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An Unreported Uterine Rupture in an Unscarred Uterus After Induced Labor With 25 μg Misoprostol Vaginally

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ABSTRACT

Uterine rupture without a former history of cesarean delivery or uterine scarring is an exceedingly rare complication in pregnancy and labor. Misoprostol is widely used to induce labor but there is a lack of knowledge about serious adverse effects. It is especially challenging to collect reports on side effects because misoprostol is not a registered drug. We report a case of a woman induced by one dose 25 μg misoprostol vaginally. Her pregnancy was uncomplicated and she had an unscarred uterus. Her labor progressed rapidly and she experienced hyperstimulation, meconium stained amniotic fluid, uterine rupture, and excessive blood loss of approximately 14 l. The child survived but is diagnosed with cerebral palsy. The case was never reported as an adverse event. This case questions the safety of misoprostol even in low dosage. It also underlines the need to report side effects to national reporting systems.

1. Introduction

Misoprostol is recommended by the Danish Association of Obstetricians and Gynecologists for induction of labor [1]. It is used off-label as Cytotec®, a medication that is currently only registered as treatment of gastric ulcers. The authors of the two latest Cochrane meta-analyses on misoprostol-induced labor underline the lack of sufficient statistical power to measure rare and serious side effects. Thus, they call on readers to report incidents of uterine rupture [2,3]. We report a case that draws attention to these issues: 1) misoprostol even when used in small doses on an unscarred uterus might cause uterine rupture and 2) side effects in the setting of off-label use should be reported to national reporting systems, where such systems are available.

2. Medical History

A woman, who had delivered her first baby via uncomplicated vaginal delivery, is induced at 42 + 0 weeks of gestation due to routine procedure in a Danish hospital in 2009. Apart from the gestation her pregnancy is normal. The patient record does not reveal the Bishops Score, but her cervix is initially described as no cervical dilatation, 2 cm in length, posterior location. At 11.53 am 25 μg misoprostol is placed in the posterior fornix of her vagina. Approximately 1 h later, at 1.00 pm after a normal CTG, she leaves the hospital according to hospital policy. She returns home to await contractions and does not receive further treatment with misoprostol. 7 h later, at eight o'clock pm she calls the hospital due to increasing labor pains. She is encouraged to stay at home. 10 min past midnight, 13 h after the misoprostol was inserted, she returns to the hospital now with strong contractions occurring every 2–3 min. She is 3–4 cm dilated, cervix is 1/2–1 cm, posterior location and soft with the fetal head present at the pelvic brim.

She is in pain, and asks for an epidural block. An external CTG is applied, classified as normal and disconnected after 13 min as she is transferred to the labor ward. Labor progresses rapidly (see Fig. 1) and 25 min after arrival at the hospital she fells an initial urge to push. Another 10 min later the water breaks; it is meconium-stained, and the cervix is now dilated to 9 cm. The fetal head is now 1 cm above the ischial spines. CTG is applied again and due to the patient record it reveals minor FHR decelerations that return to normal baseline. She receives an oxygen mask. At 1.05 am the midwife encourages her to push. The head is described as just below the spines. The descent of the head of the baby progresses normally during pushes, but it retracts between contractions. After 20 min of pushing there is still no sign of further fetal decent and the woman is asked to gasp. Due to the lack of progression an obstetrician is called and arrives at 1.35 am. The fetal head is still just below the spines. The obstetrician orders Syntocinon® (generic name oxytocin) 10 I.E. in a 1000 ml NaCl-solution. Due to the already frequent contractions the drip is started cautiously 6 ml/h that is half the standard dose. At 1.50 am the woman is again encouraged to push. It is noted in the hospital record that 'the drip is slowly increased to 24 ml/h'. Suddenly at 2.06 am there is fetal bradycardia to 75–80 beats per minute and the fetal head detracts resulting in a loss of fetal station. Simultaneously the woman starts to complain about unremitting abdominal pain and she turns pail. As the uterus is palpated uterine defense is noted and an emergent cesarean section is ordered.

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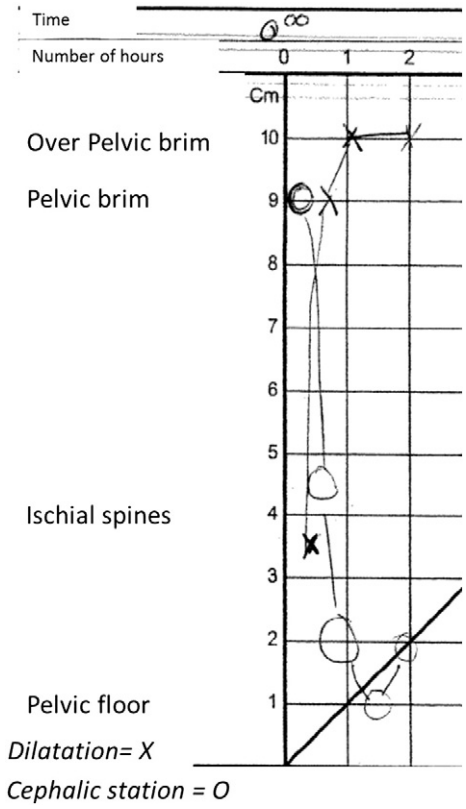

Fig. 1. Partogram: The partogram illustrates rapid progress of labor with the presenting fetal head touching the pelvic floor and then retracts. (The wording in the partogram is translated by us).

A girl is born 14 min later, Apgar 1/1, 5/10 min and pH 6.68, SBE −19 and weight 4800 g. The baby is transferred to an intensive care unit in another hospital. She receives 72 h of hypothermal treatment. At age 3 the girl is diagnosed with cerebral palsy.

The uterus is severely damaged. There is a full, posterior rupture extending from the fundus down, and there is almost a complete separation between the uterus and the vagina. The uterine scar is sewed continuously but with numerous insertions due to uncontrollable bleeding. The uterus is restored, but she bleeds 5500 ml during the operation. Two hours after the termination of the operation she is bleeding heavily again, and is re-operated. The bleeding is located at the lower part of the uterine rare side and in the left side of cervix and after several insertions hemostasis is obtained. However there is still diffuse bleeding from the fundal part. A double B-lynch suture is applied. In the patient record it is estimated that the total blood loss was 10 l. She receives 27 product with 245 ml erythrocytes, 18 product with 270 ml plasma and 9 products with 350 ml thrombocytes. She also received approximately 2.4 l NaCl solution which indicates that her blood loss might have been underestimated (total amount of IV products = 14.6 l + 2.4 l NaCl).

After the second operation she is sedated for approximately 14 h. It is noted in her patient record that she and the newborn are in a life-threatening situation. Her family members are called home from abroad due to the severity of the situation. She is discharged with the newborn 14 days after delivery.

She is never informed about the fact that she is treated with off-label medication. The family is not informed about their right to complain to the National Patient Complaint System and they are not informed about the possibility to seek compensation for the poor outcome (damaged uterus and a child with lifelong disability) from the Patient Complaint System [4,5]. Furthermore these cases (mother and baby) were not reported as an adverse incident report. After a public debate in 2012 on unreported side effects to misoprostol this family brought their case to the Patient Compensation Association and the child received a substantial economic compensation. The Patient Compensations Association stated that it was highly probable that misoprostol was the cause for these adverse events.

3. Discussion

Misoprostol is a prostaglandin E1 analog and very efficient uterotonic drug [1]. The US Food and Drug Administration (FDA) has listed a range of side effects such as hyperstimulation, uterine tetany, meconium-stained amniotic fluid, uterine rupture, maternal shock, maternal death, fetal bradycardia and fetal death [6]. Though both mother and child survived, this parturition included hyperstimulation, uterine rupture, meconium-stained amniotic fluid, life-threatening maternal hemorrhage, fetal bradycardia and threatening fetal death.

This woman previously had an uncomplicated vaginal delivery, and her current pregnancy was uneventful. It is highly unlikely to experience a uterine rupture in birth without a previously scarred uterus [7]. However high parity, malpresentation or placental abruption are predisposing factors [7–9]. External force to the maternal abdomen (i.e. Kristeller-maneuver, vacuum- or forceps assisted birth) can, in rare cases, cause rupture of an unscarred uterus [7–9]. None of these factors were present in this case.

25 μg misoprostol used vaginally is the recommended dose according to the Cochrane review [3]. Prostaglandins and other uterotonic agents can cause uterine rupture [7–10]. Several studies have found misoprostol more prone to hyperstimulation with fetal heart rate changes, meconium stained amniotic liquid and uterine rupture than other uterotonic agents [3,11] and reports on uterine rupture on previously unscarred uterus after misoprostol induction has been reported [12–17].

This birth was induced by misoprostol and thus not spontaneous. The woman experienced frequent contractions (5 in 10 min), which suggests hyperstimulation. The rapid progress of labor, her cervix dilated from 3–4 cm to 9 cm within 25 min and the fast decent of the fetal head from pelvic brim to below the ischial spines ads further to this argument.

Approximately 12 h passed from application of misoprostol to hyperstimulation and rapid progress of labor. Wing et al. [18] have noted that 'some patients appear to be quite sensitive to misoprostol, demonstrating prolonged contraction responses after a dose of the agent, sometimes in excess of 20 h after the drug'. This observation by Wing is supported by this case and we plan to publish other cases that also draw attention to possible prolonged contraction responses.

The woman received two drugs that are connected to hyperstimulation and uterine rupture. The combined use of misoprostol and Syntocinon in the presence of hyperstimulation is known to be hazardous and both drugs are connected to hyperstimulation and uterine rupture. We know that the dose of misoprostol is 25 μg, however the exact dose of Syntocinon is not reported in the patient record. However the woman only received a marginal dose of Syntocinon. According to the patient record the doctor enters the delivery room at 1.35 am and orders a Syntocinon-drip starting cautionary at 6 ml/h. 15 min later it is noted that 'the drip is raised slowly'. The drip is running at 24 ml/h at 2.06 am. This leaves a total time of 31 min. Even though the exact amount of Syntocinon is not noted in her patient record, we can give a reasonable estimate of the amount. 1) We calculated the amount of Syntocinon as the number of minutes she was treated and multiplied it with the number of ml of Syntocinon/h, and 2) we estimate that it took 5 min to install the drip, and it was then started at 1.40 am. 3) The sign of uterine rupture (fetal bradycardia and detractions of the fetal head) is noted at 2.06 am. This provides us with a timeframe of 26 min of infusion time. We furthermore assessed, that the drip was increased every 10 min, as it was noted that they increased with caution. Given the above

information we calculated the infusion as:

1.40 — 1.50 am : 6 ml / hour for 10 minutes
×(6 ml × 10 minutes / 60 minutes) = 1 ml

1.50 — 2.00 am : 12ml / hour for 10 minutes
×(12 ml. × 10 minutes / 60 minutes) = 2 ml

2.00 — 2.06 am : 24 ml / hour for 6 minutes
×(24 ml × 6 minutes / 60 minutes) = 2.4 ml.

Given the above she received a total of 5.4 ml oxytocin, which is equivalent to approximately a teaspoon (5 ml) of the Syntocinon solution (10 IE in 1000 ml NaCl).

Adding Syntocinon at a time when hyper stimulation is already present increases the risk of rupture, however as the incidence of uterine rupture in an unscarred uterus is extremely rare a causal relationship to misoprostol must be considered [3]. It is important to note, that in this case hyper stimulation was present for approximately 11/2 h prior to initiation of the oxytocin-drip and thus it is likely that misoprostol is the main contributor to the overstretched and thinning of the uterine wall. As we can only assess likelihood but never have certainty it is important that all induction agents should be reviewed in all cases of uterine rupture.

Despite medication there is one more risk factor in this case as high fetal weight is a predisposing factor for uterine rupture [9,10]. The fetal weight could be a contributing factor; however this is unlikely to be a sufficient cause for this uterine rupture, as there was no sign of obstructed labor and a fast decent of the fetal skull until below the ischial spines. This indicates sufficient space in the pelvis. The uterine rupture occurred after only a short pushing period and with no external force added.

Overall these considerations of risk factors make misoprostol a likely agent in the course of labor that led to uterine rupture.

A serious issue is the lack of reporting. All medical treatments that may cause possible severe side effects should be reported to the National Health Authorities [5,19]. With the use of an off-label agent the reporting is even more crucial, as this is the only way to gain knowledge about possible side effects. Pharmaceutical companies have the obligation to collect, share and report side effects to the authorities, however this obligation does not exist in the case of off-label use. This case had severe consequences for both mother and baby and should without doubt have been reported. The Danish Declaration on the reporting of side effects state that all side effects to off-label use should be reported to the Health Authorities [5]. Furthermore the woman was not informed about the possibility to seek compensation for the poor outcome (damaged uterus and a child with lifelong disability) from the Patient Complaint System [4].

4. Conclusion

There is a high likelihood that 25 μg misoprostol used vaginally caused hyperstimulation that consequently led to a severe uterine rupture and excessive bleeding progressing to a situation where both mother and child were in a life-threatening situation. The weight of the baby and the marginal dose of oxytocin might be contributing factors but neither of them could cause the rapid progress of labor and hyperstimulation. Multiple interventions in childbirth interact in complex ways. In this particular case misoprostol is the only intervention that had the potential to either 1) cause a uterus rupture or 2) alter the muscular tissue in such a way that a teaspoon of oxytocin solution could cause such severe trauma to the uterine muscle.

If severe side effects like this case are not reported, then it raises concern that serious and less severe side effects also remain unreported. Drugs used off-label is especially prone to underreporting of side effects and the reporting system might not allow the reporting of side effects to medication that is used off-label. Randomized trials cannot measure rare side effects and combined with insufficient reporting and a lack of pharmaceutical company responsibility for off-label use, the foundation for the widely use of misoprostol is weak.

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