PROPOSAL

Study Title: MEMBRANE SWEEPING VERSUS TRANSCERVICAL FOLEY CATHETER FOR INDUCTION OF LABOUR IN WOMEN WITH PREVIOUS CAESAREAN DELIVERY

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Organisations / Institutes:

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Sponsor:

This study is self-funded by Department of O&G, Sibu Hospital. No grant is applied.

Conflict of interest:

There is no conflict of interest among members of the study team.

BACKGROUND/LITERATURE REVIEW

Induction of labour (IOL) is an obstetric intervention to artificially initiate labour before its spontaneous onset (1, 2). It is undertaken when maternal or fetal risks of continuing pregnancy outweigh the risks of IOL (1). The methods of IOL include pharmacological method (prostaglandin), mechanical methods (transcervical Foley catheter and laminaria tents) and surgical method (amniotomy). Pharmacological method and mechanical methods are preferred choice for IOL in women with unfavourable cervix. Whereas surgical method is reserved for women with favourable cervix in which membranes are accessible.

With the global rise in Caesarean section, more and more women embark on pregnancy with previous Caesarean scar (3). It is estimated that one in every four term pregnancies requires IOL (4). With IOL in previous Caesarean section, the risk of uterine scar rupture with subsequent catastrophic maternal and neonatal outcomes is the greatest concern (5). Previous influential study (6) highlighted that IOL with prostaglandin conferred the greatest risk of uterine rupture (2.45%) in women with one previous Caesarean delivery. On the other hand, the risks of uterine rupture were lower and comparable among women whose labour induced without the use prostaglandin (0.77%) and women with spontaneous labour (0.52%). Among the various IOL methods, prostaglandin is more likely associated with shorter interval to achieve vaginal delivery and avoidance of oxytocin augmentation (7). Nevertheless, mechanical methods have lower risk of uterine hyperstimulation (7, 8) but have more risk of infection (7). As a result, obstetricians are facing dilemma on deciding the safe and effective method of IOL in women with previous Caesarean delivery.

In Sibu Hospital, membrane sweeping is routinely offered to women with previous Caesarean delivery who require IOL. This technique involves the examining finger passing through the cervix to rotate against the wall of the uterus, to separate the chorionic membrane from the decidua, or to massage around the cervix if the os is closed (1, 2). However, membrane sweeping may not exert its cervical ripening effect immediately and the delivery may be delayed by up to 8 days (9). This may render a proportion of women to resort to repeated Caesarean section for failed induction. The vaginal birth rates following membrane sweeping in women with unscarred uterus are ranging between 78%-90% (10-12). Among women with previous Caesarean delivery undergoing IOL with membrane sweeping, the reported vaginal birth rates were conflicting. A randomised controlled trial by Hamdan et al. showed vaginal

birth rate of 56.1% (13). Another comparative study by Ramya et al. reported much lower vaginal birth rate of 17.3% which could be explained by high rate of Caesarean Section for maternal request in this study (14). The average intervals from sweeping to labour onset and to delivery were about 2 days (14) and 4 days (9), respectively. Membrane sweeping did not increase the risk of maternal or neonatal infection, Caesarean section, postpartum haemorrhage and neonatal poor APGAR score, though discomfort during vaginal examination, minor vaginal bleeding and irregular contraction were frequently reported by women undergoing membrane sweeping (13, 15). No cases of uterine rupture was reported among women with scarred uterus undergoing membrane sweeping (14).

Pharmacological IOL method involving prostaglandin is avoided in Sibu Hospital in view of higher risk of scar rupture and presence of limited number of consultants to cope with this debilitating event. Non-pharmacological methods of IOL such as Foley catheter, double-balloon catheter, hygroscopic cervical dilator (laminaria tent) etc are known to have lesser risk of scar rupture. Double-balloon catheters are limited in numbers in this hospital and they are costly. Laminaria tent is not available in this hospital. Foley cathter is a consumable item in this hospital and thus is readily available all the time. Compared to double-balloon catheter, Foley catheter has equivalent cervical ripening efficacy and safety profile (16). In addition, Foley catheter is also cheaper and has shorter induction to delivery interval. All these advantages make Foley catheter an ideal method of IOL for women with previous Caesarean delivery.

Among women with previous Caesarean delivery underlying IOL with transcervical Foley catheter, the reported vaginal birth rates are ranging between 43.5%-71.4% (17-25). The retrospective cohort analysis by Bujold et al. (18) compared the risk of uterine rupture among women with previous Caesarean delivery undergoing spontaneous labour, induction by amniotomy with or without oxytocin, or preinduction cervical ripening with transcervical Foley catheter. The rates of uterine rupture were similar among the groups ((1.1% vs 1.2% vs 1.6%, $p = 0.81$). However, transcervical Foley catheter appeared to be safer than low dose oxytocin infusion for cervical ripening before amniotomy as the latter tended to be associated with risk of uterine scar dehiscence (26). Another retrospective cohort study done by Gonsalves et al. showed no case of uterine rupture among 68 women with previous Caesarean section undergoing IOL with transcervical Foley catheter insertion (25).

The transcervical insertion of balloon catheter as a 'foreign material' may theoretically increase the risk of uterine infection. But, the current data available are conflicting. Meta-analysis by Heinemann et al. (27) demonstrated that the Foley catheter was associated with a significantly higher rate of maternal infections, defined as fever, endometritis or chorioamnionitis, compared to the use of prostaglandins or oxytocin for induction of labor (7.6% vs 5%, pooled OR 1.5, 95%CI 1.07–2.09). On the other hand, Cochrane Review (8) concluded that there is no evidence of an increased risk of infectious morbidity with balloon catheters. In the PROBAAT-trial (28), comparing the Foley catheter with the use of vaginal prostaglandin E2 gel, the rate of intrapartum infection was significantly lower in women with the Foley catheter (1% vs 3%, p = 0.035). Two other trials evaluating labor induction with balloon catheters after rupture of the membranes did not show an increased risk for maternal infection (29, 30).

Maslovitz et al. (31) reported the rate of vaginal bleeding of 1.8% following transcervical Foley catheter insertion. However, the bleeding was minor with unaltered haemoglobin levels and coagulation profile. There was also no case of cervical tear which might result in postpartum haemorrhage. Besides, risk of change of fetal vertex presentation to breech was reported to be 1.3% (31). This was probably related to concomitant presence of unengaged free-floating fetus and contraction following Foley catheter insertion which resulted in flipping movement of the fetus. Risk of poor APGAR and NICU admission was not significantly higher compared to other IOL methods eg. prostaglandin and oxytocin (24, 26).

Till date, there is paucity of evidence on the superiority of membrane sweeping and transcervical Foley catherter in IOL in previous Caesarean delivery. Both methods have the same mechanism action by increasing local production of endogenous prostaglandin (1). The aim of this study is to evaluate the effectiveness of membrane sweeping and transcervical Foley catherter insertion for IOL in women with previous Caesarean delivery.

OBJECTIVES AND PURPOSE

1. General objective:
    a. To compare the effectiveness of membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.

2. Specific objectives:
    a. To compare the following induction outcomes between membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.
        i. Improvement of modified Bishop score at interval of 24 hours and 48 hours, respectively.
        ii. The requirement of oxytocin following IOL.
    b. To compare the following delivery outcomes between membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.
        i. Mode of delivery.
        ii. Overall:
            - Induction to delivery interval.
            - Oxytocin augmentation duration.
        iii. Vaginal delivery subgroup:
            - Induction to delivery interval.
            - Amniotomy to delivery interval.
            - Duration of oxytocin augmentation.
            - Vaginal delivery rate within 24 hours of induction.
            - Vaginal delivery rate between 24-48 hours of induction.
    c. To compare the maternal outcomes between membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.
        i. Uterine hyperstimulation.
        ii. Uterine rupture.
        iii. Post-partum haemorrhage.
        iv. Maternal pyrexia.
        v. Duration of hospitalization.
    d. To compare the neonatal outcomes between membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.
        i. APGAR score at 5 minutes.
        ii. Cord pH.

e. To compare women's evaluation on the care they receive between membrane sweeping and transcervical Foley catheter for IOL.

STATEMENT ON ETHICAL ISSUES

1. Institutional Review Board (IRB) Review:
    a. The study protocol will be reviewed by Medical Research Ethics Committee (MREC) of Ministry of Health, Malaysia.

2. Patient information sheet and informed consent:
    a. Written informed consent will be obtained from each subject prior to the enrollment.
    b. Subjects will be told of the objective of this study in clear laymen's term. They will be informed of their rights as subjects and that their participation is voluntary.
    c. Subjects will also be notified that if they choose to withdraw from the study at any time, they will be managed according to local protocol under Department O&G, Sibu Hospital.
    d. The information sheet specifies whom the contact if they are injuries as a result of the study, and whom to contact with general information about the study.
    e. The consent form specifies that the study staff, and governmental or regulatory authorities, have direct access to subject's medical record in order to make sure that the study is conducted correctly and the data are recorded correctly.
    f. Compliance with informed consent will be monitored by the principal investigators.

TRIAL DESIGN

1. Study location:
    a. This study will be conducted in the Department of Obstetrics and Gynaecology, Sibu Hospital, Sarawak.

2. Study design:
    a. A prospective randomised controlled trial (RCT) will be conducted.
    b. The subjects will be followed-up from time of IOL till delivery.

3. Study endpoint:
    a. The study endpoint is to confirm the superiority of membrane sweeping and transcervical Foley catheter for IOL in women with one previous Caesarean delivery.

4. Study duration:
    a. This study will be conducted from 15 November 2017 till 24 September 2018.

5. Study procedure: (see flow chart in Appendix 1)
    a. Approval will be obtained from the Medical Research & Ethics Committee, Ministry of Health Malaysia before conducting the study.
    b. Pregnant women with one previous Caesarean section who are indicated for IOL and eligible will be recruited in the study.
    c. Informed consent available in either English or Malay language (See Appendix 2) will be obtained prior to enrollment into the study. The consent will be taken by the principal investigator at time of admission in Sibu Hospital Labour Ward.
    d. A data collection form will be filled up and details including personal information will be obtained (Appendix 3).
    e. Eligible subjects will be randomly assigned to one of the treatment groups below.
        i. Group 1: IOL with membranes sweeping
        ii. Group 2: IOL with transcervical Foley catheter
    f. Blocked randomisation, in a block size of 6 and an allocation ratio of 1:1, will be performed using a computer-generated randomisation sequence by Research Randomizer (available online at https://www.randomizer.org/). The allocation assignment indicating “membrane sweeping” or “transcervical Foley catheter” will be sealed in sequentially numbered, opaque envelopes by principal investigator, . Envelopes will be kept in a locked box in Labour Ward. When study consent is signed, the next sequential envelope will be taken out from the box and opened to determine allocation.

g. This is a non-blinded study in which subjects, medical staffs, and investigators are not blinded to group assignment. This is because both IOL methods are distinctly different procedure. However, both intervention arms are considered receiving equal treatment. In term of safety, both membrane sweeping and transcervical Foley catheter are non-pharmacological in nature and thus the risk of scar rupture does not differ in both methods. In term of efficacy, there is no previous study to compare effectiveness between these two methods. Individual studies revealed that membrane sweeping is likely to reduce the need for formal IOL in post-date pregnancy and transcervical Foley catheter could improve cervical favourability.

h. IOL will be done on the next morning. Pre-induction cardiotocograph (CTG) will be performed to ensure normal fetal heart rate prior to IOL.

i. In Group 1, membrane sweeping involves the insertion of a digit past the internal cervical os followed by three circumferential passes of the digit causing separation of the membranes from the lower uterine segment. When the cervix is closed, a massage of the cervical surface for 15 to 30 seconds will be performed instead. Membrane sweeping will be undertaken twice a day at 8 to 10 hours apart.

j. In Group 2, transcervical Foley catheter No. 18 F will be inserted under aseptic technique into the endocervical canal surpassed beyond the internal os. The balloon will be inflated with 60 ml of sterile water and the catheter is plastered to patient's thigh with gentle traction. The catheter will be checked for its position and the traction at 6 hours interval. If it were expelled spontaneously, it would not be re-inserted. Otherwise, the catheter will be removed after 24 hours.

k. Post-induction CTG will be performed at 1 hour after the first membrane sweeping in Group 1 and after transcervical Foley catheter insertion in Group 2.

l. The uterine contractions, maternal temperature and fetal heart rate (via handheld Doppler device) will be monitored every 4 hours.

m. After 24 hours, improvement of modified Bishop score will be assessed.

    i. If the cervix is favourable for amniotomy, amniotomy will be performed followed by augmentation with intravenous oxytocin.

ii. If the cervix is still unfavourable and amniotomy is impossible, membrane sweeping will be continued for one more day in Group 1 whereas conservative management will be undertaken for one day in Group 2. Suitability for amniotomy will be reassessed on the next day.

n. After amniotomy, subsequent intrapartum management will be based on the hospital protocol.

o. Oxytocin augmentation will be started when desired contractions are not achieved at 2 hours after amniotomy or labour progress falls below the action line of partogram.

p. Our oxytocin infusion regime begins with 2 mU/min. An increment in dosage is made every 30 minutes until desired contractions of 3-4 in 10 minutes lasting 45-60 seconds. The maximum oxytocin dose is 16 mU/min.

q. Continuous CTG monitoring will be undertaken throughout the labour process.

r. Oxytocin augmentation will not be started or will be withheld when there is non-reassuring fetal heart rate.

s. If amniotomy is still impossible after 2 days of IOL, the ward Obstetrician will discuss with women regarding option of Caesarean section.

6. Criteria for suspending or terminating the study:

a. Transcervical Foley catheter is found to have unreasonable and significant risks to subjects. The risks include uterine rupture, maternal sepsis, severe cervical trauma, and neonatal sepsis. However, all these serious adverse outcomes were infrequent risk based on literature review. Literature review showed that the risk of uterine rupture in Foley catheter arm is comparable to women with scarred uterus undergoing spontaneous labour (18, 25). There is small risk of maternal pyrexia or infection but no case of maternal or neonatal sepsis was reported (8, 28-30). Similarly, no case of cervical trauma was reported as well (31).

7. Study instruments:

a. Data collection form which consists of:

i. SECTION A: Subjects' demographic information (gravida, parity, gestational age, maternal height and weight, body mass index, details of previous Caesarean delivery, indication of IOL).

ii. SECTION B: Subjects' induction outcomes (serial changes in modified Bishop score).

iii. SECTION C: Subjects' delivery outcomes (oxytocin requirement, mode of delivery, induction to delivery interval, overall duration of oxytocin augmentation, intrapartum details for the vaginal delivery (including instrumental delivery) subgroup, estimated blood loss, maternal and neonatal outcomes.

iv. SECTION D: 'Subjects' satisfaction on the care they received.

b. Membrane sweeping:

i. An IOL method involving the insertion of a digit past the internal cervical os followed by three circumferential passes of the digit causing separation of the membranes from the lower uterine segment.

ii. When the cervix is closed, a massage of the cervical surface for 15 to 30 seconds will be performed instead.

c. Transcervical Foley catheter:

i. An IOL method involving insertion of a balloon catheter under aseptic technique into the endocervical canal surpassed beyond the internal os.

ii. The balloon will be inflated with 60 ml of sterile water and the catheter is plastered to patient's thigh with gentle traction.

iii. Foley catheter is an indwelling catheter made of latex rubber.

d. Modified Bishop score: (see Figure 1)

i. A group of measurements made at internal examination, used to determine whether the cervix is favourable or not.

ii. The score is based on the station, dilation, effacement (or length), position and consistency of the cervix.

iii. A score of 8 or more generally indicates that the cervix is ripe (2).

Figure 1: modified Bishop score

Score	0	1	2	3
Dilatation (cm)	1	1-2	3-4	>4
Length of cervix (cm)	>4	2-4	1-2	<1
Station	-3	-2	-1	0
Consistency	Firm	Average	Soft	-

Position	Posterior	Mid/Anterior	-	-

SELECTION AND WITHDRAWAL OF SUBJECTS

1. Sample population:
    a. All pregnant women with one previous Caesarean section who are admitted to Sibu Hospital for IOL will be recruited in the study.

2. Inclusion criteria:
    a. The inclusion criteria are age at least 18 years old, gestational age ≥ 37 weeks, singleton pregnancy, reassuring fetal status and modified Bishop score ≤ 6.

3. Exclusion criteria:
    a. Women with ruptured membranes, intrauterine death, polyhydramnios, severe fetal anomalies, multiple pregnancy.
    b. Women with contraindications for IOL eg. placenta previa, suspected macrosomia, suspected cephalopelvic disproportion, non-cephalic presentation, and obstructive pelvic masses.

4. Sample size determination:
    a. We had searched electronic databases including PubMed, Cochrane Library, Scopus, Ovid, JSTOR and Google Scholar. We found that there was no study comparing the two IOL methods, thus no prior information is available for sample size calculation.
    b. Based on Julious SA (32), we will recruit 24 subjects (a sample size of 12 per group) first, then do an interim analysis and calculate the actual sample size required for a full RCT. The justifications for this interim sample size are based on rationale about feasibility, precision about the mean and variance, and regulatory considerations.
    c. With α at 0.05 and power at 0.8, the final sample size will be calculated based on the study primary outcome of induction to delivery interval. As this outcome is a continuous data, we will use the following formula by Snedecor and Cochran 1989 to calculate the sample size (including 15% of dropout rate).

$$n = 1 + 2C\left(\frac{s}{d}\right)^2$$

s = standard deviation,

d = the difference to be detected, and

C = constant

5. Consent taking:
    a. Pregnant women with one previous Caesarean section who are indicated for IOL and eligible will be recruited in the study.
    b. Participation of the subjects is voluntary and will not affect medical services.
    c. Informed consent available in either English or Malay language (See Appendix 2) will be obtained prior to enrollment into the study.
    d. The consent will be taken by the principal investigator at time of admission in Sibu Hospital Labour Ward.

6. Subject withdrawal:
    a. Criteria:
        i. Subjects may withdraw voluntarily from study at any time upon their request.
        ii. Subjects are inappropriately enrolled without fulfilling inclusion/exclusion criteria.
        iii. Subjects develop spontaneous labour before IOL procedure is undertaken.
    b. Follow up process:
        i. The withdrawn subjects will be managed according to local protocol under Department O&G, Sibu Hospital.
        ii. The withdrawn subjects data will be destroyed as it will not be used for data analysis.
    c. The withdrawn subjects will be replaced with new subjects in order to meet the required sample size.

TREATMENT AND PROCEDURES

1. Treatment and medications that are permitted during the trial:
    a. Amniotomy
    b. Oxytocin augmentation when contractions are not optimised
    c. Abdominal and vaginal examination to assess labour progress
    d. Intrapartum continuous fetal heart rate monitoring
    e. Fetal scalp sampling in the presence of non-reassuring fetal heart rate
    f. Instrumental delivery or emergency Caesarean section if indicated

2. Both IOL methods of membrane sweeping and transcervical Foley catheter do not contain drug or medication. Thus, the risk of uterine rupture is similar to spontaneous labour in women with previous Caesarean delivery. If scar dehiscence is highly suspected during labour, standard management with recourse to emergency Caesarean section will be undertaken.

3. Treatment and medications that are not permitted during the trial:
    a. Vaginal prostaglandin E2

ASSESSMENT OF EFFICACY

1. Primary outcome:
    a. Overall induction to delivery interval.
2. Secondary outcomes:
    a. Induction outcomes:
        i. Improvement of modified Bishop score at interval of 24 hours and 48 hours after induction.
        ii. Whether oxytocin augmentation is required.
    b. Delivery outcomes:
        i. Mode of delivery.
        ii. Duration of oxytocin augmentation overall and in vaginal delivery group.
        iii. Induction to vaginal delivery interval.

iv. Amniotomy to vaginal delivery interval.
v. Vaginal delivery rate within 24 hours of induction and between 24-48 hours of induction.

c. Maternal outcomes:
vi. Uterine hyperstimulation (> 5 contractions per 10 minutes for at least 20 minutes or a contraction lasting at least 2 minutes with/without abnormal fetal heart rate).
vii. Uterine rupture.
viii. Post-partum haemorrhage (estimated blood loss ≥ 500 ml).
ix. Maternal pyrexia (temperature >38.0 °C once, or 37.5 °C on two occasions 2 hours apart).
x. Duration of hospitalisation.

d. Neonatal outcomes:
i. APGAR score at 5 minutes.
ii. Cord pH.

ASSESSMENT OF SAFETY

1. No adverse events (AEs) will be expected during the course of study because there is no involvement of pharmacological drug or product. Both methods of membrane sweeping and transcervical Foley catheter do not contain drug or medication. Thus, the risk of uterine rupture is similar to spontaneous labour in women with previous Caesarean delivery. However, maternal discomfort and vaginal bleeding following membrane sweeping and unknown latex allergy following transcervical Foley catheter insertion may occur, and subjects will be informed of this risk in the informed consent.

2. All other invasive (amniotomy, fetal scalp sampling in the presence of non-reassuring fetal heart rate, instrumental delivery or emergency Caesarean section if indicated) and non-invasive procedures (maternal vital signs observation and intrapartum continuous fetal heart rate monitoring) and evaluations (abdominal and vaginal examination to assess labour progress) included in this protocol are considered to be standard of care in evaluation and management of women with one previous Caesarean delivery undergoing IOL and would have been performed as part of routine practice.

3. Report of adverse events eg. SAEs, SUSARs.
    a. When adverse event of any type occurs, local SAE/SUSAR report will be created by principal investigator and notified via SAE Platform on NMRR website.
    b. Subjects who experience SAE/SUSAR will be followed up by principal investigator and a follow up report will be submitted.
    c. For "Non-life threatening SUSARs" eg. latex allergy associated with Foley catheter insertion, vasovagal attack following membrane sweeping, and cervical tear, initial report is to be submitted within 15 calendar days followed by a follow up report.
    d. For "Life threatening SUSARs" eg. uterine rupture and maternal sepsis, initial report is to be submitted within 7 calendar days followed by a follow up report within the next 8 calendar days.

4. Process and duration of follow-up of adverse events
    a. Latex allergy associated with Foley catheter insertion
        i. Foley catheter will be removed immediately.
        ii. Steroids and anti-histamine will be administered as rescue medication.
        iii. Closed monitoring of vital signs and oxygen saturation for 24 hours.
    b. Vasovagal attack following membrane sweeping
        i. No further membrane sweeping will be performed.
        ii. Affected subject will be withdrawn from the study.
        iii. No rescue medication is needed as condition is self-limiting.
        iv. Closed monitoring of vital signs and oxygen saturation for 24 hours.
    c. Cervical tear
        i. Examination under anaesthesia will be performed immediately.
        ii. Cervical repair will be performed.
        iii. Subject will be followed up till 42 days post-delivery (completion of puerperal period).
    d. Uterine rupture
        i. Emergency laparotomy will be performed immediately.
        ii. Depend on the severity of uterine rupture, uterine repair or hysterectomy may be warranted.

iii. Subject will be followed up till 42 days post-delivery (completion of puerperal period).

e. Maternal sepsis
   i. Blood culture and high vaginal swab for culture will be taken.
   ii. Broad spectrum antibiotics will be started as rescue medication.
   iii. Unstable subjects will be nursed in intensive care unit.
   iv. Subject will be followed up till 42 days post-delivery (completion of puerperal period).

5. Compensation of adverse events
   a. In the event of a bodily injury or illness directly resulting from the membrane sweeping or transcervical Foley catheter insertion, the department will pay for reasonable and necessary treatment.
   b. The department is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, subjects' negligence or willful misconduct, the negligence or willful misconduct of the investigators or the study site or any third parties.

STATISTICS

1. All results will be analysed using the Statistical Package for Social Sciences for Windows (SPSS for Windows).

2. Normality of numerical data (Bishop score, induction to delivery interval, induction to vaginal delivery interval, amniotomy to vaginal delivery interval, duration of oxytocin augmentation, duration of hospitalisation, APGAR score at 5 minutes, cord pH, neonatal birth weight) will be assessed using Kolmogorov-Smirnov analysis. Independent T-test (data with normal distribution) or Mann-Whitney U test (if data not normally distributed) will be used to compare these outcomes between the group of membrane sweeping and group of transcervical Foley catheter.

3. Chi-square test will be used to compare:

a. The requirement of oxytocin augmentation following induction between the group of membrane sweeping and group of transcervical Foley catheter.
b. The following delivery outcomes between the group of membrane sweeping and group of transcervical Foley catheter.
    i. Mode of delivery.
    ii. Vaginal delivery within 24 hours of induction.
    iii. Vaginal delivery within 24-48 hours of induction.
    iv. The maternal outcomes (uterine hyperstimulation, uterine rupture, post-partum haemorrhage, maternal pyrexia) between the group of membrane sweeping and group of transcervical Foley catheter.

If there is at least one expected value of < 5, Yates correction will be done.

If sample size is less than 20 or (>40 but at least one expected value <5), Fisher test instead of Chi-square test will be used.

4. Statistical significance is defined as p value < 0.05.

CONFIDENTIALITY AND SECURITY OF SOURCE DOCUMENTS AND STUDY DATA

1. All of the subjects' information obtained in this study will be kept and handled in a confidential manner. When publishing or presenting the study results, subjects' identity will not be revealed without their expressed consent.

2. Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but subjects' identity will not be revealed at any time.

3. Following the trial, only the principal and co/sub investigators, and regulatory authorities but not the subjects have access to study data and findings.

4. Storage and archival of medical records and study data:
    a. Medical records will be kept in the hospital record office as following hospital policy. The investigators will only keep the study data.

b. Documents and other study materials can be accessed by staff restricted to the investigators and regulatory authorities.
c. All data and documents or study materials will be made available whenever it is requested by relevant authorities, in the presence of investigator.
d. Duration of study data storage will be 5 years after completion of study. Study data will be destroyed after period of storage.

FINANCE AND INSURANCE

1. This study is self-funded by Department of O&G, Sibu Hospital.

PUBLICATION POLICY

1. When publishing or presenting the study results, subjects' identity will not be revealed without their expressed consent in order to protect subjects' confidentiality.

2. Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but subjects' identity will not be revealed at any time.

INVOLVEMENT OF VULNERABLE SUBJECTS

1. This study does not involve vulnerable subjects.

RESULTS (Dummy tables)

Table 1: Demographic characteristics

Characteristics	Membrane sweeping	Transcervical Foley catheter	p-value
Age, years			
Parity			
Gestational age			
Ethnicity, n (%)			
Iban			
Melanau			
Bidayuh			
Malay			
Chinese			
Indian			
Others			
Foreigner			
Body mass index, kg/m^2			
Previous Caesearean section			
Tested scar			
Untested scar			
Indication of induction of labour			
Postdate			
Fetal growth restriction			
Hypertension			
Diabetes			
Others			

Table 2: Induction outcomes in two groups

Outcomes	**Membrane sweeping**	**Transcervical Foley catheter**	**p-value**
Bishop score at start of induction			
Bishop score after 24 hours of induction			
Bishop score after 48 hours of induction			
Change in Bishop score			
Oxytocin required			

Table 3: Delivery outcomes and maternal complications in two group

Outcomes	**Membrane sweeping**	**Transcervical Foley catheter**	**p-value**
Mode of delivery			
Vaginal			
Caesarean section			
Overall			
Induction to delivery interval			
Oxytocin augmentation duration			
Vaginal delivery			
Induction to delivery interval			
Amniotomy to delivery interval			
Oxytocin augmentation duration			

Within 24 hours of induction

Between 24-48 hours of induction

Indication for Caesarean section

Poor progress

Failed induction

Acure fetal distress

Suspected scar dehiscence

Others

Maternal complications

Uterine rupture

Uterine hyperstimulation

Post-partum haemorrhage

Maternal pyrexia

Duration of hospitalisation

Table 4: Neonatal outcomes in two groups

Outcomes	Membrane sweeping	Transcervical Foley catheter	p-value
APGAR score at 5 minutes			
Cord pH			
Birth weight			

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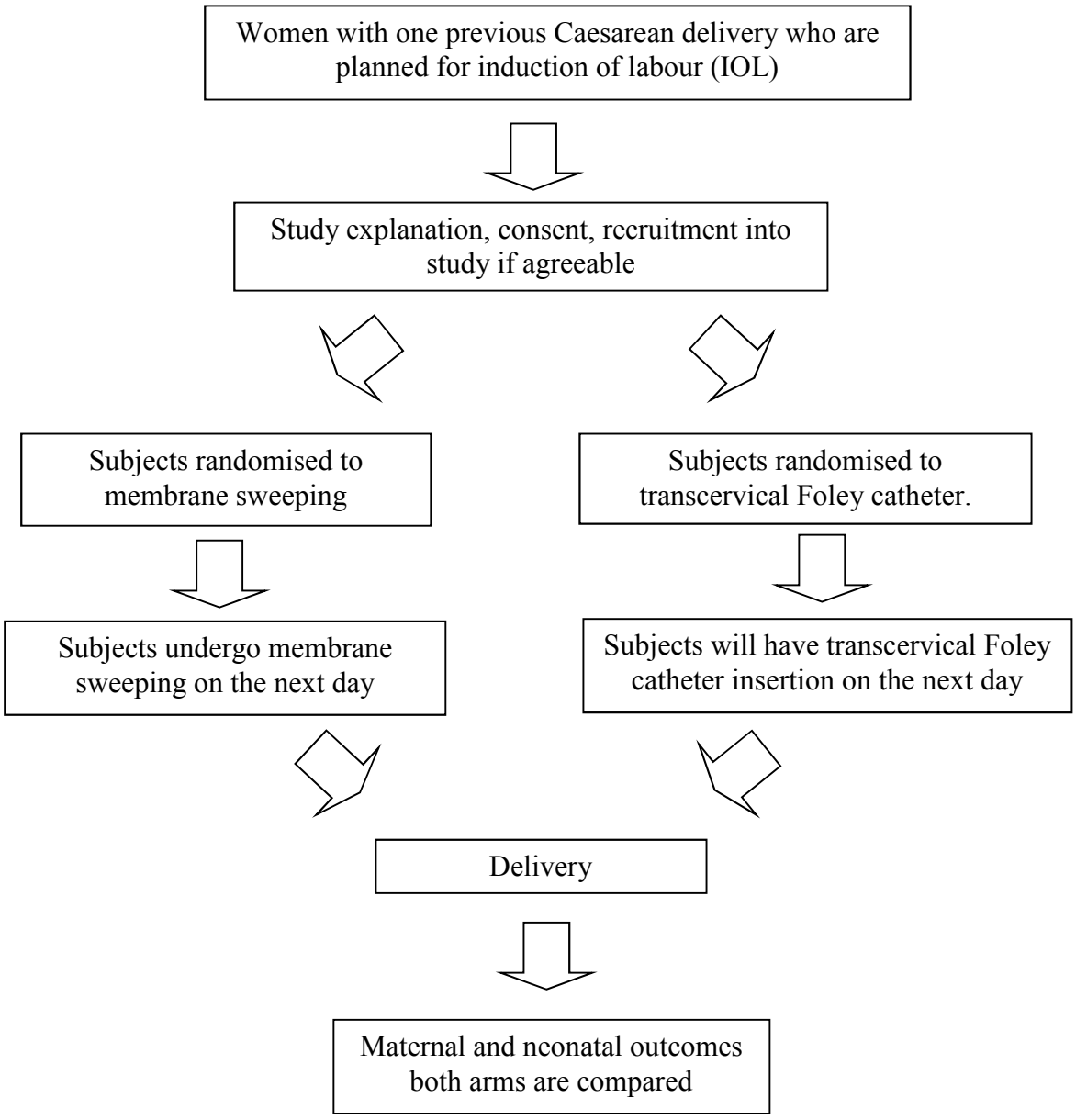
Appendix 1

Study Procedure Flow Chart



Appendix 2

PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

1. Title of study:

Membrane Sweeping versus Transcervical Foley Catheter for Induction of Labour in Women with Previous Caesarean Delivery

2. Name of investigator and institution:

Dr. Yong Soon Leong
Dr. Joyce Ting Chin Sing
Dr. Ling Tin Yee

Organisations / Institutes:
Department of Obstetrics & Gynaecology, Sibu Hospital.

3. Name of sponsor:

This research is self-funded by Department of O&G, Sibu Hospital.

4. Introduction:

You are invited to participate in a research study because you will be undergoing an induction of labour (artificial initiation of labor). The details of the research trial are described in this document. Please read through and consider this information carefully before you decide if you are willing to participate. Ask the study staff if anything is unclear or if you like more information. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form.

Your participation in this study is voluntary. If you volunteer to be in this study, you may withdraw from it at any time. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled.

This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

5. What is the purpose of the study?

Nowadays, more and more women embark on pregnancy with previous Caesarean scar. One in five pregnancies requires induction of labour. The use of non-pharmacological methods (methods without using medication) has been gaining popularity for women who are not good candidates, such as women with previous Caesarean scar, for an induction with medications such as prostaglandin. Labour induction with prostaglandin carries higher risk of uterine rupture and thus it is not routinely offered to women with previous Caesarean delivery in Sibu Hospital. Non-pharmacoloical methods of induction of labour appear to be safe in women with previous Caesarean delivery. However, various methods are available and the efficacy among them remain in doubt.

In Sibu Hospital, membrane sweeping, which is a type of non-pharmacological method, is routinely offered to women with previous Caesarean delivery who require induction of labour. However, membrane sweeping may not exert its labour induction effect immediately and the delivery may be delayed by up to 8 days. This may render a proportion of women to resort to repeated Caesarean section for failed induction.

Transcervical Foley catheter insertion is another non-pharmacological methods for labour induction. Foley catheter, which is made from latex rubber, is inserted into the womb. The balloon will be inflated and this puts pressure on the cervix and encourages dilatation. This method may successfully stimulates labour and the catheter falls out once the cervix dilates to 3 centimeters.

The benefits of the Foley catheter:

- A favourable and safe option for mothers who are hoping for a vaginal birth after Caesarean. It is estimated that 4-7 in 10 women with previous Caesarean undergoing labour induction with Foley catheter will have successful vaginal births.
- Cause the cervix to mechanically open without involving medication.
- Reduced risk of uterine rupture compared to induction with prostaglandin.
- Less risk of fetal distress compared to induction with prostaglandin.

The risks of Foley catheter:

- Vaginal bleeding (1.8%)
- Pain requiring removal of catheter (1.7%)
- Baby moving from head down to breech (1.3%)
- Fever (1%) which is lower than induction with prostaglandin.
- The risk of uterine rupture is similar to women undergoing spontaneous vaginal birth after Caesarean.

The aim of this study is to compare the effectiveness of two types of non-pharmacological methods, ie. membrane sweeping and transcervical Foley catheter for induction of labour in women with previous Caesarean delivery. As there was no previous study comparing the two methods, the actual number of subjects like you to participate in this study is yet to be decided. Thus, there will be initial 24 subjects like you participating in this study. Subsequently, the interim analysis will be conducted to decide the actual number of subjects required for this study.

6. What kind of study products will I receive?

You will be randomly (by chance, like flipping a coin) assigned to one of the treatment groups below. You have equal chance of being assigned to each of the groups.

Group 1: Induction of labour with membrane sweeping
Group 2: Induction of labour with transcervical Foley catheter

Membrane sweeping involves placing a finger into the neck of the womb and making circular, sweeping movement to separate the membranes that surround the baby, or massaging the neck of the womb if this is not possible. Membrane sweeping will be performed twice a day.

Transcervical Foley catheter involves placing a latex rubber balloon catheter into the womb and the balloon near the tip of the catheter will be inflated with 60 ml of water. The catheter will be kept for 24 hours. If it were expelled by itself, it will not be re-inserted.

7. What will I need to do if I decide to take part?

On the next day of admission, you will undergo induction of labour with either membrane sweeping or transcervical Foley catheter depends on randomised allocation. Following that, your labour contraction will be monitored every 4 hour. Your baby heart rate will be checked as well.

After 24 hours, amniotomy (artificially break the waters) will be performed. If it is not possible, membrane sweeping will be continued for one more day in Group 1 whereas conservative management will be undertaken for one day in Group 1. Suitability for amniotomy will be reassessed on the next day.

Following amniotomy, you will undergo labour as usual. Oxytocin (a drug which is used to augment the labour progress) will be given following hospital protocol if contractions are not adequate.

If amniotomy is still impossible after 2 days of effort, your obstetrician will discuss further management with you and you may be offered option of Caesarean section.

The study endpoints are duration from labour induction to delivery and final mode of delivery (whether vaginal birth or Caesarean delivery). We will observe the outcome of your delivery and your baby. Your expected duration of study participation will be from labour induction until you have delivered your baby. All the outcomes will be recorded into study clinical report form.

8. When will I receive the trial product?

Induction of labour with either membrane sweeping or transcervical Foley catheter will be carried out on the next day of admission.

9. What are the potential risks and side effects of being in this study?

Both membrane sweeping or transcervical Foley catheter insertion may cause pain and vaginal bleeding. As both methods do not contain drug or medication. Thus, the risk of uterine rupture is similar to natural labour in women with previous Caesarean delivery. You may develop fever after Foley catheter insertion but risk of severe infection has been reported unlikely. Otherwise, there will be no other major risk or side effect of being in this study. Participant with known allergy to latex will be excluded from this study.

Both membrane sweeping and transcervical Foley catheter will have no effect on an unborn child.

Please ask your study doctor if you need more information on risks and side effects.

10. What are the benefits of being in this study?

There may or may not be any benefit to you. Information obtained from this study will help to identify the most suitable method for induction of labour to be offered to women with previous Caesarean delivery in this hospital. At this moment, transcervical Foley catheter is not a routine practice in our hospital. But, membrane sweeping is routinely offered to women with previous Caesarean delivery requiring induction of labour.

11. What if I am injured during this study?

If you are injured as a result of being in this study, you should contact your study doctor. In the event of a bodily injury or illness directly resulting from the study product or a

medical procedure required for this study, the department will pay for reasonable and necessary treatment. The department is not responsible for medical expenses due to pre-existing medical conditions, any underlying diseases, any ongoing treatment process, your negligence or willful misconduct, the negligence or willful misconduct of your study doctor or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

12. Do I have to pay for the study product?

You do not have to pay for participating in this study. Similarly, no payment is available for you for participating in this study. All other drugs, medical procedure, or delivery that are not required by the study but are part of your routine medical care will have to be paid by you or your insurance.

13. Can the research or my participation be terminated early?

The study doctor may due to concerns for your safety, stop the study or your participation at any time. If the study is stopped early for any reason, you will be informed and arrangements made for your future care. You may be asked to attend a final follow-up visit.

14. Will my medical information be kept private?

All your information obtained in this study will be kept by the principal investigators and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, your identity will not be revealed without your expressed consent.

Data from the study will be archived and may be transmitted outside the country for the purpose of analysis, but your identity will not be revealed at any time.

The medical records, study data and findings can be accessed by staff restricted to the investigators and regulatory authorities but not the participants.

Your will not be informed regarding the study findings as the result will not affect your care of management.

15. Who should I call if I have questions?

If you have any questions about the study, and you want information about intervention, please contact the study doctors, Dr. Yong Soon Leong at telephone number 017-9197139 or Dr. Joyce Ting Chin Sing at telephone number 016-8948123.

We shall inform you if there is new information becomes available relevant to consent.

If you have any questions about your rights as a participant in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-2287 4032.

INFORMED CONSENT FORM

Title of Study:
Membrane Sweeping versus Transcervical Foley Catheter for Induction of Labour in Women with Previous Caesarean Delivery

By signing below I confirm the following:

I have been given oral and written information for the above study and have read and understood the information given.

I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.

I understand that my participation is voluntary and I can at anytime free withdraw from the study without giving a reason and this will in no way affect my future treatment. I am not taking part in any other research study at this time. I understand the risks and benefits, and I ***agree / disagree***(*delete which is not applicable)* to participate in the study as stated above.

I understand that I must follow the study doctor's (investigator's) instructions related to my participation in the study.

I understand that study staff, and governmental or regulatory authorities, have direct access to my medical record in order to make sure that the study is conducted correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL.

I will receive a copy of this subject information/informed consent form signed and dated to bring home.

Subject:
Signature: I/C number:

Name: Date:

Investigator conducting informed consent:
Signature: I/C number:

Name: Date:

Impartial witness:*(Required if subject is illiterate and contents of patient information sheet is orally communicated to subject)*
Signature: I/C number:

Name: Date:

Appendix 3

DEPARTMENT OF O&G, SIBU HOSPITAL, SARAWAK

DATA COLLECTION FORM

MEMBRANE SWEEPING VERSUS TRANSCERVICAL FOLEY CATHETER FOR INDUCTION OF LABOUR IN WOMEN WITH PREVIOUS CAESAREAN DELIVERY

Patient ID : .....

Name : ..... Date/time of admission: .....

IC Number : ..... Date/time of discharge : .....

MRN : .....

Age : .....

Ethnicity : ☐ Iban ☐ Melanau ☐ Bidayuh ☐ Malay

☐ Chinese ☐ Indian ☐ Other ☐ Foreigner

ALLOCATED GROUP: *(PLEASE TICK)*

MEMBRANE SWEEPING ☐ **TRANSCERVICAL FOLEY CATHETER** ☐

SECTION A: DEMOGRAPHIC INFORMATION

Gravida / Parity: ……../…… Gestational age at induction of labour: …….. weeks ……. days

EDD/REDD: ……..

Height (m): …….. Weight (kg): …… (at booking) …… (at delivery)

BMI (kg/m^2): ……

Previous Caesarean section: *(please tick)*

a) Untested scar ☐

b) Tested scar ☐

If untested scar, any previous vaginal delivery? ☐ Yes ☐ No

Indication of induction of labour: *(please tick)*

a) Postdate ☐

b) Fetal growth restriction ☐

c) Hypertension ☐

d) Diabetes ☐

e) Other ☐ *Please specify:* ……

SECTION B: INDUCTION OUTCOMES ***Modified Bishop score is used in this study*

Modified Bishop score:

a) At the start of induction ☐

b) When Foley catherter dislodged < 24 hours ☐ *(only applicable to Foley group)*

a) After 24 hours of induction ☐

b) After 48 hours of induction ☐

Achieved favourable Bishop (≥ 8) score: *(please tick)* ☐ Yes ☐ No

(if yes, proceed to sub-question;

If no, proceed to next question)

a) Interval to achieve favourable Bishop score _____ (hours)

Achieved cervix allowing amniotomy: *(please tick)* ☐ Yes ☐ No

(if yes, proceed to sub-question;

If no, proceed to next section)

a) Bishop score at that time _____

b) Os dilatation at that time _____ (cm)

c) Cervical length at that time _____ (cm)

SECTION C: DELIVERY OUTCOMES

Oxytocin required during delivery *(please tick)* ☐ Yes ☐ No

Mode of delivery: *(please tick)*

Vaginally ☐ Within 24 / 24-48 / > 48 hours of induction *(please circle)*

Instrumentation ☐ Vacuum / forceps *(please circle)*

Indication: _____

Caesarean section ☐ Indication: _____

Durations (regardless of final mode of delivery):

a) Induction to delivery _____ (hours)

b) Oxytocin augmentation _____ (minutes)

Durations (only for vaginal delivery including instrumental delivery):

a) Induction to vaginal delivery _____ (hours)

b) Amniotomy to vaginal delivery _____ (hours)

c) Oxytocin augmentation _____ (minutes)

Estimated blood loss (EBL): ……. ml

If EBL > 500ml, please mention cause: *(please tick)*

a) Uterine atony ☐

b) Perineal trauma ☐

c) Retained placenta ☐

d) Coagulopathy ☐

e) Others ☐ *Please specify:* ……..

Maternal complications: *(please tick)*

a) Uterine rupture ☐ Yes ☐ No

b) Uterine hyperstimulation ☐ Yes ☐ No

c) Post-partum haemorrhage ☐ Yes ☐ No

d) Maternal pyrexia ☐ Yes ☐ No

Neonatal outcomes:

a) APGAR score at 5 minutes _____ To: NICU / SCN / mother *(please circle)*

b) Cord pH _____

c) Birth weight _____

SECTION D: MATERNAL SATISFACTION

If you had to repeat it all over again, would you take part in the study? *(please tick)*

☐ Yes ☐ No

If no, please provide reason(s). _____

Notes:

Uterine hyperstimulation	:	*> 5 contractions per 10 minutes for at least 20 minutes or a contraction lasting at least 2 minutes with/without abnormal fetal heart rate*
Post-partum haemorrhage	:	*Estimated blood loss ≥ 500 ml*
Maternal pyrexia	:	*Temperature >38.0 °C once, or 37.5 °C on two occasions 2 hours apart*