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Up to date on oral misoprostol for induction of labour: an expert opinion on its use in Italian clinical practice

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ABSTRACT

Labour induction (IOL) is a standard practice in obstetrics, with the aim to facilitate the initiation of labour for obstetrical, maternal, or foetal indications. Among pharmacologic agents, oral misoprostol has emerged as a leading choice due to its efficacy, safety, compliance, and good outcomes compared to other methods. Recent meta-analyses have demonstrated the benefits of low-dose oral misoprostol (≤ 50 mcg) in reducing caesarean delivery rates while maintaining a favourable safety profile. Clear indications about monitoring and a systematic guideline about the use of this drug do not exist yet. This article presents a comprehensive overview of the clinical evidence, expert recommendations, and practical applications of oral misoprostol for IOL, with a particular focus on dosing protocols, monitoring strategies, combination with mechanical methods and women's opinion about the method.

INTRODUCTION

Induction of labour (IOL) is the process for artificially stimulating uterine contractions in pregnant women to start the labour and to achieve a vaginal delivery ideally within 24-48 hours, even if a definite cut-off of time to delivery does not exist [1, 2]. In the recent decades, induction rates increased expo-

nentially, due to the advanced maternal age and to the number of high-risk pregnancies. According with data from CeDAP (Certificato di Assistenza al Parto) 2023, IOL has nowadays a prevalence of 33.7% in Italy [3].
IOL is indicated for many obstetric, maternal, and foetal indications when the risk of continuing the pregnancy outweighs the risks of induction for the mother and/or for the foetus. Once after a shared decision-making process the clinician opts for labour induction, IOL typically includes cervical ripening, if needed, followed by the stimulation of uterine contractions and the subsequent management of latent and active phases of labour. When cervical ripening is indicated, mechanical and/or pharmacological (prostaglandins) interventions can be used [1].
Misoprostol is a synthetic analogue of prostaglandin (PG) E1 that is actually the only drug available for IOL that acts by two different mechanisms: firstly, it promotes cervical ripening by softening the cervix through the degradation of collagen in the connective tissue stroma; secondly it allows myometrial contractions through binding to PG receptors at the uterine smooth muscle cells [4, 5].
Many trials have evaluated the efficacy and safety of misoprostol for IOL. A systematic review by Alfirevic *et al*. of 76 randomized controlled trials (14,412 women) demonstrated that oral misoprostol is non-inferior to other methods in terms of efficacy, with a lower rate of caesarean sections compared to vaginal dinoprostone (RR 0.88, 95%CI 0.78-0.99) [6]. A recent meta-analysis by Kerr *et al*. also supported the use of low-dose oral misoprostol (50 mcg or less), showing that it resulted in fewer caesarean deliveries and increased vaginal births compared to vaginal dinoprostone, oxytocin, and the transcervical Foley catheter. Furthermore, oral misoprostol was associated with a lower incidence of hyperstimulation with foetal heart rate changes compared to vaginal misoprostol. Despite vaginal misoprostol leads to higher rates of vaginal delivery within 24 hours, oral misoprostol provided comparable outcomes with the additional benefit of fewer hyperstimulation-related foetal heart rate changes [7]. These findings suggest that low-dose oral misoprostol is an effective and safe choice for IOL, reducing the incidence of caesarean sections and promoting vaginal deliveries [6, 7].
In summary, Italian guidelines promoted by Ragonese Foundation report that the strength of the recommendations and the level of evidence regarding the use of misoprostol, demonstrates its efficacy and superiority compared with PGE2-based drugs [8].
As shown, the literature supporting the use of misoprostol for IOL is extensive, but these trials have been conducted using a wide variability in term of protocols.
Furthermore, the available data does not provide mandatory guideline regarding the timing of monitoring during misoprostol-induced labour. For this reason, the Italian Society of Perinatal Medicine (SIMP) has recently issued recommendations on monitoring timing during labour induction with various pharmacological methods, emphasizing that in the case of misoprostol, monitoring with cardiotocography should be performed prior to the initiation of the procedure as usual, 30-60 minutes after the first dose considering the peak of action of the active molecule. Thereafter the monitoring with cardiotocography may be based solely on clinical indications [9].
In this view the aim of our study is to provide a practice guideline about the use of oral misoprostol for induction of labour.

METHODS

A Panel of Italian Expert evaluated and investigated the rational basis and best practices for the use of oral misoprostol in pregnant women for cervical maturation and IOL in Italy, based on a wide clinical experience on that subject.
During the Expert Meeting, the following issues regarding the use of oral misoprostol were discussed:

- indications for IOL in childbirth and role of misoprostol;
- induction protocols and dosage schedule;
- cardiotocography monitoring;
- combination of misoprostol with other methods;
- role of woman's preference/experience in the choice of method for IOL.

Indications for IOL in childbirth and use of misoprostol

Expert opinion

It is essential to establish clear indications for IOL to minimize the risk of inappropriate inductions, associated complications, and failure induction rates. While reducing the induction rate may be desirable, it is important to acknowledge that, due to the change in population, an increase in the rate of

inductions is inevitable. When induction is indicated, misoprostol (alone or associated with mechanical methods) is generally the preferred method, whenever feasible. Specifically, patients who tend to benefit most from misoprostol compared to other induction methods, particularly pharmacological agents, include nulliparous women with an unfavourable Bishop score (BS) and obese patients. Some experts advise caution in using misoprostol in cases of foetal growth restriction (FGR) and, more broadly, in situations where there is a high risk of hypoxia due to chronic placental insufficiency.

The main universally accepted indications for IOL are [2, 10-13]:

- Post-term pregnancy (≥ 41 weeks);
- PROM at term (≥ 37 weeks). Generally, within 12-24 hours if the vaginal-rectal swab for group B S*treptococcus haemolyticus* is negative and within 6 hours if the swab is positive;
- Foetal growth restriction (FGR);
- Gestational diabetes (GDM)/pre-pregnancy diabetes (type I and II);
- Hypertensive disorders of pregnancy;
- Oligo/anhydramnios;
- Isoimmunization;
- Pregnancy cholestasis;
- Twin pregnancy (38 weeks Bichorionic, 36-37 weeks Monochorionic);
- Specific indications for maternal diseases (cardiac, renal, pulmonary…);
- Intrauterine foetal death.

New and discussed indications for IOL have been identified over the years:

- Obesity (especially Class II and III);
- Advanced maternal age (> 43 years)/heterologous assisted reproductive technology (ART);
- Suspected foetal macrosomia;
- Small for gestational age foetus (SGA).

The "induction rate" varies significantly across regions and should not be considered a reliable indicator of healthcare quality. In fact, a reduction in the induction rate does not inherently translate into improved maternal health outcomes within our population [3]. Rather than focusing on lowering the induction rate, it would be more beneficial to enhance clinical practices in the choice of appropriate indications and in the management of induced labour. By optimizing care, we can more effectively reduce unnecessary caesarean deliveries and improve overall maternal and neonatal outcomes. A strong antenatal counselling should be performed also in pregnancies complicated by life-limiting malformations, to obtain an effective IOL with a safe vaginal delivery [14-17].

According to the Expert Panel, oral misoprostol is the first choice among induction methods for the following reasons [6, 7, 18]:

- efficacy in terms of timing between induction start and delivery (time to delivery); number of vaginal deliveries within 24 h; caesarean delivery rate;
- safety: lower risk of uterine hyperstimulation and obstetric complications compared with dinoprostone and lower number of vaginal visits in case of PROM;
- direct action on myometrium and induction of contractile activity as well as cervical changes, resulting in less use of oxytocin during labour;
- good compliance (the oral route is preferred by women respect to the vaginal route or mechanical methods).

Current absolute contraindications to misoprostol use are few; in particular, previous uterine scars (no data are available) and contraindications to vaginal delivery, while relative contraindications are twin pregnancy, gestational age < 37 weeks, parity ≥ 4, even if in these cases, if well selected, the use of misoprostol can be considered. Oral misoprostol is not contraindicated in case of HDP and FGR, even if in most severe cases caution is recommended.

However, the main indications for misoprostol (post-term pregnancy, PROM > 37 weeks, GDM/obesity, advanced maternal age/heterologous ART, maternal diseases, cholestasis) account for about 75% of the total number of inductions. Therefore, misoprostol may be the first choice in three quarters of cases requiring IOL.

Obesity in pregnancy is an increasingly concerning issue, associated with higher rates of gestational hypertensive disorders, diabetes, foetal growth abnormalities and a greater need of induction of labour (IOL). Obese women also have higher rates of IOL failure [19, 20]. In comparison to non-obese, obese women experience a significantly longer first stage of labour, particularly a prolonged latent phase, which may increase the risk of caesarean delivery, maternal bleeding, and chorioamnionitis [21]. As the prevalence of obesity rises, achieving vaginal delivery becomes increasingly important due to the associated risks of caesarean delivery in this population. A study investigating the effect of obesity on misoprostol efficacy found that obese women, due to a larger volume of distribution, have lower bioavailability of misoprostol, poten-

tially reducing its effectiveness. This suggests that a higher dose of misoprostol may improve outcomes in obese women [22]. Additionally, a retrospective trial comparing misoprostol and dinoprostone for IOL in 564 obese patients showed that misoprostol was more effective, with higher cervical ripening rates (78.1% *vs* 66.7%; p = 0.002) and lower caesarean section rates (39.1% *vs* 51.3%; p = 0.003) compared to dinoprostone. Misoprostol was better tolerated and had similar peripartum complication and neonatal outcomes [23].

Induction protocols with misoprostol and dosage schedule

Expert opinion

- Both schedules of oral misoprostol (25 mcg every 2 hours or 50 mcg every 4 hours, up to a maximum of 200 mcg in 24 hours) [24, 25] are considered effective and feasible. In Italy, Angusta® (misoprostol 25 mcg tablet) is only authorized for induction of labour; any other use is considered off-label [24]. The choice of the regimen is made based on several factors such as the type of patient and the organization of the hospital.
- It is possible to repeat a second cycle of induction 12 hours after the last dose of the first cycle, if the first cycle did not result in the onset of labour. It is necessary not to exceed 200 mcg even on the second day of induction. According to the Scandinavian protocol [18], a third cycle is possible, but it is not currently used by the Expert Panel.
- In women with BMI > 30, the misoprostol schedule 50 mcg every 4 hours for 4 administrations is generally preferred, even if, since the daily dosage of the drug does not change, no significant differences have been demonstrated in terms of vaginal delivery rates. A dosage of 25 mcg seems to be more favourable from a pharmacokinetic perspective, ensuring a stable blood concentration (misoprostol has a peak at 12-60 minutes and a rapid concentration drop within 120 minutes) [6, 7].

The dual dosing regimen (25 mcg and 50 mcg) of misoprostol can be tailored based on clinical case and the internal protocols of the hospital. Many experts utilize both dosing schedules, as they demonstrate equivalent efficacy but allow for adjustment according to the specific needs of different patient populations.

In some clinical settings, when the 50 mcg dose of misoprostol is administered every 4 hours, a reduction to 25 mcg every 2 hours may be considered if there is evidence of significant uterine contractility along with a favourable Bishop score. This adjustment is intended to minimize the risk of tachysystole while continuing induction to optimize the results.

Regardless of dosages, induction with misoprostol should not be interrupted until the onset of labour.

Cardiotocography (CTG) monitoring during misoprostol administration

Expert opinion

- The misoprostol 25 mcg tablets SmPC does not specify the frequency of CTG monitoring [24]. According with SIMP consensus, the Experts suggest that monitoring should be carried out before starting the procedure, as usual, and again 30-60 minutes after the initial dose, considering the peak effect of the active compound. Subsequently, CTG can be performed based on clinical indications and at the onset of a regular contractile activity.
- It is crucial to stratify the risk for both mother and foetus. In case of conditions that may impair foetal tolerance to contractions, such as preeclampsia, FGR, abnormal Doppler velocimetry, or early gestational age, or factors that could increase the risk of tachysystole such as polyhydramnios, high parity (≥ 3), or twin pregnancies, an individualized CTG monitoring is warranted. In addition to CTG, careful clinical surveillance of the woman's overall well-being and uterine tone is essential throughout the induction process. If contractile activity is concerning, CTG monitoring may be initiated outside of the standard protocol to ensure the safety of both the mother and the foetus.

The requirements for proceeding to IOL include the availability of the CTG; qualified personnel to monitor the progress of the clinical picture, particularly in relation to blood loss, rupture of membranes and onset of labour; healthcare staff able to perform an emergency caesarean delivery; and a protocol for the management of tachysystole [9].

The effect of the drug on the foetal well-being is mediated by uterine contraction. During the drug administration, the contractile response of the uterus should always be manually assessed between administrations. Administration should not be "automatic" but only performed after exclusion of regular uterine activity. In case of misoprostol 25 mcg tablets administration, the amount of mi-

soprostol is guaranteed by the manufacturer and unintended overdosages are not expected.
Foetal and maternal monitoring is to be repeated based on additional clinical indications or at the onset of a regular contractile activity, also considering the risk factors that led to induction. To evaluate the contractile activity, CTG can be used if clinical monitoring is not feasible.
The use of CTG is crucial for identifying even minimal abnormalities of foetal response to uterine activity. However, clinical surveillance is often overlooked. All participants agree that clinical monitoring is equally important alongside CTG. It is insufficient to solely assess the CTG; regular clinical examinations of the woman, with detailed documentation of each evaluation or visit in the medical records, are essential for comprehensive care.
The minimum CTG monitoring time for the assessment of foetal well-being is 30 minutes after misoprostol administration. However, some variability in the duration of CTG monitoring was observed among Experts (up to 45 minutes after administration to intercept the peak concentration of misoprostol).

Combination of misoprostol with other methods
Expert opinion
The concomitant use, adopted by some Experts of the Panel, is performed by two protocols:
- mechanical method and misoprostol starting at the same time;
- mechanical method alone first and misoprostol administered after 6-12 hours, keeping the mechanical method in place.

The concomitant use of mechanical methods and misoprostol starting at the same time reduce the time to delivery compared with the sequential strategy; maternal and foetal outcome are similar to that observed with mechanical method alone. The mean rate of caesarean delivery with mechanical methods and misoprostol was 27% [26-29].
The sequential use is based on the positioning of the mechanical method for 12 to 24 hours and on the subsequent administration of oral misoprostol if BS < 6 at the time of removal of the mechanical method.
The combination of misoprostol with the mechanical method (either simultaneously or sequentially) is particularly recommended for cases with an unfavourable Bishop score and in obese patients.
A clinical trial compared the efficacy of low-dose oral misoprostol (25 mcg every 2 hours) combined with a Foley catheter to oral misoprostol alone for labour induction (IOL) at term in 200 women. The group of the combined IOL demonstrated significantly shorter intervals between induction and active delivery (10.67 *vs* 16.28 hours), induction and full dilation (11.49 *vs* 19.00 hours) and induction and delivery (16.85 *vs* 21.90 hours) compared to the misoprostol-only group. Additionally, a higher proportion of women in the combined group delivered vaginally within 24 hours. These results suggest that the combination of oral misoprostol and a mechanical method may be superior in labour induction [26].
Other studies also support the combined use of misoprostol and mechanical methods for IOL, reporting improved clinical outcomes, such as reduced induction-to-delivery time, less need for oxytocin, and fewer complications, particularly in high-risk cases [27-29].
Obese women appear to benefit most from the combined approach. Literature confirms that, while the rate of caesarean deliveries and adverse outcomes is comparable to misoprostol alone, the time to delivery is reduced with the combined method. A cohort study by Kehl *et al*. evaluated IOL in obese women (BMI > 35 kg/m^2) using a double-balloon catheter followed by oral misoprostol, if necessary, compared to misoprostol alone. The combination group had a significantly lower caesarean delivery rate (27.6% *vs* 37.5%, p = 0.0345), with the most pronounced reduction observed in nulliparous women (38.6% *vs* 56.9%, p = 0.0039). The abnormal CTG rate was also lower in the combination group (19.9% *vs* 30.4%, p = 0.0150). Multivariate analyses confirmed that the method of IOL, parity, and Bishop's score significantly influenced caesarean delivery rates. Thus, the sequential use of a double-balloon catheter and oral misoprostol is associated with more vaginal deliveries and fewer caesarean sections in obese women [30].

Role of woman's preference/experience in the choice of method for IOL
Expert opinion
To be positive and effective, the induction must be appropriate, informed, supported, respectful, and safe. Ensuring a positive birth experience for the woman is a goal of health care, and investing in patients' satisfaction leads to better clinical outcomes. Therefore, patients' involvement is an essential component of quality of care.
Improved communication and involvement of women in clinical decision-making is desirable.

A correct information about IOL to women and family members in weeks before the term (ideally around 36 weeks) is recommended. Topics of counselling should be: indication, timing, modality, expected time, course, possible complications, risk/benefit ratio, definition of success/failure of induction, alternative strategies in case of failed induction, pain control, monitoring in case of refusal of induction [12]. Once the woman is informed, a consent should be obtained, allowing sufficient time for the patient to decide.

It is crucial to optimize the choice of the induction method, considering the characteristics of the pregnancy and that when possible oral methods are preferred by women respect to vaginal/mechanical methods. An Italian cross-sectional study aimed at evaluating the impact of different modalities of IOL and delivery on levels of woman' satisfaction. This study showed that mode of delivery was associated with a higher rate of satisfaction among induced women. Considering mode of induction, the oral drug was associated with a higher level of satisfaction. An optimal control of pain and a quick induction were the characteristics most appreciated by women [31]. An appropriate choice of the method is associated with higher success rates of vaginal delivery, and in turn the outcome of delivery affects woman's satisfaction. The use of misoprostol can have a positive impact on both time and pain, as it significantly reduces the time to delivery and consequently the duration of pain (the need for analgesia is lower because there is less time for psychological and physical suffering and because the oxytocin use is decreased).

COMMENTS AND CONCLUSIONS

In conclusion, oral misoprostol has emerged as the first-line agent for labour induction, thanks to its proven efficacy, favourable safety profile, and patient preference. In fact, based on the current literature and considering its contraindications, misoprostol should be considered the first choice in majority of the cases where induction is indicated. Ongoing research into dosages and combined strategies, holds great promise for refining clinical practices, reducing time-to-delivery, and improving maternal and foetal outcomes in the more complex cases. In fact, tailoring of protocols is crucial to ensure "the right method for the right patient". In this way healthcare providers can enhance the overall success of the induction process.

To optimize the induction of labour, the following steps are essential:

- accurate assessment of appropriate indications for labour induction;
- selection of the appropriate induction method based on factors such as parity, Bishop score, BMI, gestational age, specific indication, and risk factors for foetal intolerance or tachysystole;
- comprehensive patient education regarding induction methods, provided before hospitalization, ideally starting from the 38th week of pregnancy;
- clear communication about the induction timeline, as many women believe that induced labour will progress rapidly;
- offering alternative methods if the initially chosen approach fails;
- assessing patient compliance with the induction plan;
- organizing the induction process based on available resources in the ward and delivery room.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

All authors: Conceptualization, writing – review & editing. S.Z., A.F., L.D.: Writing – original draft.

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