PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	MAGPOP (Mechanical cervicAl ripeninG for women with PrOlonged Pregnancies): Protocol for a randomised controlled trial of a silicone double balloon catheter versus the Propess® system for the slow release of dinoprostone for cervical ripening of prolonged pregnancies
AUTHORS	Diguisto, Caroline; Le Gouge, Amélie; Giraudeau, Bruno; Perrotin, Franck

VERSION 1 – REVIEW

REVIEWER	Chris Wilkinson Women's and Children;s Hospital 72 King William Rd North Adelaide South Australia Australia
REVIEW RETURNED	22-Feb-2017

GENERAL COMMENTS	The protocol is clear and concise, with a well elucidated hypothesis, rationale and study plan. I would like to establish why the investigators chose a study population limited to a gestation between 41 and 42 weeks. The definition of prolonged pregnancies should also include pregnancies greater than 42 weeks to be generaliseable to international practice. (Inclusion of pregnancies greater than 42 weeks, as a higher risk group, may also increase the power of the study making it more likely to demonstrate differences in primary outcome). It makes little sense to limit the study unnecessarily. I do also have some concerns as to the blinded independent committee that would adjudicate the primary outcome at the end of the study. Although the rationale for this is made very clear in the protocol, this gives an opportunity to manipulate the primary outcome post hoc, which a cynical reviewer may suspect could be used to effect the integrity of the study results. To mitigate this, the outcomes of the study with and without this "adjustment" should be reported in the published results, so that the possible effect on such potential biases can be appreciated by the reader of the article.

REVIEWER	Nisha Lakhi MD Assistant Professor, New York Medical College Director of Research, Richmond University Medical Center, Department of Obstetrics and Gynecology Staten Island, New York, 10310
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	Overall this is a well written protocol comparing two methods of labor induction for post-term pregnancies: A 10 mg vaginal insert containing dinoprostone (Prostaglandin E2) versus a silicone double balloon catheter (Cook cervical ripening balloon). Other similar studies have evaluated the above methods of labor induction, and have found no difference in absolute cesarean delivery rate, or differences in vaginal delivery within 24 hours (BJOG. 2017 May;124(6):891-899). However, these studies have shown a significant increase in uterine activity in the prostaglandin group. Study Design: The authors differ from the above studies by choosing cesarean delivery for non-reassuring fetal heart rate as the primary endpoint. I feel that this is a highly subjective primary endpoint for a study. The decision to perform a cesarean section for non-reassuring fetal heart rate can vary based on obstetrical practices and the individual obstetrician. The authors have tried to minimize this variability by having an independent committee review each case to see if it was "justified". However, this is still open to subjectivity and interpretation based on the clinical experience of the examiner. Although the study is hypothesis driven, I do not think the primary outcome is robust or objectively measurable. A Category III tracing is an obvious need for cesarean delivery, and therefore no there is no subjectivity. However interventions for a Category II tracing can be variable and subjective based on obstetrical practice and provider experience. Interventions that could influence the primary outcome, such as tocolysis or removal or the vaginal insert/balloon catheter, can also be performed and will also vary by provider experience. Also, if the authors choose non-reassuring FHR as the primary endpoint, they should consider confining the analysis to the induction phase. Other obstetrical interventions can influence fetal heart rate activity during that augmentation of labor that are independent of induction method (ex oxytocin, amniotomy) Secondary Outcomes: The secondary outcomes were well defined and measurable. The authors list suspected maternal intra or postpartum infection as a secondary outcome. I suggest also incorporating presence of intrapartum maternal fever as a secondary outcome. Maternal fever can be due to infectious or non-infectious (eg. prostaglandin induction)aetiologies. Maternal fever is strongly correlated with fetal

	tachycardia and non-reassuring FHR. This could influence cesarean delivery rate. Statistical Analysis: The power analysis is accurate, and statistical test chosen for analysis are appropriate. Results/Conclusions: Not applicable Overall Critique: I think this study has merits, in that it focuses on pregnancies that are at risk of placental dysfunction (i.e post-term pregnancies). These patients require induction of labor and studies assessing the best methods and outcomes can be clinically useful. Although this topic has been studied previously, this study may add more information, or confirm current knowledge on the topic.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

2.1 I would like to establish why the investigators chose a study population limited to a gestation between 41 and 42 weeks. The definition of prolonged pregnancies should also include pregnancies greater than 42 weeks to be generaliseable to international practice. (Inclusion of pregnancies greater than 42 weeks, as a higher risk group, may also increase the power of the study making it more likely to demonstrate differences in primary outcome). It makes little sense to limit the study unnecessarily.

=> We aimed to study perinatal outcomes for prolonged pregnancies (41+0-42+0). Pregnancies over 42 weeks are known as “post-term pregnancies”. They are associated with an even higher foetal risk than prolonged pregnancies and represent only 1% of pregnancies. The foetal risk is so high that most obstetricians in France induce delivery before 42 weeks. The French National Perinatal Survey in 2010 showed only 0.3% of women delivered ≥ 42 weeks. Not including post term pregnancies will not induce a major power loss and will allow us to obtain a homogeneous population risk-wise.

2.2 I do also have some concerns as to the blinded independent committee that would adjudicate the primary outcome at the end of the study. Although the rationale for this is made very clear in the protocol, this gives an opportunity to manipulate the primary outcome post hoc, which a cynical reviewer may suspect could be used to effect the integrity of the study results.

To mitigate this, the outcomes of the study with and without this "adjustment" should be reported in the published results, so that the possible effect on such potential biases can be appreciated by the reader of the article

=> We agree with the reviewer’s comment and have added in the secondary outcomes the rate of “caesarean deliveries for non-reassuring foetal status (as defined by investigators)”.

Reviewer 2

3.1 Although the study is hypothesis driven, I do not think the primary outcome is robust or objectively measurable. A Category III tracing is an obvious need for cesarean delivery, and therefore no there is no subjectivity. However interventions for a Category II tracing can be variable and subjective based on obstetrical practice and provider experience. Interventions that could influence the primary outcome, such as tocolysis or removal or the vaginal insert/balloon catheter, can also be performed and will also vary by provider experience.

Also, if the authors choose non-reassuring FHR as the primary endpoint, they should consider confining the analysis to the induction phase. Other obstetrical interventions can influence fetal heart rate activity during that augmentation of labor that are independent of induction method (ex oxytocin, amniotomy)

⇨ Choosing the most appropriate outcome was difficult and we agree that the outcome "The caesarean rate for non-reassuring fetal status determined by an adjudication committee" needs to be discussed as is it already done in the "main outcome" and "adjudication committee" sections.
⇨ Stratification on centre is planned to minimize bias induced by differences of obstetrical practice and provider experience.
⇨ Analyses on the induction phase will be performed as "suspicious and pathological FHR" are secondary outcomes and will be recorded for both the induction phase and the labour phase.
⇨ Meta-analysis comparing mechanical to pharmacological cervical ripening methods showed that pharmacological methods was not only associated with increased non reassuring FHR but also with more vaginal instrumental deliveries and more hospitalisation of neonates. We believe that the effect of the cervical ripening method is not limited to the induction phase which justifies the choice of our outcome which occurs in the labour phase.

3.2 The authors list suspected maternal intra or postpartum infection as a secondary outcome. I suggest also incorporating presence of intrapartum maternal fever as a secondary outcome. Maternal fever can be due to infectious or non-infectious (eg. prostaglandin induction)aetiologies. Maternal fever is strongly correlated with fetal tachycardia and non-reassuring FHR. This could influence cesarean delivery rate.

=> We agree with the reviewer's comment and have added "maternal fever during labour" in the secondary outcomes.

VERSION 2 – REVIEW

REVIEWER	Assoc Professor Chris Wilkinson Women's and Children's Hospital North Adelaide 5006 South Australia Australia
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	This is a protocol for a RCT of a double balloon catheter compared to a slow release dinoprostone system for cervical ripening in post dates pregnancies. The investigators propose using a primary outcome of caesarean section for fetal distress secondary to uterine hyperstimulation , reasoning that pharmacological cervical ripening is more likely to cause hyperstimulation and subsequent caesarean section

	particularly in post dates pregnancies, which the authors claim are "more susceptible to this." They make the distinction that that this is the first study of pharmacological versus mechanical cervical priming to exclusively study post dates pregnancy. This appears to be true, but many of the previous studies were of "low risk pregnancies" of which post dates pregnancies were a significant proportion. For example, 35 to 36% of the women in the PROBAT study(1) were induced because they were post dates. Between 69 and 75% of the women in Henry's RCT were induced because of post dates(2). 29 to 30% of Lallad's study were post dates (3). None of these studies found a difference in caesarean section, as the investigators of this protocol are hypothesising. It would perhaps be much easier and cheaper than this trial to simply conduct an IPD analysis of all post dates women in the other trials, looking at post dates as a confounder. The actual susceptibility of a fetus between 41 and 42 weeks gestation to increased caesarean section from hyperstimulation is also not really established by the investigators. The reasoning from many post dates induction protocols, is that induction between 41 and 42 weeks gestation is intended to prevent women taking their pregnancy past 42 weeks gestation, and the increased susceptibility to stillbirth, fetal distress and caesarean section that is established from good level 1 evidence past that point. (4) I note that the double ripening balloon is being inserted for 24 hours (why was 24 hours chosen, when there is level 1 evidence that there appears to be no advantage of 6 hours over 12 hours?(5)). A cynical reviewer may conclude that this is a deliberate artificial construct to even the playing field so that the time from induction to delivery for each arm is the same. This would call into question the generaliseability of the results of the trial to actual clinical practice The protocol states that if the catheter is expelled, then a new catheter is not inserted (p9 line 19) as the cervix will be at least 2 cm dilated. The authors should be careful, as a proportion of catheters will "fall out" that have not been properly inserted, particularly as the investigation is multi centre. Unless the investigators are routinely requiring that woman have a point of care ultrasound to check position of the balloons , a small number of catheters will be ineffective, and this may bias the results in favour of the dinoprostone group. I hope that these constructive criticisms may be helpful to improve this protocol. 1. Jozwiak M, Oude Rengerink K, Benthem M, van Beek E, Dijksterhuis MG, de Graaf I. Foley catheter versus vaginal prostaglandin E2 gel for induction of labor at term (PROBAAT trial): an open label, randomized controlled trial. Lancet. 2011;378:2095 - 103. 2. Henry A, Madan A, Reid R, Tracy S, Austin K, Welsh A, et al. Outpatient Foley catheter versus inpatient prostaglandin E2 gel for induction of labour: a randomised trial. BMC Pregnancy and Childbirth. 2013;13(25):11. 3. Laddad M, Kshirsagar N, Karale A. A prospective randomized comparative study of intra-cervical Foley\s catheter insertion versus PGE2 gel for pre-induction cervical ripening. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2013:217-20. 4. Gulmezoglu AM, Crowther CA, Middleton P, Heatley E. Induction

	of labour for improving birth outcomes for women at or beyond term. Cochrane Database Syst Rev. 2012;6(6):CD004945. 5. Mattingly P, Temming L, Bliss S. Cervical Ripening With a Double-Lumen Balloon Catheter for 6 Compared With 12 Hours: A Randomized Controlled Trial Obstetrics & Gynecology. 2015;125:p.71S.

REVIEWER	Nisha Lakhi MD, FACOG New York Medical College, USA
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	I think the authors have answered questions adequately. I am still weary about the potential for bias and variability in the primary outcome, but the authors have take much effort to mitigate this, and have taken steps to acknowledge the potential limitations.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

1.1 I would like to establish why the investigators chose a study population limited to a gestation between 41 and 42 weeks. The definition of prolonged pregnancies should also include pregnancies greater than 42 weeks to be generaliseable to international practice. (Inclusion of pregnancies greater than 42 weeks, as a higher risk group, may also increase the power of the study making it more likely to demonstrate differences in primary outcome). It makes little sense to limit the study unnecessarily.

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