Efficacy and safety of Misoprostol vaginal insert to induce labor beyond 40 + 0 weeks of gestation

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Abstract

Introduction

One of the most common reasons for inducing labor are pregnancies beyond 40 + 0 weeks. Prostaglandins have been proven to induce labor whilst not increasing the rate of caesarean delivery. As a vaginal insert Misoprostol was available in Germany from 2014 to 2019. Studies show that Misoprostol vaginal insert (MVI) reduces induction to delivery time as well as active labor time. But it is also known to increase uterine tachysystole. This study aimed to clarify whether MVI is safe and efficient for women with pregnancies past 40 + 0 to 42 + 0 weeks since there is a lack of studies focussing on this particular group of women.

Methods

This single centre prospective cohort study was performed between December 2014 and September 2019 at a tertiary academic centre at the Presbyterian Hospital Bergisch Gladbach, Germany. A total of 304 women between 40 + 0 to 42 + 0 weeks of gestation have been induced to labor with MVI. MVI was placed in the posterior vaginal fornix to release to release 200 µg synthetic prostaglandin E_1 in a controlled manner. Time from insertion of MVI to delivery was documented for each patient. In addition, we recorded all kinds of intervention, CTG alterations and fetal outcome. We recorded mode of delivery, the need of epidural anaesthesia as well as the rate of tocolysis to treat signs of fetal distress due to pathological heart rates. And thirdly we had an interest in fetal outcome reflected by cord blood pH-levels or admission to a neonatal clinic.

Results

75.7 % (n = 230) of women gave birth within 24 hours which means time from insertion to delivery. After MVI insertion 72.2 % (n = 140) nulliparous women and 81.8 % (n = 90) multiparous women gave birth within 24 hours. Subgroup analyses revealed that within 24 hours after removal of MVI 259 women out of 304 (85.2 %) delivered their babies. 67.8 % (n = 206) of women induced with MVI delivered vaginal.

Conclusion

MVI is an efficient and safe method to induce labor for women with pregnancies beyond 40 + 0 weeks.

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Background

Induction of labor is a common procedure in obstetrics aiming to balance maternal and perinatal risks [1]. In 2017 in Germany 21.7% of deliveries have been induced [2]. Even though it is an established procedure it frequently causes controversy regarding indications and safety. Today, obstetricians are able to choose between a variety of labor inducing treatments. On one hand, there are mechanical methods that dilate the cervix via balloon catheter to help cervical ripening. On the other hand, there are pharmacological agents such as oxytocin or alternative prostaglandins which can be administered. Which method to choose depends on several factors that have to be taken into consideration: gestational age, history of cesarean deliveries, risk factors and necessity of induction.

37.6% of women in Germany in 2017 carried their pregnancies beyond 40 + 0 weeks of gestation. 33.3% of those women were induced to labor. The tendency to induce labor increases [2]. At 41 + 4 weeks 67.6% of women received any kind of labor induction [3]. Risk factors have been identified including nulliparity, prior post-term pregnancies, carrying a male fetus and maternal obesity [4]. Several studies have demonstrated that late-term and post-term pregnancies are associated with a risk of perinatal morbidity and mortality [5, 6].

Prostaglandins have been proven to induce labor whilst not increasing the rate of cesarean sections (CS) among women with unscarred uterus [7]. There are different kinds of prostaglandins available. Most common are prostaglandin E_2 analogs such as dinoprostone or E_1 analogs like misoprostol. Misoprostol is a synthetic prostaglandin E_1 analog known to be the most effective for inducing labor even though it is marketed as an oral prophylaxis and treatment of peptic ulcer disease, so that most countries are using it off-label. Nevertheless, Misoprostol is listed by the World Health Organization in the list of essential drugs for obstetrical use and it is recommended to use for the medical treatment in pregnant women [2]. It is available for oral and vaginal administration. As a vaginal insert Misoprostol was available in Germany since 2014. It contains 200 micrograms in a controlled-release hydrogel polymer system for a single application. Studies show that Misoprostol vaginal insert (MVI) reduces time to vaginal delivery significantly, as well as active labor [8–13] even for women with an unfavourable cervix as to BISHOP scores [14], while reducing the need for oxytocin compared to dinoprostone vaginal insert or oral misoprostol [8, 10, 15].

Hyperstimulation syndrome requiring tocolysis is more common in women receiving MVI [8, 10, 11, 14, 16].

A large group of women who need to be induced to labor are women with pregnancies beyond 40 + 0 weeks of gestation. Interestingly, this cohort is under researched what prompted this study to clarify whether MVI is also safe and efficient for women carrying pregnancies beyond 40 + 0 to 42 + 0 weeks.

Materials And Methods

This single centre prospective cohort study was performed between December 2014 and September 2019 at a tertiary academic centre at the Presbyterian Hospital Bergisch Gladbach, Germany. All women

who have been induced to labor at 40 + 0 and more weeks of gestation based on first trimester ultrasound examination were included in this study analysis. Inclusion criterion was age of at least 18 years. Exclusion criteria were previous caesarean delivery or other history of uterine scarring, contraindications for prostaglandins, intrauterine growth restriction, fetal malformations, severe preeclampsia or any signs of high fetal distress.

All women who participated gave informed consent. Local ethic committee reviewed and approved this study. This study was retrospectively registered at ISRCTN registry. Baseline demographic data was collected. This data included age, parity, gestational age, gestational diabetes and BISHOP scores, among others. We also included women in this study with risk factors regarding to an insufficient placenta such as smoking, oligohydramnions as well as obesity.

Prior to MVI application every woman had a cardiotocography for thirty minutes. A vaginal examination was performed before the vaginal insert was placed to determine the cervical ripeness. We only included women with an unripe cervix presented by BISHOP scores of four or lower.

Following the manufacturer´s instructions misoprostol as a vaginal insert was placed in the posterior vaginal fornix. According to manufacturer´s instructions it has to be removed within 24 hours. Indications for removing Misoprostol were either the onset of labor (three or more contractions in ten minutes), a cervical dilatation of four centimetres, hyper frequency contractions or after an exposure time of not more than 12 hours. All women had another cardiotocography after MVI removal.

Primarily we were interested in the time period from (1) insertion to the onset of labor, (2) onset of labor until delivery and (3) duration from insertion to birth. Secondarily we recorded the mode of delivery, the need of epidural anaesthesia as well as the necessity of tocolysis to treat signs of fetal distress due to pathological heart rates. And thirdly we had an interest in fetal outcome reflected by cord blood pH-levels or admission to a neonatal clinic. Statistical analyses were performed using SPSS 26 software package.

Results

304 women with pregnancies beyond 40 + 0 weeks were included in this prospective cohort study. Induction of labor was recommended according to the national guidelines for pregnancies beyond 40 + 0 weeks of gestation with or without additional risk factors [17].

The median patient age was 33 (range 21–49 years, Table 1). Length of pregnancy was ranged from 40 + 0 weeks to 42 + 0 weeks (mean 40 + 5.7 weeks). Patients characteristics were listed in Table 1. No significant differences were observed regarding parity (nulliparous versus multiparous) and length of gestation (40 + 0 to 40 + 6 versus 41 + 0 to 42 + 0) .

Table 1
Patient characteristics

	Nulliparous n = 194 (63.8%)	**Multiparous n = 110 (36.2%)**	**40 + 0–40 + 6 n = 153 (50.3%)**	**41 + 0–42 + 0 n = 151 (49.7%)**
Age (years), mean = 32.9	31.8	34.9	32.9	33.0
Gestational diabetes, n (%)	16 (8.2%)	10 (9.1%)	17 (11.1%)	9 (6.0%)
Preeclampsia, n (%)	14 (7.2%)	6 (5.5%)	13 (8.5%)	7 (4.6%)
Membrane rupture, n (%)	25 (13.0%)	13 (11.8%)	18 (11.8%)	20 (13.2%)
Insufficient placentae n, (%)	38 (24.8%)	28 (18.5%)	43 (22.2%)	23 (20.9%)
Birthweight (g), mean (SD)	3656.5 (399.4)	3597.8 (429.7)	3546.3 (385.9)	3596.9 (433.6)

33 (10.9%) patients lost their vaginal insert. In this case according to manufacturer´s instructions women were not allowed to have another MVI placed. Out of these patients only 6 needed a switch to an alternative method of labor induction.

Overall 75.7% (n = 230) of women gave birth within 24 hours representing time from insertion to delivery. After MVI insertion 72.2% (n = 140) nulliparous women and 81.8% (n = 90) multiparous women gave birth within 24 hours (Fig. 1, Table 2). Subgroup analyses revealed that within 24 hours after removal of MVI 259 women out of 304 (85.2%) delivered their babies. No statistical difference was found between women with 40 + 0 to 40 + 6 weeks of gestation and women beyond 40 + 6 weeks.

Table 2
Efficacy and safety

	Nulliparous n = 94 (63.8%)	**Multiparous n = 110 (36.2%)**	**40 + 0–40 + 6 n = 153 (50.3%)**	**41 + 0–42 + 0 n = 151 (49.7%)**
Vaginal Birth n = 206, (67.8%)	111 (57.2%)	95 (86.4%)	103 (67.3%)	103 (68.2%)
Delivery within 24 h n = 230, (75.7%)	140 (72.2%)	90 (81.8%)	117 (76.5%)	113 (74.8%)
Time to vaginal birth (h), mean	23.02	16.9	22.01	19.59
Epidural n = 121 (39.8%)	90 (46.4%)	31 (28.2%)	54 (35.3%)	67 (44.4%)
Failed Induction n = 45 (14.8%)	30 (15.4%)	15 (13.6%)	28 (18.3%)	17 (11.3%)
CS n = 98, (32.2%)	83 (42.8%)	15 (13.6%)	50 (32.7%)	48 (31.8%)
Emergency CS n = 2, (0.6%)	2 (1.0%)	0	0	2 (1,3%)
Tocolysis n = 32 (10.5%)	21 (10.8%)	11 (10.0%)	22 (14.4%)	10 (6.6%)
Cord blood pH (mean = 7.27)	7.26	7.28	7.27	7.26
Neonatal Administration n = 10 (3.3%)	7 (3.6%)	3 (1.5%)	6 (4.0%)	4 (2.6%)

All cases in which MVI failed to induce labor (n = 45) were excluded for further analysis. In those cases, women were further induced with E_2 Gel analogs.

The median time from (1) insertion to onset of labor was 345 minutes (range 60 minutes to 1440 minutes). 374 minutes was the median time for (2) onset of labor to delivery (range 0 minutes to 3125 minutes) and 750 minutes was median time from (3) insertion to delivery (range 159 minutes to 3361 minutes).

67.8% (n = 206) of women induced with MVI delivered vaginally. 32.2% (n = 98) of induced women needed caesarean delivery. 42.9% (n = 42) of these women who needed a caesarean delivery showed signs of fetal distress. In two cases an emergency CS was required. Other reasons secondary CS has been arrested labor (45.9%, n = 45), maternal wish (8.2%, n = 8) or placental abruption 4.0% (n = 4). Tocolysis was needed in 10.5% (n = 32) of cases (Table 2). In 38.2% cases patients needed an epidural anaesthesia.

The median of cord pH levels reflecting fetal outcome was 7.27 (range 6.92 to 7.49). 5.8% of cord pH levels were below 7.15 to mirror fetal distress during labor. Only 3.3% (n = 10) of new-borns were transmitted to a neonatal clinic. The average APGAR scores after five minutes were 9.86 and 9.96 after ten minutes. The median new-borns weight was 3571.4 grams.

Discussion

According to The American College of Obstetrician and Gynaecologists (ACOG) Misoprostol as a vaginal insert is recommended to use to induce labor in pregnant women [4]. It is proven to be a reliable and safe method to support cervical ripening [15]. Unfortunately, since the end of 2019 it is no longer available in Germany.

A rather large and sensitive group of pregnant women are women with pregnancies beyond 40 + 0 weeks of gestation. In addition to their already existing risk factors the likelihood for placental insufficiency is even higher in this cohort [4]. A Cochrane database by Middleton et al. was able to show an association between induction of labor and fewer stillbirths for women carrying pregnancies beyond 41 weeks [18]. But at the same time in day-to-day clinic these women often need or even ask for induction of labor. However, there were only few data regarding this patient group [19].

To our knowledge this is the first study to focus on women with pregnancies beyond 40 + 0 weeks only. We demonstrated that Misoprostol as a vaginal insert for induction of labor in 304 women with pregnancies beyond their expected date of birth is efficient and safe.

More than 75% of women who were induced achieved vaginal birth within 24 hours. In this specific cohort with increased risks we found no higher rate of caesarean deliveries. In comparable studies for preterm induction of labor the rates in CS delivery mode were reported as 16.6–32% [8, 20]. In our cohort with a median duration of 40 + 6 weeks the rate of CS was 32.0%. This comparably high deliveries emphasize the increasing risk of fetal distress in prolonged pregnancies.

Until now literature is still controversial when it comes to the rates of caesarean deliveries and fetal outcomes after the Induction with MVI. Some research indicates significantly higher caesarean section rate and negative effects on fetal outcome [13]. Sharp et al (2019) demonstrated increasing caesarean deliveries comparing MVI with dinoprostone intravaginal gel. Other studies were able to show that there is no difference in perinatal outcome, rates of CS and vaginal operative delivery comparing MVI to oral misoprostone or dinoprostone insert [9, 11, 12, 15, 21].

For safety aspects, our group of women with pregnancies beyond 40 + 0 weeks is a high-risk population due to potential placental insufficiency during labor, which could cause fetal distress leading to unfavourable outcomes [13]. Gulmezoglu et al. summarized in a Cochrane database review that risks for mothers and their unborn babies start to increase significantly after 41 + 0 weeks [22]. Risks for meconium aspiration, caesarean delivery and perinatal morbidity start to increase significantly.

This study is mainly limited by two factors: its monocentric and single-arm design. Furthermore, this prospective trial could have had an increased value if we would have had a randomized design contrasting for example misoprostol vaginal insert with dinoprostol vaginal insert or other methods of application. In addition, a higher statistical power could be achieved with a larger cohort.

Regarding to the manufacturer's guidelines MVI is supposed to be removed at the onset of labor or after 24 hours at the latest. Catching the exact moment of onset of labor seems to be crucial to avoid hyperstimulation, although in clinical everyday it is sometimes impossible to intervene at the ideal moment. After 12 hours misoprostol vaginal insert released 50% of its effective dose. It´s biological half-life is 45 minutes. We decided to remove MVI after 12 hours at the latest to lower the risk of hyperstimulation.

Hyperstimulation after induction with misoprostol vaginal insert is a common side effect. Women who receive MVI and healthcare professionals who take care of those need to be aware of this fact. We suggest hospitalisation of women who receive MVI to ensure that they are monitored thoroughly so that in case of hyperstimulation or fetal distress midwives and responsible doctors have the chance to take care of the situation to ensure safety for mothers and their unborn babies. With this approach we were able to avoid hyperstimulation in most cases which is reflected by the use of tocolysis for approximately 10% only.

When deciding which method to choose for induction of labor there is need for an informed decision making. MVI is a very efficient and a fast method to achieve vaginal birth due to its controlled release system. Risks for hyperstimulation and need for a rapid birth need to be carefully balanced out. Women need to be informed about benefits and potential risks to be able to make informed choices. Looking at our data we strongly support further use of MVI to induce labor. From our clinical under clinical aspects the withdrawal of Misodel™ is not comprehensible.

Conclusion

Misoprostol vaginal insert is an efficient and safe prostaglandin to induce labor in women with pregnancies beyond 40 + 0 weeks of gestation.

List Of Abbrevations

MVI – Misoprostol vaginal insert

CS - Caesarean section

DECLARATIONS

Declarations

Ethics approval and consent to participate.

Local ethic committee at the academic centre at the Presbyterian Hospital Bergisch Gladbach, Germany reviewed and approved this study.

CONSENT FOR PUBLICATION

All women who anticipated gave informed consent.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

Not applicable.

FUNDING.

Not applicable.

AUTHORS CONTRIBUTION

Catharina Krause and Melanie Erices-Leclercq collected patient data. Statistics were performed by Christian Rudlowski and Sabine Lubig. Sabine Lubig was a major contributor writing the manuscript. All authors read and approved the final manuscript.

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Figures

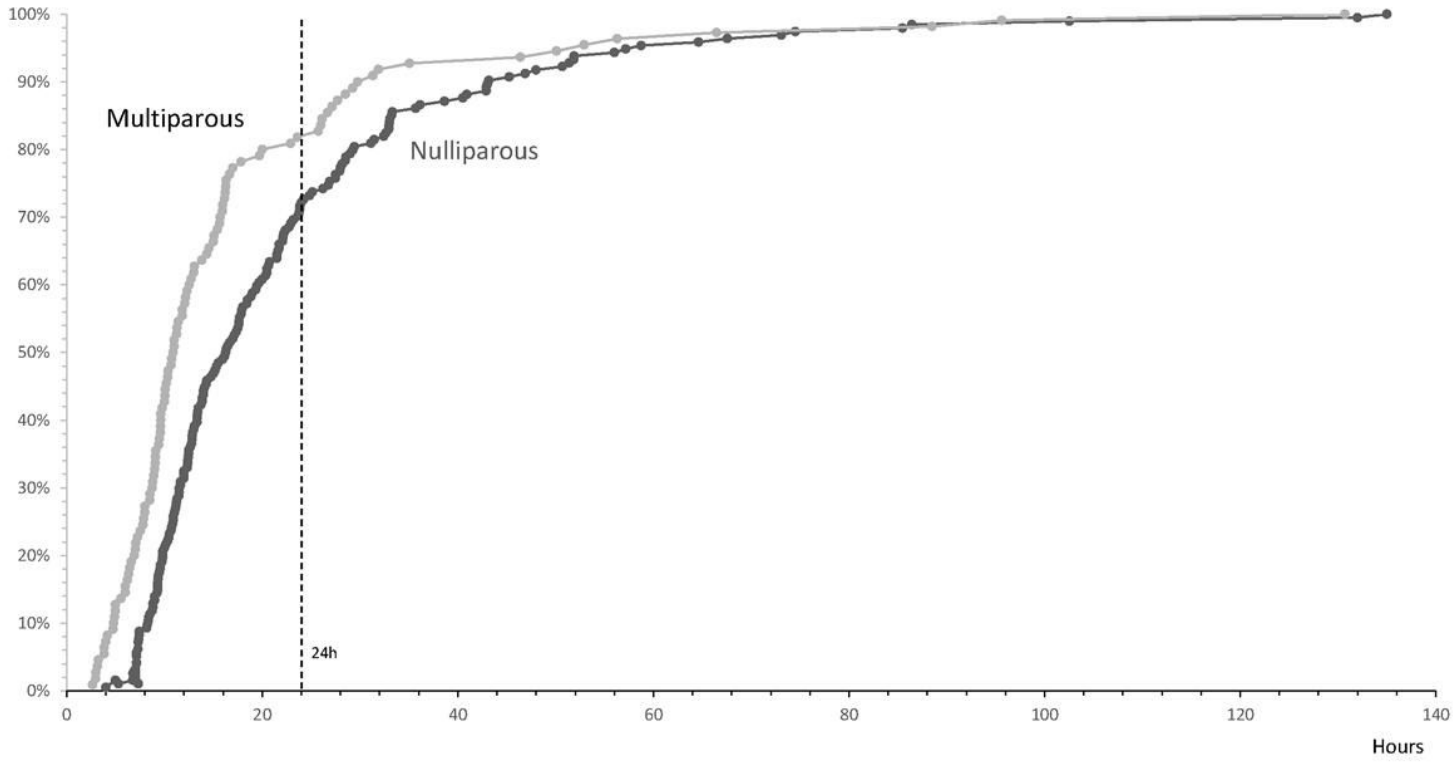

Figure 1

Duration from MVI insertion to delivery in nulli- and multiparous