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Italian Society of Gynaecology and Obstetrics (SIGO): Consensus paper on induction of labor with oral administration of Misoprostol

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INTRODUCTION

Induction of labor (IOL) is a medical procedure used to initiate labor and conclude the pregnancy. Its primary aim is to stimulate and obtain an active birth labor.
A procedure is appropriate (inappropriate) if its expected benefit if sufficiently higher (lower) than its expected cost (1-4). For this reason, IOL should only be taken into consideration when it is clearly beneficial to either mother and/or fetus and thus reduces the exposure to risks and increases maternal and/or fetal wellbeing. The risks related to IOL must be lower compared to the risks that the continuation of the pregnancy may lead to (5).
The incidence of IOL in Europe varies between 6.8% and 33% (6). This percentage varies greatly in countries worldwide and has shown a general and progressive growth in recent years. As regards the situation in Italy, statistics show that in some realities the percentage of induced labor exceeds one in every four births, with an average of 23.2% in 2017 (7).

General consensus for IOL can be found in at least three specific circumstances:

a. term pregnancy and prevention of post-term pregnancy;
b. pre-labor rupture of amniotic membranes (PROM);
c. fetal death.

Though not clearly beneficial to mother and/or fetus, IOL is being used in various other circumstances, such as:
1. hypertension (gestational, preeclampsia);
2. fetal growth restriction (IUGR/SGA);
3. cholestasis;
4. diabetes.

Other, more controversial circumstances, include:
1. request of the pregnant woman;
2. logistic and/or social purposes;
3. oligoamnios;
4. polyhydramnios;
5. fetal conditions that require a planned birth for any potential surgery.

The medical team must discuss all circumstances with the pregnant woman.

An induced labor generally tends to be longer compared to a spontaneous labor; this can impact the pregnant woman significantly from a psychological point of view (8, 9). The factors that impact the most on the outcome of an IOL are the patient's compliance to the procedure and continuity of care (10). The two main approaches to IOL are either the mechanical technique or the use of pharmacological agents, this second being the most common with the use of prostaglandins. Prostaglandins can be administered in various forms. The optimal mode and dose of administration are currently the object of various studies and scientific researches (11).
The interval of time between the beginning of an induction and the onset of active labor is one of the key factors that influences the patient's satisfaction. In fact, a study (12) comparing different variables between 450 women who labored spontaneously and 450 women who were induced demonstrates that:

1. 34.7% of women with an induced labor aren't satisfied with the information received;
2. 27.2% expect to give birth within 12 hours from the first medical procedure used for IOL;
3. the first thing 40% of the patients would change, if they were to have another induction, is the speed of the induction;
4. women that receive an IOL are generally less satisfied of their birth experience compared to women who have a spontaneous labor (70.4% *vs* 79.5%).

MISOPROSTOL

Misoprostol is a synthetic analogue of PGE1, initially used to prevent damages to the gastric mucosa and to prevent and treat gastric and duodenal ulcers. Misoprostol is economical, stable at room temperature and available in more than 80 countries worldwide, making it a fundamental drug in areas with limited resources (13). The World Health Organization (WHO) has included Misoprostol in the list of essential drugs due to its properties and its optimal profile in terms of costs and benefits, thus resulting in an extremely efficient, appropriate and economic drug (14). Misoprostol explicates its action on the cervix by stimulating contractions and facilitating cervical ripening and dilatation (15). An extended bibliography supports the evidence and recommendations that confirm Misoprostol to be superior and more efficient compared to drugs containing PGE2 (16-23). Wanting to be more specific, compared to the other classes of prostaglandins, Misoprostol shows greater efficiency and results in:

1. a shorter interval of time between induction and birth;
2. greater probability of a vaginal birth within 24h from induction;
3. greater safety in case of PROM;
4. lower risk of caesarean.

The recommended dose of Misoprostol is 25 mcg per os every 2 hours, for a maximum of 8 doses. It is recommended to dilute 200 mcg of Misoprostol in 200 ml of water and administer 25 ml of the solution every 2 hours. The administration of the drug must be preceded by at least 30 minutes of cardiotocography to ensure the wellbeing of the fetus and frequency of uterine contractions. CTG monitoring must also continue for the first hour following the administration of Misoprostol. It is important to keep in mind Misoprostol has effect after about 10 minutes of administration.
Currently, oral Misoprostol is the only form available for gynaecological use. Scientific literature suggests that oral administration of Misoprostol with low doses is linked to a lower risk of C-section and tachysystole compared to vaginal administration.

Misoprostol 25 mcg: "ANGUSTA®"

In January 2021, the pharmaceutical drug containing 25 mcg Misoprostol "ANGUSTA®" was authorized and released on the Italian pharmaceutical market under the form of tablets. This solution is therefore available at the recommended dose; due to this, no additional preparation is needed before the administration of the medicine to pregnant women. The maximum dose must not exceed 200 mcg in 24 hours (maximum 8 tablets/24h). The posology recommended on the technical data sheet (TDS) is 25 mcg every 2 hours or 50 mcg every 4 hours.

Proposed protocol for induction of labor with Misoprostol 25 mcg

Based on data from Scandinavian studies (24), it is reasonable to propose the administration of one 25 mcg tablet per os every 2 hours, for a total of 6 doses on the first day of induction. In case of failure, this procedure can be repeated on day two, with a maximum of 8 doses. It can eventually be repeated on day three with a maximum of 3 doses. According to results available in scientific literature, around 70%

of women give birth within 48 hours from the beginning of induction. Seeing as studies concerning the duration of treatment for induction and precise posology for Misoprostol are scarce, it is retained fully acceptable for centres to follow different protocols and to autonomously decide when and/or if to eventually interrupt treatment. Compared to the use of high doses (50 mcg), induction with Misoprosol 25 mcg shows a more favourable obstetric outcome and a higher probability of a successful vaginal birth. The actual percentage of an assisted birth with vacuum or forceps following IOL with Misoprostol is yet to be defined, as some studies hypothesise that low doses (25 mcg) of Misoprostol may increase this risk (25). The first dose of Misoprostol must be administered after a 30-minute reactive Non Stress Test (NST) (26). During the first day of induction, the dose may be repeated every 2 hours and up to 6 times for the Scandinavian protocol or up to 8 times according to the drug's TDS. The maximum dose on day 2 of induction is 8 doses (total 200 mcg) for both the Scandinavian protocol and the TDS, while the maximum dose on day 3 is 3 doses (75 mcg).
The uterine response to the drug must always be evaluated manually during and between the administration of the doses. Administration must not be automatic but preceded by the evaluation of any ongoing labor conditions, even in latent form, circumstance which contraindicates a new administration of the drug. It is recommended to monitor fetal wellbeing and uterine activity with a 60-minute NST after the first dose. Further monitoring of fetal wellbeing and uterine activity depends on the protocols used and the experience each medical team. Should the administration of oxytocin be made necessary, it is recommended to wait at least 4 hours from the administration of Misoprostol. Hospitals offering IOL must guarantee the possibility to proceed with an emergency cesarean section. The authors recommend paying special and close attention to multiparous women with three or more previous vaginal births or in case of a twin pregnancy.

ABSOLUTE CONTRAINDICATIONS

1. Hypersensitivity to Misoprostol or any of the excipients contained in the drug;
2. evolving labor;
3. administration of oxytocic drugs and/or other IOL procedures in the same frame time;
4. presence of uterine scars from previous surgery;
5. uterine malformations that contraindicate vaginal birth;
6. placenta previa;
7. abnormal presentation of the fetus;
8. patients with kidney failure (glomerular filtration rate 15 ml/min/1.73 m^2).

RECOMMENDATIONS

1. IOL with Misoprostol 25 mcg should only be offered in circumstances in which scientific evidence clearly points out that the benefits deriving from anticipating labor are greater than the potential risks that can derive from the procedure used for IOL itself.
2. Indications for IOL, aside from those commonly accepted such as term pregnancy, post term pregnancy, PROM and fetal death, must always be discussed and coordinated collectively by medical staff.
3. The procedure intended to be used for IOL should be thoroughly discussed with the pregnant woman prior to its onset. It is important to provide information regarding the various procedures normally brought forward throughout labor, the benefits and potential complications that could arise. The chosen procedure and the average time for labor onset and birth should be clear to the patient.
4. Informed consent must be obtained and signed by the pregnant woman prior to commencing the induction. The possibility that a full cycle of induction with Misoprostol may not be sufficient to stimulate labor and/or that the patient may not respond must be explained. If this were to be the case, the patient must also be informed that other attempts may be made using different approaches; these can either be pharmacological or mechanical. Another scenario is that in which the woman refuses to carry on the induction, opting for a C-section instead; this represents a "refusal of continuation of IOL" and not "failure of IOL".
5. The definition of "failure of IOL" is given by the inability to reach active labor (regular and efficient uterine activity with 2-4 contractions every 10 minutes, a cervix effaced by at least 80% and progressive dilation greater than 4-5 cm) after at least 15 hours of oxytocin and ruptured membranes (spontaneous or whit amniorexi).

6. Misoprostol can be considered the first pharmacological therapeutic approach in case of IOL in women that have reached 37^{+0} weeks of gestation, have a Bishop score lower than 7 and in absence of any absolute contraindications.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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