

Misoprostol for Labour Induction after Previous Caesarean Section – Forever a “No Go”?

Misoprostol zur Geburtseinleitung nach vorangegangener Sectio – ein „No-Go“ für immer?

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Abstract

Misoprostol in oral or vaginal form is an established method of labour induction worldwide. Its use after previous caesarean section is associated with a high rate of uterine rupture; according to international guidelines it is therefore contraindicated in this setting. However the evidence base for this recommendation comprises case reports, one randomised trial that was discontinued prematurely, and numerous low quality retrospective data analyses published between 1997 and 2004. New insights into e.g. resorption kinetics, dosage and application intervals, dose dependant uterine hyperstimulation rates, as well as increasing clinical experience with misoprostol have lead to a critical reappraisal of these “historical” studies. Accordingly the evidence supporting a ban on vaginal and particularly oral misoprostol for labour induction in the context of a scarred uterus is currently insufficient for a convincing guideline recommendation. In view of the clear advantages of misoprostol over prostaglandin E₂ (cheaper, more effective) a retrospective review of registry data should be conducted to determine the incidence of uterine rupture following misoprostol and the circumstances in which it occurs. A prospective, randomised trial could then be conducted on the basis of these findings (e.g. oral misoprostol vs. vaginal prostaglandin E₂); known risk factors for uterine rupture including the type of uterine scar would need to be taken into account when selecting patients for vaginal delivery. Until new data from well-designed studies are available, misoprostol will continue to be contraindicated in clinical guidelines for use in labour induction after previous caesarean section.

Zusammenfassung

Die orale oder vaginale Gabe von Misoprostol ist weltweit eine etablierte Methode zur Geburtseinleitung. Allerdings sollte Misoprostol aufgrund des hohen Risikos für eine Uterusruptur nach internationalen Leitlinienempfehlungen nicht bei Schwangeren mit vorangegangener Sectio caesarea angewendet werden. Grundlage dieser Leitlinienempfehlungen sind Fallberichte, eine randomisierte, vorzeitig beendete Studie sowie retrospektive Datenanalysen mit niedriger Qualität, die zwischen 1997–2004 publiziert wurden. Vor dem Hintergrund neuer Erkenntnisse (Resorptionskinetik, Dosierungen und Applikationsintervalle, dosisabhängige Rate uteriner Überstimulierungen) und wachsender klinischer Erfahrungen im Umgang mit Misoprostol wurden daher diese „historischen“ Studien einer kritischen Analyse unterzogen. Danach ist die Evidenz, vaginales und vor allem orales Misoprostol zur Geburtseinleitung nach vorangegangener Sectio zu verbieten, unzureichend, um daraus überzeugende, aktuelle Leitlinienempfehlungen ableiten zu können. Im Hinblick auf die evidenten Vorteile von Misoprostol (effektiver, kostengünstiger) im Vergleich zu zugelassenen, konventionellen Prostaglandin-E₂-Präparaten ist zu empfehlen, in einem retrospektiven Datenregister die Häufigkeit und Umstände von Uterusrupturen nach Misoprostol zu evaluieren. Auf der Grundlage dieses Registers könnte dann eine prospektive, randomisierte Studie (z. B. orales Misoprostol versus vaginales Prostaglandin E₂) initiiert werden, welche die Selektion für eine vaginale Geburt infrage kommender Schwangerer und die bekannten Risikofaktoren für eine Uterusruptur einschließlich der uterinen Schnittführung bei der vorangegangenen Sectio zu berücksichtigen hat. Bevor allerdings keine neuen Ergebnisse aus gut konzipierten Studien vorliegen, bleibt Misoprostol zur Geburtseinlei-

tung nach vorangegangener Sectio entsprechend aktuellen Leitlinien kontraindiziert.

Introduction

In the last 10 years the frequency of labour induction has almost doubled, current rates lying between 18 and 25% of all births; in the Netherlands the rate is as high as 33% [1], in Germany 22% in 2013 [2]. According to a 2013 nationwide survey (results from 538 hospitals) 66% of clinicians use the PGE₁ analogue misoprostol (off-label use) usually orally (95%) for labour induction [3]; according to one publication from 2011 the rate in Switzerland was as high as 78% [4].

The advantages of misoprostol over the conventional prostaglandins (PGE₂) are its stability at room temperature, easy application, quick onset of action and low cost [5]. In contrast to PGE₂ misoprostol can be used in patients with asthma and (severe) pregnancy associated hypertension/preeclampsia [6]. A recent Cochrane review [7] showed that oral misoprostol (WHO recommendation 2013: 25 µg 2 h) [8] is as effective as vaginal PGE₂ for labour induction with a comparatively lower caesarean section rate. The rate of uterine hyperstimulation is also comparable for low dose oral misoprostol and conventional prostaglandins [7]. Vaginal misoprostol (WHO recommendation 2013: 25 µg 6 h) [8] when compared to vaginal PGE₂ is associated with a higher vaginal delivery rate in 24 hours, less need for regional anaesthesia and less need for oxytocin augmentation of labour [9]. According to the 2014 Cochrane review oral misoprostol is preferable to vaginal misoprostol in view of lower rates of uterine hyperstimulation and postpartum haemorrhage, as well as better fetal outcome (5-minute Apgar score <7); misoprostol is also cheaper than PGE₂ irrespective of application route [7].

Thus most guidelines recommend misoprostol for labour induction. Recommendations include the vaginal application route [10] and either the vaginal or oral application routes [11–13]. Misoprostol was first licensed in 1985 for the treatment and prevention of gastroduodenal ulcers and according to manufacturer's information it is contraindicated in pregnancy. In Germany it was taken off the market in 2006.

Increasing caesarean section rates worldwide, which have been accompanied by increasing rates of uterine rupture, have presented clinicians with the problem, amongst others (e.g. increased rate of placental implantation pathologies), of whether labour induction in subsequent pregnancies is possible at all, and if so, which methods should be considered. 25% of patients with previous caesarean section who could be considered for vaginal delivery (trial of labour) have maternal indications or labour induction [14]. In the USA the vaginal delivery rate after previous caesarean decreased from 28.3 to 8.3% between 1996 and 2007 [15]. This development is largely due to clinicians fearing uterine rupture during trial of labour (spontaneous onset of labour or labour induction), which is associated with significantly increased neonatal morbidity (e.g. hypoxic ischaemic encephalopathy), perinatal mortality and severe maternal complications such as severe postpartum haemorrhage and need for hysterectomy [16–18].

• **Fig. 1** provides an overview of uterine rupture rates for patients with elective repeat caesarean section, with spontaneous onset of labour, and with labour induction using various methods. One of the main problems with the literature on the subject is

differing definitions of uterine rupture (symptomatic uterine rupture, scar dehiscence).

The first evidence of an increased risk of uterine rupture associated with vaginal misoprostol for labour induction after previous caesarean came from trials conducted between 1998 and 2001 and led the ACOG in 2002 [19] to consider its use contraindicated in this context; PGE₂ however, although also carrying an associated risk of uterine rupture (risk generally low), was allowed if medically indicated. Subsequently other international guidelines [11–13] have concurred with these recommendations so that today misoprostol is no longer used for labour induction after previous caesarean; its use has occasionally led to the conviction of clinicians [20] and a Pubmed literature search found no randomised trials on its use from the last 10 years.

In view of continually growing clinical experience with misoprostol for labour induction (without previous caesarean section) and the manifest advantages of this PGE₁ analogue over conventional prostaglandins (PGE₂) it is now necessary to reappraise the "historical" evidence, particularly with respect to patient selection (risk factors for uterine rupture), application route, dose and dosage interval, additional use of oxytocin for augmentation of labour and rates of uterine hyperstimulation. This article aims to encourage a critical approach to published evidence through a detailed analysis of the studies behind the above-mentioned guidelines.

Randomised Trials

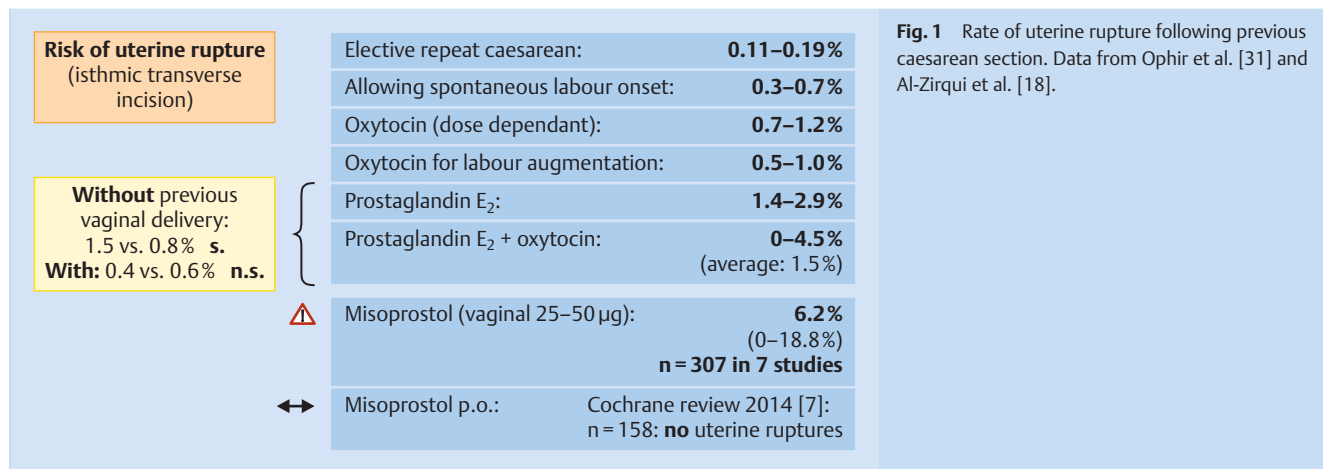
Wing et al. 1998 [21]

This randomised trial – quoted in all guidelines – is of importance as it is cited as the definitive evidence against the use of misoprostol after previous caesarean section. The publication, consisting of two case histories and a commentary, gives no detailed information on e.g. patient demographics, induction indications, initial Bishop score or uterine hyperstimulation. Due to its importance we will now discuss this publication in more detail.

Patients who were induced after previous caesarean section received either 25 µg vaginal misoprostol 6 hourly up to a maximum of 4 doses, or intravenous oxytocin according to the hospital's standard regime (not further defined). 23 patients were known to have had transverse uterine incisions, one a low vertical incision and for 13 women the type of uterine scar was unknown. The authors quote a publication by Miller et al. 1994 [22] stating that labour induction after previous caesarean section is possible even if the type of uterine scar is unknown. No cases of uterine rupture occurred in the oxytocin group (n = 21) compared to 2 out of 17 patients in the vaginal misoprostol group (11.7%).

Case 1

The cervix was initially unfavourable. After two doses of misoprostol adequate cervical ripening had occurred and oxytocin augmentation was begun (dose not stated). Approximately 22 h after the start of induction a clinical diagnosis of chorioamnionitis was made. An hour later the cervix was fully dilated and after a further two hours without any progress, in the presence of fetal tachycardia and late decelerations, the decision was made to per-



form a repeat caesarean section. Uterine hyperstimulation is not mentioned. At caesarean section a 10 cm vertical anterior uterine wall defect was found, which was management conservatively. Apart from maternal postpartum bleeding there were no maternal or neonatal complications.

Comment

Labour induction was performed in the presence of numerous unfavourable predictive factors for vaginal delivery (unripe cervix, no previous vaginal deliveries, post-term) and uncertain type of uterine scar. Labour was protracted and oxytocin administered in unknown dosage, and despite clinically verified chorioamnionitis and labour arrest with a fully dilated cervix a further two hours were waited, repeat caesarean only being performed when the CTG was pathological. In view of the vertical uterine rupture a vertical (“classical”) uterine incision at previous caesarean section can be assumed.

Case 2

This 39 year-old patient was induced with misoprostol at 36 weeks gestation because of intrauterine growth restriction and oligohydramnios. The cervix was unfavourable and the type of uterine incision at previous caesarean section was unknown. Amniotomy was performed after three doses of vaginal misoprostol when cervix was 4 cm dilated, no signs of uterine hyperstimulation being present. While an epidural catheter was being placed fetal bradycardia was diagnosed on ultrasound. Uterus rupture was suspected and urgent repeat caesarean performed. An 8 cm long transverse uterine rupture was confirmed intraoperatively and managed conservatively. There were no further maternal and no neonatal complications.

Comment

Again, the patient was induced in the presence of numerous unfavourable factors (unripe cervix, no previous vaginal deliveries, maternal age > 35 years, gestation remote from term). From the intraoperative findings the authors suspected a previous isthmic transverse incision. The trial was discontinued after the second uterine rupture with misoprostol, the authors warning against the use of misoprostol for labour induction after previous caesarean section!

Randomised Trials Including Patients with Previous Caesarean Section



Chuck et al. 1995 [23]

15 patients with previous caesarean section were included in this trial (total n = 99). Patients were between the 35th and 42nd weeks of gestation with unfavourable cervix (Bishop score = BS < 5) and were induced using either 50 µg vaginal misoprostol (4 hourly, max. 5 doses) or 0.5 mg PGE₂ intracervical gel (same dosage schedule as misoprostol); intravenous oxytocin was commenced to augment labour if there had been no progress after the 5th dose of either misoprostol or PGE₂. Rates of uterine hyperstimulation were 2 and 4% for misoprostol and PGE₂ respectively. There was no information on type of previous caesarean scar and there were no uterine ruptures.

Carlan et al. 1997 [24]

59 patients with previous isthmic transverse caesarean section were included in a study population of 467 women with unfavourable cervix (median BS = 4) induced for medical indications (mostly hypertension/preeclampsia) between the 35th and 40th weeks of gestation. Patients were given either (A) 50 µg misoprostol as a vaginal tablet or (B) 50 µg misoprostol vaginal gel (tylose); after two doses of the trial medication (dose interval 8 hours) doses were increased to 100 µg and continued up to a maximum total dose of 500 µg. Intravenous oxytocin was commenced if necessary once the BS was 7 or more (48.7 vs. 52.8%). Rates of uterine hyperstimulation were 15.8% (A) and 7.7% (B) (p = 0.05). There were no uterine ruptures.

Perry et al. 1998 [25]

A total of 127 patients between the 35th and 40th weeks of gestation with unfavourable cervix (average BS = 2) including 19 women with previous caesarean sections (type of uterine scar not stated) were induced for medical indications (41% preeclampsia, 20% post-term). Induction was either (A) with 25 µg misoprostol vaginal tablet 4 hourly until adequate contractions were established (3–4 contractions every 10 minutes); maximum 6 doses and total dose of 150 µg, or (B) intracervical Foley catheter with a filling volume of 50 ml plus 4 mg PGE₂ vaginal gel given simultaneously and repeated every 4 hours; maximum dose 12 mg. Intravenous oxytocin was commenced with increasing dose if cervical dilatation was inadequate over a period of an hour, at the earliest 4 h after the last prostaglandin dose. The in-

Table 1 Randomised trials of labour induction including patients with previous caesarean section.

Author/year	Misoprostol vag. dose/interval	Patient number	Rupture n/%	Control group	Patient number	Rupture n/%
Chuck et al. 1995 [23]	50 µg/4 h	5	0/0	0.5 mg intracervical PGE ₂ gel	10	0/0
Carlan et al. 1997 [24]	50 µg/8 h	59	0/0	–	–	–
Perry et al. 1998 [25]	25 µg/4 h	10	0/0	Foley catheter + 4 mg vaginal PGE ₂	9	0/0
Vengalil et al. 1998 [26]	25 µg/4 h	12	0/0	Foley + NaCl extraamniotic	20	0/0
Blanchette et al. 1999* [27]	25 or 50 µg/4 h	16	3 (18.8%)	0.5 mg intracervical PGE ₂ gel	9	0/0
Total		102	3 (2.9%)		48	0/0

* > 1 previous caesarean section n = 1

type of uterine scar not known n = 1

cidence of uterine hyperstimulation was significantly higher in group A than group B (11 vs. 3%; tachysystole 26 vs. 6%).

There were no uterine ruptures.

Vengalil et al. 1998 [26]

The aim of this trial (n = 250) was to compare 25 µg vaginal misoprostol (4 hourly, max. 3 doses, A) to extraamniotic application of a physiological saline solution via Foley catheter (filling volume 30 ml, B) for medically indicated labour induction with unfavourable cervix. Twelve patients with previous caesarean section were included in group A and 20 in group B (type of uterine scar not stated). Oxytocin was started if there were no contractions following the 3rd misoprostol dose and increased incrementally. The rate of uterine hyperstimulation was nearly 17% after misoprostol, and in both groups there were no uterine ruptures.

Blanchette et al. 1999 [27]

This was a prospective comparative study in which 226 women between the 39th and 42nd weeks of gestation with medical indications for induction and unfavourable cervix (average BS = 3) (cf. **Table 1**) were induced with either A: 25 or 50 µg vaginal misoprostol 4 hourly (max. 6 doses) or B: 0.5 mg PGE₂ intracervical gel 6 hourly (max. 3 doses); there were 16 patients with previous caesarean section in group A and 9 in group B. Intravenous oxytocin for augmentation of contractions was commenced as required, starting 4 hours after the last misoprostol dose and increased incrementally (no further details provided).

Group B had no uterine ruptures compared to group A with 3 uterine ruptures (18.8%) and one scar dehiscence. These patients are discussed on a case-by-case basis: 3 patients had had an isthmic transverse incision at previous caesarean section (one case with two previous caesareans); in one patient the type of uterine scar was unknown. In all cases misoprostol had been given in increasing doses (25 → 50 µg) and 2 had also received intravenous oxytocin for augmentation. None of the uterine ruptures were associated with uterine hyperstimulation. A pathological CTG was the main clinical indicator for the suspicion of uterine rupture in 3 patients. The authors warn against the use of vaginal misoprostol for labour induction after previous caesarean section despite it being more effective than PGE₂.

Retrospective Data Analyses



Plaut et al. 1998 [28]

This retrospective analysis of a computerised data pool reports on 5 cases of uterine rupture from a cohort of 89 women with previous caesarean section who received misoprostol for labour

induction, a rate of 5.6%; this was compared to a rupture rate of 0.2% amongst 423 women with previous caesarean in whom spontaneous labour was allowed to commence. Four of the 5 uterine ruptures following misoprostol are dealt with individually: 25 µg vaginal misoprostol had been given 3 hourly with up to 8 doses (200 µg); all cases had also received oxytocin in increasing dosage for augmentation. All patients had previous isthmic transverse incisions (in one case 2 incisions) and one patient had also had a vaginal delivery. Induction was performed for medical reasons near term with unfavourable cervix. Oxytocin was commenced between 3 and 6 hours after the last dose of misoprostol. There were no cases of uterine hyperstimulation concurrent with uterine rupture. Fetal bradycardia (in some cases with late decelerations) was the leading symptom for the suspicion of uterine rupture in every case; abdominal pain was an important additional indicator in 2 cases. Uterine rupture occurred at full cervical dilatation in 2 cases, in 2 cases the cervix was still unfavourable.

Cunha et al. 1999 [29]

In this retrospective comparative study from Mozambique 57 women with previous caesarean section who underwent labour induction for medical reasons using 50 µg vaginal misoprostol (5 patients receiving once-off repeat doses after 18 hours) were compared to 57 women with previous caesarean in whom spontaneous labour was allowed to commence. No data is provided on patient demographics, initial Bishop score, induction indication, whether or not oxytocin was given or type of uterine scar. There were 2 uterine ruptures in the misoprostol group (3.5%, no further details provided) compared to none in the spontaneous labour group. The authors note the possibility of selection bias (inadvertent selection of patients at the start of the study).

Bennet et al. 2000 [30]

This comparative study of vaginal misoprostol (25 µg 6 hourly, n = 39) vs. awaiting spontaneous labour (n = 560) in women with previous caesarean section was only published as an abstract and is currently not available online. Ophir et al. [31], quoting the study, state that there were 3 uterine ruptures following misoprostol (7.7%) and 13 ruptures among patients with spontaneous labour (2.3%). No further details are provided. The publication is also mentioned by Sanchez-Ramos et al. [32] in the reference list of their meta-analysis from 2000, again without any further information.

Hill et al. 2000 [33]

This retrospective analysis of patient files reports on 89 women induced with intravenous oxytocin and 48 with vaginal misoprostol (50 µg 4 hourly, max. 8 doses). All patients had an initial

BS < 7 and had previous “classical” caesarean incisions. No detailed information is provided on patient demographics, study design, induction indication or oxytocin timing and dosage. Three cases of uterine rupture (6.3%) occurring 7.5–13 hours after the last misoprostol dose are individually discussed: uterine hyperstimulation was not a feature in any; whether oxytocin was given for labour augmentation, and in what dosage, remains unclear. One uterine rupture occurred after the use of oxytocin (1.1%) with no further details being provided.

Choy-Hee and Raynor 2001 [34]

This was a retrospective analysis of 425 women from a computerised data pool. 48 women had previous caesarean sections and were induced using 50 µg vaginal misoprostol 4 hourly for up to 24 hours; intravenous oxytocin was given for augmentation if there was inadequate progress of labour, or 4 hours after the 6th misoprostol dose (45%) if contractions were insufficient. The remaining 377 women without previous caesarean section formed the control group. 35 patients had a previous isthmic transverse uterine scar, in 13 the type of scar was unknown and 12 patients had also had a previous vaginal delivery. There were **no uterine ruptures** in either group; rates of uterine hyperstimulation are not stated. The authors recommend a multicentre, retrospective study to compare misoprostol vs. oxytocin or PGE₂ vs. spontaneous labour.

Nwachaku et al. 2001 [35]

The largest prospective data analysis to date, this study examined 382 cases of labour induction in the presence of previous isthmic transverse caesarean section. Induction took place at term, with unfavourable cervix (BS ≤ 6) and as follows:

1. Cervical ripening with vaginal misoprostol 25 µg 4 hourly, max. 8 doses; when cervix ripe oxytocin augmentation from 3/4 h after the last misoprostol dose (n = 100),
2. Awaiting spontaneous onset of labour; no use of oxytocin (n = 115),
3. Only augmentation with oxytocin after spontaneous onset of labour (dose not stated, n = 167).

There were no uterine ruptures in any of the groups! Based on their results the authors call for prospective, randomised trials.

Aslan et al. 2004 [36]

In this retrospective data review 41 women with previous caesarean section (8 with two previous caesareans) who were induced using misoprostol in the 2nd and 3rd trimesters (average gestational age 26/27 weeks!), were compared to 50 women without previous caesarean with spontaneous onset of labour. Data were reviewed with respect to rates of uterine rupture. In the treatment group two doses of 50 µg misoprostol were given vaginally 4 hours apart, followed by 100 µg 4 hourly up to a maximum of 6 doses; when the cervix was 2 cm dilated or when there were regular contractions misoprostol was stopped. Intravenous oxytocin was started if progress of labour was inadequate, in the treatment group 6 hours after the last misoprostol dose. Oxytocin was required significantly more often in patients with previous caesarean section (41%) compared to no previous caesarean (20%). Initial BS was < 6 and patients known to have longitudinal uterine scars were excluded from the review.

The authors report in detail on 4 cases of uterine rupture after previous caesarean section (9.7%) with the following similarities: induction occurred in the presence of unfavourable cervix, at gestations remote from term (2 patients in the 26th week of gesta-

tion, 1 each in the 29th and 31st weeks), some patients had two previous caesarean sections, some had high dose oral misoprostol, and in all cases intravenous oxytocin was given at increasing dosage, sometimes < 4 h after the last misoprostol dose. Uterine hyperstimulation did not occur in association with rupture.

Lin and Raynor [37]

This retrospective data analysis published in 2004 included women (n = 3533) with one or more previous caesarean section who were induced after the 28th week of gestation using either oxytocin (n = 430) or misoprostol (n = 142). No information is given on misoprostol application route or dosing schedule. Rates of uterine rupture after allowing for spontaneous onset of labour and after elective repeat caesarean section were also calculated. Uterine rupture rates were: 0.5% overall (19/3533); following labour induction overall 1.2%, with oxytocin 1.2% and with misoprostol 1.4% (difference not statistically significant); following elective repeat caesarean section 0.2%; after spontaneous onset of labour 0.4%. Uterine rupture rate with oxytocin was 1.1% (4/376) after one previous caesarean section and 1.9% (1/54) after more than one previous caesarean; with misoprostol it was 0.8% (1/123) and 5.3% (1/19) respectively. Due to low patient numbers these differences were not statistically significant.

Cases of uterine rupture in association with the use of vaginal misoprostol (25 and 50 µg 3–4 hourly) have also been reported from 1997/1998 [38, 39].

Data on oral misoprostol is astoundingly sparse, two publications being quoted in a recent Cochrane review [7]:

Gherman 2001 [40]

This retrospective study without a control group was only published as a brief abstract: 10 patients with previous isthmic transverse incision were induced after the 36th week of gestation with initial BS ≤ 6 using 50 µg oral misoprostol 4 hourly up to a maximum of 6 doses. Augmentation with intravenous oxytocin was permitted (dose not stated). Five patients underwent repeat caesarean section, there were 4 spontaneous births, and one patient had a uterine rupture following 5 doses of misoprostol and an oxytocin infusion lasting 20 hours.

Aslan et al. 2004 [36]

This study of sequential doses of vaginal or oral misoprostol has already been discussed (see above).

A meta-analysis by Weeks and Alfrevic 2006 [5] also dealt with the use of oral misoprostol for labour induction after previous caesarean section. In the overall analysis of 8000 patients, 155 had a previous caesarean section, and amongst these there were no uterine ruptures.

Discussion



Medical labour induction after previous caesarean section presents obstetric clinicians with a dilemma. On the one hand vaginal delivery is achievable on average in 75% of cases (60–85% [19]), avoiding repeat caesarean section and the associated short and long term morbidity. On the other hand current guidelines draw attention to increased risk of uterine rupture with the use of oxytocin and most importantly, prostaglandins.

According to the manufacturer's product information previous caesarean section is a contraindication for the use of PGE₂ preparations for labour induction; the current “Rote Liste” (German

Table 2 Retrospective data review: vaginal misoprostol vs. awaiting spontaneous labour onset or intravenous oxytocin (excluding abstracts).

Author/year	Misoprostol dose/interval	Number of patients	Rupture n (%)	Number of patients	Rupture n/%
Plaut et al. 1998 [28]	25 µg/3 h	89	5 (5.6%)	423	0/0
Cunha et al. 1999 [29]	50 µg/18 h	57	2 (3.5%)	57	0/0
Hill et al. 2000* [33]	50 µg/4 h	48	3 (6.3%)	oxytocin i.v. n = 89	1/1.1%
Choy Hee 2001 [34]	50 µg/4 h	48	0/0	377	0/0
Nwachaku et al. 2001 [35]	25 µg/4 h	100	0/0	115	0/0
Aslan et al. 2004† [36]	50 µg/4 h → 100 µg oral/4 h	41	4/9.7%	50	0/0
Total		383	14 (3.7%)	1 111	0/0.1% (with oxytocin)

* following longitudinal “classical” uterine incision

† Patients in 2nd/3rd trimester (average gestational age 26/27 weeks)

medicines formulary) lists oxytocin in this setting as restricted use.

This being the situation, and due to clear recommendations in international guidelines as well as continuing forensic uncertainty, the use of misoprostol (off-label use) for induction after previous caesarean section can currently still be regarded as a “no go”.

If this “no go” status of misoprostol is to change in future – and because of its obvious advantages this may indeed be desirable – a critical reappraisal of “historical” studies is necessary that takes up-to-date scientific knowledge into account. In the mid to late 90s of the previous century when clinicians worldwide recognised how highly effective misoprostol is for labour induction, women with previous caesarean sections were “inadvertently” included in randomised, comparative trials; the studies report no uterine ruptures with vaginal misoprostol for labour induction [23–26].

It was only in 1999, in the comparative study by Blanchette et al. [27] that compared vaginal misoprostol (25–50 µg) to PGE₂ intra-cervical gel, that uterine rupture following misoprostol for labour induction after previous caesarean section was reported (3 out of 16 patients); one patient had two previous caesarean sections and the type of uterine scar was unknown in another. Although these results cannot be ignored, they are in contradiction to findings of 4 other comparative studies with similar induction protocols (cf. [Table 1](#)) in which uterine rupture is not reported. Thus no clear evidence can be deduced from these trials when considered together.

The only study with relevant evidence (El I) is the much quoted, randomised trial of Wing et al. [21] that had the primary aim of comparing the effectiveness of vaginal misoprostol to that of intravenous oxytocin for labour induction in women with scarred uterus; the study was stopped prematurely after 2 patients out of 17 in the misoprostol group had uterine ruptures. This early discontinuation of the trial makes a publication bias possible, at the very least, and since details of inclusion and exclusion criteria are missing – required information for randomised trials – a selection bias with unintentional selection of some patients cannot be excluded. Also, the obstetric management in case 1 can be viewed in a critical light (see commentary) since induction was evidently carried out in the presence of a longitudinal uterine scar.

In case 2 induction was performed in the presence of what today are known to be unfavourable predictive factors for vaginal delivery and risk factors for uterine rupture (see commentary).

In addition, important information on maximum oxytocin dose, interval between last misoprostol and commencement of i.v.

oxytocin as well as the presence/frequency of uterine hyperstimulation directly associated with uterine rupture is missing in both cases.

In the view of the authors it is understandable that the trial was stopped following two uterine ruptures out of 17 subjects, nevertheless the specific criteria for early discontinuation had not yet been fulfilled [41], this point being criticised in a meta-analysis by Sanchez-Ramos et al. [32]. Moreover the authors acknowledge the inaccuracy of their findings due to early discontinuation commenting: “we acknowledge ... that we may have experienced merely a statistical quirk”, yet they still deduce the explicit warning to other investigators against the use of misoprostol in studies of labour induction after previous caesarean section. This warning has continued to hold its place as a recommendation in international guidelines ever since.

The studies shown in [Table 2](#), mostly retrospective, case-control studies (misoprostol vs. awaiting spontaneous labour onset) based on computerised data pools, should be interpreted with caution because of possible selection and publication bias. Their validity is limited by imprecise data collection as well as missing data and the absence of certain essential variables. The largest trial of labour induction after previous caesarean section to date, by Lydon-Rochelle et al. 2001 [42], is an example: the finding of a high uterine rupture rate following PGE influenced the guidelines of the time, however obvious shortcomings in data collection that was based on ICD codes were subsequently proven [43,44], e.g. no differentiation between PGE₂ and misoprostol associated uterine ruptures was possible.

On closer examination of the retrospective, comparative studies their low quality is clearly evident: relevant data are missing on demographics, induction indication, initial Bishop score before induction, risk factors for uterine rupture, type of previous uterine incision, duration and maximum dose of oxytocin for augmentation of labour and interval between the last misoprostol dose and start of oxytocin infusion; all factors which can significantly influence the risk of uterine rupture. In addition, the heterogeneous study design (e.g. differing misoprostol doses and dosing intervals, differing gestational ages at induction, differing inclusion and exclusion criteria, differences in initial Bishop score before induction) and small case numbers are clearly points of critique, so that as a whole these studies provide no evidence of clinical relevance for inclusion in guidelines.

In view of the rarity of uterine rupture a study population of over 60 000 women is required to detect a 0.5% risk increase above background risk (0.5–0.7%) [7].

Ultimately, the high rates of uterine rupture described in these studies must be re-evaluated in light of more recently published, newly acquired knowledge and clinical experience with the use of misoprostol. The 2013 WHO guideline recommends vaginal misoprostol 25 µg 6 hourly for labour induction (without previous caesarean section) [8], a recommendation which is evidence based, in accordance with recent resorption kinetics knowledge, and in agreement with other guidelines [10, 12, 13]. This dosing schedule was not used in any of the retrospective, comparative studies with uterine ruptures; higher single misoprostol doses and/or shorter dosage intervals were used. The correlation between PG dose and uterine rupture risk was recently highlighted [45].

The largest retrospective study to date, that of Nwachuku et al. [35], is of interest in this regard. Among 100 women who received vaginal misoprostol (25 µg 4 hourly) for labour induction after previous exclusively isthmic transverse caesarean sections, there were no uterine ruptures. The authors explained this outcome as the result of careful patient selection and their induction protocol: labour induction only in the event of documented previous isthmic transverse incision, the use of low dose vaginal misoprostol (25 µg), continuous CTG monitoring during misoprostol application and discontinuation of misoprostol when regular contractions (<5 minutes apart) were established. In contrast, the study by Aslan et al. 2004 [36] that has the highest rupture rate of all (9.7%, 4/41) used high doses of vaginal misoprostol (50 µg) followed by 100 µg oral misoprostol 4 hourly. More detailed analysis of this study also reveals that study patients were mostly induced remote from term (average gestational age 26/27 weeks), and that 20% of induced women had multiple previous caesareans. Uterine ruptures occurred between the 26th and 31st weeks of gestation.

Augmentation of labour with intravenous oxytocin following initial induction with PGE is a further risk factor for uterine rupture, however clinical data from 8 studies is contradictory [31]: while some show a 2.5 to 5.6-fold increase in risk of rupture compared to awaiting spontaneous labour onset, others show no risk increase (synopsis in [31]). Combining the results of these studies, PGE₂ followed by oxytocin resulted in a uterine rupture rate of 1.5% compared to 0.4% for PGE₂ alone [29]. The important determining factors here are the duration and maximum dose of oxytocin. This was demonstrated in a comparative study of oxytocin dosage in patients with and without uterine rupture that showed rupture risk increased exponentially 4-fold when oxytocin dose exceeded 20 mU/min (up to 40 mU/min) [46]. Relevant clinical evidence is lacking on the risk of uterine rupture with the use of misoprostol and subsequent oxytocin augmentation after previous caesarean section.

The “uncritical” use of oxytocin should thus be warned against, not only because of increased risk of uterine rupture but also because of other maternal complications (e.g. increased rate of postpartum haemorrhage).

Evidence is also insufficient on the use of oral misoprostol for labour induction after previous caesarean section. The retrospective study by Gherman 2001 [40], published only as an abstract, in which **one** uterine rupture occurred following 50 µg oral misoprostol 4 hourly plus a lengthy oxytocin infusion for augmentation (>20 h) is in contrast to the most recent Cochrane review [7] which evaluated two further randomised trials [47, 48]. Here no uterine ruptures occurred among 158 women who received oral misoprostol for induction after previous caesarean section.

There have been no studies of oral PGE₂ for labour induction in this setting, only vaginal PGE₂. Whether the “first uterine pass effect” as known from vaginal progesterone [49], with high local uterine concentrations of active substance, also applies to vaginal misoprostol and plays a role in this context or not, is speculative. The observation that PGE₂ induced ruptures usually occur in the area of the old uterine scar, and that oxytocin induced ruptures do not, lead Buhimschi et al. [50] to hypothesise that PGs cause a local biochemical tissue loosening/resistance reduction of the scar area, a so-called “softening effect”. Interestingly there were two patients (out of 10) with uterine rupture following vaginal misoprostol included in this study. No plausible explanation for the higher rate of uterine rupture following misoprostol compared to PGE₂ is evident. The hypothesis that the higher rate of uterine rupture (compared to vaginal PGE₂) is the result of vaginal misoprostol leading to mechanical “strain” of the uterine scar in a dose dependant manner through uterine hyperstimulation is not substantiated by the quoted studies, since here uterine rupture occurred exclusively in patients without uterine hyperstimulation [21, 27, 28, 33, 36].

Conclusion and Future Perspectives

Medical induction of labour after previous caesarean section is regarded as an independent risk factor for uterine rupture, whether using oxytocin, PGE₂ or misoprostol. We aimed to critically re-evaluate the “historical” literature on the use of misoprostol in this setting with respect to the current state of knowledge, thus hoping to end years of stagnation and stimulate discussion to initiate new trials on the subject. We did **not** aim to declare the association of misoprostol and uterine rupture as harmless, nor did we intend to propagate the unconsidered use of misoprostol after previous caesarean; current guidelines should be regarded as valid and unchanged in this issue. Rather, after detailed examination of trials to date, we believe we have shown clearly that the evidence behind current guidelines against the use of misoprostol is insufficient. The question remains: should these guideline recommendations simply be accepted and fixed for the future or is there a need for the generation of new data? Since several hospitals in Germany have experience with the use of oral misoprostol for labour induction after previous caesarean section – as shown in our own 2013 nationwide survey [3] – a useful first step would be the creation of a retrospective register of uterine rupture frequency, including an analysis of the circumstances in which it occurs. These data could provide the basis for a multicentre, prospective, randomised trial (e.g. oral misoprostol vs. vaginal PGE₂) with carefully considered selection criteria for eligibility for vaginal delivery. Known risk factors for uterine rupture including type of uterine scar would need to be taken into account and continuous maternal and fetal monitoring would have to be implemented. Fitting prediction models for achieving vaginal delivery have been published repeatedly in recent years [51–53].

From an ethical point of view however, and considering our own experiences with ethics commissions, we believe such a study may well not be realisable in Germany.

Conflict of Interest

None.

References

- 1 Huisman CM, Jozwiak M, de Leeuw JW *et al.* Cervical ripening in the Netherlands: a survey. *Obstet Gynecol Int* 2013; 2013: 745159
- 2 AQUA-Institut. Geburtshilfliche Qualitätsindikatoren – Bundesauswertung nach Erfassungsjahr 2013. Göttingen: 2014; 16/1
- 3 Voigt F, Goecke TW, Najjari L *et al.* Off-label use of misoprostol for labor induction in Germany: a national survey. *Eur J Obstet Gynecol Reprod Biol* 2015; 187: 85–89
- 4 Krause E, Malorgio S, Kuhn A *et al.* Off-label use of misoprostol for labor induction: a nation-wide survey in Switzerland. *Eur J Obstet Gynecol Reprod Biol* 2011; 159: 324–328
- 5 Weeks A, Alfirevic Z. Oral misoprostol administration for labour induction. *Clin Obstet Gynecol* 2006; 49: 658–671
- 6 Weeks AD, Fiala C, Safar P. Misoprostol and the debate over off-label drug use. *BJOG* 2005; 112: 269–272
- 7 Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database Syst Rev* 2014; 6: CD001338
- 8 Tang J, Kopp W, Dragoman M *et al.* WHO recommendations for misoprostol use for obstetric and gynaecologic indications. *Int J Gynecol Obstet* 2013; 121: 186–189
- 9 Hofmeyr GI, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev* 2010; 2: CD00941 (update 2013)
- 10 ACOG Committee on Practice Bulletins – Obstetrics. ACOG Practice Bulletin No. 107: Induction of labour. *Obstet Gynecol* 2009; 114 (2 Pt 1): 386–397
- 11 WHO recommendations for induction of labour. Online: <http://wholibdoc.who.int/hg/2011WHORHR11.10eng.pdf>; last access: 30.04.2015
- 12 FIGO Misoprostol recommendations for induction of labour 2012. Online: <http://www.figo-org2012>; last access: 30.04.2015
- 13 SOGC Clinical Practice Guideline No.296: Induction of labour. *JOGC* 2013; 35: 840–857
- 14 Locatelli A, Regalia AL, Ghidini A *et al.* Risks of induction of labour in women with a uterine scar from previous low transverse caesarean section. *BJOG* 2004; 111: 1394–1399
- 15 Martin JA, Hamilton BP, Sutton PD *et al.* Births: final data for 2007. *Natl Vital Stat Rep* 2010; 58: 1–85
- 16 Landon MB, Hauth JC, Levano KJ *et al.* Maternal and perinatal outcomes associated with a trial of labor after prior caesarean delivery. *N Engl J Med* 2004; 351: 2581–2589
- 17 Chauhan SP, Martin JN, Henrichs CE *et al.* Maternal and perinatal complications with uterine rupture in 142,075 patients who attempted vaginal birth after caesarean delivery: A review of the literature. *Am J Obstet Gynecol* 2003; 189: 408–417
- 18 Al-Zirqui I, Stray-Pedersen B, Forsen L *et al.* Uterine rupture after previous caesarean section. *BJOG* 2010; 117: 809–820
- 19 ACOG Committee on Obstetric Practice. Induction of labour for vaginal birth after caesarean delivery. *Obstet Gynecol* 2002; 99: 679–686
- 20 Uphoff R. Misoprostol zur Geburtseinleitung: Haftungsrechtliche Konsequenzen. *Frauenarzt* 2014; 55: 734–740
- 21 Wing DA, Lovett K, Paul RH. Disruption of prior uterine incision following misoprostol for labor induction in women with previous caesarean delivery. *Obstet Gynecol* 1998; 91: 828–830
- 22 Miller DA, Paul RH. Vaginal birth after caesarean: A 10-year experience. *Obstet Gynecol* 1994; 84: 255–258
- 23 Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E2 gel (Prepidil gel): randomized comparison. *Am J Obstet Gynecol* 1995; 173: 1137–1142
- 24 Carlan SJ, Bouldin S, O'Brien WF. Extemporaneous preparation of misoprostol gel for cervical ripening: a randomized trial. *Obstet Gynecol* 1997; 90: 911–915
- 25 Perry KG jr., Larmon JE, May WL *et al.* Cervical ripening: a randomized comparison between intravaginal misoprostol and an intracervical balloon catheter combined with intravaginal dinoprostone. *Am J Obstet Gynecol* 1998; 178: 1333–1340
- 26 Vengalil JR, Guinn DA, Olabi NF *et al.* A randomized trial of misoprostol and extraamniotic saline infusion for cervical ripening and labor induction. *Obstet Gynecol* 1998; 91: 774–779
- 27 Blanchette HA, Nayak S, Erasmus S. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol* 1999; 180: 1551–1559
- 28 Plaut MM, Schwartz ML, Lubarsky SL. Uterine rupture associated with the use of misoprostol in the gravid patient with a previous caesarean section. *Am J Obstet Gynecol* 1999; 180: 1535–1542
- 29 Cunha M, Bulgaino A, Biquie C *et al.* Induction of labor by vaginal misoprostol in patients with previous caesarean delivery. *Acta Obstet Gynecol Scand* 1999; 78: 633–634
- 30 Bennett KA, Elmore L, Fleischman S *et al.* Prostaglandin induction in women with a prior caesarean delivery increased induction time and risk of uterine rupture. *Am J Obstet Gynecol* 2000; 182: S130
- 31 Ophir E, Odeh M, Hirsch Y *et al.* Uterine rupture during trial of labor: Controversy of induction's methods. *Obstet Gynecol Surv* 2012; 67: 734–745
- 32 Sanchez-Ramos L, Francisco L, Kaunitz AM. Cervical ripening and labor induction after previous caesarean delivery. *Clin Obstet Gynecol* 2000; 43: 513–523
- 33 Hill DA, Chez RA, Quinlan J *et al.* Uterine rupture and dehiscence associated with intravaginal misoprostol cervical ripening. *J Reprod Med* 2000; 45: 823–826
- 34 Choy-Hee L, Raynor BD. Misoprostol induction of labor among women with a history of caesarean delivery. *Am J Obstet Gynecol* 2001; 184: 1115–1117
- 35 Nwachuku V, Sison A, Quathic C *et al.* Safety of misoprostol as a cervical ripening agent in vaginal birth after caesarean section. *Prim Care Update Obstet/Gyn* 2001; 8: 244–247
- 36 Aslan H, Unlu E, Agar M *et al.* Uterine rupture associated with misoprostol labor induction in women with previous caesarean delivery. *Eur J Obstet Gynecol Reprod Biol* 2004; 113: 45–48
- 37 Lin C, Raynor BD. Risk of uterine rupture in labor induction of patients with prior caesarean section: an inner city hospital experience. *Am J Obstet Gynecol* 2004; 190: 1476–1478
- 38 Sciscione AC, Nguyen L, Manley JS *et al.* Uterine rupture during preinduction cervical ripening with misoprostol in patient with a previous caesarean delivery. *Aust N Z J Obstet Gynaecol* 1998; 38: 96–97
- 39 Bennett BB. Uterine rupture during induction of labour at term in intravaginal misoprostol. *Obstet Gynecol* 1997; 89: 832–833
- 40 Gherman RB. Trial of labor after caesarean delivery: a pilot study of oral misoprostol for preinduction cervical ripening. *Obstet Gynecol* 2001; 97 (Suppl. 1): S68
- 41 Pocock SJ. When to stop a clinical trial. *BMJ* 1992; 305: 235–240
- 42 Lydon-Rochelle M, Holt VL, Easterling TR *et al.* Uterine rupture during labor among women with a prior caesarean delivery. *N Engl J Med* 2001; 345: 3–8
- 43 Flamm DL. Vaginal birth after caesarean and the New England Journal of Medicine: a strange controversy. *Birth* 2001; 28: 276–279
- 44 Vellekoop J, Roell-Schorer EA, von Roosmalen J. Uterine scar rupture after previous caesarean section and induction of labor with prostaglandins. *Acta Obstet Gynecol Scand* 2006; 85: 132–134
- 45 Schmitz T, Pourulat A-G, Moutaffaff C *et al.* Cervical ripening with low-dose prostaglandins in planned vaginal birth after caesarean. *PLoS One* 2013; 8: e80903
- 46 Cahill AG, Stamilio DM, Odibo AO *et al.* Does a maximum dose of oxytocin affect risk for uterine rupture in candidates for vaginal birth after caesarean delivery? *Am J Obstet Gynecol* 2007; 197: 495.e1–495.e5
- 47 Carlan SJ, Bouldin S, Blust D *et al.* Safety and efficacy on misoprostol orally and vaginally: a randomized trial. *Obstet Gynecol* 2001; 98: 107–112
- 48 How HY, Leaseburge L, Khoury JC *et al.* A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of labor. *Am J Obstet Gynecol* 2001; 185: 911–915
- 49 Ziegler D, Buletti C, Monstier de B *et al.* The first uterine pass effect. *Ann N Y Acad Sci* 1997; 828: 291–299
- 50 Buhimschi CS, Buhimschi JA, Patel S *et al.* Rupture of the uterine scar during term labour! Contractility or biochemistry? *BJOG* 2005; 112: 38–42
- 51 Grobman WA, Lai Y, Landon MB *et al.* Can a prediction model for vaginal birth after caesarean also predict the probability of morbidity related to a trial of labor? *Am J Obstet Gynecol* 2009; 200: 56.e1–56.e6
- 52 Schoorel ENC, van Kuijk SMJ, Melman S *et al.* Vaginal birth after a caesarean section: the development of a Western European population-based prediction model for deliveries at term. *BJOG* 2014; 121: 194–201
- 53 Schoorel ENC, Melman S, van Kuijk SMJ *et al.* Predicting successful intended vaginal delivery after previous caesarean section: external validation of two predictive models in a Dutch nationwide registration-based cohort with a high intended vaginal delivery rate. *BJOG* 2014; 121: 840–847