

Induction of labor with oral misoprostol in nulliparous mothers of twins

Teresinha Simões¹, Pedro Condeço¹, Elsa Dias², Paula Ventura¹, Cristina Matos¹ and Isaac Blickstein^{2,*}

¹ Department of Maternal-Fetal Medicine and Neonatology, Maternity Dr. Alfredo da Costa, Lisbon, Portugal

² Kaplan Medical Center, Rehovot, Israel

Abstract

The efficacy and safety of oral misoprostol for labor induction of twins is unknown. We conducted a retrospective case-control study to evaluate the use of oral misoprostol in near term (≥ 35 weeks) twin pregnancies in nulliparas. Eligible cases were given 100 mcg oral misoprostol, which was repeated after 6 h if labor did not start. Either a third dose or diluted oxytocin infusion were given in intractable cases. Diluted oxytocin infusion was used for augmentation. Controls were nulliparas delivered at ≥ 35 weeks by elective cesarean section. The two groups were comparable in most aspects, except for fetal malpresentation, which was the major reason for avoiding induction. Of the 69 patients in whom labor was induced, 53 (76.8%) had a vaginal birth, 3 (4.3%) had a combined twin delivery, and 13 (18.8%) had a cesarean during labor. The mean length of stay of the neonates was significantly shorter among study cases, without significant difference in the frequency of delayed discharges as an overall proxy for neonatal complications. Labor induction with oral misoprostol could be offered to patients in whom near term vaginal twin delivery is unequivocally permitted and wish to deliver by the vaginal route.

Keywords: Cesarean section; labor induction; misoprostol; twins.

Introduction

Cesarean birth and labor induction for twin pregnancies increased substantially in the United States during the

last decade, and these changes in obstetrical practice have been associated with a significant decline in the rate of stillborn twins [1]. This conclusion comes from a recent retrospective cohort study of more than a million twin live births and stillbirths in the United States between 1989 and 1999, showing that the rates of labor induction and cesarean birth among twin live births increased by 138% (from 5.8 to 13.8%) and 15% (from 48.3 to 55.6%), respectively [1]. During the same period, there was a 43% decline in the stillbirth rate (from 24.4 to 13.9 per 1000 fetuses at risk). Importantly, the decline in the rate of twin stillbirths was larger at later gestational ages where the largest absolute increases in labor induction rates were observed [5]. These observations confirmed data from France and Australia, indicating that decisions to minimize fetal deaths in twin pregnancies increased preterm deliveries, and thus, lower rates of stillbirths are achieved seemingly at the price of delivering more twin infants before term [14, 15].

Further analysis of the American database suggests that in 1999 more than 15,000 live born twins were registered as being delivered after labor induction [6]. Regardless, these epidemiological studies [5, 6, 14, 15] did not consider the method of labor induction, method-related complications, or the frequency of failed inductions. At the same time the ACOG Practice Bulletin [2] included the multifetal pregnancy among obstetric circumstances that “are not contraindications to the induction of labor but do necessitate special attention”. Regrettably, this Practice Bulletin remained silent about the method of induction as well as the special attention that is required, whereas a more recent Practice Bulletin on multiple gestations [3] did not even mention the issue of labor induction in twins.

The clinical concern about labor induction in advanced twin gestations is based on the potential hyperstimulation of an overdistended uterus. This concern is represented by a paucity of published studies related to labor induction in twin gestations. These few and small-sized studies suggested that oxytocin stimulation [9, 10], intra-uterine balloon [12], or even prostaglandin E2 [19] were effective and safe for cervical ripening in the process of labor induction in twin gestations.

Over the past 15 years, data have been accumulated regarding the safety and efficacy of misoprostol (Cytotec, Searle), a prostaglandin E1 analogue, as a method for cervical ripening and labor induction [4]. More recently, stepwise oral misoprostol appears to be as effective as vaginal misoprostol for cervical ripening with a low inci-

*Corresponding author:

Dr. Isaac Blickstein

Kaplan Medical Center

Department of Obstetrics and Gynecology

76100 Rehovot/Israel

Tel.: +972-8-944 1930

Fax: +972-8-941 1944

E-mail: blick@netvision.net.il

cence of uterine hyperstimulation, no increase in side effects, a high rate of patient satisfaction, and a lower cesarean section rate [20]. The ACOG Committee Opinion on labor induction with misoprostol, which published favorable comments related to this method of induction, also remained silent about its potential application in twin gestations [1].

Based on our experience with this drug in singletons, we performed this retrospective case-control study to evaluate the use of misoprostol in near term twin pregnancies.

Material and methods

During the period September 1994–December 2004, there were 825 twin pregnancies followed and delivered at our maternity center. This figure represents 0.98% of all births. Twin pregnancies that were delivered immediately upon admission were not included in the study. During this period, information about the pregnancy and delivery was prospectively registered on a preset form and subsequently entered into a computerized system. Because the purpose of this study was to evaluate the efficacy and safety of near term labor induction in twins using oral misoprostol, and in order to avoid the confounding effect of parity, we restricted this study to nulliparous women. Hence, the study group comprised nulliparous patients delivered following oral misoprostol induction at ≥ 35 weeks' gestation. Because we were interested in outcome related to the induction process and to avoid the confounding effect of spontaneous birth, the control group comprised nulliparous patients delivered at ≥ 35 weeks' gestation by elective cesarean section.

Induction of labor was not done in patients with previous uterine surgery, an abnormal (non-vertex) presentation of the first twin, when the patient opted for an elective cesarean section, or when a vaginal delivery was contraindicated. Eligible patients for induction by misoprostol had a closed and uneffaced cervix with intact membranes. Following a detailed informed consent process, a comprehensive maternal and fetal assessment (dual fetal heart rate tracing, biophysical profile, and estimated fetal weight) to exclude cases from the induction process, oral misoprostol was given in a dose of 100 μg , which was repeated after 6 h if there were no contractions or cervical dilatation. If the second dose did not induce labor, either a third dose is given or diluted oxytocin infusion (starting with 5 and increasing up to 15 mU/min) is initiated. Cases that were successfully induced by misoprostol alone and misoprostol and oxytocin comprised the study group. Augmentation of labor was done, if necessary, by diluted oxytocin infusion. We considered an induction successful if the patient delivered by the vaginal route. Failed induction was considered if intrapartum cesarean section was performed. During labor, we rupture the membranes at a relatively early stage in order to have access for direct fetal heart rate monitoring of the presenting twin (enabling accurate dual monitoring, performed almost invariably) and to reduce uterine overdistension.

The following variables were considered for analysis: maternal age, mode of conception (spontaneous or by assisted reproduction), maternal complications during pregnancy (premature contractions and hypertensive disorders), maternal complications that indicate delivery near term (≥ 36 weeks, including semi-indications such as worsening dyspnea, sleeplessness,

severe depending edema, etc. [3]), fetal indications (such as growth aberration or oligohydramnios in one or both gestational sacs); fetal presentation (vertex–vertex or other), and frequency of monochorionic twins. We evaluated the induction method by the length of the active phase of labor (from 3 cm of dilatation to delivery) and by the need for intrapartum cesarean delivery in the study group. Postpartum hemorrhage and infectious morbidity in both study and control groups were considered as method complications. Neonatal outcomes included birth weights, 5-min Apgar scores of <7 , trauma, admission to and length of stay at the neonatal intensive care unit. The overall outcome was evaluated by the frequency of delayed discharge of the infants as a result of neonatal complications (such as respiratory distress, and need for mechanical ventilation, hyperbilirubinemia, and infection). Umbilical cord blood gases were not evaluated.

The data were evaluated using the Microsoft Excel® program (Microsoft Corporation, Redmond, Washington). We used the True EPIDAT Software (Math Archives, Round Rock, TX) to compare the induction and the elective cesarean section cases. We performed Student's *t* and chi-square tests for continuous and categorical variables, respectively. We derived the odds ratios and 95% confidence interval, as well as *P* values (considered significant if <0.05). The local Ethical Committee approved the study.

Results

During the study period, 69 patients (8.3% of the entire cohort) met the inclusion criteria for labor induction with oral misoprostol near term. The eligible control group comprised 116 (14.1%) patients. Table 1 shows the comparison of maternal and fetal characteristics between the groups. Study patients were slightly younger and comprised slightly more (borderline significance) spontaneous conceptions, but have the same frequency of pregnancy complications, mean gestational age, similar frequencies for the indication leading to induction of labor, and similar frequencies of monochorionic twins. There was a much higher frequency of vertex–vertex combination of presentations among the study group. Taken together, Table 1 suggests that the two groups were comparable in most aspects, except for fetal malpresentation, which was the major reason for avoiding inductions in these patients.

Of the 69 patients in whom labor was induced, 53 (76.8%) had a vaginal twin birth, 3 (4.3%) had a combined twin delivery (i.e., cesarean section for the second twin), and 13 (18.8%) had a cesarean delivery during labor. Combined twin delivery was done because of difficult delivery of a malpresenting twin ($n=1$) and intrapartum signs of fetal distress in the second twin ($n=2$). The indications for cesarean section during labor were arrest disorders of the active phase ($n=10$) and suspected fetal distress in the remaining 3 cases.

The mean duration of labor from the beginning of the active phase until delivery in the successful induction cases was 225 ± 153 min. This was achieved in 41 cases (59.4%) with misoprostol only, and in the remaining cas-

Table 1 Comparison between the clinical presentation of the labor induction and elective cesarean section groups. Data shown as N (%) or as mean \pm SD. Statistics are shown as P values for continuous data, and by odds ratio (95% confidence interval) for categorical data.

	Labor induction	Elective cesarean section	Statistics
N	69	116	
Maternal age (yrs)	28.5 \pm 5.4	29.3 \pm 6.6	P < 0.01
Spontaneous pregnancies	49 (75.4)	63 (54.7)	2.1 (1.04, 4.1)
Pregnancy complications			
Preterm contractions	29 (42.0)	50 (43.1)	1.0 (0.5, 1.8)
Hypertensive disorders	13 (18.8)	32 (27.5)	0.6 (0.3, 1.3)
Gestational age (d)	256.0 \pm 6.0	254.8 \pm 7.0	P = 0.27
Indication for induction*			
Semi-indications at \geq 36 weeks	46 (66.6)	91 (78.4)	0.5 (0.3, 1.1)
Maternal	14 (20.3)	28 (24.1)	0.8 (0.4, 1.8)
Fetal	8 (11.6)	20 (17.2)	0.6 (0.2, 1.6)
Stillbirth	0	3 (1.3%)	
Vertex-Vertex	56 (81.1)	28 (24.1)	13.5 (6.1, 30.5)
Monochorionic	16 (23.1)	18 (15.5)	1.6 (0.7, 3.7)

*Only major indications were considered for the analysis. Some patients may have more than one indication.

es with the addition of oxytocin induction. There were no cases of uterine hyperstimulation or uterine rupture in the study group. One case of postpartum hemorrhage and one case of postpartum infection complicated the elective cesarean group. One case of failed induction was subsequently re-operated to drain an abdominal incision hematoma.

The comparison of fetal outcome variables is shown in Table 2. There was a significantly higher birth weight of the firstborn twin (but not of the second born) in the study group. Admission to the neonatal intensive care unit was required for one infant in each group, and this was indicated for neonatal respiratory difficulties. The mean length of stay of the neonates at the hospital was significantly shorter among the study cases, although there was no significant difference in the frequency of delayed discharges as an overall proxy for neonatal complications.

Discussion

Every method for labor induction should be evaluated by its safety and efficacy. To the best of our knowledge, this is the first study discussing the use of oral misoprostol

to induce labor in twins, and hence, there are no other published studies to compare with. For this reason, we limit our discussion to the use of oral misoprostol in singletons and to other methods of labor induction in twins.

Misoprostol is an inexpensive prostaglandin E₁ analogue administered orally or vaginally, easily stored, and known to have few systemic side effects when compared to placebo, vaginal or intracervical prostaglandin E₂, and oxytocin [11]. In terms of safety, it was suggested that effective oral regimens may have an unacceptably high incidence of complications such as uterine hyperstimulation and possibly uterine rupture [4, 20], a concern that is not shared by recent studies comparing oral misoprostol to other labor induction regimens in singletons [8, 11, 13, 17]. In our present series of twin pregnancies, labor induction with oral misoprostol appears to be safe, for both mother and twins. This is of special importance since we used a seemingly higher dose of misoprostol as recommended in the literature for singleton births [1]. Moreover, in a series of 69 labor inductions in multiparas with twins managed in our hospital, no uterine hyperstimulation was encountered (data not shown).

In terms of efficacy, our results show that induction was successful in 80% of the cases eligible for induction, and in 60% of these cases (about 50% of all inductions),

Table 2 Comparison between neonatal outcomes of the labor induction and elective cesarean section groups. Data shown as N (%) or as mean \pm SD. Statistics are shown as P values for continuous data, and by odds ratio (95% confidence interval) for categorical data.

	Labor induction	Elective cesarean section	Statistics
Birth weight			
Twin A	2551 \pm 315	2450 \pm 282	P = 0.02
Twin B	2432 \pm 320	2354 \pm 482	P = 0.1
5-min Apgar < 7	0	2 (0.9%)	
Length of stay (d)	4.0 \pm 2.3	5.2 \pm 3.0	P < 0.01
Delayed discharge	10 (7.2%)	22 (9.5)	0.8 (0.3, 1.9)

labor was induced with misoprostol alone. These success rates are comparable to those reported in singletons [8, 17]. In addition, fetal outcomes were entirely comparable between the labor induction and the elective cesarean groups, and associated with an overall reduction of neonatal hospitalization (Table 2). Finally, in our series of successful inductions, vaginal birth was achieved (from the beginning of the active phase) within 225 ± 153 min, in agreement with the results of Schiff et al. [16] who found that twin gestations have a significantly shorter first stage of labor than do singleton gestations, and in contrast to the data provided by Silver et al. [18] who found that the active phase dilation in twins proceeds at a slower rate than that observed in singleton pregnancies.

Other methods exist for labor induction in twins. For example, Manor et al. [12] evaluated the efficacy and safety of labor induction using an intrauterine balloon catheter in twin pregnancies. In the series of 17 cases, vaginal delivery was achieved in 15 (88.2%) patients and all neonates had a perfect 5-min Apgar score. Suzuki et al. [19] induced labor in 17 twin gestations with oral prostaglandin E_2 , and did not report any particular side effects. However, most reports in the literature probably used artificial rupture of membranes and oxytocin stimulation as a method of induction [10].

It is evident that not all twin pregnancies are candidates for labor induction, and from our study it appears that the obstetrical decision for an elective cesarean section was primarily related to fetal malpresentation, i.e., a combination other than vertex-vertex (Table 1). It also seems that both patients and their caregivers are more reluctant to choose labor induction in non-spontaneous twin gestations (Table 1). This trend, namely, cesarean section for "premium" twin pregnancies, is quite reasonable given the impact of the history of subfertility on decision making during labor and delivery [7]. As it appears, labor induction could be offered to patients in whom near term vaginal twin delivery is unequivocally permitted and to those who prefer the vaginal to the abdominal route.

Regardless of the favorable outcome associated with labor induction in our series of nulliparas with twins, we acknowledge the fact that such a procedure needs a dedicated obstetrical team and close observation throughout the induction process as well as during labor and delivery. Obviously, larger series are needed to exclude the possibility of rare events associated with labor induction such as uterine rupture.

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