

# INDUCTION OF LABOR WITH SLOW RELEASING MISOPROSTOL, OUTCOME AND ASSOCIATION WITH CTG TRACES

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## Abstract

Medical conditions associated with pregnancy are continuously rising therefore the obstetrician is more often required to indicate termination of pregnancy for various medical reasons. Termination of pregnancy at term or near term, before spontaneous labor may be easy but sometimes can create difficulties. The following study proposes to present the induction of labor method with misoprostol at term, analysis of results, various associations between obstetrical parameters and mode of delivery including Apgar score at 1 minute.

We also present cardiotocography (CTG) traces associated with induction of labor (IOL) with prostaglandins and management.

We would like to emphasize the importance of careful case selection that can be induced, the surveillance protocol of an induced labor and the attitude suitable for each individual case.

Apart from permanent efforts to decrease the primary caesarean section rate including maternal request cesarean section, we must be aware of the existence of this group of women with various medical conditions that request IOL, for whom we are ethical and medical responsible to offer the chance of a natural vaginal delivery.

## Rezumat: Inducția travaliului cu misoprostol cu eliberare prelungită, rezultate și asocierea cu traseele CTG.

Patologia medicală asociată sarcinii recunoaște o tendință ascendentă astfel încât medicul obstetrician este pus din ce în ce mai des în fața situației în care trebuie să indice terminarea evoluției sarcinii din diverse motive. Finalizarea sarcinii la termen sau în apropierea termenului, în afara travaliului spontan, poate fi facilă, dar în unele cazuri poate ridica dificultăți. În studiul efectuat ne-am propus să prezentăm metoda de declanșare a travaliului cu misoprostol la gravidele la termen, studiul rezultatelor, diverse asocieri între parametrii obstetricali monitorizați și modul nașterii, respectiv scorul Apgar la 1 minut. Vom prezenta de asemeni și anumite trasee cardiotocografice (CTG) asociate cu inducția cu prostaglandine și conduita adoptată.

Dorim să subliniem importanța selecției atente a cazurilor care pot fi induse cu misoprostol, modul în care se urmărește un travaliu indus și atitudinea care trebuie adoptată pentru fiecare situație în parte.

Pe lângă eforturile permanente de a scădea incidența operației cezariene primare sau a celei la cerere, trebuie să avem în vedere faptul că există și acest grup de gravide cu diverse patologii pentru care suntem obligați moral și medical să le oferim șansa de a naște natural.

**Cuvine cheie:** inducție travaliu, misoprostol, prostaglandine, cardiotocografie, monitorizare travaliu

## **Introduction**

Induction of labor (IOL) refers to all techniques used to stimulate a pregnant uterus and cervix in order to accomplish delivery, before natural spontaneous labor. In Romania where the prevalence of caesarean sections is high due to multiple factors, very little attention was focused towards IOL and to the medical conditions associated with pregnancy that needs IOL.

Medical pathology associated with pregnancy is continuously increasing worldwide therefore the need of medical IOL should be the same. For example in United States between 1990 and 2012 the overall frequency of IOL has more than doubled, from 9.5 in 1990 to 23.8% in 2010 and 23.3 in 2012 (1), in Africa induction accounted for 4.4% and in Asia 12.1% of deliveries with overall success rate of over 80% (2).

In Romania pregnancy complications are continuously rising, on one hand, due to maternal age – a subpopulation that is well known that carries an elevated risk of adverse outcomes (3) and on the other hand because of the increasing pathology associated with pregnancy (obesity, diabetes, hypertension, hematologic conditions, infections, sexually transmitted diseases (STD) (4). Severe medical conditions associated with pregnancy such as severe preeclampsia and eclampsia conducts to unfavorable outcomes in low-resource settings even if they are managed appropriately (5), therefore good timing of IOL is needed to achieve good results.

The most common conditions where induction is indicated are: postterm pregnancy (defined by American College of Obstetricians and Gynaecologists – ACOG- as pregnancy beyond 42+0 weeks (6)), prelabor (premature) rupture of membranes, preeclampsia, eclampsia and HELLP syndrome, gestational hypertension, maternal diabetes (preexisting and gestational), fetal growth restriction or small for gestational age (SGA), chorioamnionitis, oligohydramnios, rhesus disease with alloimmunization, twins and fetal demise. Also, a frequent condition seen recently is elective induction after 39 weeks also known as “social” induction or “maternal request” induction, especially in multiparous pregnancies requested mainly for the time comfort,

to avoid the unexpected labor and delivery outside of the hospital for both the obstetrician and the woman. This attitude is highly discouraged due to significant increased of neonatal morbidity and the rate of cesarean delivery (7).

When IOL is performed with correct indications studies have shown that, contrary to a long-standing belief, the cesarean section rate was not increased by induction at full term, weather or not the cervix is favorable (8,9).

Contraindications for IOL include but not limited to placenta previa or vasa previa, fetal malpositions such as breech presentation, transverse or unstable lie, umbilical cord prolapse or persistent funic presentation, invasive cervical cancer, active genital herpes infection, prior classical or other high risk incision cesarean section, prior uterine rupture and cardiotocography (CTG) abnormalities. Relative contraindications include previous low segment cesarean sections which needs special maternal counseling about risks and benefits and also close monitoring during labor with low threshold for intervention in case of obstetrical complications or non-reassuring fetal heart CTG trace.

Preparation for induction includes cervical status assessment, which is quantified according to the Bishop score, the most common system used worldwide (10). Correctly scoring is very important because is well known that women with a high Bishop score (>6) have a high likelihood of vaginal delivery and those with low scores are less likely to deliver vaginally after induction than in spontaneous labor (11) but without a good value in predicting cesarean delivery (12).

There are several method of IOL, such as vaginal prostaglandins, artificial rupture of membranes (amniotomy), oxytocin and cervical ripening balloon. The indication is depending on clinical status, gestational age, associated conditions and nevertheless, maternal choice.

Membrane sweeping is a procedure that involves detaching the membranes of the inferior amniotic pole from the inferior uterine segment with the examiner’s finger in order to stimulate the natural release of prostaglandins for ripening the cervix. A meta-analysis from 2005 demonstrated that sweeping

the membranes increases the likelihood of spontaneous labor within 48 hours with no evidence of an increased risk of maternal or neonatal infection (13), even in group B streptococcus (GBS) carriers (14).

Also, nonstandard approaches have been described as methods for stimulation of labor such as sexual intercourse, herbal substances, primrose oil, acupuncture, castor oil and glucocorticoids. However, safety and efficacy has not been established yet, therefore they are not medically indicated (15,16,17,18,19,20).

Induced labor progresses differently than spontaneous labor, therefore a high degree of obstetrical care and intervention is needed in order to achieve good outcome and to prevent induction failure. The average duration of the latent phase is significantly longer in induced labors comparing with spontaneous labor (21) mainly because of an unfavorable cervix (22), however the active phase was found to be shorter in the IOL group (23). The second stage of labor was found to have similar length in both induces and spontaneous laboring groups (24).

Fetal heart monitoring and uterine activity is one of the most important parameters that needs to be carefully assessed periodically. Continuous fetal heart rate (FHR) monitoring is mandatory when uterotonic medication is administered for both preventing fetal distress and adjusting the dose.

Main side effects of IOL includes tachysystole and hyperstimulation with abnormal CTG traces, hyponatremia due to prolonged oxytocin infusion (which has a similar structure with vasopressin and can stimulate the same renal receptor conducting to water intoxication and non-eclamptic seizures (25,26)) and infection due to prolonged rupture of membranes.

Other complications may include: uterine rupture due to excessive uterine activity, mainly in patients with previous cesarean sections, and amniotic fluid embolism. Medical induction of labor nearly doubled the risk of overall cases of amniotic fluid embolism, however the condition is extremely rare (27).

Induction of labor is considered to be successful when vaginal delivery is achieved within 24 hours of oxytocin infusion. There is no standard

definition for failed induction but careful attention is needed to avoid cesarean sections in the latent phase of IOL which is incorrectly diagnosed as failed induction (28,29).

In 2012 a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development from the United States, Society of Maternal-Fetal Medicine and ACOG workshop proposed that failed induction to be defined by the following criteria (30):

- Failure to generate regular (e.g. every 3 minutes) contractions and cervical change after at least 24 hours of oxytocin administration, with artificial membrane rupture if feasible;
- First stage arrest if cervix is e" 6cm dilation with membrane rupture or e" 5cm without membrane rupture and e" 4 hours of adequate contractions, or e" 6 hours if contractions are inadequate with no cervical change.

For allowing enough time for cervical ripening for up to 24 hours and then oxytocin infusion after rupture of membranes for 12 to 18 hours, ACOG demonstrated in 2014 that many cesarean sections for failed inductions can be prevented (31).

## Material and methods

We performed an observational retrospective study in Filantropia Clinical Hospital, a tertiary Obstetrics and Gynecology University Clinic from Bucharest, Romania, with almost 4000 deliveries per year, where we promote vaginal delivery. Study was conducted between January 2016 and May 2017.

We used as inclusion criteria women with pregnancies more than 37 weeks gestation, primiparous, Bishop score less than 5, with IOL indication, without any contraindication and where induction was done with slow releasing misoprostol vaginal pessary (Misodel) (32).

Exclusion criteria were multiparous pregnancies, any IOL absolute or relative contraindications, maternal refusal for IOL, patients where the pessary felt out before planned removal, Bishop score more than 6 and patients which underwent induction with other methods apart from slow releasing misoprostol vaginal pessary.

**Table 1.** Indications for IOL (Filantropia Clinical Hospital).

Indication	Number of cases
Postdate pregnancy	9
Hypertension	6
Oligohydramnios	1
Gestational Diabetes (GDM)	4
Obstetric Cholestasis (OC)	2
Small for gestational age (SGA)	4
Fetal malformations	1
Maternal Age	3

Data was collected from institutional electronic database and from clinical notes in hardcopy. We retrieved the following data: gestational age, medical history, body mass index (BMI), reason for IOL, time interval for misoprostol insertion, adverse reactions, way of delivery, indication for cesarean sections and operative deliveries, CTG traces, Bishop score, fetal weight, Apgar score at 1 and 5 minutes, amniotic fluid aspect, neonatal complications and maternal complications.

For data processing we used SPSS Statistics (IBM, USA) and Microsoft Excel for Mac 2011 for table processing and charts.

Cardiotocography (CTG) traces were retrieved from Omniview Sisporto Central Monitoring System's archive and captured with regular Windows image software.

## Results

After applying inclusion and exclusion criteria we enrolled 35 patients from whom in 5 cases we were unable to find reliable data about indication of IOL and labor due to insufficient case documentation or failed induction so these cases were excluded. We calculated an incidence of misoprostol IOL of 0.65% (5350 deliveries with 35 misoprostol inductions).

The indications for IOL which are presented in detail in table 1 were the main indications from the literature.

According to our internal obstetrical clinical guideline we recommend IOL for postdates pregnancies at 41+3 weeks, for pregnancy complicated with poor control of hypertension after 37 weeks (we excluded from the study the group

with preeclampsia/eclampsia or gestational hypertension that needed delivery before 37 weeks because slow releasing misoprostol is contraindicated), oligohydramnios diagnosed by ultrasound scan after 37 weeks, gestational diabetes (GDM),-in women with diet controlled GDM at 39-40 weeks (according to maternal glycemic control), GDM treated with insulin at 38-39 weeks of gestation, obstetric cholestasis at 37 weeks (with documented bile acids levels > 14 umol/L and pruritus), small for gestational age (estimated fetal weight less than 10<sup>th</sup> centile), maternal age at term (IOL for maternal age more than 40 years old at 40 weeks of gestation according to latest studies and National Institute for Health and Clinical Excellence (NICE) recommendations (33,34)) and fetal malformations incompatible with life or fetal demise (Table 1).

Regarding the mode of delivery we found that the majority of cases delivered vaginally (53%, 16 cases), 20% delivered by operative vaginal delivery (5 cases with forceps -17% , 4 cases with vacuum extractor -13%) and the rest of 5 cases (17%) delivered by cesarean section due to suspected fetal compromise with abnormal CTG trace, failed to progress in active second stage of labor or failed induction (Figure 1).

Regarding the Bishop score before IOL we made 6 groups (Bishop 0 to 5) and correlated with the way of delivery. We found no significant correlation between Bishop score and the way of delivery (Figure 2) in either group.

The last parameter studied was the Apgar score at 1 minute. A correlation between the Apgar and the Bishop scores was studied and the result was that the distribution of Apgar scores at 1 minutes

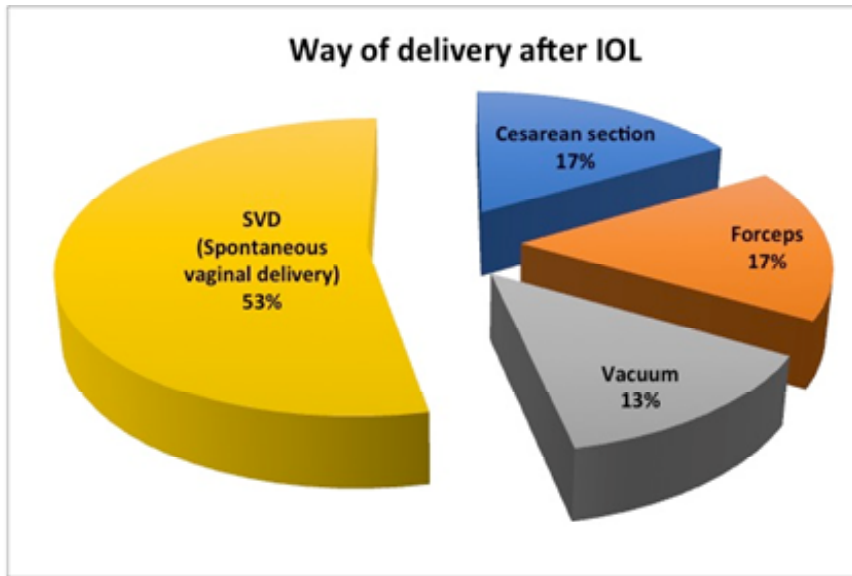


Figure 1. Way of delivery after IOL

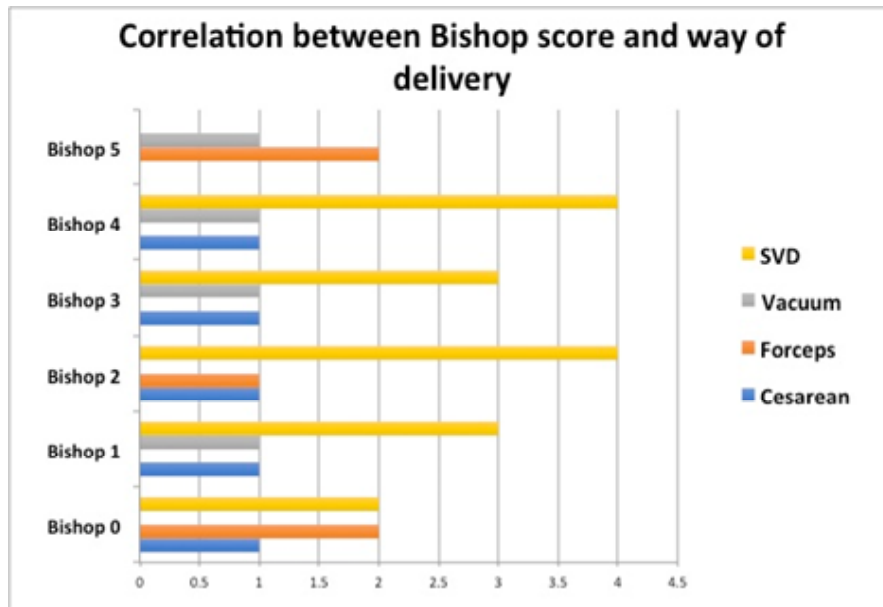


Figure 2. Correlation between the Bishop score and the way of delivery

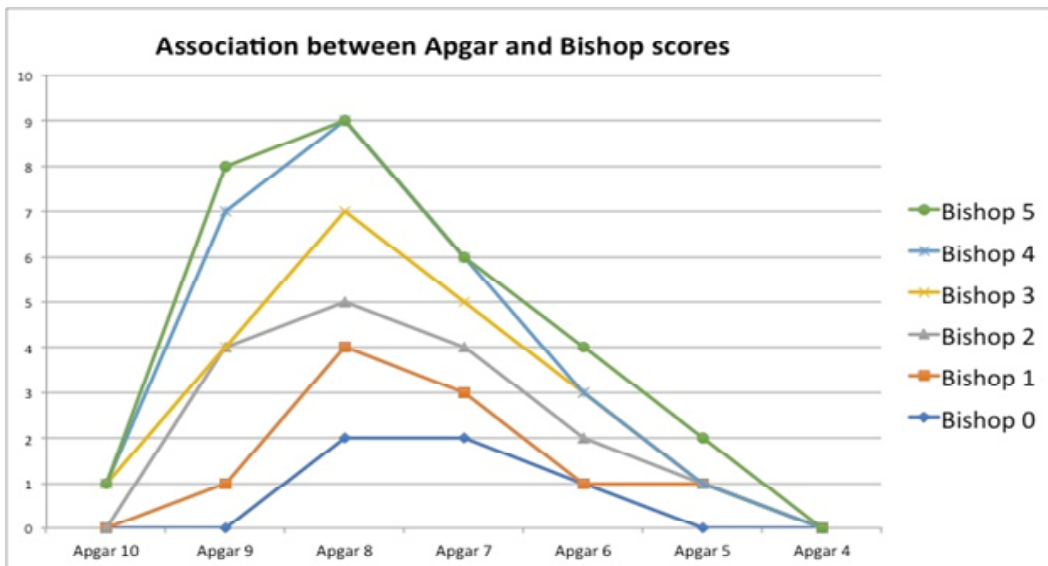


Figure 3. Association between Bishop and Apgar scores at 1 minute follow the same pattern irrespectively of Bishop score

before IOL (Figure 3).

Part of data retrieval was the CTG traces. At Filantropia Clinical Hospital we use the 2015 FIGO classification of CTG traces both as computerized analysis with Central Monitoring Station and individual human assessment (35).

According to FIGO guidelines we classify the traces into normal, suspicious or pathological, after assessment of baseline, variability, accelerations and decelerations.

From 30 traces retrieved, majority of them were normal during IOL (Figure 4) and only suspicious in active second stage (according to FIGO, however normal for second stage).

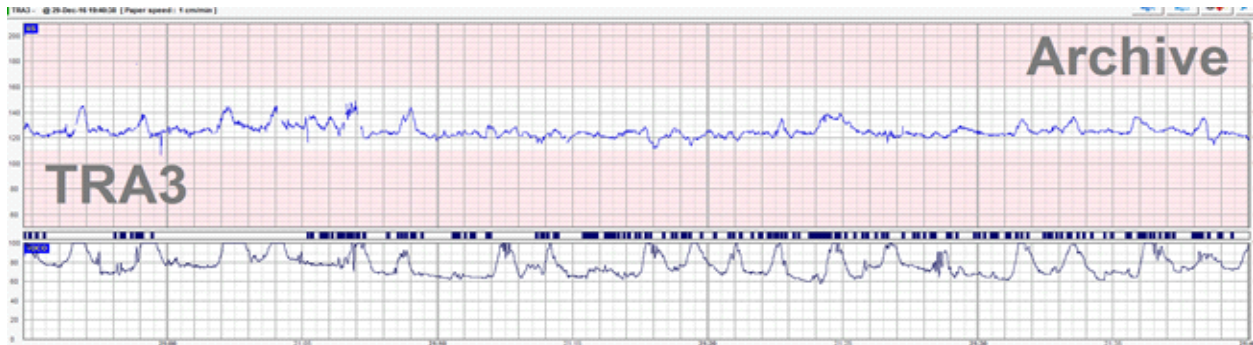
We will continue to present suspicious and pathological traces which were recorded during IOL

and our action to prevent unfavorable neonatal outcome.

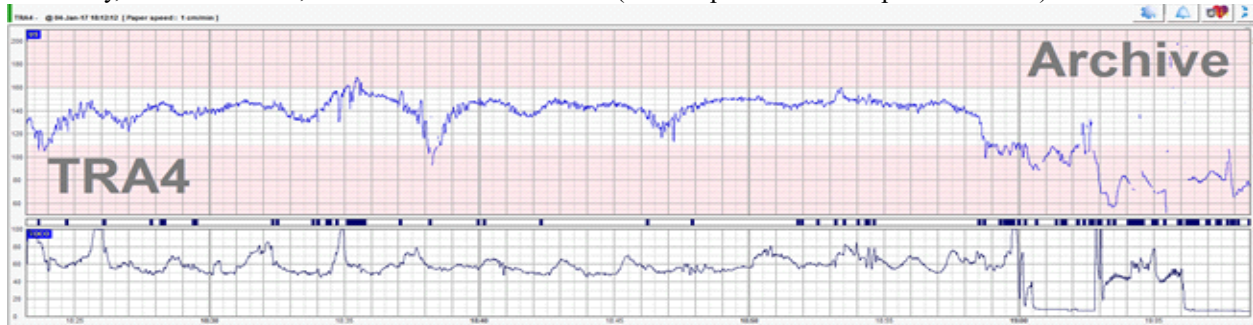
### Case 1

A 30 years old G1, P1, 41+3 weeks of gestation, Bishop 0, IOL for postdates, removal of misoprostol pessary after 6 hours due to excessive uterine activity at 5 cm dilatation, delivered after another 4 hours.

CTG trace was pathological showing raised baseline and late decelerations with prolonged deceleration, with the head at +1 station, occiput-anterior position. Healthy female was delivered by forceps for suspected fetal compromise in active second stage, 4200g with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. Cord pH of 7.15 (arterial) (Figure 4).



**Figure 4.** Normal CTG trace during IOL with misoprostol. Presence of accelerations, stable baseline, reassuring variability, no decelerations, 5 contractions in 10 minutes (Filantropia Clinical Hospital collection).



**Figure 5.** Pathological CTG trace showing raised baseline, late and prolonged decelerations (Filantropia Clinical Hospital collection).



**Figure 6.** Pathological CTG trace due to increased baseline, reduced variability and late decelerations (Filantropia Clinical Hospital collection).

**Case 2**

A 26 years old G1,P1, 41+4 weeks of gestation, Bishop 0, IOL for postdates, removal of misoprostol pessary after 2 hours due to pathological CTG trace with no cervical changes, delivered after 40 minutes.

CTG trace was pathological due to raised baseline, reduced variability and late decelerations, suggestive pattern for utero-placental insufficiency. Emergency cesarean section was performed following a prolonged deceleration, for suspected fetal compromise and a healthy male was delivered, 2800g with Apgar scores of 7 and 8. (Figures 5 and 6).

hypertension, removal of misoprostol pessary after 7 hour, started augmentation with oxytocin 1 hour later after artificial rupture of membranes at 3 cm dilatation. In active second stage after another 5 hours oxytocin augmentation was stopped due to pathological CTG (repetitive complicated decelerations with subacute hypoxia pattern). Trace showed no improvement, patient was fully dilated, head at +1, occiput-anterior position and was delivered by forceps for suspected fetal compromise. A male 2750g was delivered with Apgar scores of 6 and 8 and arterial cord pH of 7,11 (Figure 7).

**Case 3**

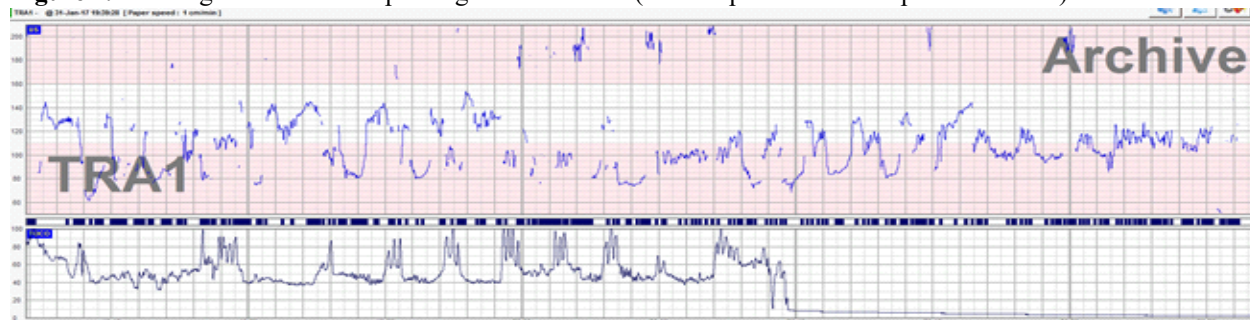
A 37 years old G1,P1, 39+5 weeks of gestation, Bishop 2, IOL for uncontrolled gestational

**Case 4**

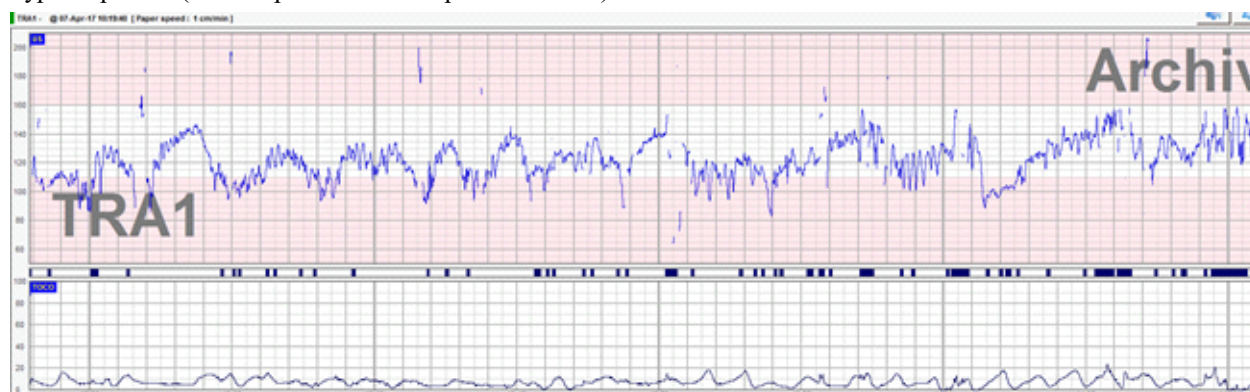
A 31 years old G1, P1, 39+4 weeks gestation, Bishop 4, IOL for GDM diet controlled. After 7 hours from misoprostol pessary insertion increased uterine



**Figure 7.** Pathological CTG due to prolonged deceleration (Filantropia Clinical Hospital collection).



**Figure 8.** Pathological CTG trace due to repetitive complicated decelerations in active second stage with subacute hypoxia pattern (Filantropia Clinical Hospital collection).



**Figure 9.** Pathological CTG due to misoprostol hyperstimulation (7 contractions in 10 minutes) and complicated variable decelerations. Trace improved after tocolysis (Filantropia Clinical Hospital collection).

activity was noticed progressing rapidly towards hyperstimulation. The pessary was removed and urgent tocolysis was performed with i.v. hexoprenaline. Trace improved, contractions ceased at 4 in 10 minutes and patient delivered vaginally 4 hours later. Uneventful delivery (Figure 9).

## **Discussions**

Laboring with slow releasing misoprostol is very different from the other methods of IOL, far more different even from other prostaglandins IOLs such as dinoprostone.

The main concern in inducing labor with misoprostol is the uterine activity and hyperstimulation, situation that can be prevented if spotted on time. If ignored or even if the intervention is delayed, fetal distress is more likely to happen and associated with an unexperienced obstetrician attending the labor ward, delivery by cesarean section is more likely.

Although in case of hyperstimulation associated with oxytocin use, stopping the infusion and hydrating the patient is as effective as tocolysis (36), the antidote for hyperstimulation must be available on labor ward for cases with hyperstimulation without oxytocin infusion. At Filantropia Clinical Hospital we routinely use i.v. hexoprenaline, but also subcutaneous 250 mcg terbutaline is highly effective (37), however not available in Romania. Atosiban was also described as being effective in emergency interventions but is prohibitively due to high costs.

Regarding monitoring, an induced labor with misoprostol, needs to be done according to underlying pathology but we routinely recommend intermittent auscultation in the latent first stage with CTG monitoring every 4 hours and continuous monitoring in case of regular contractions or active labor. According to this protocol, the timing when misoprostol pessary needs to be removed (which was 7-11 hours after insertion) is exceptionally missed. To prevent failures we also recommend active management of labor with artificial rupture of membranes after misoprostol removal, allowing 1 hour of active mobilization after which oxytocin augmentation needs to be started if dilatation is not

progressing with existing contractions. Pain management is not different from management of spontaneous labor including early epidural if requested by the patient before oxytocin augmentation.

Having known that second stage of IOL is similar to those with spontaneous labor (24), we routinely recommend minimum 1 hour of passive descent and 1 hour of active pushing if not otherwise contraindicated.

We would like to emphasize the importance of careful case selection for misoprostol IOL, the surveillance protocol of an induced labor and the attitude suitable for each individual case.

Also another large group that needs induction at term is the pre-labor rupture of membranes (PROM) group where we think IOL with misoprostol would prove benefit after 24 hours of expectant management.

## **Conclusions**

Induction of labor with slow releasing misoprostol pessary is a safe method of induction, however a high degree of attention needs to be present in order to predict and prevent possible complications and to remove the pessary not too early and also not too late. In cases of unfavorable cervix there is a high rate of failed inductions and subsequent cesarean sections when cases are being managed inappropriately.

We suggest routine use of slow releasing misoprostol in selected cases, the only prostaglandin licensed in Romania for term induction, in cases of Bishop score less than 5, having known that cervical ripening prior to active labor can raise the rate of successful vaginal delivery and also can shorten the duration of uncomfortable active labor with very good neonatal outcomes.

Apart from permanent efforts to decrease the primary cesarean section rate including maternal request cesarean section, we must be aware of the existence of this group of women with various medical conditions many of them declining pre-labor cesarean section and requesting IOL, for whom we are ethical and medical responsible to offer the chance of a natural vaginal delivery.



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