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Prospective observational study on response to induction of labor with vaginal misoprostol 200 µg and its determinants in routine clinical practice: a multicenter study

Giuseppe Ettore[1], Brigida Carducci[2], Maddalena Smid[3], Marco Liberati[4], G Benedetto Melis[5], Enrico Ferrazzi[6], Giuseppe Maria Maruotti[7], Bianca Masturzo[8], Fabio Parazzini[9], Andrea Lojacono[10]

[1]UOc Ostericia e Ginecologia P.O. Garibaldi-Neisma ARNAS Garibaldi, Catania
[2]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma
[3]Clinica Ostetrica e Ginecologica, Ospedale S.Raffaele, Milano
[4]Clinica Ostetrica e Ginecologica Università di Chieti, Chieti
[5]A.O. San Giovanni di Dio Dip. Materno Infantile Policlinico Duilio Casula Cagliari ed Università di Cagliari, Cagliari
[6]IRCCS Policlinico, Dipartimento di scienze Cliniche e di Comunità, Università di Milano, Milano
[7]Dip di Neuroscienze e Scienze Riproduttive ed Odontostomatologiche dell'Università di Napoli Federico II, Napoli
[8]II Clinica Universitaria. Città della Salute e Della Scienza, Torino
[9]IRCCS Policlinico, Dipartimento di scienze Cliniche e di Comunità, Università di Milano, Milano
[10]Clinica ostetrica e Ginecologica , Università di Brescia, Brescia

on behalf of the Italian Misoprostolo Study Group (listed in Appendix) (Giada Belluomo (Catania); Federico Prefumo, Claudia Maggi, Giorgia Mazzoni (Brescia); Caterina neri Angela Botta (Roma Gemelli); Federica Pasi (Milano S. Raffaele);Antonia Iacovelli (Chieti), Alessandra Meloni (Cagliari); Gloria Brembilla (Milano Buzzi)

ABSTRACT
Objective: Field-practice' studies on vaginal misoprostol 200 µg are scant, and only few data exist on the predictive factors for labor success with this molecule. Moreover, there are no published data on the use of vaginal misoprostol specifically referring to the Italian scenario, due to its recent introduction into the market. Here, we report the results of an Italian multicenter prospective observational study on prognostic factors of response to induction to labor with vaginal misoprostol 200 µg.
Study Design: Consecutive women treated with removable vaginal misoprostol 200 µg in nine Italian centers were enrolled. After drug insertion, vaginal examinations were performed at 6, 12, 18 and 24 hours. The modified Bishop score, the time and mode of delivery of the neonate and indication for caesarean delivery or reason for instrumented vaginal delivery were also recorded.
Results: A total of 197 women were enrolled. Of them, 117 (58.8%) were nulliparae and 71 (35.8%) had a Bishop score at insertion ≤1. Indication to induction was post-term pregnancy in 87 (43.7%) cases, fetal reasons in 33 (16.6%), maternal reasons in 82 (41.2%) and other in 14 (7.0%) cases. Vaginal birth within 24 hours from the beginning of induction was reported in 100 (50.8%) women (43.25 among nulliparae and 81.4 among parae). The median time from misoprostol insertion to vaginal delivery for women of any parity was 17.5 hours: the corresponding values in nulliparae and parae 20.0 and 13.1 hours, respectively. The caesarean delivery rate was 21.8% (43 cases). Reasons

SOMMARIO
Razionale ed obiettivi: Gli studi sul misoprostolo per via vaginale 200 µg nella pratica clinica sono scarsi e esistono solo pochi dati sui fattori predittivi di successo dell'induzione al travaglio con questa molecola. Inoltre, non vi sono dati pubblicati sull'uso del misoprostolo vaginale che si riferiscano specificamente allo scenario italiano, a causa della sua recente introduzione sul mercato. Qui, riportiamo i risultati di uno studio osservazionale prospettico multicentrico italiano sui fattori prognostici di risposta all'induzione al travaglio con misoprostolo vaginale 200 µg.
Metodi: Sono state arruolate le donne consecutivamente indotte con misoprostolo vaginale 200 µg in nove centri italiani. Dopo l'inserimento del farmaco, è stata eseguita valutazione vaginale a 6, 12, 18 e 24 ore. Sono stati inoltre registrati il punteggio Bishop modificato, il timing e la modalità di parto, l'indicazione al taglio cesareo o al parto operativo vaginale.
Risultati: sono state arruolate 197 donne. Di queste, 117 (58,8%) nullipare e 71 (35,8%) con un Bishop Score all'inserzione ≤1. L'indicazione all'induzione è stata la gravidanza post-termine in 87 casi (43,7%), indicazioni fetali in 33 (16,6%), indicazioni materne in 82 (41,2%) e altre in 14 (7,0%). Il parto per via vaginale entro 24 ore dall'inizio dell'induzione è stato osservato in 100 (50,8%) donne (43,25 tra nullipare e 81,4 tra pluripare). Il tempo medio dall'inserimento del misoprostolo al parto vaginale indipendentemente dalla parità è stato di 17,5 ore: nelle nullipare 20,0 ore e nelle pluripare e 13,1 ore,

Corresponding Author: Giuseppe Ettore
Giuseppe.ettore@gmail.com

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for caesarean delivery in women treated with the 200-µg misoprostol were: pathologic fetal health rate pattern in 23 patients (53.5%), lack of efficacy in eight (18.6%), prolonged labor in eight subjects (18.6%), maternal request in three (7.0%), and maternal hypertension in one (2.3%). Parity was associated successful induction (RR vs nullipara: 4.26). There were no fetal, maternal or neonatal deaths. Tachysystole requiring intervention occurred in 58 cases (29.4%).
Conclusions: Misoprostol 200 µg VDR is an effective and safe approach to induction of labor, regardless of several factors including Bishop' score, age and maternal BMI.

Keywords: Misoprostol; labor induction; vaginal delivery; predictive factors

rispettivamente. Il tasso di taglio cesareo è stato del 21,8% (43 casi). Le ragioni del taglio cesareo nelle donne trattate con misoprostolo vaginale 200 µg sono state: alterazioni della frequenza cardiaca fetale in 23 pazienti (53,5%), fallimento dell'induzione in 8 (18,6%), travaglio prolungato in 8 soggetti (18,6%), richiesta materna in 3 (7,0%) e ipertensione materna in 1 paziente (2,3%). La parità risulta essere associata al successo dell'induzione (RR vs nullipara: 4,26). Non ci sono stati decessi fetali, materni o neonatali. La tachisistolia che ha richiesto l'intervento medico si è verificata in 58 casi (29,4%).
Conclusioni: il dispositivo vaginale a base di Misoprostolo 200 µg è un approccio efficace e sicuro all'induzione del travaglio, indipendentemente da diversi fattori tra cui il Bishop score, l'età e l'IMC materno.

INTRODUCTION

Induction of labor is a common obstetrical intervention: recent data show that in Italy approximately 20% of labors are induced[1]. In case of induction, childbirth occurs vaginally in approximately 60–70% of cases, regardless of how induction is performed[2,3]. Traditionally, the Bishop score and parity were considered the main predictors of response to induction[4]. Moreover, the risk of failure to induce is greater among nulliparous women[5]. Recently, other factors were suggested as prognostic response factors including age and body mass index (BMI)[6].

Multiple approaches to induction of labor exist. Overall, prostaglandins represent the preferred agent in labor induction, but mechanical methods are also used[7]. Among different prostaglandins, misoprostol has the ability to mimic the changes of spontaneous labor and has been used off-label for over 30 years as a labor-induction agent, and is now registered in Europe in the form of a single controlled-release vaginal insert containing 200 µg, and approved for labor induction beyond 37 0/7 weeks' gestation[8,9]. The efficacy and safety of this agent have been extensively investigated[8,10,11]. However, 'field-practice' studies on vaginal misoprostol 200 µg are scant, and only few data exist on the predictive factors for labor success with this molecule – while most available evidence on predictive factors is gathered from other prostaglandins. Moreover, there are no published data on the use of vaginal misoprostol specifically referring to the Italian scenario, due to its recent introduction into the market.

Here, we report the results of a multicenter prospective observational study on prognostic factors of response to induction to labor with vaginal misoprostol 200 µg in routine clinical practice.

PATIENTS AND METHODS

Setting and patients

This was a prospective, multicenter observational cohort study, which started in September 2016 and ended in September 2017. Consecutive women treated with removable vaginal misoprostol (vaginal delivery system [VDS]; Mysodelle, Ferring Pharmaceuticals, Saint-Prex, Switzerland) 200 µg in nine Italian centers were enrolled provided they met the following criteria: age >18 years; 37 weeks of gestation or more in which induction was clinically indicated; single fetus pregnancy in cephalic presentation; and modified Bishop's score[12] less than or equal to 4 at induction. Exclusion criteria were as follows: active labor; hypersensitivity to the active substance or to any of the excipients; suspicion or evidence of foetal impairment prior to induction (e.g., failed stress or stress test, meconium staining or diagnosis or history of non-reassuring fetal state); prior oxytocin and/or other labor inducing agents administration; suspicion or evidence of uterine scar resulting from previous uterine or cervical surgery; uterine malformations (such as uterus bicorns); placenta previa or unexplained vaginal bleeding after 24 weeks of gestation; and signs or symptoms of corioamniosite. The research was authorized by the Ethics Committee of participating centers. All women provided written informed consent.

The objective of the study was to investigate the efficacy of misoprostol 200 µg in the induction of labor in the study population and the determinants of response.

For the purpose of this study induction response was defined as: vaginal childbirth within 24 h from the beginning of induction.

Treatment

According to the observational design of the study, all decisions relating to the use of misoprostol 200 µg VDS and the management of labor and childbirth were exclusively at the discretion of the experimenters in accordance with their usual practice.

Misoprostol 200 µg was placed in the posterior vaginal fornix. Women were invited to rest on a bed for at least 30 minutes after insertion and were continually monitored for uterine and fetal heart rate activity.

The vaginal insert was removed at the onset of active labor (defined according to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine[13] as three or more contractions in 10 minutes, lasting 45 seconds or longer resulting in cervical change or reaching 4-cm dilatation with any frequency of contractions); at the completion of the 24-hour dosing period; at the occurrence of any antepartum adverse event; or at maternal request. Oxytocin administration was allowed 30 minutes after removal of the insert if the patient was not in active labor and had reassuring fetal status.

Treatment interventions, including tocolysis and amnioinfusion, used to treat tachysystole, fetal heart rate abnormality, or both, were applied, where appropriate, according to the standard practice of each center. Fetal heart rate activity patterns and uterine contractile abnormalities were defined according to FIGO[14].

Assessments

After drug insertion, vaginal examinations were performed at 6, 12, 18 and 24 hours (if delivery had not occurred) although the insert had been removed, the woman was in active labor, or a caesarean delivery was planned. The modified Bishop score was recorded at each time point. The time and mode of delivery of the neonate and indication for caesarean delivery or reason for instrumented vaginal delivery were also recorded.

Women and neonates were observed for adverse events till hospital discharge. Before hospital discharge, women were asked about their satisfaction about delivery using a 5-point scale.

Sample size and statistical analysis

In total, 200 patients were planned to be enrolled. Indeed, considering an expected rate of induction failures (defined for the objective of this protocol: not vaginal childbirth within 24 h from the beginning of induction) in the population as a whole equal to approximately 45%[15], with this sample size we were able to identify non-rare factors in the population (i.e., present one-third of the study population) that increase the risk of failure of about 50% (relative risk [RR]: 1.5).

Data were analyzed by descriptive statistics. The correlation between a number of factors – age, weight, height, BMI, parity, sonographic data and indication to induction – and the response to induction were evaluated using the analysis of relative risks and the relative confidence limits to 95%.

RESULTS

A total of 200 women were enrolled; in three cases entry criteria were not respected and in one case labor started before drug insertion, and therefore the present report includes 197 cases.

Table 1 summarizes patients' characteristics. The mean age and the mean BMI before pregnancy were 32.5 years and 24.2 kg/m2, respectively. A total of 117 (58.8%) women were nulliparae and 71 (35.8%) had a Bishop score at insertion ≤1. Indication to induction was post-term pregnancy in 87 (43.7%) cases, fetal reasons in 33 (16.6%), maternal reasons in 82 (41.2%) and other in 14 (7.0%) cases.

Table 1
Characteristics of 197 study patients

Characteristics	n	%
Age, mean (range); years	32.5 (19–46)	
BMI before pregnancy, mean (range); kg/m2	24.3 (16.5–59.4)	
Weight gain in pregnancy, mean (range); kg	13.6 (0–35)	
Previous pregnancy: – 0 – 1+	 117 80	 59.4 40.6
Previous delivery: – 0 – 1 – 2+	 154 33 10	 78.2 16.8 5.0
Smoking in pregnancy: – Yes – No	 9 190	 4.6 95.4
Assisted reproductive techniques: – Yes – No	 10 187	 5.1 94.9
Gestational hypertension: – Yes – No	 14 183	 7.1 92.9
Gestational diabetes: – Yes – No	 42 155	 21.3 78.7
Gestational week at induction: – 36 – 37 – 38 – 39 – 40 – 41	 2 8 31 42 29 85	 1.0 4.1 15.7 21.3 14.7 43.2
Bishop score at insertion of vaginal misoprostol 200 µg: – 0 – 1 – 2 – 3 – 4	 42 28 71 41 15	 21.3 14.2 36.0 20.8 7.6
Reason for induction: – Post-term pregnancy – Fetal – Maternal – Other	 86 33 82 14	 43.6 16.7 41.6 7.1

Induction of labor

Table 2 shows the efficacy outcomes in the total series and strata of parity. Vaginal birth within 24 h from the beginning of induction was reported in 100 (50.8%) women (43.25 among nulliparae and 81.4 among parae). The median time from misoprostol insertion to vaginal delivery for women of any parity was 17.5 hours: the corresponding values in nulliparae and parae 20.0 and 13.1 hours, respectively.

The caesarean delivery rate was 21.8% (43 cases). Reasons for caesarean delivery in women treated with the 200-µg misoprostol were: pathologic fetal health rate pattern in 23 patients (53.5%), lack of efficacy in eight (18.6%), prolonged labor in eight subjects (18.6%), maternal request in three (7.0%), and maternal hypertension in one (2.3%).

The rates of caesarean delivery were 26.7 (23/85), 9.1(3/33), 20.7 (17/82) and 21.4(3/14) when the indication was post-term pregnancy, fetal, maternal and other, respectively. Instrumental vaginal deliveries occurred in 17 cases.

Parity was significantly associated with the risk of successful induction: in comparison with nullipare the relative risk of successful induction among parae was 4.26 (**Table 3**).

Table 2

Efficacy outcomes in the total series and strata of parity. Values in brackets represent range or percentage, as appropriate

	Total (n=197)	**Nulliparae, total (n=154)**	**Parae, total (n=43)**
Median time to vaginal delivery (h) (n=154)	17.5 (12.1–19.6)	20.0 (13.7–30.9)	13.1 (10.0–17.5)
Median time to any delivery (h) (n=197)	18.0 (12.3–30.7)	20.8 (13.7–32.9)	13.1 (10.0–17.5)
Median time to active labor (h) (n=182)	13.7 (9.8–23.7)	15.8 (10.1–24.8)	10.6 (7.7–12.8)
Women requiring pre-delivery oxytocin	64 (32.5%)	62 (39.7%)	2 (4.6%)
Incidence of vaginal delivery in 12 h	38 (19.3%)	21 (13.6%)	17 (39.5%)
Incidence of vaginal delivery in 24 h	100 (50.8%)	65 (42.2%)	35 (81.4%)
Incidence of any delivery within 12 h	47 (23.9%)	29 (18.8%)	18 (41.7%)
Incidence of any delivery within 24 h	125 (63.4%)	88 (57.1%)	37 (86.0%)
Incidence of vaginal delivery	154 (78.2%)	113 (73.4%)	41 (95.4%)
Instrumental vaginal delivery	17 (8.6%)	17 (11%)	0 (0%)

Table 3

Relative risk of successful induction/vagina delivery within 24 h) according to selected factors

Factors	**Successful induction, n (%)**		**RR (95% CI)**
	Yes	**No**	
Age (years): – <35 – ≥35	 65 (65.0) 35 (35.0)	 62 (63.9) 35 (36.1)	 1 0.98 (0.65–1.47)
BMI: – >25 – ≥25	 67 (67.0) 33 (33.0)	 64 (66.0) 33 (34.0)	 1 0.98 (0.64–1.48)
Parity: – 0 – 1 or more	 65 (65.0) 35 (35.0)	 89 (91.8) 8 (8.2)	 1 4.26 (1.28–6.7)
Bishop's score: – 0–2 – 3–4	 72 (35.4) 28 (64.6)	 69 (36.1) 28 (63.9)	 1 0.9 (0.6–1.5)
Indication to induction: – Post-term gestational week – Fetal – Maternal – Other	 46 (46.0) 16 (16.0) 39 (39.0) 7 (7.0)	 40 (41.2) 17 (17.5) 43 (44.3) 7 (7.2)	 1.10 (0.74–1.63)† 0.95 (0.55–1.62) 0.90 (0.60–1.34) 0.98 (0.46–2.12)

In some cases, the sum does not add up the total due to missing values.

†Reference category: any other indication.

Table 4

Neonatal outcomes and adverse events.

	n	**%**
Uterine tachysystole*	58	29.4
Tocolysis use	32	16.2
Amnioinfusion	5	2.5
Meconium-stained liquor	37	18.8
Antibiotic use	14	7.1
Epidural anesthesia	92	46.7
Post-partum blood loss (ml), median (IQR)	300 (200–500)	
Other maternal adverse events: • Uterine atonic • Postpartum elliptic crisis • Postpartum hemorrhage • Uterine hypertonus • Fever in labor • Sepsis (suspected) • Postpartum hypotension	8 1 1 1 1 2 1 1	4.1 0.5 0.5 0.5 0.5 1.1 0.5 0.5
Neonatal birth weight, grams	3472	±443
1-min Apgar score: • <7 • ≥7 5-min Apgar score • <7 • ≥7	 8 189 1 195	 4.1 95.9 0.5 99.5
pH value, mean (SD)	7.2 (±0.1)	
Lactate (mmol/L), mean (SD)	5.2 (±3.8)	
BE value (mmol/L), mean (SD)	-5.8 (±3.3)	
Neonatal ICU admission	8	4.1

*Defined as >5 contractions in 10 min, averaged over three consecutive 10-min periods.

Table 5
Patient's satisfaction.

	n	%
Very satisfied	53	27.0
Satisfied	102	52.0
Neither satisfied nor dissatisfied	24	12.2
Not satisfied	15	7.7
Totally not satisfied	2	1.0

The sum does not add up the total due to missing values

Safety
There were no fetal, maternal or neonatal deaths. The adverse event "tachysystole requiring intervention" occurred in 58 cases (29.4%). Other safety outcomes are presented in **Table 4**.
Patient's satisfaction
Table 5 shows the results of questionnaire on patient's satisfaction about induction, trial and delivery. Overall, 79% of women declared to be satisfied or very satisfied.

DISCUSSION

This study shows that vaginal misoprostol 200 µg is an effective modality of induction of labor. Moreover, it is well accepted by woman, with the wide majority of patients satisfied or very satisfied about induction and delivery. Remarkably, parity, but not age and BMI or indication to induction, was a determinant of successful induction. It should be also underlined that despite the high rate of tachysystole observed, due to the clinical management, no major adverse maternal or fetal event were reported. Concern regarding an increased risk of uterine hyperstimulation with the use of misoprostol has been reported and associated with possible lacerations or uterine ruptures and the need for attentive fetal monitoring[16-19]. Our observation suggests that the use of vaginal misoprostol is safe; in addition, the reduced time to delivery could be an advantage for the health system.

We must acknowledge that this is an observational, non-comparative trial, and such it does not offer information on the comparative efficacy of vaginal misoprostol versus other modalities of induction. However, the goal of this study is to offer an evaluation of the efficacy and safety of vaginal misoprostol in the routine practice in Italy, a country in which misoprostol has been recently marketed and now is not commonly used. Along this line, we have included all the women consecutively treated with vaginal misoprostol in the participating centers during the study period.

Remarkably, our study offers information on the determinants of response to vaginal misoprostol, an issue poorly investigated too far and for which prospective studies have been advocated since available data are based on studies using different drugs for induction than vaginal misoprostol[20]. Indeed, it is possible that different drugs or formulations can show different response rates in some subgroups of patients (e.g. obese vs non-obese women).
Historically, the Bishop score and parity were considered the main indicator of response to induction[5].

Recently, however, other factors have been suggested as prognostic factors for response. Among these the most important in clinical practice are age and maternal weight[21,22]. For example, in a retrospective study conducted in the USA that included 80 nulliparous women who had been treated for induction of labor with Bishop score unfavorable factors associated with a favorable outcome of induction of labor were the age, lower BMI and lower maternal weight[23]. In our study, only parity was a determinant of successful after induction with vaginal misoprostol; remarkably, misoprostol 200 µg was effective regardless of other factors, such as Bishop' score, age and maternal BMI. Knowing the determinants of response to induction is extremely important in the routine practice. For example, quantifying the role of maternal age can lead to identify a group of women in which anticipating the induction may reduce the rate of failure. Midwives' workload is very high in Italy, as maternity resources are insufficient and require an attentive channelling. Use of a method for induction with a high success rate may help to reduce caesarean procedures and may further help in a setting where supportive care during labor by midwives may be inadequate to control stress and pain[24,25].

CONCLUSION

Misoprostol 200 µg VDR is an effective and safe approach to induction of labor, regardless of several factors including Bishop' score, age and maternal BMI.

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