Oral misoprostol alone compared to oral misoprostol followed by oxytocin in India: a multicentre randomised trial in women induced for hypertension of pregnancy.

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Abstract

Objective: To assess whether, in those requiring ongoing uterine stimulation after cervical ripening with oral misoprostol and membrane rupture, augmentation with low dose oral misoprostol is superior to intravenous oxytocin. **Design:** Open-label, superiority randomised trial **Setting:** Government hospitals in India **Population:** Women induced with oral misoprostol for hypertensive disease in pregnancy and requiring ongoing induction after membrane rupture **Methods**: Participants received misoprostol (25mcg orally two hourly) or titrated oxytocin through an infusion pump. **Main Outcome Measure:** Caesarean birth **Results**: 520 women were randomised and the baseline characteristics were comparable between the groups. The caesarean section rate was not reduced by the use of misoprostol (misoprostol 32.3% vs oxytocin 27.3%; adjusted odds ratio 1.226 (95% CI 0.81-1.85, p=0.33)). There were no differences in rates of hyperstimulation, fetal heart rate abnormalities, or maternal side effects, although the geometric mean time from randomisation to birth was 31 minutes longer with misoprostol. Fewer babies in the misoprostol arm were admitted to the special care unit (10 vs 21 in the oxytocin group) and there were no neonatal deaths in the misoprostol group, compared to 3 in the oxytocin arm. Women's acceptability ratings were high in both study groups. **Conclusion**: Following cervical preparation with oral misoprostol and membrane rupture, the use of ongoing oral misoprostol for augmentation did not significantly reduce caesarean rates compared to oxytocin. The method, however, was safe for both mother and baby.

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ABSTRACT

Objective : To assess whether, in those requiring ongoing uterine stimulation after cervical ripening with oral misoprostol and membrane rupture, augmentation with low dose oral misoprostol is superior to intravenous oxytocin.

Design: Open-label, superiority randomised trial

Setting: Government hospitals in India

Population: Women induced with oral misoprostol for hypertensive disease in pregnancy and requiring ongoing induction after membrane rupture

Methods : Participants received misoprostol (25mcg orally two hourly) or titrated oxytocin through an infusion pump.

Main Outcome Measure: Caesarean birth

Results : 520 women were randomised and the baseline characteristics were comparable between the groups. The caesarean section rate was not reduced by the use of misoprostol (misoprostol 32.3% vs oxytocin 27.3%; adjusted odds ratio 1.226 (95% CI 0.81-1.85, p=0.33)). There were no differences in rates of hyperstimulation,

fetal heart rate abnormalities, or maternal side effects, although the geometric mean time from randomisation to birth was 31 minutes longer with misoprostol. Fewer babies in the misoprostol arm were admitted to the special care unit (10 vs 21 in the oxytocin group) and there were no neonatal deaths in the misoprostol group, compared to 3 in the oxytocin arm. Women's acceptability ratings were high in both study groups.

Conclusion : Following cervical preparation with oral misoprostol and membrane rupture, the use of ongoing oral misoprostol for augmentation did not significantly reduce caesarean rates compared to oxytocin. The method, however, was safe for both mother and baby.

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INTRODUCTION

Hypertensive disease in pregnancy is a major cause of maternal deaths.[1] Many of the deaths could be prevented by timely and effective delivery, but labour induction itself carries risks. Identifying a safe and effective method suitable for low- and middle-income settings is a critical public health intervention.

Low dose oral misoprostol (LDOM) is a highly effective method of induction. Oral administration of 25 micrograms every 2 hours has received a strong recommendation by both WHO and NICE for cervical preparation.[2,3] Cochrane reviews of LDOM found that it is more effective than the commonly used vaginal dinoprostone gel,[4,5] and it has the added advantages of being heat stable and low cost in many settings.

Standard practice for induction is to use a prostaglandin (e.g. misoprostol or dinoprostone) for cervical preparation. Once active labour commences and the amniotic membranes rupture, the prostaglandin is replaced with an intravenous infusion of oxytocin if required.[6] The infusion is titrated every 30 minutes to stimulate uterine contractions sufficient to progress labour, but not so much as to cause hyperstimulation. In many countries, electronic infusion pumps are not available, and oxytocin is administered through a gravity drip infusion. These poorly regulated infusions require constant supervision as inadvertent overdosing can lead to hyperstimulation, with associated maternal and fetal risks.[7,8] There is a need, therefore, to identify cost-effective means of induction in which the uterotonic can be administered in a safe and standardised way.

In the Cochrane review of LDOM for labour induction, the LDOM was continued into active labour in 2 studies, whilst in the remaining 57 the stimulation was changed to oxytocin after artificial membrane rupture.[4,9] The main outcomes following continued use of LDOM into active labour were equivalent or better than in the comparator arms.

Use of ongoing LDOM allows women to be free to mobilise in labour, unrestricted by an intravenous infusion, and it could empower women to be more involved in their care. There could also be significant health system savings with less use of equipment and staff time.

Despite its promise, an induction protocol continuing LDOM into labour has never been directly compared to the standard oxytocin regimen in a randomised trial. The study objective was to assess whether, in those requiring ongoing uterine stimulation after cervical ripening with oral misoprostol and membrane rupture, augmentation with LDOM is superior to intravenous oxytocin.

Funding

Funding was provided by the MRC, Foreign, Commonwealth and Development Office (FCDO), National Institute for Health Research (NIHR) and Wellcome Trust (MR/R006/180/1) and included external peer review. The funder attended Trial Steering Committee meetings, but otherwise played no part in the conduct of the research or writing the paper.

Methods

Study design

This was a pragmatic, parallel group, open-label, superiority randomised control trial of two protocols for labour induction among women with hypertension of pregnancy. All women underwent initial cervical preparation with low dose oral misoprostol; and those who required ongoing induction after membrane rupture were randomised in a 1:1 ratio to LDOM or intravenous oxytocin. The study protocol has been published,[10] but brief methods are outlined below.

Participants

Women planning to give birth in three government hospitals in central India were recruited to this trial: Government Medical College, Nagpur and Daga Memorial Women's Hospital Nagpur, and Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha. Women with an indication for induction due to hypertensive disease, irrespective of gestation, and who required cervical preparation for an unfavourable cervix (Bishop's score [?] 6) were recruited prior to the start of induction. All consenting women then underwent cervical preparation with LDOM 25mcg 2 hourly. However, only those who subsequently required augmentation following artificial rupture of membranes were randomised. Most did not have prior ultrasound unless growth restriction was suspected clinically prior to the development of hypertension or if the onset was before 34 weeks' gestation. Those with a previous caesarean section, age <18 years old, known intrauterine fetal death, or multiple pregnancy were excluded.

Randomisation and masking

Potential participants were informed of the study through posters in the antenatal areas and labour ward. Once a clinical decision was made for induction, the woman was provided with an own-language information sheet and a brief slide presentation to view on a tablet. If she was unable to read, a member of the research team read the forms to her in her own language in the presence of family members and/or friends. If she wished to participate, then she signed (or placed a thumb print) on the consent form. If she then required ongoing induction after membrane rupture as part of the induction process, she was randomised to receive misoprostol or oxytocin without the need for additional written consent.

For randomisation, the next consecutive, sequentially numbered opaque envelope containing the allocation was drawn from the trial dispenser by the research assistant and opened. The treatment allocation was generated independently using a computerised pseudo-random number generator, stratified by centre with random block sizes of 4, 6 and 8. Neither participant, researcher nor clinical team were blinded to the allocated treatment.

Procedures

Induction for all women commenced with cervical preparation using 25 mcg oral misoprostol tablets (Cipla Ltd, Goa, India) every 2 hours. Once painful contractions started, labour monitoring commenced with assessments every 30 minutes with a vaginal examination every 4 hours. The next dose of oral misoprostol was omitted when 3 or more moderate or strong contractions occurred every 10 minutes. Artificial rupture of membranes (ARM) was performed as per routine clinical practice when the cervix was 2cm dilated. If spontaneous rupture of membranes occurred before that point, then the cervical preparation doses of misoprostol were stopped. If contractions were inadequate, then LDOM could be restarted as part of the randomised trial.

After membrane rupture, if contractions continued at 3 in 10 or more and there was progressive cervical change (defined as at least 1cm every 2 hrs) then no further LDOM was used, and the participants were not randomised. If, however, the contractions reduced to less than 3 in 10 or if there was no progressive cervical change, then the woman was randomised to either continued LDOM or an oxytocin infusion. This was the point of trial entry. If the cervix was still not favourable for ARM after 24 hours of cervical preparation, then the decision regarding the ongoing management was by the clinical team but was usually a caesarean birth.

The misoprostol 25mcg was given orally every 2 hours in the absence of adequate uterine activity. There was no titration of the misoprostol dose, but the next dose was withheld in the presence of regular uterine

activity and only restarted if contractions became inadequate or if there was inadequate cervical change (<1cm every 2 hours). For the oxytocin infusion, 5IU oxytocin (Pfizer Limited, Nani Daman, India) in 500 mL of Ringer's lactate was given through an electronic infusion pump at a rate of 2 mU/min, and increased every 30 min by 2 mU/min to a maximum of 20mU/min until there were 3-4 contractions every 10 min. If there was any suspicion of fetal distress due to excessive uterine activity, then the oxytocin infusion was stopped, and the participant was put in a left lateral position and continuous electronic fetal heart rate monitoring started.

Maternal and fetal monitoring was conducted on a one-to-one basis by graduate research assistants, specifically trained on fetal monitoring and uterine contraction strength. Intermittent electronic fetal monitoring was done every 30 minutes with continuous electronic fetal monitoring in case of abnormality. Continuous fetal monitoring was also used routinely in high-risk women when available. In case of hyperstimulation, staff were instructed to commence electronic fetal monitoring and, in the event of abnormality, reduce the dose of oxytocin.

Outcomes

Outcomes were based on the Cochrane Collaboration induction of labour generic protocol[11] and the induction of labour core outcome set.[12] The primary outcome was caesarean birth. Secondary outcomes addressed the success of the induction process, maternal mortality and morbidity, and neonatal morbidity and mortality. Measures of success included the randomisation to birth interval, duration of hospital stay and satisfaction. Data was collected using REDCap (Vanderbilt University, Tennessee, USA). A qualitative study, situational analysis and health economic analysis were also conducted and will be reported separately.

Sample size calculation

In a previous study of labour induction conducted in this population, 157 (52%) women required uterine stimulation after membrane rupture with intravenous oxytocin (standard practice), of whom 49 (31%) had a caesarean birth.[12] In a systematic review of LDOM, those whose induction was continued after membrane rupture with LDOM had 42% less caesarean sections than those who changed to oxytocin (15% vs 26%).[5] Using this data, it was estimated that a total sample size of 520 women would provide (a) 90% power to detect a reduction in the CS rate from 31% to 18.5% (RR 0.6), or (b) 80% power to detect a reduction in the CS rate from 31% to 20% (RR 0.65) in those women who receive LDOM (superiority; two sided α=0.05). It was proposed to approach and gain consent from 1000 women of whom an estimated 520 would require ongoing induction after cervical preparation. At the point of requiring uterotonics for ongoing induction, consented women would be randomized to either a protocol of continued LDOM (n=260) or the standard oxytocin infusion (n=260).

Statistical analysis

The primary outcome was CS, analysed according to the intention-to-treat principle. The primary outcome measure was evaluated using logistic regression models, initially unadjusted and then after adjustment for pre-determined important potential confounding variables and covariates. Effect sizes are presented as the odds ratio in CS delivery rates between the two study treatment arms with its 95% confidence interval. Secondary outcome measures were also evaluated unadjusted and then, where possible, adjusted for the same pre-determined variables and covariates using logistic regression, ordinal (ordered) logistic regression, Poisson regression, Cox proportional hazards and standard regression models according to data type. Stata was used for all analyses.

A formal interim analysis was performed by an independent data and safety monitoring committee (IDSMC) after 214 women were randomised, whilst safety data was reported bi-annually. Stopping rules for the interim analysis were in accordance with O'Brien and Fleming.[13] The IDSMC had the authority to request further interim analyses if indicated but this was not exercised.

The study was sponsored by the University of Liverpool, registered with ClinicalTrials.gov (NCT03749902) and the Clinical Trial Registry, India (CTRI/2019/04/018827). Consumer representatives reviewed the

protocol and participant-facing documentation at all stages, and a representative sat on the Trial Steering Committee.

RESULTS

Overall, 1033 women were recruited to participate in the MOLI study between 6th of January 2020 and the 14th July 2022 when the sample size was reached (Figure 1). Two of the participating government hospitals, located in Nagpur, India, recruited participants from the launch of the study in 2020 till the trial ended. Recruitment was temporarily halted on 19th March 2020 due to the COVID-19 pandemic, before restarting again from 1stOctober 2020 with additional precautions against infection for participants and staff in line with Indian government recommendations. A third site, Mahatma Gandhi Institute of Medical Science in Sevagram, was added and began enrolling patients in February 2021.

Of the 1033 women, 520 required ongoing induction after membrane rupture following cervical preparation with LDOM. These women were randomised to receive either continued LDOM (n = 260) or oxytocin infusion (n = 260). There was no missing data or loss to follow-up. Prior to randomisation, the participants had received a mean (s.d.) of 2.9 (1.7) and 3.0 (1.7) doses of LDOM respectively for cervical preparation. Membrane rupture was spontaneous in 65 (25.0%) and 60 (23.1%) respectively; the remainder underwent artificial membrane rupture.

The two randomised groups were well matched by age, parity, and severity of disease (Table 1). Most women had not given birth previously, were close to their ultrasound-estimated delivery date and mild non-proteinuric hypertension.

The primary outcome of caesarean section (CS) was similar in the two arms: 84 (32.3%) for women who had ongoing induction with LDOM and 71 (27.3%) for those who received oxytocin infusion (adjusted odds ratio 1.226 (95% confidence interval 0.814 - 1.847); p = 0.329 (Table 2)). The most common reasons for CS were progress failure in the 1st stage of labour and fetal heart rate abnormalities; no statistically significant differences were detected between the two study arms. In an exploratory subgroup analysis, the preterm gestations showed a statistically significant increase in CS in the misoprostol group (Figure 2).

Rates of fetal heart rate abnormality and meconium-stained liquor were similar in each group. There were no cases of uterine hyperstimulation (contractions >5 in 10 minutes), no differences in the rates of placental abruption, postpartum haemorrhage, manual removal of placenta, receipt of blood products, or hypertensive complications. No woman in either group experienced a uterine rupture, admission to intensive care or death.

Women in the LDOM group took a statistically longer time to give birth (geometric mean time from randomisation to birth 225 versus 194 minutes in the oxytocin group; Figure 4), with the difference driven by those who had normal vaginal births. There was no statistically significant difference for those who underwent CS.

Fewer babies allocated to the LDOM group were admitted to the special care baby unit (Table 3); while these babies tended to spend more time there, this difference was not statistically significant (p=0.510). Furthermore, there was no statistically significant difference between the babies receiving ventilation, resuscitation, or intubation. All other neonatal outcomes were similar between the two arms. Three babies died neonatally and all were in the oxytocin arm. The causes of death were septicaemia (a 2.5kg baby), asphyxia (a 1.7kg baby with severe hypoxic-ischaemic encephalopathy with pulmonary bleed and with cardiovascular arrest), and severe growth restriction (1.1kg baby with a severe pulmonary bleed). None were thought to be related to the study medications.

After giving birth, participants in both groups showed high levels of acceptability with their augmentation method (Figure 3, Table 4). Only 16 (6.2%) of the women in each group would not be happy to have the same method used again for future inductions if needed. There was no difference between groups in their

acceptability ratings on the time taken to give birth, the amount of pain during the induction and birth, or their anxiety.

DISCUSSION

Main Findings

To the best of our knowledge, this is the first randomised trial to compare the safety and efficacy of an induction protocol in which LDOM was used instead of oxytocin following membrane rupture. It demonstrates that in this setting, ongoing induction with LDOM after membrane rupture did not reduce the caesarean section rate. It was however safe, with some evidence that it may even be safer than the oxytocin.

Strengths and Limitations

The strengths of this study are that it was conducted to international standards with UK sponsor oversight and regular monitoring visits to ensure compliance. The presence of a one researcher, allocated to each recruited woman throughout her induction and labour ensured that the data was fully collected and that hyperstimulation, a factor that is often poorly recorded, could be accurately assessed every 30 minutes throughout the labour. Although this process lessened the study's external validity, it ensured that the study had complete follow-up and no missing data, despite being conducted in busy delivery units. The inclusion of two teaching hospitals in an urban and rural setting, and a district hospital allowed us to assess the effect of the intervention across three different types of delivery settings. A detailed comparison of the trial data between the study sites will be published elsewhere.

It is very difficult to blind a study in which a titrated infusion is compared with an oral tablet, and an open label study is prone to clinician and researcher bias. Furthermore, the use of a placebo infusion would have nullified any mobility effect of the use of LDOM for ongoing induction after membrane rupture. Nevertheless, bias is particularly a risk in this study where some clinicians reported being anxious about the risks of LDOM in labour and being reluctant to give over 3 doses. This could have led to an excess of CS in the LDOM group after 6 hours, but this was not seen in the survival curves (Figure 4).

Interpretation

There are no previous randomised trials comparing these two stimulation methods during labour induction, although the regimen has been previously described.[9,14] There are also one randomised trial in which low dose oral misoprostol has been used for augmentation of spontaneous labour to accelerate slow progress.[15] In that study the LDOM group had lower rates of tachysystole than the oxytocin – but there was no difference in any other maternal or neonatal outcome. On the basis of the small size of studies and the potential risks of misuse, WHO recommended that it should not be used for augmentation.[16]

This study supports the previous evidence that suggest that LDOM is a safe and effective method of ongoing stimulation after cervical preparation with LDOM, although the reduction in CS that had been anticipated was not achieved. Although this study was not powered for neonatal outcomes, the safety signals in special care baby unit admission and neonatal deaths are both in favour of LDOM. Safety of induction is especially important in settings where there are cases of undetected growth restriction. In this study, the three babies who died were all small (2.5kg, 1.7kg and 1.1kg) and would have been vulnerable to intrauterine hypoxia even in the absence of hyperstimulation. Given the historical concerns with misoprostol, the increased risk of this patient population, and the lack of previous studies on this method, it was important to provide close individual monitoring to detect and treat any hyperstimulation. It was not however detected in either arm. Induction with LDOM is recognised to have very low rates of hyperstimulation, equivalent to balloon catheter cervical preparation,[4] so the absence of hyperstimulation in over 500 women undergoing labour induction is not surprising.

Ongoing induction with an oxytocin infusion is a complex process, and not only requires an infusion pump and intravenous set, but also close skilled supervision by an appropriately trained maternity care worker to monitor and titrate the dose. The opportunity to replace this whole process with a tablet that can be taken

orally is attractive to clinical staff, labouring women and health service funders alike. Qualitative and health economic assessments to formally assess these issues have been conducted and will be published separately. However, the maternal satisfaction scales in this study suggest that replacing an intravenous infusion method with an oral tablet did not affect satisfaction rates. This mirrors the qualitative study which found that women prioritised the safety of their babies over any particular method of induction.

The simplicity of the LDOM protocol could also have adverse consequences if it encouraged labour induction or augmentation in the community or by unskilled birth attendants. There have been reports of adverse outcomes from unauthorised intrapartum use of both oxytocin and misoprostol in the community,[17,18] and the rate of adverse events is likely to be worsened by the frequent confusion over dosage and routes for both agents. National health care regulators should ensure that the public and informal health care workers are informed about the risks of unregulated use of misoprostol in labour, so that woman and their babies are not put at risk.

Further research is needed to understand whether these positive results can be replicated in other settings. The simplified induction protocol using an oral medication combined with the very low rate of hyperstimulation makes use of LDOM particularly attractive for low resource settings where fetal monitoring and close intrapartum medical supervision cannot be guaranteed for monitoring and titration of the oxytocin dose. LDOM is also an attractive protocol for high resource settings where de-medicalisation of maternity care is valued by many and there are fewer concerns regarding its unregulated use by informal health care workers.

CONCLUSIONS

In this study of ongoing labour induction after cervical preparation with LDOM and membrane rupture, the use of LDOM as an alternative to oxytocin infusion did not reduce the need for caesarean section. No cases of uterine hyperstimulation were seen in either group and the maternal and neonatal outcomes were reassuring with LDOM. Satisfaction rates in both groups were high and comparable, even though the time to birth was, on average, 31 minutes longer with LDOM than with oxytocin. We conclude that ongoing labour induction with LDOM is a safe and effective option after cervical preparation with LDOM and membrane rupture.

ADDITIONAL INFORMATION

Contributors

The idea for the study evolved from the former INFORM study conducted by the same investigator group. ADW led the grant application, chaired the trial management group and wrote the first draft of the paper; he is the study guarantor. SM, HB, BF, TE, SL, MTu, ZA, BW and ADW wrote the grant application. SM was the lead investigator in India, whilst MTa, SP and PVS were the site principal investigators with local responsibility for study conduct and data collection. KL and HB (replaced in Jan 2021 by JD) were the trial managers. BF was the trial statistician and conducted the analysis. SM, KL, HB/JD, BF, BW and ADW formed the trial management committee. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Data Sharing

The data from this study will be confidential until the database is closed at the end of the study. Following this the study investigators will have exclusive access to the data until the publication of the results in a journal. Once this has happened, the database will be open to other researchers upon request. Open access databases will also be sought so as to maximise the availability of our research data with as few restrictions as possible, in line with MRC and Wellcome Trust policy. The consent form included a clause for women to give their permission for anonymous data to be used for future research studies.

Declaration of Interests

Professor Weeks runs an information website called misoprostol.org on a voluntary basis which receives no income. He also acted as a scientific advisor to Norgine from 2021-2. In this role he received no personal

remuneration other than travel expenses, but money was paid to the University of Liverpool for his time. The other authors declare that they have no competing interests.

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Trial Steering Committee: A Shennan (Chair), L Marions, A Medina-Lara, U Sharma; Independent Data and Safety Monitoring Committee: D Elbourne (Chair), A Muthal-Rathore, J Vogel, C Sutton. We thank the MRC, Wellcome Trust, NIHR and UK government for providing funding for the study through the Joint Global Health Trials scheme.

Ethics approval and consent to participate

This trial underwent peer review as part of the funding process. It is sponsored by the University of Liverpool (Brownlow Hill, Liverpool L69 7ZX, UK; UoL001374) which oversees the study quality and has final responsibility for the study conduct. The study was approved by the Institutional Ethics Committees at Government Medical College Nagpur (1724 EC/Pharmac/GMC/NGP), Spandan Heart Institute and Research Center (MOLI Study), the Mahatma Gandhi Institute of Medical Sciences (MGIMS/IEC/OBGY/96/2020) and the University of Liverpool (UoL001374). The study is insured by the sponsor (for harm arising from protocol design) and by the recruiting sites (for clinical negligence). The study is registered with ClinicalTrials.gov (NCT03749902) and Clinical Trial Registry, India (CTRI/2019/04/018827). All women enrolled in the trial provided informed written consent.

REFERENCES

1. World Health Organization, United Nations Children's Fund (UNICEF) & United Nations Population Fund. (2023). Improving maternal and newborn health and survival and reducing stillbirth: progress report 2023. World Health Organization.

2. World Health Organization. WHO recommendations for induction of labour. Geneva: World Health Organization; 2011.

3. National Institute of Clinical and Care Excellence (NICE). Inducing Labour (NICE Guideline NG207). NICE, November 2021.

4. Kerr RS, Kumar N, Williams MJ, Cuthbert A, Aflaifel N, Haas DM, Weeks AD. Low-dose oral misoprostol for induction of labour. Cochrane Database of Systematic Reviews. 2021 Jun 22;6(6):CD014484.

5. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, Navaratnam K, Caldwell DM. Labour induction with prostaglandins: a systematic review and network meta-analysis. BMJ. 2015 Feb 5;350:h217.

6. World Health Organization. Reproductive Health. Managing complications in pregnancy and childbirth: a guide for midwives and doctors. 2nd edition. World Health Organization; 2017.

7. Dujardin B, Boutsen M, De Schampheleire I, Kulker R, Manshande JP, Bailey J, Wollast E, Buekens P. Oxytocics in developing countries. International Journal of Gynecology & Obstetrics. 1995 Sep 30;50(3):243-51.

8. Lovold A, Stanton C, Armbruster D. How to avoid iatrogenic morbidity and mortality while increasing availability of oxytocin and misoprostol for PPH prevention? International Journal of Gynaecology & Obstetrics. 2008 Dec;103(3):276-82.

9. Hofmeyr GJ, Alfirevic Z, Matonhodze B, Brocklehurst P, Campbell E, Nikodem VC. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. BJOG: An International Journal of Gynaecology & Obstetrics. 2001 Sep 1;108(9):952-9.

10. Bracken, H., Lightly, K., Mundle, S., Kerr, R., Faragher, B., Easterling, T., Leigh, S., Turner, M., Alfirevic, Z., Winikoff, B., & Weeks, A. (2021). Oral Misoprostol alone versus oral misoprostol followed by oxytocin for labour induction in women with hypertension in pregnancy (MOLI): protocol for a randomised controlled trial. BMC Pregnancy and Childbirth, 21(1), 537.

11. Hofmeyr, GJ, et al. Methods for cervical ripening and labour induction in late pregnancy: generic protocol. The Cochrane Library (2009).

12. Dos Santos F, Drymiotou S, Antequera Martin A, Mol BW, Gale C, Devane D, Van't Hooft J, Johnson MJ, Hogg M, Thangaratinam S. Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. BJOG: An International Journal of Obstetrics & Gynaecology. 2018;125(13):1673-1680.

13. O'Brien, PC, Fleming, TR. A Multiple Testing Procedure for Clinical Trials. Biometrics. 1979 35 (3): 549–556.

14. Dallenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. American Journal of Obstetrics and Gynecology 2003;188(1):162-7.

15. Ho M, Cheng SY, Li TC. Titrated oral misoprostol solution compared with intravenous oxytocin for labor augmentation: a randomized controlled trial. Obstetrics and Gynecology. 2010 Sep;116(3):612-618.

16. World Health Organization. WHO recommendations for augmentation of labour. Geneva: World Health Organization; 2014.

17. Forna F, Titulaer P, Sesay S, Conteh S, Muoghalu S, Kanu P, Moses F, Kenneh S, Kayita J. Prevalence of use of highly concentrated oxytocin or "pepper injection" in labor among clinicians undergoing emergency obstetric training in Sierra Leone. International Journal of Gynecology & Obstetrics. 2020 Dec;151(3):450-455.

18. Kujabi ML, Mikkelsen E, Housseine N, Obel J, D'Mello BS, Meyrowitsch DW, Hussein K, Schroll JB, Konradsen F, van Roosmalen J, van den Akker T, Maaløe N. Labor augmentation with oxytocin in low- and lower-middle-income countries: a systematic review and meta-analysis. American Journal of Obstetrics and Gynecology Global Reports. 2022 Oct 21;2(4):100123.

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