in a geometric manner as planned unless uterine contraction frequency was five or more per 10 minutes in which case infusion rate would be maintained to sustain contraction frequency of four to five per 10 minutes. Infusion was continued for a total of 6 hours. Study women were on continuous electronic fetal monitoring throughout the 6-hour infusion.

In the event of contraction frequency of six or more per 10 minutes over two consecutive 10-minute periods but without fetal heart rate abnormality (tachysystole), infusion rate would be halved every 10 minutes until contraction frequency of five or less per 10 minutes was achieved. In women with uterine hyperactivity (i.e. tachysystole or a prolonged contraction of ≥2 minutes) and fetal heart rate pattern abnormality, the following management sequence was suggested with escalation as dictated by clinical response: 1) stop infusion, 2) perform vaginal examination and attempt to remove dinoprostone pessary if still present, 3) administer terbutaline 0.25 mg subcutaneously for tocolysis and 4) expedite delivery by caesarean section if necessary. Any such occurrence was recorded as an adverse trial event.

Women given vaginal dinoprostone for cervical ripening and labour induction in our hospital were normally only reassessed vaginally after 6 hours to institute further management. We also recorded any indicated vaginal assessment and any analgesia needed during the 6-hour infusion as trial events. Intramuscular pethidine (75 mg) and promethazine (25 mg) were routinely offered as first-line analgesia at this point, with epidural analgesia also available if needed.

Infusion was stopped after 6 hours following which another sterile vaginal assessment was performed and Bishop score recorded. At this assessment, depending on cervical findings, a further dinoprostone can be administered if the cervix remained unfavourable, amniotomy performed or no action taken if contractions are strong and good progress has been made. Following amniotomy or spontaneous rupture of membranes, oxytocin augmentation would be started if labour progress was unsatisfactory as determined by partogram assessment with a 2-hour delay action line. If a second dinoprostone pessary was administered, another vaginal assessment was performed 6 hours later. Once membranes had ruptured or labour had become established, vaginal assessment was performed at least 4 hourly.

We allowed a maximum of two dinoprostone pessaries per day. In the event that cervical status remained unfavourable after two doses of dinoprostone and amniotomy was not possible, women who were well and with a reactive CTG were normally rested overnight.

Up to four doses of dinoprostone pessary over 2–3 days might be used in our hospital in nonurgent labour inductions, provided the women and their babies remained well during the labour induction process. However, some women might opt for a caesarean delivery after two doses of dinoprostone had failed to achieve cervical ripening. Decision to perform a caesarean delivery was made based on our usual obstetric practice, and the indication for caesarean delivery was recorded.

Data were entered into a statistical software package SPSS version 11 (SPSS Inc., Chicago, IL, USA), and GraphPad Instat and QuickCalcs software (GraphPad Software Inc., San Diego, CA, USA) were also used for data analysis. SISA software (Quantitative Skills, Hilveraum, the Netherlands) was used to perform Fisher's exact test with larger than 2×2 data sets. The Kolmogorov–Smirnoff test was used to check for normal distribution. The t test was used to analyse means and distributions, and the Mann–Whitney U test was used to check for consistency in the event that t test was applied to non-normal data or ordinal data. Relative risk (RR) and its 95% confidence interval were calculated using GraphPad Instat. Numbers needed to treat (NNT) and its 95% confidence interval were generated with GraphPad Quickcalc. $P < 0.05$ in any test was considered statistically significant, and all test used two-sided results. Analysis was performed per protocol and on intention-to-treat basis.

Results

Two hundred and twenty-seven nulliparas were approached. Two hundred and twenty agreed to participate and were randomised (Figure 1). However, due to infringements of the inclusion criteria, 12 women (7 randomised to oxytocin and 5 to placebo) were excluded after randomisation and opening of their treatment allocation envelopes. Thus, 105 women allocated oxytocin and 103 women allocated to placebo were available for per-protocol analysis. All women received allocated treatment.

The characteristics of study women are listed in Table 1. There was no significant difference ($P > 0.05$) in any recorded characteristic between women randomised to oxytocin and those randomised to placebo infusion (Table 1). This finding remains consistent even if we had taken into account the 12 women excluded due to infringement of inclusion criteria (intention-to-treat analysis).

The distributions of the VAS pain and birth process satisfaction scores, mean change in Bishop score after 6 hour of infusion, total number of dinoprostone pessary used and the Apgar score at 5 minute were nonparametric when assessed using the Kolmogorov–Smirnoff test.

Primary outcome and secondary outcomes are reported in Table 2. Vaginal delivery within 24 hours of labour

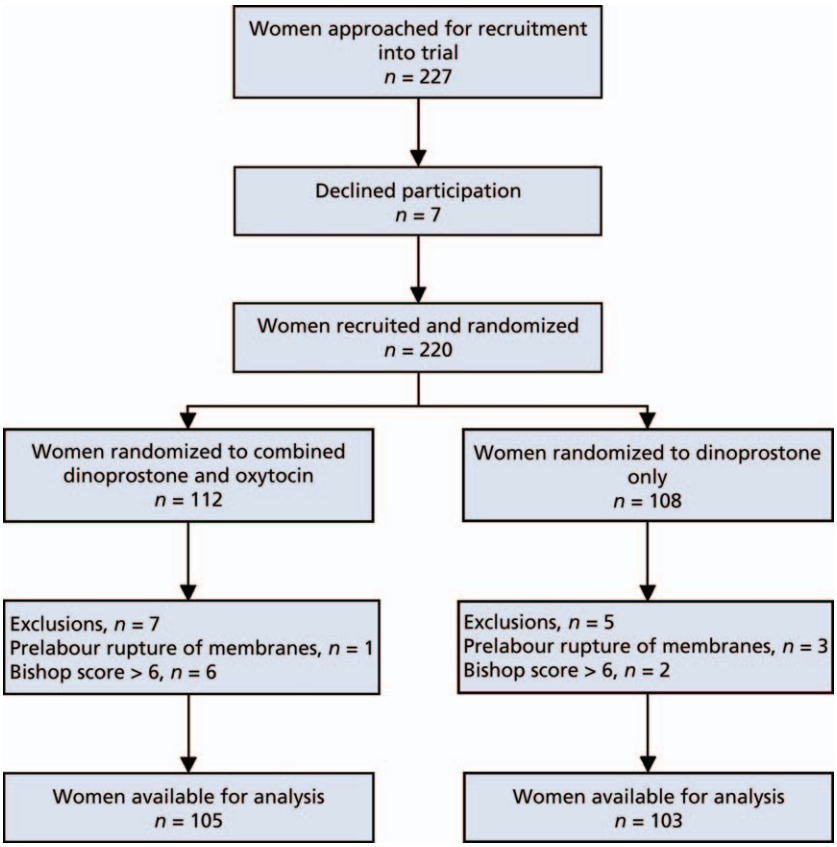

Figure 1. Recruitment flow chart for randomised trial of combined vaginal dinoprostone and oxytocin infusion for 6 hours versus vaginal dinoprostone alone at initiation of labour induction in nulliparas with unfavourable Bishop score.

induction was not significantly increased with concurrent oxytocin infusion (48.6 versus 35.9%, RR 1.4, 95% CI 1.0–1.9; $P = 0.07$), but this was a borderline result. Inclusion of 12 women excluded due to inclusion criteria infringements (intention-to-treat analysis) did not change this finding (50.0 versus 38.0%, RR 1.3, 95% CI 0.97–1.9; $P = 0.08$).

Women allocated to oxytocin infusion were less likely to need a further dinoprostone pessary (NNT = 5, 95% CI 2.7–9.2). There was no significant reduction in the caesarean delivery rate (41.9 versus 44.7%, RR 0.94, 95% CI 0.69–1.28; $P = 0.78$). They expressed better satisfaction with their birth experience (median score of 3 versus 5 on a 10-point VAS, $P = 0.007$). However, they reported worse VAS pain score at end of the 6-hour infusion (median score of 5 versus 4 on a 10-point VAS, $P < 0.001$) and were more likely to receive analgesia during the 6-hour infusion (number needed to harm is 7, 95% CI 3.9–16.3). Intramuscular pethidine and promethazine analgesia were administered as required; no study women needed epidural analgesia during the 6-hour infusion.

There was no significant difference in the occurrence of uterine hyperstimulation syndrome (tachysystole or prolonged contraction with fetal heart rate abnormality) between the two groups—with two women in the oxytocin arm and one in the placebo arm. These women responded rapidly to the reduction or stopping of the trial infusion. No woman needed removal of dinoprostone pessary, terbutaline injection or expedited delivery due to uterine hyperstimulation syndrome. One woman allocated to saline placebo needed an emergency caesarean section during the 6-hour infusion period for fetal heart rate decelerations on CTG but without uterine hyperactivity.

There was no significant difference in meconium-stained liquor. Umbilical cord blood pH was marginally lower (mean 7.26 ± 0.08 SD versus mean 7.28 ± 0.07 SD; $P = 0.044$) in women allocated oxytocin, but the number [%] of babies with umbilical cord arterial blood pH < 7.1 (3 [2.9] versus 8 [7.8], $P = 0.13$) and the number [%] of neonatal admissions to a neonatal unit (6 [5.7] versus 12 [11.7], $P = 0.15$), although not significantly different, were lower in women assigned to oxytocin. Apgar score at 5 minutes and the incidence of neonatal jaundice were not different. There was no perinatal mortality in this study.

Two women, both allocated to oxytocin, had somewhat unusual management of their labour induction, which

Table 1. Characteristics of study women stratified according to treatment allocation to combined dinoprostone and oxytocin or dinoprostone only at initiation of labour induction in nulliparas with unfavourable Bishop score

	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103
Age (years)*	27.9 ± 3.6	27.8 ± 3.9
	28 [5]	27 [5]
Age ≥ 35 years	6 (5.7)	8 (7.8)
Gravidity*	1.3 ± 0.7	1.2 ± 0.5
	1 [0]	1 [0]
Gestational age*	40.0 ± 1.3	40.0 ± 1.2
Gestational age > 40 weeks	52 (49.5)	49 (47.6)
Gestational age determined by		
Dates and confirmed by ultrasound	97 (92.4)	90 (87.4)
Early ultrasound only	8 (7.6)	11 (10.7)
Dates only	0 (0)	2 (1.9)
Ethnicity		
Malay	63 (60.0)	58 (56.3)
Chinese	20 (19.0)	13 (12.6)
Indian	19 (18.1)	27 (26.2)
Others	3 (2.9)	5 (4.9)
Indication for labour induction**		
Prolonged pregnancy ≥ 41 weeks	40 (35.7)	32 (29.6)
Diabetes	41 (36.6)	43 (39.8)
Hypertension	13 (11.6)	14 (13.0)
Nonreassuring fetal status***	14 (12.5)	16 (14.8)
Others	4 (3.6)	3 (2.8)
Height (cm)	156 ± 6	155 ± 6
Height < 150 cm	16 (15.4)	22 (21.4)
Body mass index	30.3 ± 5.2	30.3 ± 4.3
Preinduction Bishop score*	4.2 ± 1.3	4.2 ± 1.3
	4 [1]	4 [1]
Birthweight (kg)	3.15 ± 0.44	3.13 ± 0.41
Delivery blood loss (ml)*	348 ± 163	351 ± 178
	300 [150]	300 [150]

Data are represented as mean ± SD, median [interquartile range] and *n* (%). Analyses were by *t* test for comparison of means and Fisher's exact test for categorical data sets. Mann–Whitney *U* test was used to check consistency with *t* test for nonparametric data. $P > 0.05$ for all variables.
*Nonparametric data.
**Total indications added up to 220 because seven women on the combined treatment arm and five women on the dinoprostone only arm had two indications for induction of labour.
***Nonreassuring fetal status includes oligohydramnios, reduced fetal movements, intrauterine growth restriction, suboptimal CTG and suboptimal umbilical artery Doppler profile.

resulted in significant skewing in the analysis for the mean induction-to-delivery interval. One woman was allowed nine 'rest' days following initial failed induction and another had two rest days. Without correction for the above unusual management, mean ± SD induction-to-delivery time was 26.7 ± 30.2 versus 26.2 ± 14.2 hours ($P = 0.87$) for oxytocin-assigned versus placebo-assigned women, respectively. If rest days given to the two women assigned to oxytocin were disregarded in the induction-to-delivery calculation, the result would be 24.2 ± 16.3 versus 26.2 ± 14.2 hours ($P = 0.36$).

Inclusion of the 12 excluded women into the analysis did not significantly change the finding on any secondary outcomes (data not shown), with one exception: the mean increase in Bishop score after 6 hours of oxytocin infusion (2.4 ± 1.8 versus 1.9 ± 1.7, $P = 0.036$; Table 2), but this finding was no longer significant (2.3 ± 1.7 versus 1.9 ± 1.7, $P = 0.08$) when all randomised women were analysed.

Discussion

Frontloading with oxytocin infusion for 6 hours concurrent with vaginal dinoprostone at the initiation of labour induction compared with vaginal dinoprostone alone was associated with a better birth process satisfaction score even though

Table 2. Outcomes in randomised trial of concurrent intravenous oxytocin infusion for 6 hours with vaginal dinoprostone versus placebo saline infusion and vaginal dinoprostone at the initiation of labour induction in nulliparas with Bishop score ≤ 6

Outcomes	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103	*P* value	RR (95% CI)
Primary outcome				
Vaginal delivery within 24 hours	51 (48.6)	37 (35.9)	0.07	1.4 (1.0–1.9)
VAS for satisfaction with birth process[*,†]	3.2 ± 2.4	4.1 ± 2.4	0.007	
	3 [4]	5 [4]	0.007[‡]	
Outcomes during labour induction				
Mean change in Bishop score (first 6 hours)[†]	2.4 ± 1.8	1.9 ± 1.7	0.036	
	2 [3]	2 [2]	0.041[‡]	
Analgesic requirement (first 6 hours)	26 (24.8)	9 (8.7)	0.003	2.8 (1.4–5.8)
Total doses of vaginal dinoprostone used	1.6 ± 0.8	1.9 ± 0.9	0.01	
	1 [1]	2 [1]	0.03[‡]	
Need for repeat vaginal dinoprostone	39 (37.1)	63 (61.2)	0.001	0.61 (0.45–0.81)
Uterine hyperstimulation[§]	2 (1.9)	1 (1)	1.0	1.96 (0.18–21.3)
Need for vaginal examination (within initial 6 hours)	10 (9.5)	4 (3.9)	0.17	2.45 (0.79–7.57)
Indication for vaginal examination within initial 6 hours			0.17	
Pain	3	1		
Spontaneous rupture of membranes	5	2		
Vaginal delivery	2	0		
Unprovoked fetal heart decelerations	0	1		
VAS for pain at 6 hours[‖,†]	5.5 ± 2.3	4.2 ± 2.3	<0.001	
	5 [3]	4 [4]	<0.001[‡]	
Intrapartum outcomes				
Meconium-stained liquor	16 (15.4)	17 (17.0)	0.85	0.92 (0.49–1.72)
Intrapartum epidural anaesthesia	58 (55.2)	62 (60.2)	0.49	0.92 (0.73–1.16)
Oxytocin augmentation	76 (72.4)	77 (74.8)	0.75	0.97 (0.82–1.14)
Duration of oxytocin augmentation (hours)	8.0 ± 3.7	7.9 ± 4.3	0.90	
Delivery outcomes				
Vaginal delivery within 12 hours	15 (14.3)	9 (8.7)	0.28	1.6 (0.7–3.6)
Mode of delivery				
Caesarean section	44 (41.9)	46 (44.7)	0.52	
Instrumental vaginal	17 (16.2)	11 (10.7)		
Normal vaginal	44 (41.9)	46 (44.7)		
Indications for caesarean delivery				
Failed induction of labour	15 (34.1)	10 (21.8)	0.34	
Failure to progress during labour	13 (29.5)	22 (47.8)		
Nonreassuring fetal status	11 (25.0)	10 (21.7)		
Others	5 (11.4)	4 (8.7)		
Neonatal outcomes				
Admission to neonatal unit	6 (5.7)	12 (11.7)	0.15	0.49 (0.19–1.26)
Indication for neonatal admission			0.33	
Meconium aspiration	0	4		
Neonatal tachypnoea	2	1		
Hypoglycaemia	1	1		
Observation	3	6		
Apgar score at 5 minutes	9.8 ± 0.4	9.8 ± 0.6	0.64	
	10 [0]	10 [0]	0.57[†]	
Apgar score < 7 at 5 minutes[¶]	0 (0)	1 (1)	0.50	
Umbilical cord arterial blood pH	7.26 ± 0.08	7.28 ± 0.07	0.044	
Umbilical cord arterial blood pH < 7.1	3 (2.9)	8 (7.8)	0.13	0.37 (0.10–1.35)
Neonatal jaundice	30 (28.6)	29 (28.2)	1.0	1.01 (0.66–1.56)

(*continued*)

Table 2. (*Continued*)

Outcomes	Dinoprostone and oxytocin, *n* = 105	Dinoprostone only, *n* = 103	*P* value	RR (95% CI)
Postdelivery outcomes				
Postpartum haemorrhage ≥ 500 ml	14 (13.3)	15 (14.6)	0.84	0.91 (0.47–1.8)
Blood transfusion¶	2 (1.9)	0 (0)	0.50	
Fever ≥ 38°C#	22 (21.0)	33 (32)	0.084	0.65 (0.41–1.04)
Delivery-to-discharge interval (days)	1.6 ± 1.1	1.5 ± 1.0	0.47	

Data are represented as *n* (%), mean ± SD or median [interquartile range]. Analyses were by *t* test for means and Fisher's exact test for categorical data. Mann–Whitney *U* test was also performed for nonparametric data to check for consistency with the *t* test.
*10-point VAS, with 0 representing complete satisfaction and 10 representing total dissatisfaction with the birth process.
†Nonparametric distribution of data.
‡Mann–Whitney *U* test for nonparametric data.
§Uterine hyperstimulation defined as six or more contractions in 10 minutes with fetal heart rate abnormality.
||10-point VAS, with 0 representing no pain and 10 representing unbearable pain.
¶RR not calculated as one cell has zero as value.
#Any fever of ≥38°C noted from commencement of labour induction to hospital discharge.

vaginal delivery within 24 hours, mean induction-to-delivery interval and overall caesarean delivery rate were not significantly different.

A 6-hour oxytocin infusion regimen was chosen for this study because it fitted well with our induction of labour management plan where a routine reassessment was performed 6 hours after commencement of induction to consider further intervention. It was also felt that 6 hours of oxytocin infusion should be sufficient exposure for an effect.

Maternal satisfaction with the birth process VAS score was significantly correlated with the induction-to-delivery interval (Spearman's rho = 0.43, $P = 0.01$); shorter induction-to-delivery interval correlated with higher satisfaction. We believe that although vaginal delivery within 24 hours was not significantly higher, this was a borderline result, and as corrected mean induction-to-delivery time was also shorter, although not significantly so, these factors might be sufficient to result in women allocated to oxytocin assigning a better VAS birth process satisfaction score.

Our study design was different from that of previous studies[9–12] of concurrent oxytocin with prostaglandin for labour induction in women with an unfavourable cervix in that we planned to administer oxytocin for only 6 hours at initiation of labour induction compared with earlier studies where oxytocin infusion once started usually continued until delivery. We were interested in applying oxytocin in this manner as a previous study from our centre has shown that a single membrane sweep at initiation of formal labour induction in conjunction with either vaginal dinoprostone or amniotomy has beneficial effects,[5] and we were interested to establish whether 'frontloading' with oxytocin at initiation of labour induction would have similar benefits by tipping women into labour more effectively. Labour once established is probably self-sustaining and is thought to involve a self-perpetuating cascade of endogenous release of prostaglandins.[14]

We used a lower maximum dose (up to 16 mu/minute) oxytocin infusion regimen than in previous studies where maximum oxytocin infusion rate permitted ranged from 36[10] to 40[9] mu/minute, and two other studies had no specified upper limit, although infusion rate more than 30 mu/minute was uncommon.[11,12] We had opted for a lower oxytocin dose regimen to minimise risk of uterine hyperstimulation syndrome and also as infusion rate of 16 mu/minute is effective in nearly 90% of women.[15] It is possible that a higher maximum oxytocin dose regimen or a longer infusion period may be more effective in reducing induction-to-delivery time.[10–12] However, one other previous trial that employed a higher maximum oxytocin dose has also not shown a shorter induction-to-delivery time with concurrent oxytocin infusion and vaginal prostaglandin for labour induction, but different prostaglandin agents (slow-release dinoprostone plus oxytocin infusion versus multidose misoprostol) were used in the treatment arms, making it difficult to compare directly with our study.[9]

To the best of our knowledge, our study is unique in determining the effect of frontloading with concurrent oxytocin that used an identical dinoprostone regimen in opposing arms at initiation of labour induction. Three of the four previous randomised studies we have identified that involved concurrent oxytocin and prostaglandin for labour induction used different prostaglandin regimens in the opposing arms.[9,11,12] The fourth study compared early concurrent oxytocin infusion with sustained-release prostaglandin with

late oxytocin infusion after removal of the prostaglandin sustained-release device.[10]

Concurrent low-dose oxytocin infusion for 6 hours with vaginal dinoprostone at initiation of labour appeared to be safe. Although in women assigned to oxytocin the mean umbilical cord blood pH was significantly lower (7.26 versus 7.28), the pH difference of 0.02 was marginal and was probably clinically irrelevant as proportion of cases with severe acidosis pH < 7.1 and the neonatal admission rate although not significantly different actually were less in women allocated to concurrent oxytocin. Also, babies with Apgar score at 5 minutes <7 were rare (occurred in only one baby of a woman assigned to saline infusion). In addition, previous studies that used higher maximum oxytocin doses have not reported uterine hyperstimulation,[9–12,16] supporting further the impression that concurrent oxytocin and vaginal prostaglandin for labour induction in women with an unfavourable cervix is safe.

There was no indication from our study that caesarean delivery rate could be significantly reduced by concurrent oxytocin and dinoprostone in nulliparas with an unfavourable cervix at high risk for caesarean delivery. Our caesarean rate was 41.9 versus 44.7% for concurrent use of oxytocin with dinoprostone versus dinoprostone pessary only, respectively. A powered study on caesarean delivery rate as primary outcome would require 4987 women in each arm using the caesarean rate achieved in this study. Previous trials have achieved similar results with regards to caesarean delivery rate.[9–12]

Our overall caesarean delivery rate of more than 40%, which was rather high, might be due to the high-risk profile in terms of caesarean delivery of our study population, e.g. all study women were nulliparas[4,17] with low Bishop score ≤ 6,[18] all were Asian,[19] 40.4% had labour induction for diabetes in pregnancy,[20] 34.6% for gestational age ≥ 41 weeks,[17] 14.4% for antenatal nonreassuring fetal status[20] and 13% for hypertension[20]—all these characteristics are established independent risk factors for caesarean delivery at induction of labour.

Although treatment allocation was blinded from study women and providers, it was possible that assigned treatment could be deduced by women or their providers as pain was significantly increased and more women needed analgesia during the 6-hour infusion in the concurrent oxytocin group. We did not study frequency or strength of uterine contractions, but concurrent oxytocin and prostaglandin has been reported to produce more frequent and stronger contractions more quickly.[16]

The labour induction regimen in our centre where we were prepared to allow a longer latent phase in women who required prolonged cervical ripening is in keeping with a recent report that a latent phase of 18 hours or even longer is acceptable and does not result in greater risk of blood transfusion, hysterectomy or prolonged hospitalisation.[21] We believe our findings are widely generalisable as vaginal dinoprostone for cervical ripening and labour induction in nulliparas with an unfavourable cervix is common[22] and oxytocin is universally available.

We did not demonstrate a significantly higher labour induction success rate (defined as vaginal delivery within 24 hours) with concurrent oxytocin infusion and dinoprostone pessary but a rate of 48.6 versus 35.9% ($P = 0.07$) with an absolute difference of 12.7%, a borderline significant P value and with the reported increased maternal birth process satisfaction is probably clinically significant. It is possible that our study remained underpowered as we used a beta of 0.2 in our power calculation. Larger studies in this clinically important area are warranted.

Medically indicated induction of labour in nulliparas with an unfavourable cervix remains a considerable clinical challenge associated with a lengthy process and a high caesarean delivery rate.

Conclusion

Concurrent oxytocin infusion with prostaglandin at induction of labour in nulliparas appears to be safe and can improve woman satisfaction with the birth process. However, the optimal maximum infusion rate of oxytocin and its duration of infusion should be subjected to further study. ■

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Effect of Coital Activity on Onset of Labor in Women Scheduled for Labor Induction

A Randomized Controlled Trial

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OBJECTIVE: To estimate the effect of coitus on the onset of labor.

METHODS: Women with a nonurgent labor induction at term were recruited. Women randomly assigned to the advised-coitus group were encouraged to have sex to promote the onset of labor. Controls were neither encouraged nor discouraged regarding coitus. Participants kept a coital and orgasm diary until delivery, and standard obstetric care was provided to both groups. Primary outcomes were reported coitus and spontaneous labor. Secondary outcomes included reported orgasms, initial Bishop score at the admission for induction, preterm rupture of membranes, use of dinoprostone, oxytocin, or epidural, meconium-stained amniotic fluid, cesarean delivery, maternal fever, and neonatal morbidity.

RESULTS: One hundred eight and 102 women randomly assigned to advised-coitus and control groups, respectively, were available for analysis. Women assigned to the advised-coitus group were more likely to report coital activity before delivery (60.2% compared with 39.6%, relative risk 1.5, 95% confidence interval 1.1–2.0; P=.004), but the spontaneous labor rate was no different (55.6% compared with 52.0%, relative risk 1.1, 95% confidence interval 0.8–1.4; P=.68). Cesarean delivery rate and neonatal and other secondary outcomes were also not different.

CONCLUSION: Among women scheduled for labor induction who were advised to have sex, the increase in sexual activity did not increase the rate of spontaneous labor.

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LEVEL OF EVIDENCE: I

Labor induction has been increasing since the early 1990s,[1] and the rate is running at about 20% for pregnancies at term.[2,3] Induction of labor compared with spontaneous labor is associated with adverse maternal outcomes, including at least a doubling in the caesarean delivery rate,[4,5] 25–50% increase in instrumental vaginal delivery rate,[3,5] higher postpartum hemorrhage rate,[5] and prolonged labor.[5] Neonates born after induced labor are more likely to have low Apgar score and low umbilical cord blood pH.[5]

Coital activity at term in healthy women has been reported to be associated with a shortened gestation and less requirement for labor induction for prolonged pregnancy, and there is a direct correlation between the amount of coital activity and expedited onset of labor.[6] However, these findings are not consistently reported.[7] Although having sex is commonly believed to hasten labor,[8] between 20% and 80% of pregnant women have safety concerns.[6]

Biologic plausibility for sexual activity to promote labor onset is supported by the presence of prostaglandin E in semen,[9] observed effect of breast stimulation on labor onset,[10] and association of uterine activity with orgasm during sexual intercourse in pregnancy.[11] A Cochrane review on sexual intercourse for cervical ripening and induction of labor identified only one study with 28 women, from which no meaningful conclusions can be drawn.[12]

We sought to investigate a situation in which the woman had an appointment to undergo a nonurgent labor induction at term whether the couple can be persuaded to have vaginal sexual intercourse as a natural method of promoting the onset of labor. We felt that, with labor induction imminent, the motiva-

tion would be highest in these couples to respond positively to advice. As a consequence, we anticipated that some couples who would otherwise be abstinent could be persuaded to have sex and those couples who would be sexually active anyway would increase their rate of coital activity. We hypothesized that the increased coital activity would increase the rate of onset of spontaneous labor.

MATERIALS AND METHODS

A randomized trial was performed in which a group of women already given an appointment for nonurgent labor induction at term and advised to have vaginal sex was compared with a control group where sex was neither encouraged nor discouraged. Ethical approval for the study was granted by the University of Malaya Medical Centre Medical Ethics Committee.

We recruited women from our antenatal clinic on the same day that they were given an appointment for labor induction for nonurgent reasons. Appointments were usually made one week in advance. After randomization and allocated counseling, women were allowed to return home so that the opportunity for sexual activity in their home environment existed.

Inclusion criteria were induction of labor scheduled at term (37 weeks or later), a viable singleton fetus, intact membranes, and cephalic presentation. We excluded women with a previous cesarean scar and known gross fetal anomaly.

A previous study from our hospital has shown that 58% of women were sexually active at term. Assuming that advice to have sex was heeded by an additional 20% of women with alpha of 0.05 and power of 80%, 94 women were needed in each arm. Assuming a 10% dropout rate, 209 women in total were needed for the study. Data from the 2003 birth cohort of our hospital indicated that 56% of women who entered the 40th gestational week would be delivered within the next week. Assuming that advising women to have sex increased the spontaneous labor rate by 20–76%, with alpha of 0.05 and power of 0.8 as above, 97 women were needed in each arm.

Women who had been given an appointment for labor induction were identified by antenatal nursing staff and directed to a single investigator (C.M.Y.), who recruited the women. Written consent was obtained from all women.

Randomization was carried out in randomized blocks of 8 or 12 with a computerized random number generator by another investigator (P.C.T.) who also prepared the numbered opaque envelopes containing the individual random allocation to either the advised-coitus group or the no-advice group. The numbered envelopes were used in strict chronological sequence, and an envelope, once opened, was not reused.

We kept the counseling to a single investigator (C.M.Y.) to standardize the process. The counselor-investigator was clearly identifiable to the women as a doctor. Women randomly assigned to the advised-coitus group were told that sexual intercourse in late pregnancy was safe and could promote onset of labor. They were told that induced labor was associated with operative delivery and a more prolonged process compared with spontaneous labor. They were asked to have sex as frequently as possible before their appointment for labor induction. They were also required until delivery to keep a daily diary on vaginal sexual intercourse and orgasms they achieved during sex. Women who wanted more information after the standard counseling were given a response that was supportive of having sex.

For women randomly assigned to no advice, counseling was kept as short as possible. These women were told that sex was safe but the effect was unclear on promotion of labor onset. We also asked them to keep the same diary. To keep our approach to the control group as neutral as possible, women allocated to the no-advice group (control) who wanted additional information were referred to the information leaflet given to all study women.

The allocation of women to the advised-coitus or control groups was not revealed to providers. Recruitment took place between December 2005 and June 2006. Study women received standard obstetric care.

In our center, labor was induced with vaginal dinoprostone if the cervix was unfavorable, and amniotomy was performed if the cervix was favorable. Our standard management for labor induction and intrapartum care has been described previously.[13] In the event of premature rupture of membranes at term (PROM), women were given either the option of immediate action, usually an oxytocin infusion, or the option to wait up to 24 hours for spontaneous labor as an inpatient.

The charts of women in our study were obtained after their delivery; admission and delivery details were then transferred to a standard data sheet. Women who did not submit their diaries within a few days after their labor induction appointment were contacted by telephone to obtain diary data. If the women were delivered elsewhere, we obtained as much clinical data from the women as we could by telephone.

Primary outcomes were 1) coital activity from the diaries and 2) the onset of labor. The onset of labor

was defined as 1) spontaneous regular contractions leading to cervical changes of at least 3 cm dilatation or 2) PROM, on or before the original appointment date for labor induction. All women who presented after the original appointment date were considered as having failed the outcome even if they were subsequently admitted in spontaneous labor or with PROM. Similarly, we consider all cases of prelabor cesarean delivery as a failed outcome regardless of timing of birth admission.

Secondary outcomes included cesarean delivery, reported orgasms, initial Bishop score at the admission for birth, PROM, use of dinoprostone, use of oxytocin infusion during labor, maternal fever, epidural use in labor, meconium-stained liquor, and various neonatal measures.

Analysis was by intention to treat. Data were entered into SPSS 13 (SPSS Inc, Chicago, IL), and GraphPad Instat (GraphPad Software Inc, San Diego, CA) was also used for data analysis. The *t* test was used to analyze means and the Kolmogorov-Smirnov test to check distribution. Fisher exact test was used for categorical 2×2 data sets, χ^2 for larger categorical data sets, and relative risk and its 95% confidence interval calculated with GraphPad Instat. $P<.05$ in any test was considered statistically significant, and all tests used two-tailed results.

RESULTS

During our recruitment period of December 2005 to June 2006, 219 women were sent to the investigator for recruitment out of a maximum 569 women who were given an induction of labor appointment. The smaller number was due to investigator availability and study population criteria. Four women declined the invitation to participate. Another five women, all allocated to the control group, decided to withdraw from the study at the counseling phase, a decision we felt might have been due to their counseling having been kept as short and as neutral as possible. This left 210 women for analysis: 108 women assigned to the advised-coitus group and 102 to the no-advice control group (Fig. 1).

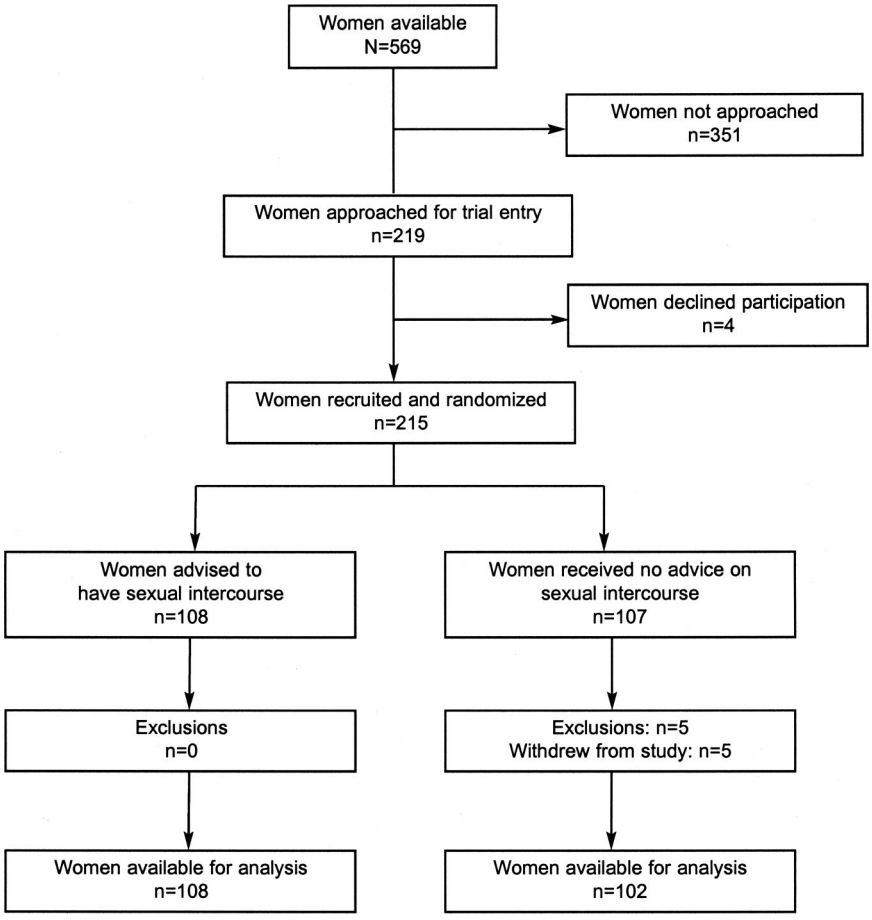

Fig. 1. Recruitment flow chart for randomized trial of advising sexual intercourse to women scheduled for labor induction at term.
Tan. Coitus and Spontaneous Labor. Obstet Gynecol 2007.

Three women who delivered elsewhere were contacted by phone, but data obtained were incomplete. For one woman who delivered at home, data were also incomplete. Another woman did not submit her diary and could not be contacted by telephone, but her chart was available.

The characteristics of study women included in the analysis are shown in Table 1. There was no significant difference in any characteristic between the randomized groups.

More women advised to have sex reported coital activity: 60.2% compared with 39.6% (relative risk 1.5, 95% confidence interval [CI] 1.1–2.0, P=.004) compared with controls, but spontaneous labor onset was no different: 55.6% compared with 52.0% (relative risk 1.1, 95% CI 0.8–1.4, P=.68) (Table 2). Of the 105 women who reported at least one episode of vaginal sex after randomization, 87 (82.9%) reported having at least one orgasm during the study period.

Table 3 shows the clinical presentation of study women at their admission for delivery, stratified according to allocated intervention and timing of delivery admission in relation to appointment date for labor induction. There were no significant differences between the randomized groups with reference to timing of admission for birth or spontaneous labor (PROM included), as well as for presentation at admission for birth (χ^2 P=.21 and P=.49, respectively).

Table 4 shows the secondary outcome measures; there were no differences in cesarean delivery rate or maternal fever. Neonatal outcome was also not different.

Table 1. Characteristics of Study Women Stratified According to Treatment Allocation at Time of Scheduling of Appointment Date for Labor Induction

	Advised-Coitus Group (n=108)	Control Group (n=102)
Age (y)	29.0±4.4	29.8±4.6
Ethnicity		
Malay	66 (61.1)	64 (62.7)
Chinese	21 (19.4)	14 (13.7)
Indian	18 (16.7)	17 (16.7)
Others	3 (2.8)	7 (6.9)
Gravidity	2 [2]	2 [2]
Parity	0 [1]	1 [1]
Nulliparas	58 (53.7)	50 (49)
Gestation at recruitment (wk)	39.7±1.2	39.6±1.1
Gestation at scheduled labor induction (wk)	40.7±1.1	40.6±1.1
Recruitment to scheduled labor induction interval (d)	6.6±3.5	7.1±3.1
Gestational age determined by		
Menstrual dates (supported by ultrasonography)	95 (88.0)	87 (85.3)
Ultrasonography only	13 (12.0)	15 (14.7)
Indication for labor induction at recruitment*		
Prolonged pregnancy (41 wk or more)	72 (64.3)	60 (57.7)
Diabetes	31 (27.7)	37 (35.6)
Hypertension	5 (4.5)	5 (4.8)
Others	4 (3.6)	2 (1.8)

Data are expressed as mean±standard deviation, median [interquartile range], and number (%).

Analyses by t test for comparison of means, Fisher exact test for 2×2 categorical data sets and χ^2 test for larger than 2×2 categorical data sets. P>.05 for all analyses.

* Total indications were 216 because six women (four allocated to advised-coitus group and two to control group) had two indications for labor induction.

DISCUSSION

We have demonstrated that it was feasible to motivate women at term who were scheduled for labor induction to have vaginal sex to promote labor. We had taken care to have as controls a group that is not negatively influenced about sex; 39.8% of women assigned to the control group reported coital activity, although this percentage is smaller than the 58% that reported coital activity in a previous study of healthy women at term from our center.[6] The previous study covered vaginal sex from 36 weeks of gestation to delivery, whereas the recruitment-to-birth admission interval in our current study population was only 4.7±3.4 days (mean±standard deviation). However, the spontaneous labor rate was not different: 55.6% compared with 52.0% when comparing the randomized groups.

A post hoc analysis on reported coitus compared with spontaneous labor onset was performed to explore the possibility that our study might be underpowered. Although statistical significance was not achieved, the spontaneous labor rate was higher in women who reported no coitus (60.6% compared with 46.7%, relative risk 1.3, 95% CI 1.0–1.7, P=.052). This finding differed from that of an observational study from our center that excluded from analysis women who had labor induction for any medical indications apart from those indicated by prolonged pregnancy.[6] A possible explanation for our post hoc finding might be that women close to spontaneous labor onset had reduced libido and consequently less coitus; the mean recruitment-to-admission interval was only 4.7 days in our study.

A recent study has indicated that women who are sexually active at term have slightly longer gestations and slightly lower Bishop scores.[7] Orgasm has also

Table 2. Primary Outcomes After Randomization to Advised-Coitus or to No-Advice Control Group

	Advised-Coitus Group (n=108)	Control Group (n=102)	Relative Risk (95% Confidence Interval)	*P*
Coitus reported*	65 (60.2)	40 (39.6)†	1.5 (1.1–2.0)	.004
Mean±standard deviation (d)	1.2±1.3	0.8±1.3		.032
Median [interquartile range] (d)	1 [2]	0 [1]		.005
Range (d)	0–5	0–7		.004
Spontaneous labor‡	60 (55.6)	53 (52.0)	1.1 (0.8–1.4)	.68

Data are expressed as n (%), except where otherwise indicated.
Analysis is by Fisher exact test for categorical data sets, *t* test, and Mann Whitney *U* test.
* At least 1 day with coital activity after randomization.
† One woman assigned to control group did not submit coital diary and could not be contacted to obtain diary data.
‡ Spontaneous labor included women presenting with premature rupture of membrane on or before the scheduled date for labor induction. No spontaneous labor outcome group included all women not in spontaneous labor by appointment date for labor induction, labor induction earlier than planned for any reason, and all prelabor cesarean delivery regardless of timing.

Table 3. Presenting Feature According to Randomization and Timing of Final Admission for Birth

		Presenting Clinical Feature (at Admission for Birth)		
Intervention	Timing of Admission for Birth in Relation to Original Scheduled Date for Labor Induction	Spontaneous Labor	Premature Rupture of Membranes	Labor Induced
Advised-coitus group (n=107)*				
Before	58 (54.2)	43 (74.1)†	12 (20.7)†	3 (5.2)‡
On scheduled date	45 (42.1)	4 (8.9)†	1 (2.2)†	40 (88.9)§
After	4 (3.7)‖	2 (50.0)†	0 (0)†	2 (50.0)
No-advice group (n=102)				
Before	43 (42.2)	35 (81.4)†	7 (16.3)†	1 (2.3)‡
On scheduled date	55 (53.9)	11 (20.0)†¶	0 (0)†	44 (80.0)
After	4 (3.9)‖	0 (0)†	1 (25.0)†	3 (75.0)

Data are expressed as n (%).
* One woman allocated to the advised-coitus group delivered elsewhere, and the date of her admission for birth was missing.
† Premature rupture of membranes considered as spontaneous of labor.
‡ Four women had labor induced prior to scheduled date for induction: admission with contractions without cervical changes (three women: two assigned to advised-coitus and one to control group) and subjective reduction in fetal movements (one woman randomly allocated to advised-coitus group).
§ Includes two women who had prelabor cesarean delivery without any attempt at labor induction indicated by suspected macrosomia in a diabetic pregnancy and face presentation at vaginal assessment prior to induction.
‖ Eight women did not have their labor induced on the scheduled date for induction: five women did not attend appointment for induction for personal nonmedically related reasons (three randomly assigned to advised-coitus and two to control group), two woman had their appointment delayed by provider due to reinterpretation of estimated date of delivery (one each assigned to advised-coitus and control group), and one woman's status could not be determined (assigned to control).
¶ One woman delivered at home and was subsequently admitted to hospital.

been reported to be associated with a lower occurrence of preterm delivery.[14] Our post hoc analysis was more consistent with these findings.

Of women in our study who reported having sex during the study period, 82.9% also reported at least one episode of orgasm. Therefore, regardless of its effect on labor onset, sex at term was orgasmic for a large majority of sexually active women in the study.

Adverse neonatal outcome was uncommon in our study and was no different between the randomized groups. Post hoc analysis, stratified according to coital activity to maximize power, similarly showed no difference in neonatal outcome.

Our study has some shortcomings. We relied on reported coital activity, and we could not independently verify the reports. That having been said, we did not see any indication that women were systemically biased in their reporting. Women were typically counseled without their partners being present, and we also did not record partner involvement during the study. Ideally, the couple should be seen together, because the male partner is often the main initiator of sex during pregnancy.[15] Our study also involved a single investigator doing all the counseling, which was helpful for standardization of the delivery of our intervention but which might reduce generalizabil-

Table 4. Secondary Outcomes of Women Assigned to Advised-Coitus or No-Advice Control Group

Outcome	n*	Intervention: Advised-Coitus Group	Intervention: No-Advice Group	*P*
Any reported orgasm	209	56 (51.9)	31 (30.7)	.002
Days with reported orgasms		1.0±1.2	0.6±1.2	.024
Recruitment to admission for birth interval (d)	210	4.3±3.2	5.2±3.6	.065
Postpartum blood loss	205	303±164	313±213	.73
Blood loss 500 mL or greater		13 (12.4)	13 (13.0)	1.0
Umbilical cord blood pH	203	7.3±0.08	7.3±0.07	
pH less than 7.1		1 (1.0)	1 (1.0)	1.0
Apgar score at 5 min	206	9.9±0.4	9.8±0.5	
Apgar score less than 7 at 5 min		0 (0)	0 (0)	.17†
Birth weight (kg)	207	3.3±0.44	3.2±0.46	.19
Initial Bishop score at delivery admission	205	4.2±2.6	4.0±2.4	.59
Mode of delivery	210			
Normal vaginal		74 (68.5)	74 (72.5)	.75
Instrumental vaginal		7 (6.5)	7 (6.9)	
Cesarean		27 (25.0)	21 (20.6)	
Indications for cesarean delivery	48			
Nonreassuring fetal status		5 (14.8)	7 (33.3)	.12
Failure to progress		17 (63.0)	7 (33.3)	
Failed induction		1 (3.7)	4 (19.0)	
Others		4 (14.8)	3 (14.3)	
Fever‡	206	19 (17.9)	25 (25.0)	.24
PROM§	209	13 (12.1)	8 (7.8)	.36
Any dinoprostone use	210	39 (36.1)	44 (43.1)	.33
Any oxytocin use during labor	209	57 (53.3)	56 (54.9)	.89
Epidural	209	35 (32.4)	26 (25.7)	.36
Meconium stained liquor‖	208	16 (14.8)	10 (10)	.40
Neonatal admission	210	2 (1.9)	3 (2.9)	.68
Indications for neonatal admission	5			
Fractured humerus (shoulder dystocia)		1		
Neonatal grunting		1		
Low Apgar score at 1 min			2	
Observation			1	

Data are expressed as mean±standard deviation or n (%).
Analysis by the *t* test for means, Fisher exact test for 2×2 categorical data sets, and χ^2 test for larger data sets.
* Incomplete data in some parameters are due to combinations of the following reasons: nonsubmission of coital diary (one), delivery at home (one), delivery in other hospitals (three), and failure to perform umbilical cord blood gas analysis (one).
† *P* value not calculated as two zero cells.
‡ Fever defined as temperature of 38°C or greater on at least one occasion from any time during labor until hospital discharge.
§ Premature rupture of membranes (PROM) as initial presentation at admission for birth.
‖ Any meconium seen up to delivery.

ity. Based on the findings of our study, women scheduled for induction of labor at term should not be given advice to have sex for the purpose of promoting labor onset.

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Coitus and orgasm at term: effect on spontaneous labour and pregnancy outcome

Tan P C, Yow C M, Omar S Z

ABSTRACT

Introduction: Coitus and orgasm in late pregnancy are believed to facilitate the onset of labour. We aim to evaluate the relationship at term of reported coitus and orgasm with spontaneous labour.

Methods: Women at term scheduled for non-urgent labour induction were asked to keep a coitus and orgasm diary. These women were recruited for a randomised trial on the effect of coitus to promote spontaneous labour. For this analysis, the women were categorised into coitally-active and abstinent groups according to their coital diary. Spontaneous labour prior to the date of scheduled labour induction was the primary outcome. Labour, delivery and neonatal outcome were also evaluated. Multivariable logistic regression analysis was used to control for significant variables.

Results: On univariate analysis, the inverse association of coitus with spontaneous labour was borderline (odds ratio [OR] 0.6; 95 percent confidence interval [CI] 0.3–1.0; p-value is 0.052). Orgasm was not associated with spontaneous labour (p-value is 0.33). After adjustment, coitus (adjusted OR 0.4; 95 percent CI 0.2–0.8; p-value is 0.009) displayed a significant inverse association with spontaneous labour. Coitus and orgasm were not associated with any other adverse pregnancy outcome.

Conclusion: Women who reported coitus were less likely to go into spontaneous labour prior to their scheduled labour induction. Reported coitus and orgasm were not associated with adverse pregnancy outcome.

Keywords: coitus, orgasm, pregnancy outcome, spontaneous labour

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INTRODUCTION

Sexual intercourse to promote labour onset is biologically plausible as prostaglandin E is present in semen,[1] breast stimulation promotes labour onset[2] and uterine activity is provoked by orgasm during sexual intercourse in pregnancy.[3] Coitus in healthy women at term is associated with a shorter gestation and a lesser need for labour induction for prolonged pregnancy, and the frequency of coitus is positively correlated with an expedited onset of labour.[4] However, these findings are not consistently reported.[5] Although having sex is widely believed to facilitate the onset of labour,[6] safety concerns are expressed by 20%–80% of pregnant women.[4]

We recently reported on an intervention trial where women scheduled for non-urgent labour induction were randomised to an advise-vaginal-sex-to-promote-labour group or to a control group. This study showed that physician advice can increase reported coitus but the rate of spontaneous labour was not affected.[7] The facilitation of labour onset at term is important as about 20% of term pregnancies are terminated by the induction of labour,[8,9] and induced labour is associated with prolonged labour,[10] Caesarean delivery[10,11] and poorer neonatal outcome.[10] A secondary analysis was performed on the data from the previously-reported randomised trial,[7] to evaluate further the effect of reported coitus and orgasm on spontaneous labour and other pregnancy outcomes.

METHODS

The methodology for the randomised trial was previously reported.[7] In brief, term women were recruited from the antenatal clinic after they had been given a non-urgent appointment for labour induction, which was typically one week in advance. After randomisation, counselling by a physician and instruction on keeping a diary to record coitus and orgasm activities, the women were allowed home. Orgasm was not defined for the subjects and the data was based on self reporting in a diary. Women randomised to the advise-sex group were encouraged to have vaginal sex to promote labour onset prior to their scheduled labour induction. For the control group, coitus was neither encouraged nor discouraged. Recruitment for the trial took

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Table I. Characteristics of 209 women stratified according to reported coitus and orgasm.

	Coitus (n = 105)	No coitus (n = 104)	p-value	Orgasm (n = 87)	No orgasm (n = 122)	p-value
Age (years)	29.3 ± 4.4	29.3 ± 4.6	1.0	29.1 ± 4.3	29.5 ± 4.6	0.57
Age ≥ 35 years	14 (13.3)	12 (11.5)	0.83	10 (11.5)	16 (13.1)	0.83
Ethnicity						
Malay	71 (67.6)	58 (55.8)	0.19	61 (70.1)	68 (55.7)	0.061
Chinese	15 (14.3)	20 (19.2)		8 (9.2)	27 (22.1)	
Indian	13 (12.4)	22 (21.2)		13 (14.9)	22 (18.0)	
Others	6 (5.7)	4 (3.8)		5 (5.7)	5 (4.1)	
Gravidity	2.1 ± 1.4	2.0 ± 1.1	0.62	2.1 ± 1.4	2.1 ± 1.2	0.99
	2 [2]	2 [2]	0.90	2 [2]	2 [2]	0.50
Parity	0.9 ± 1.3	0.7 ± 0.9	0.19	0.9 ± 1.3	0.8 ± 1.0	0.37
	0 [1]	0 [1]	0.53	0 [1]	0 [1]	0.78
Nullipara	54 (51.4)	54 (51.9)	1.0	45 (51.7)	63 (51.6)	1.0
Gestation at recruitment (weeks)	39.6 ± 1.3	39.7 ± 1.1	0.65	39.6 ± 1.3	39.7 ± 1.1	0.60
Gestation at recruitment > 280 days	75 (71.4)	71 (68.3)	0.65	63 (72.4)	83 (68.0)	0.54
Gestation at scheduled LI (weeks)	40.6 ± 1.1	40.6 ± 1.1	0.82	40.6 ± 1.1	40.6 ± 1.1	0.68
Recruitment to scheduled LI interval ≥ 7 days	61 (58.1)	46 (44.2)	0.053	51 (58.6)	56 (45.9)	0.092
Gestational age determined by						
Menstrual dates (supported by US)	94 (89.5)	88 (84.6)	0.31	79 (90.8)	103 (84.4)	0.21
US only	11 (10.5)	16 (15.4)		8 (9.2)	19 (15.6)	
Indication for LI at recruitment						
Prolonged pregnancy (≥ 41 weeks)	66 (62.9)	62 (59.6)	0.67	55 (63.2)	73 (59.8)	0.67
Others*	39 (37.1)	42 (40.4)		32 (36.8)	49 (40.2)	
Randomisation to						
Advise-coitus group	65 (61.9)	43 (41.3)	0.004	56 (64.4)	52 (42.6)	0.002
Control group	40 (38.1)	61 (58.7)		31 (35.6)	70 (57.4)	

Data is expressed as mean and standard deviation, no. (%) and/or median [interquartile range].
US: ultrasonography; LI: induction of labour
Analyses by *t*-test for comparison of means, Mann-Whitney U test for ordinal data, Fisher's exact test for 2 × 2 categorical datasets and chi-square test for larger than 2 × 2 categorical datasets.
* Include diabetes mellitus in pregnancy, hypertension and more than one listed indication.

place between December 2005 and June 2006. The women were provided with standard obstetric care.

After delivery, the coitus and orgasm diaries were collected (or for those women who did not deliver at our centre, the data was collected by telephone) and the charts obtained. The admission and delivery details were transferred to a standard data sheet. The women were categorised into two groups based on reported coital activity during the study period (between recruitment and admission for birth) for this analysis. Reported orgasm was taken as another variable. The primary outcome was spontaneous labour onset which was defined either as spontaneous regular contractions leading to cervical changes of at least 3 cm dilatation, or prelabour rupture of membranes on or before the original appointment date for labour induction. The secondary outcomes, including recruitment to hospital admission for birth interval, recruitment-to-delivery interval, the Bishop Score on admission, premature membrane rupture, the use of dinoprostone or oxytocin during labour, meconium liquor, epidural anaesthesia, mode of delivery, postpartum blood loss, umbilical cord pH, Apgar score, neonatal admission and maternal fever, were also considered.

In our centre, women with otherwise uncomplicated pregnancies were usually offered induction of labour for prolonged pregnancy ≥ 41 weeks' gestation. Women with gestational diabetes mellitus were offered induction at 40 weeks' gestation if they were well controlled on diet alone and at 38 weeks' gestation if they were on insulin. The trial was approved by the Medical Ethics Committee of the University of Malaya Medical Centre, Malaysia. The Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA) and GraphPad Instat software (GraphPad Software Inc, San Diego, CA, USA) were used for data analysis. The student's *t*-test was used to compare the means of continuous variables, Mann-Whitney U test for ordinal data, Fisher's exact test for categorical 2 × 2 datasets and chi-square for larger categorical datasets, and the odds-ratio (OR) and its 95% confidence interval (CI) were calculated. Multivariable logistic regression analysis was used, incorporating all the covariables with crude $p \leq 0.1$ to the primary outcome of spontaneous labour. $p < 0.05$ in any test was considered statistically significant, and all the tests used two-sided results.

Table II. Outcomes stratified according to reported coitus.

Outcome	Total* no.	Coitus (n = 105)	No coitus (n = 104)	Odds ratio (95% confidence interval)	p-value
Onset of spontaneous labour†	209	49 (46.7)	63 (60.6)	0.6 (0.3–1.0)	0.052
Recruitment to admission interval (days)	208	5.7 ± 3.8	3.8 ± 2.6		< 0.001
Recruitment to delivery interval (days)	209	6.1 ± 4.1	4.6 ± 3.2		0.005
Postpartum blood loss	204	314 ± 214	303 ± 161		0.69
Blood loss ≥ 500 ml		14 (13.7)	12 (11.8)	1.2 (0.6–2.4)	0.83
Umbilical cord blood pH	202	7.3 ± 0.07	7.29 ± 0.08		0.12
Cord blood pH < 7.1		0 (0)	2 (2.0)	‡	0.24
Apgar score at five minutes	205	9.9 ± 0.3	9.8 ± 0.5		0.028
Apgar score < 7 at five minutes		0 (0)	0 (0)	‡	‡
Birth weight (kg)	206	3.2 ± 0.4	3.2 ± 0.5		0.65
Initial Bishop score at admission	204	3.9 ± 2.5 4 [4]	4.3 ± 2.5 5 [4]		0.26 0.26
Bishop score < 5 at admission		60 (58.8)	48 (47.1)	1.3 (1.0–1.6)	0.12
Mode of delivery	209				
Normal vaginal		73 (69.5)	74 (71.5)		0.73
Instrumental vaginal		6 (5.7)	8 (7.7)		
Caesarean section		26 (24.8)	22 (21.2)		
Indications for caesarean	48				
Non-reassuring foetal status		5 (19.2)	6 (27.3)		0.58
Failure to progress		15 (57.7)	9 (40.9)		
Failed induction		3 (11.5)	2 (9.1)		
Others		3 (10.4)	5 (22.7)		
Fever§	205	22 (21.4)	22 (21.6)	1.0 (0.6–1.7)	1.0
PROM¶	208	7 (6.7)	14 (13.5)	0.5 (0.2–1.2)	0.17
Any dinoprostone use	209	48 (45.7)	35 (33.7)	1.4 (1.0–1.9)	0.09
Any oxytocin use during labour	208	59 (56.7)	54 (51.9)	1.1 (0.9–1.4)	0.58
Epidural	208	27 (25.7)	34 (33.0)	0.8 (0.5–1.2)	0.29
Meconium-stained liquor**	207	12 (11.4)	14 (13.7)	0.8 (0.4–1.7)	0.68
Neonatal admission	209	2 (1.9)	3 (2.9)	0.7 (0.1–3.9)	0.68

Data is expressed as mean and standard deviation, no. (%) and/or median [interquartile range].
Analysis by the *t*-test for means of continuous data, Mann-Whitney U test for ordinal data, Fisher's exact test for 2 × 2 categorical datasets and chi-square test for larger datasets.
*Incomplete data in some parameters due to combinations of the following: delivery at home (one), delivery in other hospitals (three), omission to do umbilical cord blood gas analysis (one).
†Spontaneous labour is defined as the presentation to hospital for birth with either regular contractions and cervical dilatation ≥ 3cm, or confirmed rupture of membranes on/before the scheduled date for induction of labour.
‡p-value or odds ratio was not calculated for at least one zero cell in the 2 × 2 table.
§Fever is defined as temperature ≥ 38°C on at least one occasion from any time during labour until hospital discharge.
¶Prelabour rupture of membranes as initial presentation at admission for birth.
**Any meconium seen up to delivery.

RESULTS

Of the 215 women randomised, five withdrew from the trial very shortly after randomisation, and another woman did not return her diary of coital activity and orgasm, leaving 209 cases for analysis. Of the 209 women, 105 reported coitus, 104 were abstinent and spontaneous labour occurred in 112 (53.6%). The characteristics of the women were stratified according to the reported coitus or orgasm, as listed in Table I. All the listed characteristics were similar except for the randomised allocation to the advise-sex or control group, as previously reported.[7] A recruitment to a scheduled induction interval ≥ 7 days was borderline with regard to reported coitus and orgasm (p = 0.053 and p = 0.092), respectively.

Analyses of reported coitus and outcomes are listed in Table II. The mean Apgar score at five minutes were marginally higher (9.9 ± 0.3 vs. 9.8 ± 0.5; p = 0.028) in the reported coitus group. Mean intervals from recruitment to hospital admission and to birth were longer among women who reported coitus. Onset of spontaneous labour was borderline; 46.7% vs. 60.6% (OR 0.6, 95% CI 0.3–1.0; p = 0.052) with fewer women who reported coitus presenting in spontaneous labour by the appointment date for labour induction. No other adverse outcome was associated with

Table III. Outcomes stratified according to reported orgasm.

Outcome	Total* no.	Orgasm (n = 87)	No orgasm (n = 122)	Odds ratio (95% confidence interval)	p-value
Onset of spontaneous labour†	209	43 (49.4)	69 (56.6)	0.8 (0.4–1.3)	0.33
Recruitment to admission interval (days)	208	5.9 ± 3.9	3.9 ± 2.8		< 0.001
Recruitment to delivery interval (days)	209	6.2 ± 4.2	4.7 ± 3.3		0.003
Postpartum blood loss	204	321 ± 231	300 ± 153		0.45
Blood loss ≥ 500 ml		13 (15.5)	13 (10.8)	1.5 (0.7–3.4)	0.40
Umbilical cord blood pH	202	7.31 ± 0.07	7.29 ± 0.08		0.12
Cord blood pH < 7.1		0 (0)	2 (1.7)	‡	0.51
Apgar score at five minutes	205	9.9 ± 0.3	9.8 ± 0.5		0.15
Apgar score < 7 at five minutes		0 (0)	0 (0)	‡	‡
Birth weight (kg)	206	3.2 ± 0.4	3.2 ± 0.5		0.72
Initial Bishop score at admission	204	4.0 ± 2.5	4.2 ± 2.5		0.64
		4 [4]	4.5 [4]		0.69
Bishop score < 5 at admission		48 (57.1)	60 (50.0)	1.3 (0.8–2.3)	0.32
Mode of delivery	209				
Normal vaginal		60 (69.0)	87 (71.3)		0.41
Instrumental vaginal		4 (4.6)	10 (8.2)		
Caesarean section		23 (26.4)	25 (20.5)		
Indications for caesarean	48				
Non-reassuring foetal status		4 (17.4)	7 (28.0)		0.31
Failure to progress		14 (60.9)	10 (40.0)		
Failed induction		3 (13.0)	2 (8.0)		
Others		2 (8.7)	6 (24.0)		
Fever§	205	21 (24.7)	23 (19.2)	1.4 (0.7–2.7)	0.39
PROM¶	208	6 (7.0)	15 (12.3)	0.5 (0.2–1.4)	0.25
Any dinoprostone use	209	38 (43.7)	45 (36.9)	1.3 (0.8–2.3)	0.39
Any oxytocin use during labour	208	48 (55.8)	65 (53.3)	1.1 (0.6–1.9)	0.78
Epidural	208	24 (27.6)	37 (30.6)	0.9 (0.5–1.6)	0.76
Meconium stained liquor**	207	10 (11.5)	16 (13.3)	0.8 (0.4–2.0)	0.83
Neonatal admission	209	2 (2.3)	3 (2.5)	0.9 (0.2–5.7)	1.0

Data is expressed as mean ± standard deviation, no. (%) and/or median [interquartile range].
Analysis by the *t*-test for means of continuous data, Mann-Whitney U test for ordinal data, Fisher's exact test for 2 × 2 categorical datasets and chi-square test for larger datasets.
*Incomplete data in some parameters due to combinations of the following: delivery at home (one), delivery in other hospitals (three), omission to do umbilical cord blood gas analysis (one).
†Spontaneous labour is defined as presentation to hospital for birth with either regular contractions and cervical dilatation ≥ 3 cm, or confirmed rupture of membranes on/before the scheduled date for induction of labour.
‡p-value or odds ratio was not calculated for at least one zero cell in the 2 × 2 table.
§Fever is defined as temperature ≥ 38°C on at least one occasion from any time during labour until hospital discharge.
¶Prelabour rupture of membranes as initial presentation at admission for birth.
**Any meconium seen up to delivery.

reported coitus. Analyses of reported orgasm and outcomes are listed in Table III. Mean intervals from recruitment to hospital admission and to birth intervals were longer among women who reported orgasm. Reported orgasm was not associated with spontaneous onset of labour (p = 0.33). No adverse outcome was associated with reported orgasm.

We further analysed the effect of increasing exposure to coitus by subdividing women who reported coitus into subgroups of those who had only reported coitus on one day and those who reported coitus on two or more days in their diaries. Spontaneous labour rates were 63/104 (60.6%) vs. 28/48 (58.3%) vs. 21/57 (36.8%) for abstinence, one day of coitus reported and ≥ two days of reported coitus, respectively (chi-square test, p = 0.012; and chi-square test for trend, p = 0.006).

Univariate and adjusted analyses of covariables to onset of spontaneous labour as the primary outcome are shown in Table IV. On univariate analysis, maternal age ≥ 35 years, recruitment at gestation > 280 days, recruitment to scheduled induction of labour interval ≥ 7 days, induction of labour indicated by prolonged pregnancy and reported coitus had a p < 0.1, and were incorporated into the model for multivariable logistic regression analysis. Reported orgasm did not show a significant

Table IV. Variables stratified according to spontaneous onset of labour before the scheduled labour induction.

	Spontaneous onset of labour*		Odds ratio (95% confidence interval)	p-value	Adjusted odds ratio (95% confidence interval)†	Adjusted p-value†
	Yes (n = 112)	No (n = 97)				
Maternal age (years)	28.6 ± 4.3	30.2 ± 4.5		0.007		
Age ≥ 35 years	9 (8.0)	17 (17.5)	0.4 (0.2–1.0)	0.057	0.5 (0.2–1.2)	0.12
Gravidity	2.0 ± 1.1	2.2 ± 1.5		0.32		
	2 [1]	2 [2]		0.95		
Parity	0.7 ± 0.9	0.9 ± 1.3		0.17		
	1 [1]	0 [2]		0.77		
Nulliparous	55 (49.1)	53 (54.6)	0.8 (0.5–1.4)	0.49		
Ethnicity						
Malay	72 (64.3)	57 (58.8)		0.46		
Chinese	19 (17.0)	16 (16.5)				
Indian	18 (16.1)	17 (17.5)				
Others	3 (2.7)	7 (7.2)				
Gestation at recruitment (weeks)	39.8 ± 1.0	39.5 ± 1.3		0.088		
Gestation at recruitment > 280 days	86 (76.8)	60 (61.9)	2.0 (1.1–3.7)	0.023	0.6 (0.2–1.8)	0.38
Recruitment to induction interval (days)	7.4 ± 3.1	6.1 ± 3.4		0.003		
Interval ≥ 7 days	70 (62.5)	37 (38.1)	2.7 (1.5–4.7)	0.001	2.9 (1.6–5.4)	0.001
Indication for labour induction						
Prolonged pregnancy	80 (71.4)	48 (49.5)	2.6 (1.4–4.5)	0.002	3.1 (1.2–8.2)	0.023
Others‡	32 (28.6)	49 (50.5)				
Randomised to advise-coitus group§	60 (53.6)	48 (49.5)	1.2 (0.7–2.0)	0.58		
Coitus reported¶	49 (43.8)	56 (57.7)	0.6 (0.3–1.0)	0.052	0.4 (0.2–0.8)	0.009
Orgasm reported¶	43 (38.4)	44 (45.4)	0.8 (0.4–1.3)	0.33		

Data is expressed as mean ± standard deviation, no. (%) and/or median [interquartile range].
Analysis by Student *t*-test continuous variables, Mann-Whitney U test for ordinal data, Fisher's exact test, chi-square test and multivariable logistic regression incorporating all covariables with unadjusted $p < 0.1$.
*Spontaneous labour is defined as the presentation to hospital for birth with either regular contractions and cervical dilatation ≥ 3 cm, or confirmed rupture of membranes on/before the scheduled date for induction of labour.
†Adjusted odds ratios and p-values shown for variables incorporated in the multivariable logistic regression analysis.
‡Include diabetes mellitus in pregnancy, hypertension, non-reassuring foetal status and more than one indication listed.
§Random allocation to advise-coitus or control group of randomised trial.
¶Vaginal sex or orgasm reported by the women in the interval between recruitment into the randomised trial and admission for birth.

association with spontaneous labour ($p = 0.33$). Following adjustment, recruitment to scheduled induction ≥ 7 days, labour induction indicated by prolonged pregnancy and reported coitus were independently associated with onset of spontaneous labour.

DISCUSSION

Our finding that reported coitus at term was associated with a reduced spontaneous labour rate was unexpected. Similarly unexpected was the inverse trend of spontaneous labour rates with frequency of reported coitus. Uterine activity in the immediate period after coitus is increased in women at high risk of preterm labour;[12] similarly, we had anticipated that women at term should be physiologically most receptive to stimuli to promote labour onset. Prospective studies on the effect of coitus at term on labour onset have produced mixed results: one has shown a positive impact[4] while the other has not shown any association.[5] Sexual intercourse has been reported to have a protective effect on preterm labour in certain circumstances,[13-15] but most studies have reported no association.[16-22] Other reports on coitus in pregnancy have even demonstrated an increased risk of prematurity[23] with the adverse effect most marked in women at high risk of preterm delivery.[24,25] The effect of coitus on both term and preterm labour appears unsettled in the literature.

We have not found reported orgasm to be associated with labour onset. Orgasm has been reported to be potentially protective of preterm birth[14,21] but more intense orgasm might increase the risk of prematurity,[26] while other reports have not found any association.[22,24] The five-minute Apgar score was significantly higher in women who had reported coitus, but this small difference was unlikely to have any clinical importance, as no neonate had a five-

minute Apgar score of ≤ 6. Neither umbilical cord blood pH nor neonatal admission rates were any different. It was reassuring that no other adverse association to reported coitus or orgasm was found. Our study was not adequately powered to examine the rarer but potentially serious adverse outcomes like abruption placenta or intrauterine deaths.

The rationale behind our finding of an inverse association between reported coitus and frequency of coitus to spontaneous labour onset, might be complex. The median interval for recruitment to admission for birth was 3.5 vs. 4 days for sexually-active and abstinent women, respectively, showing a significant difference. The time period available for sexual intercourse was particularly limited in a substantial proportion of abstinent women before their onset of spontaneous labour. This suggests that abstinence might be a consequence of imminent labour limiting the opportunity for coitus. It is also plausible that abstinence might be caused by reduced libido due to preceding symptoms or signs of imminent labour, like uterine contractions and vaginal discharge (e.g. passage of a show). Therefore, the inverse association of reported coitus with spontaneous labour might be due to selection caused by a lack of opportunity or by reduced libido, rather than coitus having a direct biological effect on prolonging gestation.

Although there is some data to indicate that the risk of preterm labour might decrease with coitus or orgasm during pregnancy, there is little biological rationale to account for this observation. Similarly at term, biological mechanisms for coitus delaying the onset of labour have not been developed. Labour onset is still incompletely understood; a delay in labour onset mediated via the hypothalamic-pituitary-endocrine axes is speculative, though possible. The possibility of a Type 1 statistical error in our finding also cannot be discounted as our analyses were of a secondary nature.

Our analysis had some additional limitations – we did not validate whether coitus or orgasm had actually occurred as we relied on the self-reported diaries recorded by the women. We also did not have the data to address the issue of libido or other motivational factors that might influence coitus. Our finding was consistent with coitus having an inverse relationship with spontaneous onset of labour at term; the rationale for the observation might however be complex. Further research to clarify the effect of coitus and orgasm on the onset of labour at term is needed.

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Concurrent Dinoprostone and Oxytocin for Labor Induction in Term Premature Rupture of Membranes

A Randomized Controlled Trial

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OBJECTIVE: To estimate the effect of concurrent vaginal dinoprostone and oxytocin infusion against oxytocin infusion for labor induction in premature rupture of membranes (PROM) on vaginal delivery within 12 hours and patient satisfaction.

METHODS: Nulliparas with uncomplicated PROM at term, a Bishop score less than or equal to 6, and who required labor induction were recruited for a double-blind randomized trial. Participants were randomly assigned to 3-mg dinoprostone pessary and oxytocin infusion or placebo and oxytocin infusion. A cardiotocogram was performed before induction and maintained to delivery. Dinoprostone pessary or placebo was placed in the posterior vaginal fornix. Oxytocin intravenous infusion was commenced at 2 milliunits/min and doubled every 30 minutes to a maximum of 32 milliunits/min. Oxytocin infusion rate was titrated to achieve four contractions every 10 minutes. Primary outcomes were vaginal delivery within 12 hours and maternal satisfaction with the birth process using a visual analog scale (VAS) from 0 to 10 (higher score, greater satisfaction).

RESULTS: One hundred fourteen women were available for analysis. Vaginal delivery rates within 12 hours were 25 of 57 (43.9%) for concurrent treatment compared with 27/57 (47.4%) (relative risk 0.9, 95% confidence interval 0.6–1.4, *P*=.85) for oxytocin only; median VAS was 8 (interquartile range [IQR] 2) compared with 8 (IQR 2), *P*=.38. Uterine hyperstimulation was 14% compared with 5.3%, *P*=.20; overall vaginal delivery rates were 59.6% compared with 64.9%, *P*=.70; and induction to vaginal delivery interval 9.7 hours compared with 9.4 hours *P*=.75 for concurrent treatment compared with oxytocin, respectively. There was no significant difference for any other outcome.

CONCLUSION: Concurrent vaginal dinoprostone and intravenous oxytocin for labor induction of term PROM did not expedite delivery or improve patient satisfaction.

CLINICAL TRIAL REGISTRATION: Current Controlled Trials, www.controlled-trials.com, ISRCTN74376345

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LEVEL OF EVIDENCE: I

Premature rupture of membranes (PROM) at term occurs in about 8% of term pregnancies.[1] Expedited labor induction in PROM reduces chorioamnionitis, endometritis, and neonatal infection.[2] Oxytocin infusion compared with prostaglandin for labor induction is associated with less chorioamnionitis and neonatal infection, but epidural anesthesia and the requirement for internal fetal monitoring is increased.[3] Recent guidance supports the use of oxytocin infusion as the first-line labor induction method in PROM.[1]

Premature rupture of membranes, nulliparity, and induction of labor are recognized major risk factors for failure to progress during the first stage of labor.[4] Induction of labor in PROM compared with when membranes are intact is associated with a longer second stage and a higher rate of cesarean delivery due to failure to progress.[5] Neonatal intensive care admission, variable decelerations, and pri-

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mary cesarean delivery rates are positively correlated with a longer admission-to-labor-onset interval in women with PROM.[6] Nulliparas with PROM and unfavorable cervices needing labor induction remain a clinical challenge.

Concurrent oxytocin infusion with prostaglandin in the labor induction of nulliparas with intact membranes at term has been shown to improve maternal satisfaction[7] and is associated with a shorter induction-to-delivery interval and reduced drug costs.[8] Concurrent oxytocin and prostaglandin for labor induction with intact membranes does not increase the risk of adverse outcomes due to uterine hyperstimulation.[7–11] There is a paucity of information on concurrent therapy in term PROM labor induction.

We hypothesized that concurrent treatment will result in a faster and more satisfactory labor in PROM labor induction. We sought to estimate the effect of front-loading a single dose of vaginal dinoprostone in nulliparas with PROM and unfavorable cervices who are receiving titrated oxytocin infusion as the standard method for induction of labor.

MATERIALS AND METHODS

We performed a double-blind randomized trial of a single dose of 3-mg dinoprostone pessary and titrated intravenous oxytocin infusion compared with placebo pessary and titrated intravenous oxytocin infusion. The study was approved by the University of Malaya Medical Centre Medical Ethics committee (Institutional Review Board Reference No. 607.9). All participants provided written informed consent. Enrolment was from November 12, 2007, to December 1, 2008. Participants were followed up until hospital discharge. Potential candidates for labor induction were identified by care providers in our delivery suite after the diagnosis of uncomplicated PROM at term and a decision to induce labor. Women were given verbal and written information before recruitment and randomization. All participants gave written consent.

Inclusion criteria were ruptured membranes confirmed clinically by the demonstration of pooling of liquor at the upper vagina on speculum assessment, nulliparity (no previous delivery with more than 20 weeks of gestation), gestational age more than 36 weeks, unfavorable Bishop Score 6 or less,[7–10] less than one contraction in 15 minutes if any was present, singleton fetus in cephalic presentation, a reassuring cardiotocogram, and decision already reached to induce labor. Exclusion criteria were previous uterine incision, meconium-stained liquor, known severe fetal anomaly, maternal asthma, and allergy to prostaglandin. In our center, women with confirmed uncomplicated PROM were given the options of immediate labor induction or expectant inpatient management for up to 24 hours.

The randomization sequence was generated by a computerized random number generator in blocks of 8 and prepared by an investigator (P.C.T.). Allocation to treatment arms was effected by the sequential opening of sealed numbered envelopes, each containing either 3-mg dinoprostone pessary or an identical-looking placebo pessary. The sealed numbered envelopes were made up periodically as required and kept in a refrigerator until use.

The allocated pessary was inserted into the posterior fornix. At the same time, oxytocin infusion at 2 milliunits/min was started for all participants. Oxytocin infusion was doubled every 30 minutes to a maximum of 32 milliunits/min or until four contractions in 10 minutes was achieved.

Continuous cardiotocogram monitoring was maintained throughout the induction and labor. Standard management of labor induction and labor was applied as previously described.[12] Antibiotic prophylaxis against early onset neonatal Group B streptococcal sepsis was routinely administered during labor if PROM of 18 hours or more was reached or maternal fever 38°C or more developed. The usual prophylactic regimen was an initial dose of 2 g of ampicillin intravenously followed by 1 g ampicillin intravenously every 4 hours until delivery.

In the event of a nonreassuring cardiotocogram associated with uterine hyperactivity, the following actions were suggested: reduce or stop oxytocin infusion, remove pessary (if still present), administer subcutaneous terbutaline for tocolysis or expedite operative delivery depending on individual circumstances and the severity of the cardiotocogram abnormality. The cardiotocogram was assessed by a blinded investigator after delivery to identify hyperstimulation and cardiotocogram abnormalities.

Participants' characteristics and outcomes were extracted onto a standardized case report form. Case notes and hospital records were scrutinized after delivery to retrieve relevant clinical outcome data.

Primary outcomes were 1) vaginal delivery within 12 hours of induction and 2) maternal satisfaction score for the birth process obtained within 24 hours of delivery. A visual analog scale (VAS) with a range of 0 to 10, with higher score denoting greater satisfaction, was used to gauge maternal satisfaction. Secondary outcomes were induction-to-delivery interval, mode of delivery, analgesia use in labor, uterine hyperstimulation (eg, uterine tachysystole—defined as

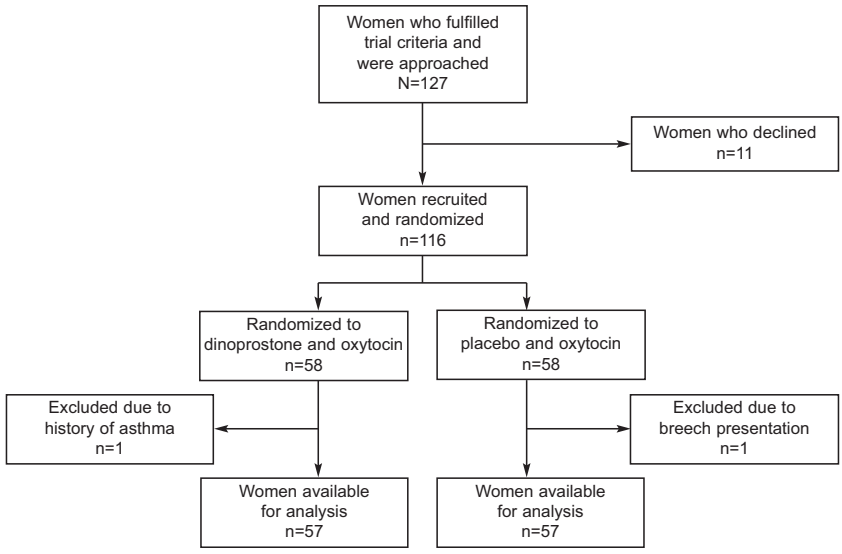

Fig. 1. Trial recruitment and flow.
Tan. Concurrent Dinoprostone and Oxytocin in PROM. Obstet Gynecol 2009.

six or more uterine contractions per 10 minutes over two consecutive 10-minute periods without fetal heart rate abnormalities; uterine hypertonus–uterine contraction lasting more than 2 minutes; or hyperstimulation syndrome–defined as six or more uterine contractions per 10 minutes with fetal heart rate abnormalities), meconium stained liquor, peridelivery blood loss and blood transfusion, maternal fever from recruitment to discharge (temperature 38°C or more), various neonatal outcomes (special care nursery admission, umbilical cord blood pH and base excess, Apgar score, and phototherapy).

Because a study of concurrent oxytocin and prostaglandin for PROM labor induction was not available at trial inception to our knowledge, power calculation was based on a study of labor induction in women with intact membranes using concurrent oxytocin with prostaglandin compared with prostaglandin, which showed a 39% compared with 15% vaginal delivery rate at 12 hours for nulliparas.[8] Setting significance at 5%, power at 80%, and one-to-one recruitment ratio, 53 women were required in each arm. Allowing for a 10% dropout rate, we planned to recruit a total of 116 women.

Analysis was performed on intention-to-treat basis. Data were entered into SPSS 15 (SPSS Inc., Chicago IL). GraphPad Instat software (GraphPad Software Inc., San Diego CA) was also used. The one-sample Kolmogorov-Smirnov test was used to check for normality of data distribution. The Student *t* test was used on continuous data, and the Mann-Whitney *U* test was used for ordinal and nonnormally distributed data. Fisher exact test was applied for 2×2 categorical data sets and χ^2 test for larger than 2×2 categorical data sets. Relative risk (RR) and its 95% confidence interval (CI) were calculated using GraphPad Instat (using Fisher exact test). All tests used were two-tailed. A $P<.05$ in any test was considered significant.

RESULTS

Figure 1 displays the recruitment flow. One hundred sixteen women were randomly assigned: 58 to dinoprostone and oxytocin and 58 to placebo and oxytocin. All assigned women received allocated treatment. One woman allocated placebo was found to be in breech presentation cesarean delivery was offered, accepted, and quickly performed. Another woman allocated to dinoprostone was discovered to have a history of asthma soon after pessary insertion, and the pessary was immediately removed. Labor induction was continued with oxytocin only. These two women were excluded. There were another five women (four with Bishop score 7 and one with Bishop score 8), four of whom were assigned to concurrent therapy and one to oxytocin only who despite not fulfilling inclusion criterion of Bishop Score 6 or less were included. The errors incurred in the summation of their Bishop score from its various components were not discovered until at data analysis (they were thought to have a Bishop score of 6 when recruited). These five participants were managed as per trial protocol throughout their induction and labor.

Patient characteristics are listed in Table 1. The groups were comparable in all characteristics except for maternal age. The women assigned to concurrent dinoprostone and oxytocin was younger (mean

Table 1. Patient Characteristics

Characteristic	Dinoprostone and Oxytocin (n=57)	Oxytocin (n=57)	*P*
Age	26.9±2.9	28.5±4.2	.017
Gravidity	1 [0]	1 [0]	.50
Gestational age (wk)	39.0±1.0	38.8±1.1	.34
Ethnicity			.21
Malay	35 (61.4)	31 (54.4)	
Chinese	9 (15.8)	16 (28.1)	
Indian	12 (21.1)	7 (12.3)	
Others	1 (1.8)	3 (5.3)	
PROM to induction interval (h)	6.5 [10.2]	4.3 [10.8]	.27
Bishop score	5 [1]	4 [1]	.11
Antenatal risk factors			
None	47 (82.5)	47 (82.5)	.38
Gestational diabetes	6 (10.5)	6 (10.5)	
Anaemia	2 (3.5)	1 (1.8)	
Hemoglobin E disease	0 (0)	1 (1.8)	
Minor valvular heart disease	0 (0)	2 (3.5)	
Hypertension	2 (3.5)	0 (0)	
Birth weight (kg)	3.0±0.5	3.0±0.4	.49

PROM, premature rupture of membranes.

Data are mean±standard deviation, median [interquartile range], or n (%). Analysis by Student *t* test for continuous data, Mann Whitney *U* test for ordinal data and nonnormally distributed data, and Fisher's exact test for categorical data (2×2 data sets) or χ^2 test (larger than 2×2 data sets).

age±standard deviation 26.9±2.9 years compared with 28.5±4.2 years; *P*=.017).

Outcomes are shown in Table 2. There were no significant differences in the predefined primary outcomes: vaginal delivery rates within 12 hours were 25 of 57 (43.9%) compared with 27 of 57 (47.4%) (relative risk 0.9, 95% CI 0.6–1.4, *P*=.85) and median VAS satisfaction score was 8 (interquartile range 2) compared with 8 (interquartile range 2), *P*=.38 for concurrent treatment compared with oxytocin only, respectively.

There was no significant difference in any of the secondary outcomes recorded. Induction-to-delivery interval and mode of delivery were very similar. Although not significant, 14% (compared with 5.3%; *P*=.20) of women assigned to concurrent treatment had uterine hyperstimulation, and 8.8% (compared with 1.8%; *P*=.44) of them also required stoppage of oxytocin infusion due to uterine hyperactivity. One woman allocated to oxytocin only also required terbutaline tocolysis for uterine hyperstimulation syndrome. There was no cesarean delivery indicated by uterine hyperstimulation syndrome within the trial.

Two women assigned to concurrent treatment had significant morbidity. In one woman, labor was induced 9.5 hours after PROM. Intrapartum, she had epidural anesthesia, developed a fever of 40.1°C, and was treated with intravenous ampicillin. She had a normal vaginal delivery 7 hours after labor induction. A combination of a cervical tear and uterine atony caused a primary postpartum hemorrhage with cumulative blood loss of 3 L. She required multiple uterotonics, examination under anesthesia, cervical suturing, and eventually laparotomy and bilateral internal iliac ligation to control persistent bleeding from the cervix. Blood transfusion was given, and she spent several days in the intensive care unit. Her neonate was also admitted to the special nursery for suspected congenital pneumonia. The mother made a full recovery, with an intact uterus. Her neonate also recovered fully. Her provider requested the identity of the allocated treatment at the time of these complications and her treatment was revealed to the provider. In the second woman, labor was induced 2 hours after PROM, and an epidural was placed during labor. Labor was slow, and progress arrested at 9-cm cervical dilatation. A healthy 4.1-kg neonate was delivered by cesarean delivery 19 hours after induction. During the cesarean delivery, hemorrhage due to uterine atony was noted. Uterine atony did not respond to multiple uterotonics. A B-Lynch suture was performed to control hemorrhage. Blood loss was 1.5 L, and blood was transfused. The mother made a full recovery, with an intact uterus.

One woman assigned to placebo had a prolonged episode of fetal bradycardia on cardiotocogram soon after commencement of labor induction that required removal of the pessary and stoppage of oxytocin infusion. However, there was no evidence of uterine hyperactivity at the time of fetal bradycardia. She eventually had a cesarean delivery.

There was no significant difference in any neonatal outcome recorded. There were four neonatal admissions–three newborns were from women assigned to placebo and one from a woman assigned to concurrent therapy. These admissions were indicated by respiratory distress (2) and presumed sepsis (2); there was no admission for birth asphyxia. All four recovered fully. There was a single baby with umbilical arterial cord blood pH <7.1 but did not need admission. No neonate had an Apgar score less than 7 at 5 minutes. Phototherapy for neonatal jaundice was less commonly encountered for the neonates of women assigned to concurrent therapy, 3.5% compared with 8.8% (RR 0.4, 95% CI 0.1–2.0; *P*=.44), but this difference was not significant.

Table 2. Outcomes

Outcome	Dinoprostone and Oxytocin (n=57)	Oxytocin (n=57)	RR (95% CI)*	*P*
Primary outcomes				
Vaginal delivery within 12 h	25 (43.9)	27 (47.4)	0.9 (0.6–1.4)	.85
Visual analog scale†	8 [2]	8 [2]		.38
Secondary outcomes				
Induction to delivery interval (h)	10.6±4.2	10.2±4.3		.68
Induction to vaginal delivery interval (h)	9.7±3.6 (n=34)	9.4±4.2 (n=37)		.75
Mode of delivery				
Vaginal delivery	34 (59.6)	37 (64.9)		.70
Cesarean delivery	23 (40.4)	20 (35.1)		
Spontaneous vaginal	30 (52.6)	29 (50.9)		.46
Instrumental vaginal	4 (7.0)	8 (14.0)		
Indication for operative delivery				1.0
Failure to progress	17 (63.0)	18 (64.3)		
Fetal distress	10 (37.0)	10 (35.7)		
Uterine hyperstimulation	8 (14)	3 (5.3)	2.7 (0.7–10)	.20
Comprising				
Uterine hyperstimulation syndrome	4 (7)	1 (1.8)		
Uterine hypertonus	0 (0)	1 (1.8)		
Tachysystole	4 (4)	1 (1.8)		
Oxytocin infusion stopped due to uterine hyperstimulation	5 (8.8)	2 (3.5)	2.5 (0.5–12)	.44
Total oxytocin infused intrapartum (units)	2.5 [3.7]	3.1 [5.7]		.83
Epidural analgesia	35 (61.4)	33 (57.9)	1.1 (0.8–1.4)	.85
Pethidine analgesia	20 (35.1)	24 (42.1)	0.8 (0.5–1.3)	.56
Meconium-stained liquor in labor	1 (1.8)	0 (0)	‡	1.0
Maternal fever	4 (7.0)	1 (1.8)	4.0 (0.5–34.7)	.36
Delivery blood loss (mL)	390±410	340±200		.38
Postpartum hemorrhage (500 mL or more)	10 (17.5)	8 (14.0)	1.3 (0.5–2.9)	.80
Blood transfusion	4 (7.0)	1 (1.8)	4.0 (0.5–34.7)	.36
Induction to discharge interval (d)	3.2±1.6	2.9±1.0		.99
Apgar score at 5 minutes	10 [0]	10 [0]		.65
Apgar score at 5 minutes less than 7	0 (0)	0 (0)	‡	‡
Arterial cord blood pH§	7.29±0.08	7.27±0.07		.25
Cord arterial blood pH less than 7.1§	1 (1.8)	0 (0)	‡	1.0
Cord arterial blood base deficit (mmol/L)§	6±4	6±3		.86
Neonatal admission for special care	1 (1.8)	3 (5.3)	0.3 (0.04–3.1)	.62
Phototherapy for jaundice	2 (3.5)	5 (8.8)	0.4 (0.1–2.0)	.44

RR, relative risk; CI, confidence interval.

Data are mean±standard deviation, median [interquartile range], or n (%). Analysis was by Student *t* test for continuous data, Mann-Whitney *U* test for ordinal data, and Fisher exact test for categorical data (2×2 data sets) or χ^2 test (larger than 2×2 data sets).

* Placebo plus oxytocin group served as referent.

† Visual analog scale from 0 to 10, with 0 representing complete dissatisfaction to 10 representing complete satisfaction with the birth process.

‡ No result because one or more cells contain a zero.

§ Umbilical cord arterial blood not analyzed in two patients, one from each group.

DISCUSSION

Our study showed that the front loading of vaginal dinoprostone concurrently with oxytocin infusion to induce labor in term PROM did not hasten delivery or decrease operative delivery compared with oxytocin infusion. Intrapartum analgesic need was similar. Maternal satisfaction with the birth process was also similar.

Concurrent prostaglandin and oxytocin to induce labor in the context of intact membranes has been shown to result in a shorter induction-to-delivery interval but has not significantly decreased the cesarean delivery rate.[8,10,11] Maternal satisfaction is also higher with concurrent therapy.[7] Membrane sweeping in conjunction with dinoprostone or amniotomy at labor induction (intact membranes) has been shown to shorten induction-to-delivery interval, increase spontaneous vaginal delivery rate, and improve maternal satisfaction.[12] Our finding was in contrast to the positive effect on delivery timing that concurrent front-loading regimens have in labor induction when membranes were intact. This difference

might be due to the fact that we were comparing concurrent therapy against oxytocin in this study. Previous trials of concurrent prostaglandin and oxytocin for labor induction with intact membranes typically compared against prostaglandin arms. We titrated the rate of oxytocin infusion against uterine contractions. This meant that any slack in uterine activity would be quickly dealt with by an increased delivery of oxytocin, leaving little room for dinoprostone to demonstrate optimization of uterine activity.

Also, membrane rupture is associated with the considerable local release of prostaglandin at the site of membrane.[13] At term PROM, 72% would go into labor spontaneously within 24 hours[14] suggesting PROM alone is an effective pathway for labor onset for many. The landmark TERMPROM trial[15] has shown that immediate induction with oxytocin compared with prostaglandin is associated with significantly shorter time to active labor, duration of active labor and interval of membrane rupture to delivery, suggesting that the criterion standard agent to use in term PROM labor induction should be oxytocin even without considering its advantage of less infective morbidity.[16] Our finding of no benefit and of possible harm with concurrent use of dinoprostone and oxytocin might be explained by the rationale that PROM has released the optimal amount of prostaglandin for synergism with titrated oxytocin infusion to ripen the cervix and successfully induce labor. Additional exogenous prostaglandins in conjunction with oxytocin stimulation might tip the uterine response toward hyperactivity.

Overall, the cesarean delivery rate in our trial was 38%, and 63% of the cesarean deliveries were indicated by failure to progress. A previous trial from our center of concurrent oxytocin infusion and vaginal dinoprostone compared with vaginal dinoprostone for labor induction of term nulliparas with intact membranes and unfavorable cervices reported cesarean delivery rates of 41.9% compared with 44.7%, respectively.[7] These cesarean rates were high and broadly similar to that of this study. A major challenge is still in place to find an effective labor induction regime in high-risk nulliparas with unfavorable cervices with and without PROM.

There were two women from the concurrent therapy group with significant morbidity due to hemorrhage due in part to uterine atony. Prolonged exposure to prostaglandin does not result in oxytocin receptor down-regulation or reduction in myometrial contractility in an animal model.[17] Oxytocin receptor down-regulation and desensitization occurs with prolonged exposure to oxytocin,[18,19] but the total oxytocin infused is nonsignificantly lower in the concurrent therapy group. Induction-to-delivery interval was also very similar. There was no clear rationale to account for an excess of uterine atony with concurrent therapy. No woman required emergency cesarean delivery for uterine hyperstimulation syndrome, a more immediate adverse effect anticipated of concurrent therapy.

Our study has limitations. The mean age of women in the randomized groups was slightly but significantly different. We believe that this is a chance event. Controlling for maternal age in the analysis did not make any difference to the effect of concurrent therapy on the primary outcome of vaginal delivery within 12 hours of labor induction. Trial participants were heterogeneous, comprising women who opted for immediate labor induction on confirmation of PROM and those who opted for initial expectant management but later required labor induction. Power calculation was based on labor induction in women with intact membranes, where a relatively large treatment effect on delivery within 12 hours has been demonstrated with concurrent therapy.[8] Our study would be underpowered if the treatment effect were more modest. However, we did not observe any trend of more effective labor induction with concurrent therapy in our analysis.

Concurrent treatment with single-dose vaginal dinoprostone and titrated oxytocin infusion is no better than placebo pessary and similarly titrated oxytocin infusion in inducing labor for PROM at term in nulliparas with unfavorable cervices. There is concern about increased uterine hyperstimulation with concurrent therapy.

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Serial Membrane Sweeping at Term in Planned Vaginal Birth After Cesarean

A Randomized Controlled Trial

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OBJECTIVE: To estimate the effect of serial membrane sweeping on the onset of labor in women who planned vaginal birth after cesarean (VBAC).

METHODS: Women at term with one transverse lower segment cesarean delivery who were suitable for and who planned VBAC were approached to participate. Participants were randomly assigned to weekly membrane sweeping or weekly vaginal assessment for Bishop score until delivery. Participants and delivery providers were blinded to the allocated treatment. Standard obstetric care was given to all participants. The primary outcome was onset of labor which was defined as the presence of spontaneous regular and painful contractions that cause cervical dilation to at least 3 cm or prelabor rupture of membranes. Secondary outcomes included induction of labor and repeat cesarean delivery.

RESULTS: One hundred eight women were randomly assigned to membrane sweeping and 105 to control. The spontaneous labor rate was 78.5% compared with 72.1% (relative risk [RR] 1.1, 95% confidence interval [CI] 0.9–1.3; *P*=.34), the induction of labor rate was 12.1% compared with 9.6% (RR 1.3, 95% CI 0.6–2.8; *P*=.66), and the all-cause cesarean delivery rate was 40.2% compared with 44.2% (RR 0.9, 95% CI 0.7–1.2; *P*=.58) for the membrane sweeping and control groups, respectively. Gestational age at delivery (mean±standard deviation) of 39.6±1.0 weeks for the membrane sweeping group compared with 39.6±0.9 weeks for the control group (*P*=.84) was no different.

CONCLUSION: Serial membrane sweeping at term in women who planned VBAC has no significant effect on the onset of labor, pregnancy duration, induction of labor, or repeat cesarean delivery.

CLINICAL TRIAL REGISTRATION: ISRCTN, isrctn.org, ISRCTN55163179.

(Obstet Gynecol 2009;114:745–51)

LEVEL OF EVIDENCE: I

Membrane sweeping at term is effective in expediting delivery and reducing the need for formal induction of labor.[1] Recent guidance suggests that membrane sweeping can be offered at term to promote labor and avoid induction of labor for prolonged pregnancy.[2,3] Induction of labor is associated with a failed trial of vaginal birth after cesarean (VBAC) resulting in a repeat cesarean delivery.[4] Induction of labor and scarred uteri are associated with uterine rupture, which in turn massively increases the risk of neonatal mortality.[5] The rates of cesarean delivery in women undergoing planned VBAC were 33%, 26%, and 19% for induced, augmented, and spontaneous labor groups, respectively.[6] The risk of uterine rupture for planned VBAC delivery was 102, 87, and 36 per 10,000 attempts for induced, augmented, and spontaneous labor groups, respectively.[7]

Induction of labor at planned VBAC is acceptable after careful counseling and risk assessment,[8–10] but misoprostol should not be used.[8,10] The Bishop score is inversely correlated with successful induction of labor at planned VBAC.[11]

Prolonged pregnancy (after 39 weeks of gestation) after a previous cesarean delivery is associated with stillbirth.[12] Prior cesarean delivery is also associated

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with an excess risk of explained stillbirths.[13] However, other studies have not demonstrated an increased risk of subsequent stillbirth after a cesarean delivery.[14,15]

A PubMed search (http://www.ncbi.nlm.nih.gov/pubmed/) that used the terms *previous cesarean* and *membrane sweeping* without any limits from 1966 until May 2, 2009, did not identify any article. There is a paucity of data within the context of membrane sweeping after a cesarean delivery.

Promoting earlier onset of labor within term in women planning VBAC can be advantageous, because the need for induction of labor may be avoided, and prolongation of pregnancy further into late term with its risk of stillbirth may be reduced. We hypothesize that serial membrane sweeping is effective in initiating labor in women planning VBAC. The objective of our research, therefore, was to estimate the effect of serial membrane sweeping on the onset of labor in women who planned VBAC.

MATERIALS AND METHODS

The trial was conducted in a university hospital located in Kuala Lumpur, Malaysia. More than 5,000 women deliver at our center each year. In a recent report from our center, 1,000 consecutive women with one previous cesarean delivery who were suitable for VBAC were identified over a 3.5-year period from 2002 to 2005. A total of 76.8% of these women underwent planned VBAC, and 71.2% of those who attempted VBAC were delivered vaginally.[16] Many women who delivered at our center fulfilled eligibility criteria of this study and our provider base was also supportive of planned VBAC.

Ethical approval for the trial was obtained from the Medical Ethics Committee of the University of Malaya Medical Center. This study was performed in compliance with the Declaration of Helsinki. All participants provided written informed consent. The trial ran from September 2007 to November 2008.

Women with one transverse lower segment cesarean scar, a singleton pregnancy, cephalic presentation, intact membranes, and gestational age more than 36 weeks who were agreeable to VBAC and passed specialist assessment for VBAC were approached to participate at their routine antenatal visit. Exclusion criteria were obstetric contraindications to VBAC (eg, placenta previa, suspected macrosomia, suspected cephalopelvic disproportion, abnormal fetal lie, and obstructive pelvic masses).

Guidance data from a previous trial of membrane sweeping in women who planned VBAC was not available for sample size calculation. The spontaneous labor rate in women who underwent a trial of VBAC in our center was 87.5%.[17] A Cochrane review indicates 1 in 8 (12.5%) would not require formal induction of labor if membrane sweeping were performed,[1] hence we estimated a 98% spontaneous labor rate with serial membrane sweeping and with alpha at 0.05 and power at 80%, sample size calculation indicated 95 subjects would be required in each arm. Allowing for a 10% dropout rate, at least 211 women were needed for an adequately powered study.

Investigators recruited participants with the support of other specialist staff to counsel participants on suitability for VBAC. After consent, participants were randomly allocated by the sequential opening of numbered sealed opaque envelopes indicating "Sweep" or "No Sweep." These numbered envelopes were prepared by an author (M.H.) in blocks of 50 using a computer-generated randomization sequence (available online at http://www.random.org/).

Immediately after randomization, women assigned to "sweep" had their cervix stretched and membranes stripped from the lower uterine segment in the manner as previously described.[18] Women assigned to "no sweep" had a gentle vaginal examination for their Bishop score.

Weekly follow-up sessions based at the antenatal clinic with the investigators were arranged to repeat membrane sweeping or vaginal examination until delivery. The Bishop score was recorded at each session. Blinding of participants and delivery providers was effected by a policy of not revealing allocated treatment to them unless requested for an important clinical need. There was no request to unblind during the trial. All participants received standard management by delivery providers.

In our center, induction of labor for prolonged pregnancy is typically offered at 41 weeks of gestation.[19] Induction of labor for diabetes that required drug treatment is offered at 38 weeks and for gestational diabetes adequately controlled by diet, induction of labor is offered at 40 weeks.[20] Upon prelabor rupture of membranes, women were offered either immediate uterine stimulation, typically with oxytocin, or expectant inpatient management for up to 24 hours.[21] All women with a previous cesarean delivery who were offered formal induction of labor were counseled about a higher risk of scar rupture and of unplanned cesarean delivery and the option of a planned repeat cesarean delivery was given.

Our labor ward setup was fully compliant with recent major guidelines[10,22] for the conduct of a trial of labor after cesarean. The labor during planned VBAC was continuously monitored by electronic cardiotocography. Our protocol for planned VBAC permitted

induction of labor with vaginal dinoprostone, augmentation of labor with oxytocin, and no specific time limit for a trial of labor, and the decision on emergency cesarean delivery was made at the discretion of the faculty provider on duty.[16]

The primary outcome was the onset of spontaneous labor. Spontaneous labor was defined as 1) regular painful contractions that resulted in cervical dilation of at least 3 cm of or 2) confirmed prelabor rupture of membranes.[23] Other outcome measures were cesarean delivery, formal induction of labor, recruitment to delivery interval, gestational age at delivery, gestational age at delivery 40 weeks or more and 41 weeks or more, number of membrane sweep or control sessions conducted, Bishop score at each session, unscheduled hospitalization, significant antepartum hemorrhage, prostaglandin and oxytocin use, maternal fever intrapartum and postpartum, blood loss at delivery, duration of hospitalization, epidural analgesia and neonatal outcomes of umbilical artery blood pH, Apgar score at 5 minutes, and birth weight.

Data were entered into statistical software package SPSS 15 (SPSS Inc., Chicago, IL). Analysis was by intention to treat. Normal distribution of continuous data was checked with the one-sample Kolmogorov-Smirnov test. Normally distributed continuous data were analyzed with the Student *t* test. Two-by-two categorical data sets were analyzed with Fisher exact test and larger categorical data sets with the χ^2 test. Ordinal data and nonnormally distributed continuous data were analyzed with the Mann-Whitney *U* test. Kaplan-Meier survival curve analysis was performed to compare recruitment-to-delivery interval (cases that did not result in spontaneous labor were censored) and the Cox-Mantel log rank test was used to analyze the survival distributions. All tests were two-tailed and $P<.05$ was considered significant.

RESULTS

Two hundred thirteen women were recruited: 108 women were randomly assigned to membrane sweeping and 105 to control vaginal examination. Two women (one each from membrane sweeping and control arms) were lost to follow-up, because they did not deliver at our center and attempts to make contact were unsuccessful. This left 211 women for analysis. All participants received their allocated treatment.

The flow of participants through the trial is shown in Figure 1.

Table 1 shows the characteristics of the participants in the two trial arms. Participants in the membrane sweep and control arms were similar ($P>.05$) in their characteristics.

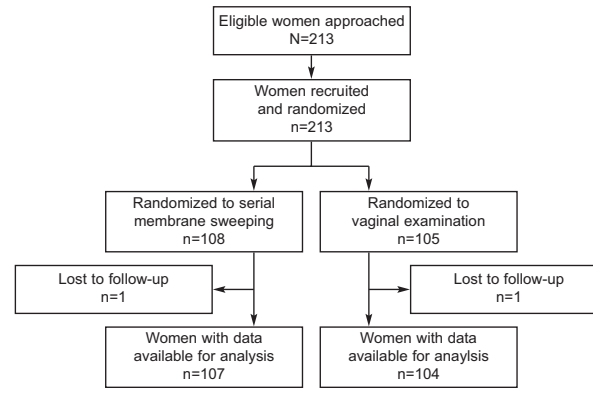

Fig. 1. Trial recruitment flowchart.

Hamdan. Serial Membrane Sweeping in Planned VBAC. Obstet Gynecol 2009.

Table 2 shows the analysis of the primary outcome of spontaneous onset of labor. Spontaneous onset of labor rate was 78.5% compared with 72.1% (relative risk [RR] 1.1, 95% confidence interval [CI] 0.9–1.3); $P=.34$) for membrane sweeping and control arms, respectively; there was no significant difference. The proportion of participants offered induction of labor was 14% compared with 16.3% (RR 0.9, 95% CI 0.5–1.6; $P=.7$) and who took the offer on and underwent induction of labor was 12.1% compared with 9.6% (RR 1.3, 95% CI 0.6–2.8; $P=.66$) for membrane sweeping and control arms, respectively. The overall planned cesarean delivery rate was 9.3% (membrane sweep) compared with 16.3% (control) (RR 0.6, 95% CI 0.3–1.2; $P=.15$). Of the planned cesarean deliveries before onset of spontaneous labor, 23 of 29 (79.3%) were due to maternal preference.

Analyses of secondary outcomes are listed in Table 3. All-cause cesarean delivery rate was not significantly different at 40.2% compared with 44.2% (RR 0.9, 95% CI 0.7–1.2; $P=.58$) for membrane sweeping and control, respectively. The indications for repeat cesarean delivery were similar. Mean (±standard deviation) recruitment-to-delivery interval at 16±8 days compared with 16±7 days ($P=.98$) and mean gestational age at delivery of 39.6±1.0 weeks compared with 39.6±0.9 weeks ($P=.84$) were virtually identical. Bishop score tended to be more favorable at subsequent treatment sessions in the membrane sweeping arm, but the median number of treatment sessions and the presenting cervical dilatation at the birth admission were no different. Epidural analgesia during labor was more commonly used by the membrane sweeping arm (31.8% compared with 19.2% $P=.04$). Frequency of unscheduled hospitalizations, significant antepartum bleeding, dinoprostone

Table 1. Characteristics of 213 Women After One Cesarean Delivery Randomly Allocated to Weekly Membrane Sweeping or Gentle Vaginal Examination

	Membrane Sweep (n=108)	Vaginal Examination (n=105)	*P*
Age (y)	30.7±3.5	31.5±3.9	.11
Gravidity	3 [1]	2 [2]	.68
Parity	1 [1]	1 [1]	.81
Any prior vaginal delivery	36 (33.3)	37 (35.2)	.78
Prior vaginal birth after cesarean	23 (21.3)	23 (21.9)	1.0
Ethnicity			.43
Malay	74 (68.5)	68 (64.8)	
Indian	18 (16.7)	24 (22.9)	
Chinese	13 (12.0)	8 (7.6)	
Others	3 (2.8)	5 (4.8)	
Interval since cesarean (y)	3.5±2.3	3.7±2.6	.62
Gestational age at recruitment (wk)	37.3±0.4	37.3±0.4	.62
Height (cm)	156±6	155±6	.38
Weight at recruitment (kg)	71±12	71±14	.97
Body mass index	29±5	29±5	.92
Bishop score at recruitment	1 [1]	1 [2]	.18
Indication for previous cesarean			.99
Failure to progress	33 (30.6)	32 (30.5)	
Nonreassuring fetal status	33 (30.6)	30 (28.6)	
Malpresentation	25 (23.1)	13 (22.8)	
Others	17 (15.7)	17 (16.2)	

Data are mean±standard deviation for continuous data, median [interquartile range] for ordinal data, and n (%) for categorical data.

Analysis by Student *t* test for continuous data, Mann Whitney *U* test for ordinal data, Fisher exact test for 2×2 categorical data sets, and χ^2 test for larger categorical data sets.

use for induction of labor, oxytocin use in labor, maternal fever, postpartum hemorrhage, and the duration of hospital stay were similar. Neonatal outcomes were also no different. No participant had a uterine rupture.

Kaplan-Meier survival curve analysis of recruitment-to-delivery interval, after censoring cases that did not result in spontaneous labor, showed no difference between the trial arms (Cox-Mantel log rank test, *P*=.82).

Post-hoc analysis stratifying women according to those with and without prior vaginal birth did not show a major difference in their response to serial membrane sweeping with regard to spontaneous onset of labor rate or to all-cause cesarean delivery. In women without prior vaginal births, comparing membrane sweeping with control, spontaneous onset of labor rate was 49 of 71 (69%) compared with 42 of 68 (61.8%) (RR 1.1, 95% CI 0.9–1.4; *P*=.38 and all-cause cesarean delivery rate was 37 of 71 (52.1%) compared with 41 of 68 (60.3%) (RR 0.9, 95% CI 0.6–1.2; *P*=.39). In women with prior vaginal birth, comparing membrane sweeping with control, spontaneous onset of labor was 35 of 36 (97.2%) compared with 33 of 36 (91.7%) (RR 1.1, 95% CI 0.9–1.2; *P*=.61) and all-cause cesarean rate was 6 of 36 (16.7%) compared with 5 of 36 (13.9%) (RR 1.2, 95% CI 0.4–3.6; *P*=1.0). Our post-hoc analysis showed that women with prior vaginal delivery generally had better outcome as expected.[9]

DISCUSSION

Serial membrane sweeping at term in women who planned VBAC did not increase the rate of onset of spontaneous labor or expedite delivery. Our findings are in contrast to the Cochrane meta-analysis of 22 membrane sweeping trials with its conclusion of reduced duration of pregnancy and with RR 0.59 of the pregnancy continuing to beyond 41 weeks with membrane sweeping.[1] Serial membrane sweeping resulted in a nonsignificant RR 1.1 (95% CI 0.9–1.3) for spontaneous onset of labor in our study. Indeed, there were proportionately more pregnancies delivered at or beyond 40 and 41 weeks in the membrane sweeping arm, although these differences were not significant.

The definition of spontaneous onset of labor used in this study included prelabor rupture of membranes.[23] Post-hoc analysis showed a more marked effect of membrane sweeping if the definition of labor was confined to achieving spontaneous regular painful uterine contractions and a cervical dilation of at least 3 cm. Spontaneous onset of labor rate was 75.7% compared with 63.5% (RR 1.2, 95% CI 1.0–1.43; *P*=.07), but this difference was also nonsignificant. Our data suggest that the effect, if any, of serial membrane sweeping to promote onset of labor in women planning VBAC is more modest than demonstrated by the Cochrane meta-analysis, but the trials covered by the Cochrane review typically enrolled low-risk women.[1]

Cesarean delivery rate was also no different, with serial membrane sweeping RR 0.9 (95% CI 0.7–1.2) in our study. The Cochrane meta-analysis[1] similarly did not demonstrate a significant reduction in cesarean delivery rate, with membrane sweeping RR 0.9 (95% CI 0.7–1.15), their relative risk is very similar to ours. Our study was not powered to estimate the

Table 2. Primary Outcome

	Sweep (n=107)	Control (n=104)	RR (95% CI)	*P*
Spontaneous labor*	84 (78.5)	75 (72.1)	1.1 (0.9–1.3)	.34
Contracting and cervix 3 cm or more dilated	81 (75.7)	66 (63.5)		
Prelabor rupture of membranes	3 (2.8)	9 (8.7)		
Not in spontaneous labor	23 (21.5)	29 (27.9)		
Offered indicated† induction of labor	15 (14)	17 (16.3)	0.9 (0.5–1.6)	.70
Accepted	13 (12.1)	10 (9.6)	1.3 (0.6–2.8)	.66
Opted for planned cesarean	2 (1.9)	7 (6.7)		
Planned cesarean‡	8 (7.5)	12 (11.5)		
Overall planned cesarean	10 (9.3)	19 (16.3)	0.6 (0.3–1.2)	.15

RR, relative risk; CI, confidence interval.
Data are n (%) except where otherwise indicated. Analysis by Fisher exact test.
* Spontaneous labor defined as having achieved regular contractions and cervical dilatation of at least 3 cm or confirmed prelabor rupture of membranes regardless of cervical or contraction status.
† Indications for induction of labor: postmature (18 total, 9 in each group), gestational diabetes (8 total, 6 in sweep and two in control group), nonreassuring fetal status (four in control group), pregnancy induced hypertension (one in control group), others (one in control group).
‡ Indications for planned cesarean delivery: (women offered induction of labor for obstetric indications but opted for planned cesarean delivery were excluded from this group) maternal request only (14), nonreassuring fetal status (two), preeclampsia (one), malpresentation (one), others (two).

effect of serial membrane sweeping on cesarean delivery.

We attempted to maintain blinding of the participants by performing vaginal examinations for their Bishop score in the control group. This measure should also eliminate the pure effect of vaginal examination, if any, as opposed to membrane sweeping in promoting onset of labor. Membrane sweeping is more uncomfortable than obtaining the Bishop score,[1,18] and therefore, the degree of blinding within the participants achieved by performing a control vaginal examination is probably incomplete.

The Bishop score was more favorable in the serially membrane swept arm at the second and fourth weekly sessions ($P<.01$ at both these sessions) and borderline at the third session ($P=.06$). It should be noted that the attrition rate was high from weekly session to weekly session as participants were delivered in the interim. The same investigator obtained both the Bishop score and performed the membrane sweeping. This protocol raised the possibility of investigator bias for the Bishop score. Also, because the Bishop score was obtained at the same time as membrane sweeping within a single digital vaginal procedure, there was the potential for the perceived cervical dilation subscore to be inflated by cervical stretching during membrane sweeping.[18] Cervical dilation was no different during the initial vaginal examination at hospitalization for birth when this was assessed by blinded delivery providers. Hence, the finding of more favorable Bishop scores at later treatment sessions in the membrane swept arm should be interpreted with some circumspection.

Epidural analgesia use was significantly higher in women assigned to serial membrane sweeping. There is no clear rationale for this effect because induction of labor rate, cervical dilation at hospitalization for birth, and oxytocin use during labor were similar across both trial arms. Given the multiple secondary outcomes assessed, there is the possibility of a type 1 statistical error with this analysis.

Our study has other limitations. A significant proportion of participants changed their mind about attempting VBAC. Although appropriately selected VBAC is supported by major guidelines,[9,10,22] when faced with the prospect of labor, induction of labor, or uterine stimulation for PROM, 29 of 211 (14%) of our participants opted for repeat cesarean delivery. These dropouts would reduce the power of our study as well as complicate interpretation of the overall repeat cesarean delivery rates. Our trial protocol was pragmatic, and given the diversity of opinion among obstetricians on the role of induction of labor in VBAC,[24] these dropouts were ethically unavoidable, because maternal choice must be given. Our participants are also heterogeneous, comprising lower-risk women with prior vaginal birth as well as women without vaginal birth who were at increased risk of unplanned repeat cesarean and uterine rupture.[9] Given the favorable outcome of planned VBAC in women with prior vaginal birth[9] (this observation was also supported by our post-hoc analysis), inclusion of these lower-risk women may have further reduced power.

Although a significant reduction in cesarean delivery rate in high-risk women without prior vaginal

Table 3. Secondary Outcomes

	Sweep (n=107)	Control (n=104)	RR (95% CI)	*P*
Maternal outcome				
Mode of delivery				.83
Spontaneous vaginal	60 (56.1)	54 (51.9)	1.1 (0.8–1.4)	.58
Instrumental vaginal	4 (3.7)	4 (3.8)		
Cesarean delivery	43 (40.2)	46 (44.2)	0.9 (0.7–1.2)	.58
Indication for cesarean				
Nonreassuring fetal status	15 (34.9)	15 (32.6)		.66
Failure to progress	12 (27.9)	9 (19.6)		
Maternal choice or request	13 (30.2)	16 (34.8)		
Malpresentation	2 (4.7)	2 (4.3)		
Others	1 (2.3)	4 (8.7)		
Number of sweep/control sessions	2 [1]	2 [1]		.75
Bishop score				
Session 2	2 [2] (n=81)	1 [1] (n=87)		<.01
Session 3	2 [2] (n=52)	1 [2] (n=45)		.06
Session 4	3 [1.5] (n=18)	1 [1] (n=11)		<.01
Session 5	3 [0] (n=1)	0 [0] (n=1)		*
Cervical dilation on admission for labor or induction of labor (cm)	2.5±1.9 (n=92)	2.4±1.7 (n=86)		.69
Hospital admission (unscheduled) after randomization	3 (2.8)	2 (1.9)	1.4 (0.2–8.6)	1.0
Reported significant antenatal vaginal bleeding after randomization	3 (2.8)	3 (2.9)	1.0 (0.2–4.7)	1.0
Prostaglandin for labor induction	5 (4.6)	2 (1.9)	2.4 (0.5–12)	.45
Oxytocin for induction or augmentation	14 (13.1)	9 (8.7)	1.5 (0.7–3.3)	.38
Intrapartum fever 38°C or more	2 (2.2) (n=90†)	3 (3.7) (n=82†)	0.6 (0.1–3.5)	.67
Postpartum fever 38°C or more	10 (9.9) (n=101‡)	6 (6.1) (n=99‡)	1.6 (0.6–4.3)	.44
Delivery blood loss (mL)	375±184	346±148		.22
Postpartum hemorrhage (500 mL or more)	21 (21.2) (n=99)	23 (23.5) (n=98)	0.9 (0.5–1.5)	.73
Recruitment to delivery interval (d)	16±8	16±7		.98
Gestational age at delivery (wk)	39.6±1.0	39.6±0.9		.84
Gestational age at delivery 40 wk or more	44 (41.1)	42 (40.4)	1.0 (0.7–1.4)	1.0
Gestational age at delivery 41 wk or more	14 (13.1)	8 (7.7)	1.7 (0.7–3.9)	.26
Duration of hospital stay for birth (d)	2.4±1.9	2.4±1.5		.78
Epidural analgesia in labor	34 (31.8)	19 (19.2)	1.7 (1.1–2.8)	.04
Neonatal outcome				
Birth weight (kg)	3.2±0.4	3.3±0.4		.63
Umbilical cord artery pH at birth	7.31±0.06	7.30±0.06		.35
Umbilical cord artery pH less than 7.1	1 (0)	(0)	§	.49
Apgar score at 5 min	10 [0] (n=100)	10 [0] (n=101)		.31
Apgar score 6 or less at 5 min	0 (0) (n=100)	0 (0) (n=101)	§	§

RR, relative risk; CI, confidence interval.

Data are mean±standard deviation for continuous data, median [interquartile range] for ordinal data, and n (%) for categorical data except where otherwise specified. Analysis by Student *t* test for continuous data, Mann Whitney *U* test for ordinal data, and Fisher exact test for 2×2 categorical data sets.

* No meaningful analysis, because only one patient in each group.

† Intrapartum maternal temperature not recorded in planned cesarean delivery, and some data are missing.

‡ Some data are missing.

§ Relative risk not calculable, because at least one cell with zero value.

birth was not demonstrated, using our post-hoc analysis data for all-cause cesarean delivery rate of 52.1% (membrane sweeping) compared with 60.3% (control), we calculated that a powered study of serial membrane sweeping would require 574 women in each arm.

Serial weekly membrane sweeping at term in women who planned VBAC was not associated with significantly increased spontaneous onset of labor rate or improved secondary outcomes. However, further study of membrane sweeping in high-risk women without prior vaginal birth and planning VBAC may be warranted, because these women are at the highest risk of unplanned repeat cesarean deliveries and uterine rupture in the event of formal induction of labor.

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Effect of Membrane Sweeping on Cervical Length by Transvaginal Ultrasonography and Impact of Cervical Shortening on Cesarean Delivery

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Objectives—The purpose of this study was to evaluate cervical length changes after membrane sweeping and the effect of cervical shortening on pregnancy outcomes.

Methods—Low-risk women at 40 weeks' gestation undergoing membrane sweeping to expedite labor were recruited. Participants were scheduled for labor induction at 41 weeks' gestation. Transvaginal ultrasonography was performed immediately before and after membrane sweeping to measure the cervical length. Three presweep and postsweep cervical lengths were measured. The shortest lengths before and after the sweep were taken as the representative lengths. The effect of membrane sweeping on cervical length was analyzed. Multivariable logistic regression analysis was performed to evaluate the effect of cervical shortening on labor induction and the mode of delivery.

Results—For the 160 participants, the mean presweep cervical length ± SD was 21.0 ± 10.0 mm; the postsweep length was 23.8 ± 10.9 mm, an average increase of 2.8 ± 0.6 mm ($P < .001$). Cervical shortening after membrane sweeping was noted in 53 of 160 cases (33%). Cervical shortening was associated with a reduction in all-cause cesarean delivery but not labor induction on bivariate analysis. After adjustment for maternal age, parity, presweep Bishop score, postsweep cervical length, oxytocin augmentation, epidural analgesia, and meconium-stained fluid, cervical shortening after membrane sweeping was independently predictive of a reduction in cesarean deliveries (adjusted odds ratio, 0.24; 95% confidence interval, 0.06–0.90; $P = .034$).

Conclusions—Membrane sweeping was associated with lengthening of the cervix. A shortened cervix after sweeping was independently predictive of vaginal delivery.

Key Words—cervical length; cesarean delivery; induction of labor; membrane sweeping; transvaginal ultrasonography

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Abbreviations

CI, confidence interval; OR, odds ratio; RR, relative risk; TVU, transvaginal ultrasonography

Sweeping of the membranes at term is associated with a shorter pregnancy and reduces the number of pregnancies continuing beyond 41 and 42 weeks. One per 8 women who have membrane sweeping will avoid formal induction of labor, but the cesarean delivery risk is not significantly reduced after membrane sweeping.[1]

Membrane sweeping has been shown to release endogenous prostaglandins and increased phospholipase A3[2] and oxytocin levels (Ferguson reflex).[3] The uterine contraction frequency is increased after membrane sweeping.[2] It has also been postulated that a mechanically dilated and disrupted cervix after membrane sweeping may offer less resistance to further dilation during labor induction.[4]

At induction of labor, transvaginal ultrasonography (TVU) of the cervix compared with the Bishop score has at least equal utility in predicting cesarean delivery, and TVU is better tolerated.[5] Labor induction after 41 completed weeks compared with expectant management is associated with fewer perinatal deaths.[6] Labor induction at term may also reduce the risk of shoulder dystocia, meconium aspiration syndrome, and preeclampsia.[7] However, labor induction compared with spontaneous labor is associated with at least double the cesarean delivery rate,[8,9] a 25% to 50% increase in the instrumental vaginal delivery rate,[9,10] postpartum hemorrhage,[9] and longer labor.[9]

The National Institute of Health and Clinical Excellence induction of labor guideline recommends that before formal induction of labor, women should be offered a vaginal examination for membrane sweeping.[11]

There appeared to be a paucity of reported data on the effect of membrane sweeping on immediate cervical changes as a marker of physical disruption to the cervix. We sought to evaluate the immediate effect of membrane sweeping on the cervical length using TVU and the effect of cervical shortening after membrane sweeping on labor induction and the mode of delivery.

Materials and Methods

The study was conducted a the University of Malaya Medical Center. Ethics approval was obtained from the University of Malaya Medical Center Medical Ethics Committee (Approval date, August 29, 2007; approval number 608.2). Informed and written consent was obtained from participants. The study was conducted from April 2008 to November 2009.

Healthy women were approached and recruited into the study when they presented at the antenatal clinic for their routine appointment at 40 weeks' gestation. They were given an appointment for labor induction at or after 41 weeks' gestation for prolonged pregnancy, as standard practice in our center.[12] Other inclusion criteria were a singleton fetus, a cephalic presentation, intact membranes, and a reassuring fetal status by cardiotocography. Exclusion criteria were the presence of painful uterine contractions (>1 in 30 minutes), previous cesarean delivery, antepartum hemorrhage, known gross fetal anomalies, contraindications to vaginal delivery (eg, placenta previa and breech presentation), and unwillingness to undergo TVU. They were offered a single membrane sweep to expedite labor with TVU of the cervix performed immediately before and after membrane sweeping.

After recruitment, participants were transferred to a private area where the TVU and membrane sweeping were performed. Participants were instructed to empty their bladder. Transvaginal ultrasonography was performed by 3 investigators (N.H.S., N.V., and S.S., all with at least 5 years of TVU experience) using an Acuson Sequoia 512 machine with a 4- to 8-MHz transvaginal probe (Philips Healthcare, Bothell, WA). A sagittal image of the entire cervical canal was acquired as described previously.[13] When a clear sagittal view of the entire cervix was seen, a 6-second saved ultrasonographic sequence was started, and the probe was gently moved if necessary to maintain the requisite view. After successful capture of the cervical imaging sequence, the probe was gently withdrawn to defocus the cervical image, and the above process repeated to obtain the second and third 6-second presweep cervical imaging sequences. The imaging sequence was marked only by a unique number (from a list of 1–1200) whose order of assignment was generated randomly online using an electronic generator via http://www.random.org.

Membrane sweeping was performed as previously described in a report from our center4 by a single investigator (P.P.K., who was not involved in TVU). The presweep Bishop score was determined in the same digital vaginal procedure as membrane sweeping. Postsweep TVU was then repeated as described above by the same sonographer, and 3 additional 6-second imaging sequences were saved. The entire process of TVU of the cervix, membrane sweeping, and another TVU examination was typically completed within 5 to 10 minutes.

After completion of recruitment for the study, the entire library of saved image sequences was read in random order by a single investigator (P.C.T., with more than 10 years of TVU experience) over several sittings. The 6-second sequence was viewed, and the best image frame on visual inspection was chosen for cervical length measurement. The cervical length was measured only once from the selected image frame. The assessor was therefore "blinded" to whether the images were obtained before or after a sweep and whether they came from any particular participant; this was done to avoid bias and reinterpretation. The cervical length was measured from the internal to external os in a straight line.[14] The shortest cervical lengths of the 3 obtained before and after the sweep were taken as

Author: *P* values missing here and below? Please add if applicable.

the representative lengths, respectively.[5,15] Cervical shortening was defined as a postsweep cervical length of less than the presweep length as determined by TVU.

Participants' demographic data were entered on a standard case report form. Case notes were retrieved after delivery, and pregnancy outcome data were similarly entered. In cases of missing data, other hospital data sources were searched, and if required, the participants were contacted by telephone.

Labor induction and the mode of delivery were the predefined main outcomes assessed in comparison with cervical shortening after sweeping. Labor was considered induced if amniotomy or a dinoprostone pessary[4,5] was used before onset of spontaneous labor, as previously defined.[16] Rupture of membranes was considered onset of labor.[16]

A study from our center of TVU in women at term and about to undergo labor induction showed a mean cervical length ± SD of 22 ± 9 mm.[5] With the use of a paired *t* test, setting $P < .05$ as the level of significance and 80% power and assuming a 2-mm shortening of the cervical length after sweeping and the SD of the difference in the response of matched pairs to be 9 mm, 161 women were required for a suitably powered study.

Data were entered into the statistical software package SPSS version 16 (SPSS Inc, Chicago, IL). Normal distribution of continuous data was checked with a 1-sample Kolmogorov-Smirnov test. A paired *t* test was used to analyze presweep and postsweep cervical length changes. Normally distributed continuous data were analyzed with the Student *t* test. Non-normally distributed continuous and ordinal data were analyzed using a Mann Whitney *U* test. Categorical 2 × 2 data sets were analyzed with a Fisher exact test, and data sets larger than 2 × 2 were analyzed with a χ^2 test. A multivariable logistic regression analysis incorporating all covariables with crude $P \leq 0.1$ on bivariate analysis was planned if cervical shortening was associated with labor induction or surgical delivery to evaluate whether cervical shortening was an independent predictor of labor induction or cesarean delivery. All statistical tests were 2 sided. $P < .05$ was considered significant.

Results

Among the 161 participants recruited, imaging sequences were completely lost for 1 participant. Of the remaining 960 saved image sequences, 6 (0.1%) did not yield images suitable for cervical length measurement, but at least 1 presweep and 1 postsweep cervical length was obtained from each participant. Five participants did not deliver in our center. Four were contactable by telephone to obtain basic pregnancy outcome data, but some secondary outcomes were unobtainable. All 5 were included in the analysis because TVU data were available.

For the 160 participants with TVU data, the mean presweep TVU cervical length was 21.0 ± 10.0 mm; the postsweep TVU cervical length was 23.8 ± 10.9 mm; and the average increase in length was 2.8 ± 0.6 mm ($P < .001$, paired t test).

Table 1 displays characteristics and pregnancy outcomes versus cervical shortening after membrane sweeping. Cervical shortening was not associated with any characteristic (including the Bishop score and presweep TVU cervical length). Cervical shortening was significantly associated with a reduction in surgical delivery (cesarean and instrumental vaginal versus spontaneous vaginal delivery; relative risk [RR], 0.44; 95% confidence interval [CI], 0.21–0.92) and cesarean delivery (cesarean versus vaginal delivery; RR, 0.40; 95% CI, 0.16–0.97) but not labor induction (RR, 0.86; 95% CI, 0.52–1.42). Cervical shortening was not associated with a number of other outcomes, including the pregnancy duration and condition of the neonate.

Table 2 displays the recorded variables that may affect cesarean delivery. On bivariate analysis, the maternal age, parity, presweep Bishop score, postsweep cervical length, cervical shortening, after membrane sweeping, recruitment-to-hospital admission interval, oxytocin use in labor, epidural analgesia use in labor, and meconium-stained fluid all had crude $P \leq .1$. All of these covariables were included in the multivariable logistic regression model. After adjustment, only being parous (adjusted odds ratio [OR], 0.22; 95% CI, 0.06–0.82; $P = .024$) and cervical shortening after sweeping (adjusted OR, 0.24; 95% CI, 0.06–0.90; $P = .034$) were independently predictive of a reduction in cesarean delivery. These findings remained consistent when labor induction was included in the model. If we considered only variables available at the point of membrane sweeping (ie, maternal age, parity, presweep Bishop score, postsweep cervical length, and cervical shortening after sweeping), cervical shortening (adjusted OR, 0.30; 95%, CI 0.09–0.96; $P = .042$), being parous **(adjusted OR, 0.15; 95% CI, 0.04–0.55)**, and a favorable Bishop score of 5 or higher (adjusted OR, 0.32; 95% CI, 0.11–0.91) were independently associated with a reduction in cesarean delivery.

A similar analysis was performed using surgical delivery (cesarean and instrumental vaginal delivery) versus spontaneous vaginal delivery as dichotomous outcomes. Being parous (adjusted OR, 0.14; 95% CI, 0.04–0.46; $P =$

Author: In Table 1, please verify P >.99 as changed from 1.00; P cannot equal 1, per American Medical Association guidelines.

.001), a favorable Bishop score of 5 or higher (adjusted OR, 0.38; 95% CI, 0.14–0.98), and cervical shortening after sweeping (adjusted OR, 0.25; 95% CI, 0.09–0.74; P = .012) were independently predictive of spontaneous vaginal delivery. After factoring in the other covariables (postsweep cervical length, meconium-stained fluid, and labor induction separately) that were included in the multivariable logistic regression model for cesarean delivery as stated above, being parous and cervical shortening were still consistently predictive of spontaneous vaginal delivery (adjusted $P < .05$), but a favorable Bishop score was no longer significantly predictive with the more inclusive models comprising more covariables.

Cervical shortening on TVU after membrane sweeping was not associated with a decrease in labor induction. The Bishop score, presweep and postsweep cervical length, and recruitment-to-hospital admission interval were associated with labor induction on bivariate analysis. After adjustment, none of these variables were independently predictive of labor induction.

Table 1. Characteristics and Pregnancy Outcomes Stratified According to Cervical Shortening Versus No Cervical Shortening on Transvaginal Ultrasonography After Membrane Sweeping

Parameter	Cervical Shortening[a] (n = 53)[b]	No Cervical Shortening[a] (n = 107)[b]	Relative Risk (95% Confidence Interval)[c]	*P*
Characteristic				
Age, y	27.9 ± 4.0	27.8 ± 4.6		.88
Gravidity	2 [1.5]	2 [2]		.54
Parity	0 [1]	0 [2]		.44
Parous	23 (43.4)	52 (48.6)	0.86 (0.56–1.36)	.61
Gestation at recruitment, wk	40.3 [0.5]	40.3 [0.6]		.83
Bishop score (before sweeping)	5 [3.5]	5 [2]		.39
Bishop score ≥5	29 (54.7)	60 (56.1)	0.96 (0.62–1.50)	>.99
Presweep cervical length, mm	22.7 ± 10.5	20.1 ± 9.6		.13
Pregnancy outcome	n = 52[b]	n = 107[b]		
Recruitment-to-delivery interval, d	2 [5]	3 [5]		.73
Gestation at delivery (weeks)	40.9 ± 0.6	40.9 ± 0.5		.95
Induction of labor	15/52 (29.4)	36/107 (33.6)	0.86 (0.52–1.42)	.59
Oxytocin in labor	18/51 (25.3)	53/103 (51.5)	0.69 (0.45–1.04)	.062
Epidural analgesia in labor	11/51 (21.6)	27/107 (25.2)	0.85 (0.46–1.58)	.69
Meconium stained liquor	9/50 (18.0)	16/104 (15.4)	1.17 (0.56–2.46)	.82
Mode of delivery				.057
Spontaneous vaginal	45 (86.5)	74 (69.2)		
Instrumental vaginal	2 (3.8)	7 (6.5)		
Cesarean delivery	5 (9.6)	26 (24.3)	0.40 (0.16–0.97)	.033
Surgical delivery	7/52 (13.5)	33/107 (30.8)	0.44 (0.21–0.92)	.020
Indication for surgical delivery				.86
Nonreassuring fetal status	5 (71.4)	21 (63.6)		
Failure to progress	2 (28.6)	11 (33.3)		
Other	0 (0.0)	1 (3.0)		
Peridelivery blood loss, mL	300 [150]	300 [187.5]		.98
Postpartum hemorrhage (≥500 mL)	4/51 (7.8)	11/104 (10.6)	0.74 (0.25–2.22)	.78
Hospital stay, d	2 [1]	2 [1]		.11
Birth weight, kg	3.3 ± 0.4	3.2 ± 0.4		.61
Apgar score at 5 min	10 [0]	10 [0]		.55
Umbilical artery pH	7.27 [0.12]	7.30 [0.10]		.29
Umbilical artery pH ≤7.1	3/48 (6.3)[d]	4/103 (3.9)	1.61 (0.37–6.91)	.68

Data are mean ± SD, number (percent), and median [interquartile range]. Analysis was by a Student *t* test for normally distributed continuous data, Mann-Whitney *U* test for non-normally distributed data or ordinal data, and Fisher exact test for categorical data.

[a]Cervical shortening was determined by transvaginal ultrasonography for cervical length performed immediately before and after membrane sweeping.

[b]The denominator is shown where it is less than n because of unavailable data.

[c]The relative risk and 95% confidence interval are shown for 2 × 2 categorical data sets.

[d]One case of prelabor intrauterine death was excluded because the umbilical artery cord blood gas value was not obtained.

Discussion

The cervix appeared to lengthen slightly by 2.8 mm on average ($P < .001$, paired t test) when assessed by TVU immediately after membrane sweeping. However, shortening of the cervix was observed in 33% of participants.

We performed an online PubMed search on April 14, 2010, using the search terms *membrane sweeping* and *TVU* together without any limit: no item was found. The search terms *membrane sweeping* and *Bishop score* together retrieved 11 articles. None of the retrieved articles were primary studies on the predictive value of the Bishop score on the pregnancy outcome after membrane sweeping.

We had postulated that the cervix might shorten by 2 mm after membrane sweeping when calculating the sample size for this study. Our hypothesis that membrane sweeping might shorten the cervix came from the observation in a randomized trial that the cervix was more likely to be dilated when a Bishop score assessment was performed concurrently with membrane sweeping4 compared with participants assigned to no membrane sweeping.

As noted, cervical lengthening after membrane sweeping was contrary to our expectation. Membrane sweeping by its nature is physically disruptive to the cervix because the cervix is typically stretched during the process. It would appear that the stretching resulted in a perceptible increase in cervical dilatation on digital assessment[4] but was translated into minor lengthening of the cervix when assessed by TVU. A possible explanation is that the fetal head is pushed off the cervix during membrane sweeping, and this alleviated head compression on the cervix. Hence, the uncompressed cervix may appear to lengthen, countering any shortening that might occur as a consequent of the physical disruption of the cervix from sweeping. Cervical length changes were not associated with the Bishop score or presweep cervical length. The Bishop score and presweep cervical length are indirect indicators of accessibility of the internal os and membranes for efficient digital lifting of the membranes from the lower uterus. The inference is that a mechanically satisfactory sweep might not be a substantial mediator of cervical length changes.

Secondary analysis from a randomized trial of membrane sweeping at term to expedite labor onset at term showed that a more favorable Bishop score at membrane sweeping is independently predictive of spontaneous labor.[17] Our finding was similar with regard to the Bishop score versus labor induction for prolonged pregnancy, but after adjustment, the result was not significant.

Cervical length on TVU at 37 weeks is predictive of prolonged pregnancy and cesarean delivery indicated for

Table 2. Predictors of Cesarean Delivery at and After Membrane Sweeping

Characteristic	Cesarean Delivery (n = 31)[a]	Vaginal Delivery (n = 128)[a]	Relative Risk (95% Confidence Interval)[b]	*P*	Adjusted Odds Ratio (95% Confidence Interval)[c]	Adjusted *P*[c]
Age, y	26.6 ± 4.5	28.0 ± 4.3		.10	1.05 (0.92–1.18)	.48
Parity	0 [0]	1 [2]		<.001		
Parous	5 (16.1)	69 (53.9)	0.30 (0.13–0.68)	<.001	0.22 (0.06–0.82)	.024
Gestation at recruitment, wk	40.4 [0.6]	40.3 [0.5]		.43		
Presweep Bishop score	4 [4]	5 [3]		<.001		
Presweep Bishop score ≥5	8 (25.8)	80 (62.5)	0.41 (0.22–0.76)	<.001	0.43 (0.14–1.32)	.14
Presweep cervical length, mm	22.5 ± 9.5	20.6 ± 10.1		.35		
Postsweep cervical length, mm	26.8 ± 10.7	23.1 ± 10.9		.09	1.01 (0.96–1.07)	.66
Postsweep cervical shortening	5 (16.1)	47 (36.7)	0.44 (0.19–1.01)	.033	0.24 (0.06–0.90)	.034
Recruitment-to-hospital admission interval, d	4 [5]	2 [4]		.036	1.06 (0.90–1.24)	.49
Induction of labor	11 (35.5)	40 (31.3)	1.14 (0.66–1.95)	.67		
Oxytocin use in labor	20/29 (69.0)	51/125 (40.8)	1.69 (1.22–2.34)	.007	1.32 (0.43–4.05)	.63
Epidural analgesia in labor	14/30 (46.7)	24/128 (18.8)	2.49 (1.47–4.21)	.003	1.57 (0.53–4.65)	.41
Meconium-stained fluid	8/29 (27.6)	17/125 (13.6)	2.02 (0.97–4.24)	.091	2.13 (0.68–6.65)	.19
Birth weight, kg	3.2 ± 0.4	3.3 ± 0.4		.53		

Data are mean ± SD, number (percent), and median [interquartile range]. Analysis was by a Student *t* test for normally distributed continuous data, Mann-Whitney *U* test for non-normally distributed data or ordinal data, and Fisher exact test for categorical data. Multivariable logistic regression analysis was performed incorporating variables with $P \leq 0.1$ on bivariate analysis.

[a]The denominator is shown where it is less than n because of unavailable data.

[b]The relative risk and 95% confidence interval are shown for 2 × 2 categorical data sets.

[c]The adjusted odds ratio and adjusted *P* value are shown where the variable was included in the multivariable logistic regression model.

failure to progress.[18] Cervical length is also predictive of the onset of spontaneous labor in nulliparous women and successful vaginal delivery in both nulliparous and parous women with prolonged pregnancy.[19] Cervical length and cervical shortening after membrane sweeping were not significantly predictive of labor induction in our patients, who all had membrane sweeping, in contrast to the previous reports on the effect of the cervical length in women who did not have membrane sweeping. The Bishop score and cervical length on TVU were not independent predictors of cesarean delivery (Table 2).

We found that cervical shortening after sweeping was independently predictive of a reduction in all-cause cesarean and surgical deliveries. This finding was robust across a number of multivariable logistic regression analysis models controlling for various covariables. Labor induction compared with spontaneous labor is typically associated with higher cesarean and instrumental vaginal delivery rates.[9] The reduction in the cesarean delivery risk that we found in association with cervical shortening after membrane sweeping did not appear to be mediated by a decrease in labor induction.

Cervical shortening after membrane sweeping was not related to the Bishop score or initial cervical length, nor was labor induction associated with it. Cervical shortening was probably not an indicator of effective membrane sweeping either. These data suggested that cervical shortening after membrane sweeping was not a good initial indicator of the cascade of events leading to labor onset. However, cervical shortening was an independent predictor of vaginal delivery. We postulate that cervical shortening after membrane sweeping might be a dynamic demonstration of cervical pliability. A pliable cervix would be more likely to result in a vaginal birth when labor starts.

There were limitations and strengths to our study. We analyzed all-cause cesarean deliveries, and most were indicated by a nonreassuring fetal status. An analysis based on cesarean deliveries indicated by failed induction or failure to progress in labor would provide stronger support to our hypothesis that cervical shortening after sweeping is a dynamic measure of cervical pliability. With only 11 cesarean deliveries indicated by failure to progress, the number was too small for meaningful interpretation: 2 of 47 (4.1%) versus 9 of 60 (10%) ($P = .33$ for cervical shortening versus no-shortening groups, respectively, excluding all other cesarean deliveries from the analysis). However, the clinical decision to perform a cesarean delivery can be complex, and slow labor is often part of the equation in deciding that the situation is no longer reassuring and cesarean delivery is indicated. Our sample size calculation was based on cervical changes and not labor induction or the mode of delivery. The 95% CI (0.06–0.90) after adjustment for cervical shortening as a predictor of cesarean delivery was broad, and the upper limit was close to unity. A type 1 statistical error was possible. However, our data were strengthened by the fact that all cervical length measurements used were made by a blinded investigator who was randomly presented with saved image sequences, which minimized bias and provided consistency. Membrane sweeping and the Bishop score were performed by a single investigator, hence minimizing variability.

Because membrane sweeping is recommended before formal labor induction at term to facilitate the onset of labor,[11] TVU assessment for cervical shortening at the time of membrane sweeping may be a well-tolerated and useful tool for counseling women on their risk of cesarean delivery. When assessed by TVU, the cervix typically lengthens after membrane sweeping at late term. A shortened cervix is an independent predictor of vaginal delivery but not labor onset. Cervical shortening after membrane sweeping may be a dynamic demonstration of cervical pliability at subsequent labor. This finding needs to be confirmed.

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Coitus to expedite the onset of labour: a randomised trial

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Objective To evaluate the effect of suggesting coitus as a safe and effective means to expedite labour on pregnancy duration and requirement for labour induction.

Design A randomised trial.

Setting Antenatal clinic in a university hospital in Malaysia.

Population Women from 35 weeks of gestation with an uncomplicated singleton pregnancy.

Methods The advise-coitus arm was counselled that coitus at term is a safe, natural and effective means to initiate labour and to avoid labour induction. The control arm was told coitus was safe. Both arms were asked to record coital activity.

Main outcome measures Pregnancy duration and labour induction.

Results The intervention to delivery interval (mean ± SD) was 3.2 ± 1.4 versus 3.3 ± 1.3 weeks ($P = 0.417$), with a gestational age at delivery of 39.4 ± 1.2 versus 39.5 ± 1.2 weeks ($P = 0.112$), and with labour induction rates of 126/574 (22.0%) versus 120/576 (20.8%) ($P = 0.666$) for the advise-coitus and control arms, respectively, with no statistical difference between the groups. Coitus prior to delivery was more often reported in the advise-coitus arm compared with the control arm: 481/574 (85.3%) versus 458/576 (79.9%) (RR 1.5, 95% CI 1.1–2.0, $P = 0.019$). Also, the median (interquartile range) reported number of coital acts of 3 (2–5) versus 2 (1–4) ($P = 0.006$) was higher for the advise-coitus arm. Other pregnancy and neonatal outcomes did not differ between the groups.

Conclusions Labour onset and labour induction did not differ in the advise-coitus arm.

Keywords Coitus, induction of labour, onset of labour, randomised trial, sexual intercourse.

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Introduction

Sexual intercourse is commonly believed to hasten labour.[1] Semen contains prostaglandin E,[2] breast stimulation has been shown to hasten the onset of labour,[3] and coitus and orgasm stimulates uterine activity,[4] thereby underpinning the expectation that sexual activity at term may expedite labour.

In a prospective diary-based study from our centre, coitus at term in healthy women is associated with a shortened gestation and fewer labour inductions, and there is a direct correlation between the frequency of coitus and expedited onset of labour,[5] which provided the impetus for this trial.

A Cochrane review on sexual intercourse for cervical ripening and induction of labour identifies only a small trial with 28 women, from which no meaningful conclusions can be drawn.[6] A recent systematic review on the methods of labour induction published in 2011 cites only the same Cochrane review, demonstrating the sparse literature currently available concerning the relationship between sexual intercourse and induction of labour.[7]

The UK's National Institute of Clinical Excellence (NICE) antenatal care guideline states that 'pregnant woman should be informed that sexual intercourse in pregnancy is not known to be associated with any adverse outcomes',[8] reflecting the accumulated literature on the safety of coitus in pregnancy. However, 20–80% of pregnant women may have safety concerns about sexual intercourse during pregnancy.[5]

We postulate that couples can be reassured about the safety of coitus in late pregnancy and persuaded to engage in coitus as a natural method to initiate labour, so as to avoid labour induction or to hasten an anticipated birth. We

anticipate that promoting coitus as a means of expediting labour will be most effective in women who have been recently abstinent, as this population starts from a zero base. We performed a randomised trial to evaluate the effect of advising vaginal intercourse to expedite labour amongst pregnant women in late pregnancy on their pregnancy duration and need for labour induction.

Methods

Ethical approval for the trial was obtained from the University of Malaya Medical Centre Medical Ethics Committee (approval number 547.3, dated 16 August 2006). Written consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki by the World Medical Association on experimentation in human subjects. The trial was registered in a public trial registry (registration number ISRCTN 82333699) before the start of enrolment.

The charts of women attending the antenatal clinic in our hospital were reviewed by a research nurse to ascertain whether they fulfilled the inclusion criteria of gestation of 35–38 weeks, with a straightforward pregnancy (i.e. viable, singleton and cephalic presentation, with no placenta praevia, antepartum haemorrhage, ruptured membranes, previous caesarean section, hypertension, diabetes, significant medical history, fetal growth restriction, fetal anomalies or previous stillbirth). Women at 35–36 weeks of gestation were approached preferentially to give the maximal opportunity for coitus after enrolment. Women who fulfilled the criteria were approached and given an information leaflet about the study.

At the initial contact stage with potential participants, the study was presented as an activity study on coitus in late pregnancy to minimise any influence on control group behaviour. The potential participants were then asked about their coital activity in the last 6 weeks. Women who said they had been coitally active or who declined to answer were excluded. We also excluded women who said they did not have a current male partner or who had medical contraindication to coitus (e.g. human immunodeficiency or hepatitis-B positive – our antenatal population was universally screened).

The methodology and intervention for this trial is adapted from and closely mirrored that of an earlier trial performed at our centre on advising coitus in women scheduled for a non-urgent induction of labour.[9] We decided to proceed with this trial as the proposed study population and circumstances are widely divergent from those of the earlier trial,[9] and a prospective study of coitus from 36 weeks of gestation onwards, also carried out at our centre with a similar study population and circumstances, has shown a strong correlation between coitus and the onset of labour.[5] The groundwork and funding for this trial was in place before the non-significant result of the earlier trial was reported.

As 99% of the parturients at our centre are married,[10] and the use of condoms by married couples for the purpose of preventing sexually transmitted disease in those not already known to be infected is believed to be rare in our setting, we did not advise on or obtain any information on condom use in this trial.

Eligible women who were willing to participate then had a one-to-one session with a practicing medically qualified member of the research team, who obtained their written consent and randomly allocated them to the intervention or control groups. The counsellor was clearly identified to the women as a medical doctor. The counsellors involved in providing the intervention were trained on the intervention protocol, which is as described below.

During counselling, women assigned to the advise-coitus arm were told that vaginal intercourse at term can be used as a natural method to safely expedite labour, and may hence reduce the need for induction of labour. They were further told that frequent intercourse can be more effective. They were advised to start vaginal intercourse after 36 weeks of gestation. Women who wanted more information after the standard counselling were consistently informed that vaginal intercourse at term is a natural, safe and effective method for initiating labour. For women allocated to the control group, interaction after randomisation was kept as short as possible, with the impression given that the women were participating in a diary-based activity study of coitus. The controls were told that sexual intercourse is safe but its effect on labour was uncertain. To keep our approach to the control arm as neutral as possible, controls that wanted additional information were referred to the common information leaflet given to all participants. The allocation of women to the advise-coitus or control arms was not revealed to providers. There was no further intervention. All participants subsequently received standard obstetric care.

The randomisation sequence was in random blocks of eight or 12, with a 1:1 ratio, generated using a computerised random number generator (www.random.org) by N.S. and P.C.T. Numbered opaque envelopes were prepared containing the allocation to either advise-coitus or control groups, which were opened in sequence to effect randomisation. An additional information leaflet was given to participants allocated to advise-coitus. This leaflet reinforced the information given in the advice or counselling session. All participants were given a simple diary sheet, instructed to regularly update their vaginal intercourse diary by circling days where vaginal intercourse had occurred and to return the diary by hand to postnatal ward staff or to use the stamped addressed envelope after delivery.

Prelabour rupture of membranes (PROM) was defined as confirmed liquor amnii leakage, as evidenced by amniotic fluid trickling through the cervix at speculum examination, or the observation of amniotic fluid discharging from the introitus in the absence of uterine contractions at the time of first occurrence. In the event of PROM, women were given the option of immediate labour induction or to wait up to 24 hours for spontaneous labour as an inpatient. If required for PROM, labour induction was typically performed with oxytocin infusion or vaginal dinoprostone. Labour induction was also offered for prolonged but otherwise uncomplicated pregnancy at 41 weeks of gestation, with either vaginal dinoprostone if the cervix was unfavourable or amniotomy followed by oxytocin infusion when the cervix was favourable (typically for a Bishop score > 6). We defined induction of labour (IOL) as the application of these standard techniques to procure labour. The standard management for labour induction and intrapartum care in our institution has been described previously.[11]

Labour was deemed to be established when contractions were at least once every 4 minutes and the cervical dilation was at least 3 cm. Oxytocin given after established labour was considered to be for labour augmentation. The length of active labour was taken as the interval from the time of diagnosed established labour to the time of delivery.

The charts of participants were retrieved after their delivery for their hospitalisation, labour and delivery details to be extracted onto a standardised case report form. Women who did not submit their coital diaries after delivery or who delivered in other hospitals were contacted by telephone to obtain as much coitus and birth data as possible.

Primary outcomes were: (1) duration of pregnancy (as represented by gestational age at delivery and the interval between intervention and delivery); and (2) rate of induction of labour. Secondary outcomes included any non-birth related hospitalisation since randomisation, PROM, method of labour induction, indication for labour induction, length of labour, epidural analgesia use in labour, oxytocin augmentation, mode of delivery, indications for operative delivery, maternal hospital stay, Apgar score at 5 minutes, arterial cord blood pH, admission to the neonatal care unit and indication for neonatal admission.

Our sample size was calculated based on the following rationale: in an earlier report, 20/84 women (23.8%) who were abstinent from 36 weeks of gestation to birth required IOL for prolonged pregnancy, compared with 5/116 women (4.3%) who reported coitus during that time.[5] In abstinent women allocated to the control group, we assume a background 5% coitus rate before delivery and their IOL rate would thus be $[(0.238 \times 0.95) + (0.043 \times 0.05)] = 22.8\%$. We postulated that if one in three allocated to advise-coitus, could be persuaded towards coitus, then $[0.05 + (0.95 \times 0.333)] = 36.7\%$ would be coitally active, and their IOL rate would be $[(0.238 \times 0.633) + (0.043 \times 0.367)] = 16.6\%$. Applying IOL rates of 22.8 versus 16.6%, with $\alpha = 0.05$, a power of 0.8 and a 1:1 recruitment ratio, and applying the chi-square test, 649 women in each arm would be required. Factoring in a 20% drop-out rate, a total of 1623 women would be required for the study.

Our public hospital delivers about 5000 women per year, of which about 4675 (93.5%) would have attended for prior antenatal care as booked cases.[10] We expect 42% to be abstinent at 35–36 weeks of gestation.[5] Factoring in a 20% exclusion rate because of criteria infringement, we anticipated 1570 suitable women to be available for enrolment each year. Assuming a 70% enrolment pick-up rate, 1099 women per year could be recruited. The trial enrolment target of 1623 participants was achievable in 18 months. The study was funded for 12 months by an internal research grant from the University of Malaya. Because of a far slower rate of enrollment than anticipated, funding was secured for another 12 months. After this funding was exhausted (after 40 months of enrollment), we decided to perform an analysis of the data with 1200 women enrolled to determine if the trial should be continued. The funder played no role in the trial design, conduct, data analysis or drafting of the article.

Data were entered into SPSS 17 (SPSS Inc., Chicago, IL, USA) for data analysis. We excluded those mistakenly recruited who did not satisfy the inclusion criteria. Analysis was performed by intention to treat. For comparison of means and distribution of continuous data we used the Student t test, for ordinal data or non-normally distributed data we used the Mann–Whitney U test, for 2×2 categorical data sets we used Fisher's exact test and for categorical data sets larger than 2×2 we used the chi-square test. Tests were two sided and $P < 0.05$ in any test was considered to be statistically significant.

Results

Enrolment into the trial was from 28 March 2008 to 15 June 2011, and the last participant was discharged from hospital following admission for childbirth on 19 July 2011. The recruitment and in-trial flow chart is depicted in Figure 1. A total of 1200 women were enrolled onto the study, and 25 women were excluded because of study criteria infringements discovered after randomisation. Pregnancy outcomes were extracted from the women's charts, hospital central records or obtained through telephone contact if the woman did not deliver at our hospital. Pregnancy outcomes were unobtainable in another 25 women because they did not deliver at our hospital and could not be contacted by telephone. In a further 13 women, we could trace pregnancy outcomes from their charts but they did not return their coital diaries and they could not be further contacted by

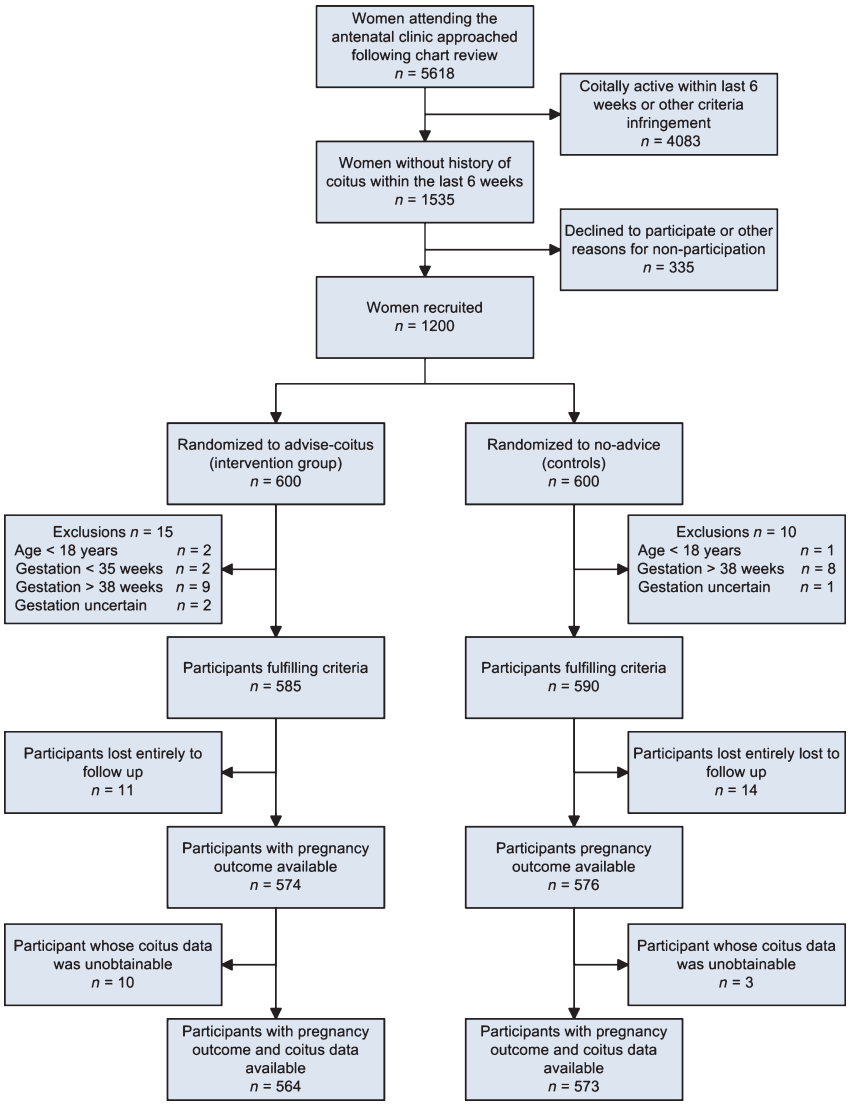

Figure 1. Recruitment flow chart into a randomised trial of promoting coitus in late pregnancy.

telephone to obtain their coitus data. Of the 1200 trial participants, 1086 (90.5%) went on to deliver at our hospital. Only 144/1200 (12.0%) of the participants returned their coitus diaries (four returned diaries contained no useful data); for the remainder, coitus data were obtained via telephone contact. However, post-hoc analysis showed that the proportion of women reporting 'any coitus' was similar in the returned diary and telephone contact groups: 80.7 versus 82.8% ($P = 0.552$).

The characteristics of participants analysed on an intention-to-treat basis ($n = 1175$) are shown in Table 1. There was no significant difference in any characteristic between the trial arms.

Primary outcomes of pregnancy duration and labour induction rate, as well as the data of main outcomes such as reported coitus, are displayed in Table 2. Pregnancy duration, as represented by the gestational age at delivery of 39.4 ± 1.2 versus 39.5 ± 1.2 weeks ($P = 0.112$), the intervention to delivery interval of 3.2 ± 1.4 versus 3.3 ± 1.3 weeks ($P = 0.417$) and the labour induction rates of 126/574 (22.0%) versus 120/576 (20.8%) (RR 1.1, 95% CI 0.8–1.4, $P = 0.666$) did not differ across the advise-coitus versus control trial arms.

Coitus 481/574 (85.3%) versus 458/576 (79.9%) (RR 1.5, 95% CI 1.1–2.0, $P = 0.019$) was more frequently reported and the coital frequency reported [median 3 (IQR 2–5) versus 2 (IQR 1–4), $P = 0.006$] was higher in the advise-coitus arm compared with the control arm. Although participants appeared to respond to the suggestion to use frequent coitus, presumably to expedite labour onset, there was no significant impact downstream on pregnancy duration or need for labour induction.

Table 1. Characteristics of trial participants, stratified according to treatment allocation (advise coitus or control).

	Advise coitus *n* = 585	Control *n* = 590
Age (years)	29.1 ± 3.9	28.9 ± 3.6
Ethnicity		
Malay	237 (40.5)	261 (44.2)
Chinese	178 (30.4)	187 (31.7)
Indian	141 (24.1)	118 (20.0)
Others	29 (5.0)	24 (4.1)
Gravidity	1 (1–2)	1 (1–2)
Parity	0 (0–1)	0 (0–1)
Nulliparous	350 (59.8)	364 (61.7)
Gestation at recruitment (weeks)	36.2 ± 0.8	36.2 ± 0.7

Data expressed as mean ± standard deviation, number (%) and median (interquartile range). Analyses by Student's *t* test for comparison of means for continuous data, Mann–Whitney *U* test for ordinal data, Fisher's exact test for 2 × 2 categorical data sets and chi-square test for larger than 2 × 2 categorical data sets. $P > 0.05$ for all analyses.

As labour typically followed shortly after PROM in a previous trial report on coitus in pregnancy from our centre,[5] PROM was considered as the onset of labour. Our protocol for uncomplicated PROM allowed patient choice of immediate labour induction or an inpatient wait of up to 24 hours for spontaneous labour before labour induction. Hence, the labour induction rate following PROM was dependent on this choice. If we took PROM to be the onset of labour, the spontaneous labour rates were 503/574 (87.6%) versus 497/576 (86.3%) (RR 1.1, 95% CI 0.8–1.6, $P = 0.278$) for the advise-coitus compared with the control arms, respectively, again with no statistical difference between the groups.

Table 3 shows the secondary outcome measures of the two trial arms. There was no significant difference in non-birth related hospitalisations after enrolment, interval between enrolment to admission for birth, rate of PROM, indication for labour induction, need for oxytocin augmentation of labour, length of active labour, mode of delivery, indication for caesarean delivery, hospital stay for delivery, postpartum blood loss, umbilical arterial cord pH, Apgar score at 5 minutes, birthweight, perinatal mortality rate or neonatal intensive care admission rate between the trial arms. The three cases that resulted in perinatal mortality all presented with intrauterine deaths and macerated stillbirths, without obvious external malformations. In one of these cases, the fetus was probably growth restricted, with a birthweight of 2.23 kg at 38 weeks of gestation, and herpes simplex IgM was only detected in the maternal serum at presentation for fetal death after routine investigation. In the other two cases, the intrauterine deaths remained unexplained after routine investigations. Autopsies were not performed, in accordance with parental requests. All three women reported coitus, and post-hoc analysis after categorisation into women that reported coitus versus women who reported abstinence showed no difference in perinatal mortality rate (3/939 [0.3%] versus 0/198 [0%], $P = 1.00$); in contrast, the neonatal unit admission rate of 10/938 (1.1%) versus 7/198 (3.5%) (RR 0.3, 95% CI 0.1–0.8, $P = 0.018$) was higher in abstinent women. The latter finding may be a 'false-positive' type-1 error. The similarity in occurrence rates of all the secondary outcomes within the trial and the *post hoc* analysis based on reported coitus on neonatal outcomes would suggest that coitus in late pregnancy is safe but ineffective in initiating labour.

Post hoc, we also compared the pregnancy duration and labour induction rate of the coitally active versus abstinent participants. Intervention to delivery interval was (mean ± SD) 3.3 ± 1.3 versus 3.2 ± 1.3 weeks ($P = 0.563$)

Table 2. Main outcomes after randomisation to advise-coitus or control groups.

	Advise coitus *n* = 574	Control *n* = 576	RR (95% CI)	*P*
Labour induction*	126 (22.0)	120 (20.8)	1.1 (0.8–1.4)	0.666
Gestational age at delivery (weeks)	39.4 ± 1.2	39.5 ± 1.2		0.112
Intervention to delivery interval (weeks)	3.2 ± 1.4	3.3 ± 1.3		0.417
Coitus reported**	481 (85.3)***	458 (79.9)***	1.5 (1.1–2.0)	0.019
Frequency of reported coital acts****	3 (2–5)***	2 (1–4)***		0.006

Data expressed as number (%), mean ± standard deviation or number (%) and median (interquartile range). Analysis is by Fisher's exact test for categorical data sets, Student's *t* test for continuous data and Mann–Whitney *U* test for ordinal data.
*Defined as the use of vaginal prostaglandin, amniotomy or oxytocin infusion to induce labour, regardless of indication.
**At least one coital act reported in the period between randomisation and delivery.
***Ten participants assigned to advise-coitus group ($n = 564$) and three participants assigned to control group ($n = 573$) did not submit a coital diary, and could not be contacted to obtain coital data, but pregnancy outcomes were obtained from clinical charts.
****Number of reported coital acts in the period between randomisation and delivery.

Table 3. Secondary outcomes of women randomised to advise-coitus or control groups.

Outcome	*n**	Intervention		RR (95% CI)	*P*
		Advise coitus *n* = 574	No advice *n* = 576		
Additional hospital admission before birth	1149	52 (9.1)	57 (9.9)	0.9 (0.6–1.3)	0.687
Interval from intervention to admission for birth (weeks)	1150	3.2 ± 1.3	3.2 ± 1.3		0.522
PROM	1150	94 (16.4)	80 (13.4)	1.2 (0.9–1.7)	0.250
Indications for induction of labour	245				0.118
PROM		64 (51.2)	50 (41.7)		
Non-reassuring fetal status		26 (20.8)	28 (23.3)		
Prolonged pregnancy		23 (18.4)	26 (21.7)		
Others		12 (9.6)	16 (13.3)		
Epidural analgesia	1150	141 (24.6)	130 (22.6)	1.1 (0.9–1.5)	0.455
Oxytocin augmentation	1150	152 (26.5)	148 (25.7)	1.0 (0.8–1.4)	0.788
Length of active labour (hours)	1024	4.9 ± 3.6	4.8 ± 3.6		0.762
Mode of delivery	115				0.482
Spontaneous vaginal	0	421 (73.3)	414		
Instrumental vaginal		52 (9.1)	(71.9)		
Caesarean section		101 (17.6)	46 (8.0)		
Indications for caesarean			116 (20.1)		0.050
Non-reassuring fetal status		36 (35.6)	57 (49.1)		
Failure to progress		27 (26.7)	34 (29.3)		
Failed induction		13 (12.9)	9 (7.8)		
Malpresentation		8 (7.9)	9 (7.8)		
Miscellaneous		16 (16.8)	7 (6.0)		
Timing of caesarean					
After spontaneous labour	57 (56.4)	61 (52.6)			0.814
After induced labour	37 (36.6)	45 (38.8)			
Planned electively	7 (6.9)	10 (8.6)			
Maternal hospital stay for delivery (days)	1149	1.9 ± 1.5	1.9 ± 2.5		0.743
Peridelivery blood loss	1065	316 ± 189	323 ± 207		0.532
Blood loss ≥1000 ml		6 (1.1)	11 (2.1)	0.5 (0.2–1.5)	0.232
Umbilical cord blood pH	102	7.28 ± 0.08	7.29 ± 0.09		0.274
pH ≤7.1	2	16 (3.1)	20 (4.0)	0.8 (0.4–1.5)	0.500
Apgar score at 5 minutes	1064	10 [10–10]	10[10–10]		0.405
Apgar <7 at 5 minutes		1 (0.2)	1 (0.2)	1.0 (0.1–16)	1.00
Birthweight (kg)	1149	3.12 ± 0.41	3.12 ± 0.41		0.941
Perinatal mortality	1150	1 (0.2)	2 (0.3)	0.5 (0.05–5.5)	1.00
Neonatal admission	1149	5 (0.9)	12 (2.1)	0.4 (0.1–1.2)	0.094
Indications for neonatal admission	17				
Observation		1	5		
Suspected meconium aspiration		0	4		
Low Apgar score		1	1		
Jaundice		2	1		
Lower limb deformity		0	1		
Congenital pneumonia		1	0		

Data expressed as number (%), mean ± standard deviation or median (interquartile range). Analysis by the Student's *t* test for means, Fisher's exact test for 2 × 2 categorical datasets, chi-square test for larger data sets or Mann–Whitney *U* test for ordinal data.
*$n < 1150$ because of incomplete data for some variables.

in the 939 participants who reported coitus compared with the 198 who were abstinent. Labour induction rates were 195/939 (20.8%) versus 49/198 (24.7%) (RR 0.8, 95% CI 0.6–1.1, $P = 0.217$. Women in the trial whose labour was induced reported fewer episodes of coitus, median [IQR] 2 [1–4] versus 3 [1–5] [$P = 0.03$]). We then performed a multivariable logistic regression analysis to evaluate the risk factors for labour induction, incorporating frequency of reported coitus,

recruitment to delivery interval, ethnicity, premature rupture of membranes and nulliparity into the model (these variables had $P < 0.1$ on bivariate analyses against labour induction). After adjustment, the frequency of reported coitus (as a continuous variable) was not independently associated with labour induction (AOR 0.94, 95% CI 0.87–1.02, $P = 0.11$). With these findings, and also taking into account the primary outcome results, as shown in Table 2, we concluded that it would be futile to continue with the trial.

Discussion

We observed a significant difference in reported coital activity in the advise-coitus group compared with the control group of 85.3 versus 79.9% (RR 1.5, 95% CI 1.1–2.0, $P = 0.019$). This effect is consistent with the results of a previous trial that investigated advising coitus to women scheduled for a non-urgent labour induction, which reported rates of coitus of 60.2 versus 39.6% (RR 1.5, 95% CI 1.1–2.0, $P = 0.004$) in the advised-coitus versus control arms, respectively.[9] The frequency of reported coital activity was also higher in the advise-coitus group in the current trial. These findings demonstrate that coital activity at term can be influenced by medical advice. However, despite the increase in reported coitus, there was no observed impact on the onset of labour or the labour induction rate in our current trial or in the earlier trial.[9] This lack of correlation between reported coitus and downstream outcome of labour onset is also reported by a prospective study.[12]

We specifically targeted women who were recently abstinent from coitus in the anticipation that any advice promoting coitus would have the greatest impact within this group of women as they started from a zero base in coital activity, and that abstinent controls would largely continue to be abstinent by inclination. Our sample size calculation was modelled on anticipated coitus rates of 36.7 and 5.0% for advise-coitus and control arms, respectively. The observed reported coitus rates were far higher in both groups (85.3 and 79.9%), and the difference between the groups was far smaller than postulated – this difference of just 5.4% would have diminished the impact of the trial intervention on downstream primary outcomes of pregnancy duration and labour induction rate. However, *post hoc* analysis comparing women who reported coitus with those who reported abstinence did not reveal any major differences in pregnancy duration or labour induction rate between these groups.

Sexual activity including vaginal sex towards the end of pregnancy is reported by 62% in the third trimester, 40% in the 2 weeks before labour and 17% in the 2 days before labour.[13] In a recent survey, over half of the postpartum women reported self-application of non-prescribed methods of inducing labour, which included sexual intercourse and nipple stimulation,[14] revealing a huge underlying demand to shorten pregnancy. The relatively high (85.3%) reported coitus rate in our advise-coitus arm could result from our underestimation of the inherent demand to shorten pregnancy and the willingness to apply a medically sanctioned method, which was presented as safe, effective and natural. We postulate that the also high (79.9%) reported coitus rate in the control arm might be because of an increased awareness of coitus from trial participation, allayed safety concerns, as we stressed that coitus was safe, even in the control arm, and hence reinforcement of the folk belief that coitus can initiate labour.[1] As the interval between trial recruitment and admission for birth was more than 3 weeks on average, it was also possible that the positive reinforcement for coitus given to the advise-coitus arm might also have percolated through to the control arm via social interaction across the trial arms, as we did not forbid such discussions.

Although human ejaculate weakens chorioamniotic membranes,[15] the association of sexual intercourse in late pregnancy and PROM is not consistently reported.[16–18] Our study showed no significant difference in PROM (16.4 versus 13.4%; $P = 0.25$) between the groups, similar to a previous trial report,[9] and consistent with another study that concluded that there were no sexual positioning or sexual activities that were significantly related to PROM.[19]

In our present study, there was no significant difference in length of labour, need of oxytocin, mode of delivery, postpartum haemorrhage, Apgar score at 5 minutes, cord arterial blood pH, admission to neonatal unit and perinatal mortality across the trial arms. These findings suggest that coitus at term is safe and is entirely in keeping with prior reports that coitus is not associated with adverse pregnancy outcome.[20,21]

There are strengths and limitations in our trial. Our enrolment was in excess of a thousand participants, and the results of analyses, including post-hoc analyses, were consistent across the full range of outcomes. Hence our finding that suggesting coitus to initiate labour is ineffective is likely to be robust. The promotion and control sessions were conducted by a few medically qualified members of the investigating team. Although these individuals were instructed and trained, an identical delivery of the intervention in an interactive environment was improbable. However, participants were randomised and using several doctor-counsellors should provide a robust test of the intervention's effectiveness. Although we did not document the presence of the male partner during the counselling sessions, the male partner was usually absent, which is not ideal, as coitus is an activity for the couple together. However, the high reported coitus rates from our data would imply that in our population, the absence of the male partner in the counselling session is not a major impediment to the uptake of advice in favour of coitus. We had a major problem with the return of the coitus diaries. Only 12% of

the responses that we eventually obtained on coital activity were from diary return, the remainder were oral reports taken over the telephone, after the event, and were restricted to participants' recollection of the number of coital acts in the period between trial enrolment and delivery. This delayed recall might have affected results, but women who recalled their sexual activity during pregnancy would typically report fewer episodes of intercourse.[22] Moreover, there was not a significant difference in reported coitus between the diary return and telephone contact groups.

We believe our findings are generalisable as coitus is widely believed to expedite labour,[1] and many women apply this method on their own accord.[14]

Conclusion

Suggesting coitus during late pregnancy to expedite labour is not effective in achieving an earlier onset of labour or in reducing the rate of labour induction.

Disclosure of interests

There is no conflict of interest to declare by any author.

Contribution to authorship

PCT and NS conceived the study. NS planned the study. NSO, ESY and one other performed the intervention. NSO collected and entered the data, assisted by ESY. PCT and NSO performed the data analysis and drafted the article. SZO supervised the entire process. All authors were involved in the critical refinement of the article. All authors approved the final version.

Details of ethics approval

Ethical approval for the trial was obtained from the University of Malaya Medical Centre Medical Ethics Committee (approval number 547.3, dated 16 August 2006). The trial was registered in a public trial registry (registration number ISRCTN 82333699) before the start of enrolment.

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Immediate Compared With Delayed Oxytocin After Amniotomy Labor Induction in Parous Women

A Randomized Controlled Trial

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OBJECTIVE: To compare immediate with delayed (4 hours) oxytocin infusion after amniotomy on vaginal delivery within 12 hours and patient satisfaction with the birth process.

METHODS: Parous women with favorable cervixes after amniotomy for labor induction were randomized to immediate titrated oxytocin or placebo intravenous infusion in a double-blind noninferiority trial. After 4 hours, study infusions were stopped, the women were assessed, and open-label oxytocin was started if required. Maternal satisfaction with the birth process was assessed with a 10-point visual numerical rating scale (lower score, greater satisfaction).

RESULTS: Vaginal delivery rates at 12 hours were 91 of 96 (94.8%) compared with 91 of 94 (96.8%) (relative risk 0.98, 95% confidence interval [CI] 0.92–1.04, P=.72), and maternal satisfaction on a visual numerical rating scale (median [interquartile range]) was 3 [3–4] compared with 3 [3–5], P=.36 for immediate compared with delayed arm, respectively). Cesarean delivery, maternal fever, postpartum hemorrhage, uterine hyperactivity, and adverse neonatal outcome rates were similar between arms. The immediate oxytocin arm had a shorter amniotomy-to-delivery interval of 5.3±3.1 compared with 6.9±2.9 hours (P<.001) and lower epidural analgesia rate of 2.9% compared with 9.9% (relative risk 0.3, 95% CI 0.1–1.0, P=.046), but fetal heart rate abnormalities on cardiotocogram were higher, 28.6% compared with 16.8% (relative risk 1.7 95% CI 1.0–2.9, P=.048). In the delayed arm, oxytocin infusion was avoided by 35.6%.

CONCLUSIONS: Immediate or delayed oxytocin infusions are reasonable options after amniotomy for labor induction in parous women with favorable cervixes. The choice should take into account local resources and the woman's wish.

CLINICAL TRIAL REGISTRATION: ISRCTN Register, http://isrctn.org, ISRCTN51476259.

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LEVEL OF EVIDENCE: I

In contemporary practice within a well-resourced setting, approximately 20% of viable pregnancies have their labor induced.[1] Compared with spontaneous labor, labor induction is associated with a higher rate of cesarean delivery of 11.4% compared with 22.0%[1] attributable predominantly to an unfavorable Bishop's score at admission.[2]

Labor occurs within 24 hours of amniotomy for labor induction in 90.1% of women.[3] However, a Cochrane review concludes that data are lacking about the value of amniotomy alone for induction of labor, but there remain clinical scenarios in which amniotomy alone may be desirable and appropriate and this method is worthy of further research.[4] Another Cochrane review states that amniotomy and oxytocin infusion can induce labor, but the optimal timing of oxytocin infusion after amniotomy is not known.[5] Antepartum use of oxytocin in nulliparas is associated with severe maternal and neonatal morbidity.[6] Oxytocin use increases the risk of uterine hyperactivity[7] and neonatal jaundice[8]; trading slight prolongation of induction to delivery interval for fewer complications by reducing oxytocin use can be a prudent strategy.[9]

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Increased parity and a favorable cervix as assessed by a higher Bishop's score are associated with successful labor induction.[10,11] We hypothesize that in parous women with favorable cervixes, after amniotomy for labor induction, a 4-hour period to await labor may reduce antepartum oxytocin use and oxytocin-related adverse events without affecting the proportion of women delivered within 12 hours of amniotomy or their satisfaction with the birth process. We performed a double-blind randomized trial to test our hypothesis.

PATIENTS AND METHODS

The trial was performed in a full-service university hospital with an annual delivery rate of approximately 6,000 women in Kuala Lumpur, Malaysia. Ethical oversight was provided by the University of Malaya Medical Centre medical ethics committee (Approval Reference No. 733.18, dated July 22, 2009). The trial was conducted in accordance with the Declaration of Helsinki (2000) for human studies. Written informed consent was obtained from each participant. The trial was registered with the ISRCTN trial register with the identifier ISRCTN 51476259 before its commencement.

Previous trials have shown that in subanalyses confined to parous women, immediate oxytocin after amniotomy was associated with a 93%[12] and a 1-hour delay associated with a 95%[13] delivery rate within 12 hours. Taking a 12-hour vaginal delivery rate of 95% for immediate oxytocin and assuming a noninferiority margin of 10% for the 4-hour delay arm, one-to-one ratio, α of 0.05 and power of 90%, and factoring in a dropout of 20%, a total of 205 women were needed.

Primary outcomes were vaginal delivery rate within 12 hours of induction and maternal satisfaction score for the birth process obtained within 24 hours of delivery. Participants were asked within 12 hours of delivery and after their transfer to the postnatal ward to score on a visual numerical rating scale of 1 (denoted as most satisfied) to 10 (denoted as most dissatisfied), their rating of their birth process. Secondary outcomes were amniotomy-to-delivery interval, mode of delivery, opiate or epidural analgesia use in labor, prenatal oxytocin use, uterine hyperactivity, intrapartum and postpartum fever (temperature 38°C or greater), delivery blood loss, maternal antibiotic use, amniotomy-to-hospital discharge interval, and various neonatal outcomes (special care nursery admission, umbilical cord blood pH and base excess, Apgar score, phototherapy for jaundice, and intensive care admission).

The randomization sequence was generated using a computerized random number generator in blocks of 40 by an investigator (P.C.T.). Allocation to treatment arms of immediate or delayed oxytocin was affected by the sequential opening of sealed numbered envelopes.

Potential recruits for the trial were identified by health care providers in our delivery suite when they were admitted for labor induction. Inclusion criteria were parous women (at least one vaginal birth at greater than 24 weeks of gestation), age 16 years or older, singleton pregnancy in cephalic presentation, gestation 37 weeks or greater, Bishop's score 6 or greater with cervical dilation 2 or greater (suitable for amniotomy), intact membranes, and a reassuring cardiotocogram. Gestational age estimations were all supported by ultrasonographic dating. Exclusion criteria were previous uterine incision or injury (cesarean delivery, myomectomy, or perforation), gross fetal anomaly, and contraindication for vaginal birth. Potential recruits were given the patient information sheet to read and, if agreeable, consented and randomized after their amniotomy. In our center, the standard labor induction technique for women with favorable cervixes was amniotomy followed by immediate oxytocin infusion or a period of up to 4 hours to await labor onset before starting oxytocin infusion as required depending on the health care provider.

The study drug was prepared by a research assistant who was not involved in the subsequent care of the participant. For women assigned to immediate oxytocin infusion, 10 units of oxytocin were added to a standard container of 500 mL Hartmann's solution (oxytocin concentration of 20 milliunits/mL) and the container labeled as "study drug." For women assigned to delayed oxytocin, an identical container of 500 mL placebo Hartmann's solution was labeled as "study drug."

For both arms, study drug infusion was started as soon as possible after amniotomy and randomization, started at a rate of 3 mL/h (ie, 1 milliunit/min for the immediate oxytocin arm). The infusion rate was doubled every 30 minutes to a maximum of 48 mL/h (ie, 16 milliunits/min for the oxytocin arm) or until three to four moderate contractions per 10 minutes were achieved at which point the infusion rate was maintained. Continuous electronic fetal heart rate monitoring was maintained throughout the induction and labor.

After 4 hours, infusion of the study drug was stopped for both arms. In the interim, vaginal assessment was performed if clinically indicated (typically for symptom or sign of second stage or in response to nonreassuring cardiotocogram). If the woman was still undelivered at 4 hours, vaginal examination was performed to assess cervical dilation

and to determine whether labor was in the active phase (defined as cervical dilation 4 cm or greater and contraction frequency three or more per 10 minutes). In the event of a nonreassuring cardiotocogram associated with uterine hyperactivity, the following actions were suggested: reduce or stop study drug infusion, administer subcutaneous 250 micrograms terbutaline as tocolysis, or expedite operative delivery depending on individual circumstances and the severity of the cardiotocogram abnormality.

At the 4-hour postamniotomy assessment, if labor was not in the active phase, open-label oxytocin infusion was started at 2 milliunits/min and infusion titrated according to our local protocol (infusion rate doubled every 30 minutes as needed to achieve contraction frequency of three to four per 10 minutes or to a maximum infusion rate of 32 milliunits/min). If labor was already in the active phase, the decision was left to the health care provider whether to continue with open-label oxytocin infusion starting at 2 milliunits/min and the rate infusion titrated further according to contraction frequency and labor progress. It has been shown that stopping oxytocin infusion after labor is already in the active phase is not associated with a significantly longer duration of the active phase and the second stage of labor.[14]

Standard management of labor induction and labor was applied for all participants as previously described for our center[15]; vaginal assessment was performed at least 4 hourly and the decision for cesarean and instrumental vaginal delivery was made based on the usual obstetric indications.

Participants' characteristics and outcomes were extracted onto a standardized case report form. Case notes and hospital records were scrutinized after delivery to retrieve relevant clinical outcome data. Participants were followed up until hospital discharge.

The cardiotocogram was assessed after delivery by an investigator (M.Z.S.) based on the following criteria for classification as fetal heart rate abnormality: fetal heart rate deceleration (greater than 15 beats per minute [bpm] below baseline for greater than 15 seconds), sustained tachycardia (greater than 160 bpm for more than 15 minutes), baseline bradycardia (less than 100 bpm for more than 15 minutes), or reduced baseline variability (less than 3 bpm for more than 15 minutes) and the following criteria for uterine hyperactivity: tachysystole (six of more contractions in 10 minutes over two consecutive 10-minute periods) or hypertonus (sustained contraction 2 minutes or longer).

Data were entered into SPSS 17. Analysis was based on intention to treat. The Kolmogorov-Smirnov test was used to check for normality of data distribution. Normally distributed continuous data were analyzed with the Student's t test. Two-by-two categorical data sets were analyzed with the Fisher's exact test and larger categorical data sets with the χ^2; ordinal data and non-normally distributed continuous data were analyzed with the Mann-Whitney U test. Time to vaginal delivery analysis was performed with the Mantel-Cox log rank test[16,17] after censoring for cesarean delivery. All tests were two-sided and $P<.05$ was considered significant.

RESULTS

The trial enrollment period was from February 5, 2010, to May 25, 2012. The latest hospital discharge of a participant or neonate was on May 30, 2012. Trial recruitment was stopped after targeted sample size was achieved. The trial recruitment flow is as shown in Figure 1. Study drug infusion was started for all participants as allocated. There were no withdrawals or dropouts.

Table 1 shows the characteristics of the participants stratified according to their randomization to either immediate or delayed oxytocin arms. There was no significant difference in the participants' basic characteristics, indication for labor induction, presence of meconium at amniotomy, and in their amniotomy-to-commencement-of-study-drug infusion time interval across the trial arms.

Table 2 shows the result for the two primary outcomes. The vaginal delivery rate within 12 hours of amniotomy (after excluding a total of 16 cesarean deliveries) was 91 of 96 (94.8%) compared with 91 of 94 (96.8%) (relative risk 0.98, 95% confidence interval [CI] 0.92–1.04, $P=.72$) and the medians (interquartile ranges) scores for satisfaction with the birth process were 3 (3–4) compared with 3 (3–5) ($P=.36$) for the immediate compared with 4-hour delay arms,

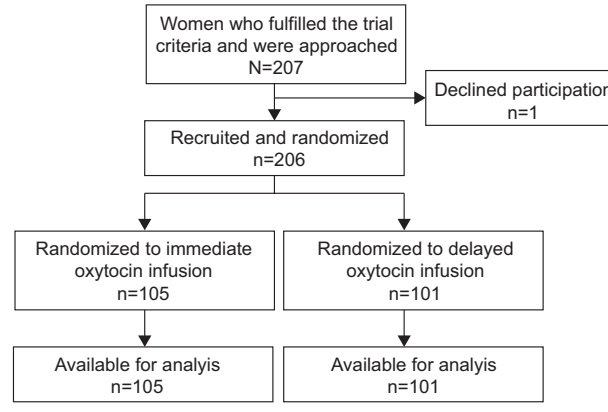

Fig. 1. Trial recruitment.

Tan. Immediate Compared With Delayed Oxytocin After Amniotomy. Obstet Gynecol 2013.

Table 1. Characteristics of Trial Participants According to Randomization to Immediate or Delayed (for 4 Hours) Oxytocin Infusion After Amniotomy for Labor Induction in Parous Women With Favorable Cervixes

Characteristic	Immediate (n=105)	Delayed (n=101)	*P*
Age (y)	32.3±4.4	31.7±4.9	.34
Gestation (wk)	39.5±1.2	39.4±1.3	.81
Parity	2 (1–3)	1 (1–2)	.20
Gravidity	3 (2–4.5)	3 (2–4)	.09
Bishop's score	7 (6–8)	7 (6–8)	.47
Ethnicity			.78
Malay	77 (73.3)	69 (68.3)	
Indian	13 (12.9)	13 (12.4)	
Chinese	10 (9.5)	11 (10.9)	
Other	5 (4.8)	8 (7.9)	
Indication for labor induction			.47
Diabetes in pregnancy	31 (29.5)	33 (32.7)	
Nonreassuring fetal status*	25 (23.8)	29 (28.7)	
Hypertension in pregnancy	19 (18.1)	14 (13.9)	
Prolonged pregnancy	14 (13.3)	17 (16.8)	
Miscellaneous†	16 (15.2)	8 (7.9)	
Meconium stained liquor at amniotomy	4 (3.8)	2 (2.0)	.68
Amniotomy to start of study drug infusion (min)	28±24	29±22	.89

Data are mean±standard deviation, median (nterquartile range), or n (%) unless otherwise specified.

Analysis performed using Student *t* test for continuous variables, Mann-Whitney *U* test for ordinal data, Fisher's exact test for 2×2 categorical data sets, and χ^2 test for larger than 2×2 categorical data sets. All statistical tests are two-sided.

* Growth restriction, oligohydramnios, reduced fetal movement, or nonreassuring antenatal cardiotocograph.

† Poor obstetric history, leukorrhea, indeterminate antepartum hemorrhage, previous shoulder dystocia, unstable lie, maternal personal factors.

respectively. Delayed oxytocin infusion was noninferior to immediate oxytocin on the primary outcomes.

Figure 2 depicts the curves for vaginal delivery rate over time for both trial arms (Mantel-Cox test *P*=.01, cesarean delivery censored) with a shorter amniotomy to vaginal delivery interval for the immediate oxytocin arm (mean±standard deviation amniotomy to delivery 5.3±3.1 compared with 6.9±2.9 hours, *P*<.001), but by 10 hours after amniotomy, vaginal delivery rates had converged at approximately the 90% mark.

Table 3 shows the result for secondary outcomes. Immediate oxytocin infusion compared with delayed oxytocin was associated with a shorter amniotomy to vaginal delivery interval, delivery before planned review at 4 hours and delivery by 6 hours, labor proceeding to the active phase by 4 hours, and requirement for epidural analgesia (number to treat needed to benefit of 17, 95% CI 8–285). Delayed oxytocin was associated with a lower incidence of fetal heart rate anomalies on cardiotocogram (number to treat needed to benefit of nine, 95% CI 4–232), particularly in the first 4 hours after amniotomy, but no decrease in the incidence of uterine hyperactivity. Cesarean delivery rate, opiate analgesia use, maternal fever and antibiotic use, postpartum blood loss, manual removal of placenta rate, amniotomy to hospital discharge interval, and neonatal outcomes (Apgar score at 5 minutes, umbilical cord arterial blood parameters, antibiotic use, phototherapy for jaundice, intensive care unit admission) were similar across the trial arms. Of the women allocated to delayed oxytocin, 35.6% avoided oxytocin infusion altogether because amniotomy alone was sufficient to induce labor and achieve delivery. Terbutaline was not used because there was no case of uterine hyperstimulation syndrome (concomitant uterine hyperactivity and fetal heart rate abnormality). There were no important unintended harmful events in either arm.

DISCUSSION

Only a small number of labor induction trials addressing the timing of starting oxytocin infusion after amniotomy have been performed.[12,13,18] In our

Table 2. Primary Outcomes of Randomized Trial of Immediate or Delayed (for 4 Hours) Oxytocin Infusion After Amniotomy for Labor Induction in Parous Women With Favorable Cervixes

	Immediate (n=105)	Delayed (n=101)	*P*	RR (95% CI)
Satisfaction with birth process*	3 (3–4)	3 (3–5)	.36	
Vaginal delivery within 12 h of amniotomy	91/96 (94.8)†	91/94 (96.8)†	.72	0.98 (0.92–1.04)

RR, relative risk; CI, confidence interval.

Data are median (interquartile range) or n/N (%) unless otherwise specified.

Analysis performed using Mann-Whitney *U* test for ordinal data and Fisher's exact test for 2×2 categorical data set. All statistical tests are two-sided.

* Satisfaction with the birth process is assessed using a 10-point (1–10) visual numerical rating scale at 24 hours after birth; low score indicates higher satisfaction.

† Nine women allocated to immediate oxytocin and seven women assigned to delayed oxytocin infusion were delivered by cesarean and were excluded from the analyses.

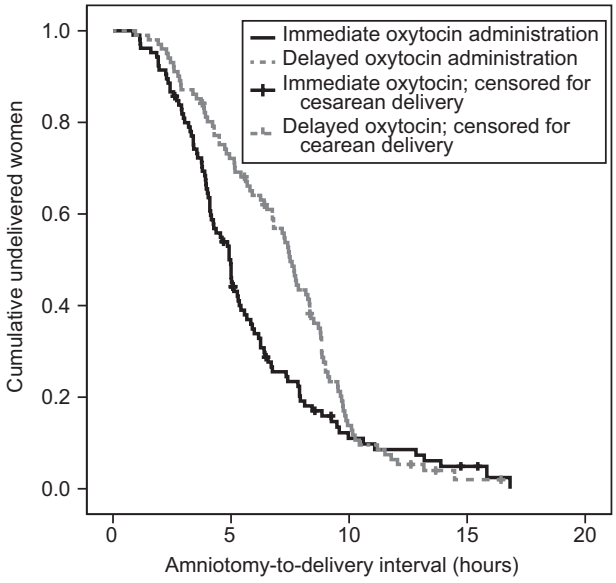

Fig. 2. Time-to-delivery analysis.

Tan. Immediate Compared With Delayed Oxytocin After Amniotomy. Obstet Gynecol 2013.

trial of parous women with favorable cervixes, a 4-hour delay compared with immediate oxytocin infusion was associated with a similar vaginal delivery rate at 12 hours after amniotomy and maternal satisfaction with the birth process. In contrast, in an early study of a mixed population of nulliparous and parous women, immediate compared with delayed (24 hours) oxytocin infusion after amniotomy for labor induction results in a vaginal delivery rate at 12 hours of 85.5% compared with 35.5% in favor of the immediate oxytocin arm[12]; however, the bulk of the deficit in the 12-hour delivery rate was contributed to by nulliparous women.

Although the amniotomy-to-delivery latency was shorter in the immediate oxytocin arm and the epidural rate was also lower in our current trial, maternal satisfaction score with the birth process was not affected. Maternal satisfaction was unaffected probably because the mean increase in the amniotomy-to-delivery interval was only 1.6 hours (mean 5.6 compared with 6.9 hours; Table 3). This time gap probably comprised a fairly comfortable latency with limited uterine activity because by 4 hours, the deficit in the active phase of labor rate was 36.7% (71.4% compared with 34.7%; Table 3) in favor of the immediate oxytocin arm. We did not record the amniotomy-to-labor interval in our trial. An earlier study reported a latency to labor difference of 2 hours (mean 2.25 compared with 4.25 hours) between the early (1-hour delay) oxytocin compared with delayed (up to 24 hours) infusion arms of a mixed study population of nulliparous and parous women after amniotomy for labor induction in favor of early oxytocin infusion.[13] An earlier labor induction trial at our center of concurrent dinoprostone and oxytocin infusion compared with dinoprostone in nulliparas with unfavorable cervixes showed greater maternal satisfaction with the birth process despite a higher pain score, increased analgesia use rate, and only a trend toward higher vaginal delivery rate at 24 hours for the concurrent therapy arm[19] suggesting that maternal satisfaction in labor induction is a complex outcome as was also shown in our current trial.

Early oxytocin infusion after amniotomy for labor induction in nulliparous women resulted in greater maternal satisfaction, a shorter amniotomy-to-delivery interval, and a better 12-hour vaginal delivery rate (of 77.1% compared with 58.1%).[18] In our population of parous women who were more rapidly responsive to amniotomy, a shorter amniotomy-to-delivery interval but with convergent 90% vaginal delivery rates by 10 hours after amniotomy, immediate oxytocin infusion did not affect maternal satisfaction score. Selo-Ojeme et al[18] report a borderline result for increased cardiotocogram abnormality for their immediate oxytocin arm (39.3% compared with 29%, relative risk 1.5, 95% CI 0.8–1.7, P=.07) and no increase in uterine hyperactivity. We found a significant increase in minor cardiotocogram abnormalities (predominantly early fetal heart rate decelerations), which did not translate into increased operative delivery rate or adverse neonatal outcome and similarly no increase in uterine hyperactivity. Selo-Ojeme et al did not find a difference in epidural analgesia rates, although their rates were high (52.4% compared with 54.8%) as would be expected for their exclusively nulliparous study population compared with rates of 2.9% compared with 9.9% in our population of parous women (which was significantly different in favor of immediate oxytocin).

We did not find a significant association between immediate and delayed oxytocin on phototherapy for neonatal jaundice: 9.6% compared with 5.0% (P=.28, relative risk 1.9, 95% CI 0.7–5.4). Previous studies have shown that the relationship between intrapartum oxytocin exposure and subsequent neonatal jaundice is tempered by consideration of gestational age,[20] use of dextrose solution as a diluent, and neonatal hyponatremia.[21] In our trial, gestational age between the arms was similar and we only used Hartmann's solution as a diluent.

Our trial has strengths and limitations. Amniotomy alone and a delay in oxytocin infusion would have the best chance of producing a good outcome in

Table 3. Secondary Outcomes of Randomized Trial of Immediate or Delayed (for 4 Hours) Oxytocin Infusion After Amniotomy for Labor Induction in Parous Women With Favorable Cervixes

	Immediate (n=105)	Delayed (n=101)	*P*	RR (95% CI)
Amniotomy to vaginal delivery interval (h)*	5.3±3.1	6.9±2.9	<.001	
Delivered before planned review at 4 h after amniotomy	46 (43.8)	24 (23.8)	.003	1.8 (1.2–2.8)
Delivered by 6 h after amniotomy	72 (68.6)	38 (37.6)	<.001	1.8 (1.4–2.4)
Mode of delivery			.91	
Spontaneous vaginal	94 (89.5)	92 (91.1)		
Instrumental vaginal	2 (1.9)	2 (2.0)		
Cesarean	9 (8.6)	7 (6.9)	.80	1.2 (0.5–3.2)
Indication for operative delivery			>.99	
Nonreassuring fetal status	8/11 (72.7)	6/9 (66.7)		
Failure to progress	3/11 (27.3)	3/9 (33.3)		
Epidural analgesia in labor	3 (2.9)	10 (9.9)	.046	0.3 (0.1–1.0)
Opiate analgesia in labor	61 (58.1)	51 (50.5)	.33	1.2 (0.9–1.5)
Oxytocin use in induction or labor	105 (100)	65 (64.4)	<.001	1.5 (1.3–1.8)
Oxytocin use: open-label	23 (21.9)	65 (64.4)	<.001	0.3 (0.2–0.5)
Maternal fever (38°C or greater) in labor	0 (0)	0 (0)	†	†
Maternal fever (38°C or greater) after delivery	1 (1.0)	0 (0)	1.00	†
Blood loss 500 mL or greater	5 (4.8)	4 (4.0)	1.00	1.2 (0.3–4.4)
Amniotomy to discharge interval (d)	1.5±1.1	1.5±1.3	.93	
Maternal antibiotic use	13 (12.4)	10 (9.9)	.66	1.3 (0.6–2.7)
Apgar score at 5 min	10 (10–10)	10 (10–10)	.14	
Apgar score lower than 7 at 5 min	1 (1.0)	0 (0)	1.00	†
Umbilical artery cord pH‡	7.31±0.07	7.31±0.08	.31	
Umbilical artery pH 7.1 or less‡	0 (0)	3 (3.1)	.11	†
Umbilical artery base deficit (mmol/L)‡	4.5±2.7	4.6±2.8	.83	
Base deficit 8 mmol/L or greater‡	12 (11.5)	11 (11.2)	1.00	1.0 (0.5–2.3)
Phototherapy for neonatal jaundice	10 (9.6)	5 (5.0)	.28	1.9 (0.7–5.4)
Neonatal intensive care admission	1 (1.0)	0 (0)	1.00	†
Neonatal antibiotics	0 (0)	0 (0)	†	†
Birth weight (kg)	3.2±0.4	3.1±0.4	.09	
Manual removal of placenta	3 (2.9)	0 (0)	.25	†
Active phase of labor§ by 4 h after amniotomy	75 (71.4)	35 (34.7)	<.001	2.1 (1.5–2.8)
Uterine hyperactivity‖ up to 4 h after amniotomy	2 (1.9)	1 (1.0)	1.00	1.9 (0.2–21)
Uterine hyperactivity‖ during entire labor	3 (2.9)	1 (1.0)	.62	2.9 (0.3–27)
Fetal heart rate anomaly on cardiotocograph¶ up to 4 h after amniotomy	15 (14.3)	2 (2.0)	.002	7.2 (1.7–31)
Fetal heart rate anomaly on cardiotocograph¶ during entire labor	30 (28.6)	17 (16.8)	.048	1.7 (1.0–2.9)
Cardiotocogram anomaly			.17	
Predominantly early deceleration	24 (80)	10 (58.8)		
Predominantly bradycardia	1 (3.3)	3 (17.6)		
Mixed heart rate pattern anomaly	5 (16.7)	4 (23.5)		

RR, relative risk ; CI, confidence interval.

Data are mean±standard deviation, n (%), n/N (%), or median (interquartile range) unless otherwise specified.

Analysis performed using Student *t* test for continuous variables, Mann-Whitney *U* test for ordinal data, Fisher's exact test for 2 × 2 categorical data sets, and χ^2 test for larger than 2×2 categorical data sets. All statistical tests are two-sided.

* Nine women allocated to immediate oxytocin and seven women assigned to delayed oxytocin infusion were delivered by cesarean and were excluded from the these analyses.

† Not calculable because one or more cells contain a zero value.

‡ Umbilical cord arterial blood gas not performed in four participants as a result of machine malfunction (one in immediate and three in delayed oxytocin arm).

§ Active phase of labor is defined as established when contraction frequency is at least 3 in 10 minutes and cervical dilation is at least 4 cm or the participant had already delivered.

‖ Tachysystole (six or more contractions in 10 min over two consecutive 10-min periods) or hypertonus (sustained contraction 2 min or longer) with or without fetal heart rate abnormality on the cardiotocograph.

¶ Fetal heart rate deceleration (greater than 15 beats per minute [bpm] below baseline for more than 15 seconds), sustained tachycardia (greater than 160 bpm for more than 15 minutes), baseline bradycardia (less than 110 bpm for more than 15 minutes), or reduced baseline variability (less than 3 bpm for more than 15 minutes).

our trial population of parous women with favorable cervixes in contrast to earlier studies of mixed parity women or nulliparas only, which have all demonstrated shorter latency to delivery with early oxytocin.[12,13,18] Our findings should be generalizable to any similar population managed in a contemporary delivery suite. Our double-blind design minimized possibility of bias, although it was possible the intervention might be discernible because oxytocin produces contractions sooner than placebo. Our sample size had 90% power of demonstrating noninferiority (margin, difference of 10%) in the 12-hour postamniotomy delivery rate. However, our sample size was not large enough to detect a difference in an important outcome like cesarean delivery. To have 80% power to detect a difference in cesarean delivery rate of 8.6% compared with 6.9%, a future trial requires a sample size of 7,766.

Immediate compared with delayed oxytocin of 4 hours was associated with a similar vaginal delivery rate at 12 hours and similar maternal satisfaction. The induction-to-delivery interval was shorter, and there was less need for epidural analgesia but more cardiotocogram abnormalities with immediate oxytocin. Operative delivery and neonatal adverse outcome rates were not different. More than one-third of women allocated to delayed oxytocin avoided antepartum oxytocin infusion. These mixed findings suggested that the timing of oxytocin infusion after amniotomy for labor induction in a parous woman with a favorable cervix should take into account local resources and the woman's choice.

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Appendix D

Guidelines For The Doctor Of Philosophy Degree Programme By Prior Publication

1. Programme Of Study

The programme of study shall be classified as Degree of Doctor of Philosophy by Prior Publication, that is, a programme of study leading to the submission of a thesis comprising published works and additional papers integrating the work.

2. Admission Requirements

(1) The candidate shall be as follows:

(a) Professor, Reader, Associate Professor or Lecturer who at the time of application for admissions, have served not less than three years as a teacher of the University and are still active in the service in the University;

(b) Graduates of the University having the minimum qualifications as follows:

(i) a Master's degree; or
(ii) a Bachelor of Medicine or Dentistry degree; or

(c) An individual who through prior publication and contribution towards the body of knowledge, is accepted by the Senate as a scholar in the field.

(2) The candidate must **not** already hold a doctoral degree from the University or any other university in the same discipline or area of research.

3. Application

(1) The candidate is required to submit a written application together with a curriculum vitae to the Registrar. The application shall include the following:

(a) At least five samples of published work which are prefaced by a critical summary of approximately 3,000 words about the publications. The critical summary should document the theme or research focus that relates the selected

publications, demonstrate their coherence and identify the contribution to the advancement of knowledge of the research which they represent. It should also indicate the methodology adopted in the research.

(b) A detailed list of the papers which will be submitted for examination, together with a synopsis of about 1,000 words which summarises the most important findings for each paper concerned.

(2) The faculty will appoint the following to consider the quality and coherence of the papers to be submitted, ascertain the parts contributed by the applicant and the likelihood the submission will meet the criteria for an award:

(a) Dean – Chairman

(b) Deputy Dean (Higher Degree)

(c) Head of Department

(d) A senior academic staff in the relevant field; and

(e) A representative of the Senate.

(3) The applicant is required to attend an interview by the Panel.

(4) Should the Faculty agree that the work submitted is consistent with the level of a PhD research, the application shall be recommended for the Senate's approval.

4. **Registration**

The candidate must renew his candidature not later than week seven of the relevant semester.

5. **Duration Of Study**

Minimum period	:	6 months
Maximum period	:	24 months

6. **Structure Of Programme Of Study**

The candidate is required to submit papers published in high impact journals (e.g. ISI journal) in the form of a thesis for examination.

7. **Supervision**

(1) At least one supervisor in the relevant field will be appointed for the candidate.

(2) The role of the supervisor will be to:

(a) guide the candidate in the selection of publications for inclusion in the submission;

(b) guide the candidate as to whether further publications are needed;

(c) guide the candidate in the preparation of the thesis including the coherence of the body of work to be submitted;

(d) advise the candidate in relation to any research training requirements.

(3) A candidate shall be required to submit a progress report at the end of each semester to his supervisor in accordance with the prescribed procedure.

8. **Format Of Thesis**

(1) The thesis may comprise published papers and/or manuscripts accepted for publication by high impact journals (e.g. ISI journals). Papers that have been used in the submission for another research degree cannot be accepted.

(2) The number of papers and/or manuscripts cannot be less than five. Such papers should be published within 10 years prior to the date of submission.

(3) Where the papers have more than one writer, the candidate must be the main writer of at least four out five papers.

(4) Normally, the thesis shall include the following in addition to the components required of a standard thesis:

(a) list of publications and/or manuscripts;

(b) acknowledgments of joint writers and evidence of permissions; and

(c) published papers and accepted manuscripts.

Each published paper or submitted manuscript must begin with a clear statement of the contribution made by each writer of any jointly written paper.

(5) The thesis shall be prefaced by a synopsis which summarises the most important findings presented in each published paper or submitted manuscript. It should indicate how the included works are thematically linked or tied to a particular research framework and how, when considered together, they contribute significantly to knowledge in the discipline.

(6) The "Introduction" chapter should contain:

(a) description of research problem investigated;

(b) objectives of the study; and

(c) account of research progress linking the research papers.

The account of research progress must link together the various papers submitted as part of the thesis so that the reader can understand the logic behind the progression of the research programme.

(7) The "Literature Review" chapter must contain, in accordance with discipline norms, a critical review of relevant literature, identify the knowledge gaps and the relationship of the literature to the programme of research.

(8) The "Conclusion" chapter establishes the cumulative effect of the papers, the significance of the findings and the knowledge claim in the thesis.

(9) Published or accepted papers must be presented coherently in the thesis according to the requirements of the University of Malaya (Degree of Doctor of Philosophy) Regulations 2007 including any accompanying declarations.

9. **Examination**

(1) A candidate shall give at least three months' notice in writing to the Faculty prior to the submission of his thesis for examination.

(2) A candidate shall submit five copies of his published work in the form of a thesis for examination.

(3) Three examiners with expertise in the field concerned of whom at least two are external examiners are appointed to examine the thesis.

(4) The Committee of Examiners shall recommend that the thesis of the candidate:

(a) has achieved sufficient merit to be awarded the Degree without any corrections; or

(b) has achieved sufficient academic merit to be awarded the Degree subject to the candidate making minor corrections within six months without any reexamination. The minor corrections do not include any amendments to the published papers; or

(c) has not achieved sufficient academic merit and the candidate has failed in the examination of his thesis.

(5) A viva-voce examination is compulsory.

(6) After all amendments have been made, the candidate shall submit three final copies of the thesis in print format (one copy should be original) and an electronic copy which shall be the property of the University.

10. **Award Of Distinction For Thesis**

A thesis qualifies to be awarded a distinction if:

(a) a distinction is recommended in the reports of all the examiners; and

(b) it is recommended by the Committee of Examiners.

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