Effect of Premature Rupture of Membranes on Induction of Labor: 
A Historical Cohort Study

Einfluss des vorzeitigen Blasensprungs auf den Erfolg 
der Geburtseinleitung: eine historische Kohortenstudie

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Key words
induction of labor, misoprostol, premature rupture of membranes, cesarean section

Schlüsselwörter
Einleitung der Geburt, Misoprostol, vorzeitiger Blasensprung, Kaiserschnitt

ABSTRACT
Objective The aim of this study was to assess the influence of premature rupture of membranes (PROM) on the induction of labor.

Material and Method This historical cohort study analyzed 1861 inductions of labor at term using misoprostol which occurred between 2010 and 2015. Exclusion criteria included intrauterine fetal death, previous cesarean section, and fetal structural or chromosomal anomalies. Induction of labor for PROM (PROM group) was compared to induction for other indications (no-PROM group); the primary outcome measure was the cesarean section rate.

Results The cesarean section rate for the PROM group was significantly lower (21.9% vs. 26.3%, p = 0.029). The induction-to-delivery interval was shorter (mean: 972 [854–6734] min vs. 1741 [97–10 834] min, p < 0.0001) and the rates of vaginal birth within 24 hours (80.9 vs. 52.0%, p = 0.0001) and 48 hours (98.4 vs. 85.3%, p = 0.0001) were higher in the PROM group. The impact of PROM on the cesarean section rate was not significant in multivariate analysis; however, PROM was found to have the greatest effect on the induction-to-delivery interval (p < 0.0001).

Conclusion Premature rupture of membranes significantly affects various outcome measures when delivery is induced, particularly the induction-to-delivery interval.

ZUSAMMENFASSUNG
Ziel Ziel dieser Arbeit war es herauszufinden, inwieweit ein vorzeitiger Blasensprung (PROM) den Erfolg einer Geburtseinleitung beeinflusst.

Material und Methode In dieser historischen Kohortenstudie wurden 1861 Geburtseinleitungen am Termin mit Misoprostol zwischen 2010 und 2015 analysiert. Zu den Ausschlusskriterien gehörten unter anderem ein intrauteriner Fruchttod, eine vorherige Sectio caesarea oder strukturelle respektive chromosomale Anomalien. Geburtseinleitungen wegen eines PROM (PROM-Gruppe) wurden mit Geburtseinleitungen aus anderen Indikationen (Kein-PROM-Gruppe) verglichen; der primäre Zielparameter war die Kaiserschnitt-Rate.
Introduction

Premature rupture of membranes (PROM) after week 37 + 0 of gestation occurs in around 8–10% of all births [1]. In around 40% of cases, regular contractions only start after more than 24 hours.

Induction of labor is indicated in the absence of contractions as it reduces maternal and infant infection rates and may obviate the need to transfer the infant to a children’s hospital post partum. It is also associated with higher satisfaction levels and no increase in cesarean section rates [2,3].

A number of options are available to induce labor; medications to induce labor include oxytocin and prostaglandins, and a balloon catheter may be used for mechanical induction. The pharmaceutical information for prostaglandin E2 medication states that all forms of treatment after rupture of the "chorioamniotic membrane" should proceed “with care”, without expanding on the possible problems that could occur. Administration of the synthetic prostaglandin E1 analog misoprostol is the most effective medication to induce labor [4–7], and its use after PROM has been studied in detail [5,8–12]. Although previous studies did not find higher infection rates following the use of balloon catheters [13], they are not commonly used. Moreover, inducing labor with a balloon catheter is not beneficial compared to the administration of misoprostol alone – and should therefore not be used in this context [14]. As vaginal applications are generally associated with a higher risk of infection, oral administration (misoprostol) appears to be the preferred method of administration [15].

There are numerous studies on the efficacy of various procedures to induce labor, but these studies often ignore the fact that the occurrence of PROM itself could be a decisive factor influencing the induction of labor.

The aim of this study was therefore to investigate to what extent premature rupture of membranes affects the induction of labor.

Material and Method

This historical cohort study analyzed the induction of labor using misoprostol in singleton term pregnancies delivered at the University Gynecology Hospitals of Erlangen (2011–2015) and Mannheim (2010–2013).

Inclusion and exclusion criteria

Exclusion criteria included fetal breech presentation, intrauterine fetal death, previous cesarean section, and the presence of fetal structural or chromosomal anomalies. The induction of labor with mechanical procedures such as balloon catheters was not included in the analysis.

Procedure in routine clinical practice

Gestational age was determined based on the last menstrual period; presumed gestational age was then reviewed using the crown-rump length measured in the first trimester of pregnancy and corrected where necessary [16]. Induction of labor for PROM was compared with induction of labor for other indications. Rupture of membranes was diagnosed clinically using the standard in–house guidelines of the participating hospital or – if clinical findings were ambiguous – based on the detection of biomarkers (e.g. insulin-like growth factor-binding protein 1 [IGFBP-1]). Antibiotic prophylaxis with penicillin or clindamycin for patients allergic or intolerant to penicillin was initiated at twelve hours after PROM and administered until delivery of the infant. Prophylactic antibiotics were only administered immediately if Group B streptococci were detected.

In the group who had labor induction for PROM, induction of labor started at 12–24 hours after rupture of membranes. The Bishop score was determined before inducing labor with misoprostol. Misoprostol was administered orally. The initial dose was 50 µg, with repeat doses administered after four and eight hours in the absence of contractions. On the second day of labor induction, oral misoprostol was increased to 100 µg per dose, with a maximum of three administrations over a 24 hour period and a minimum interval of four hours between each administration. On the third day, 100 µg misoprostol tablets were administered vaginally.

Outcome measures

The primary outcome measure was the cesarean section rate. Secondary outcome measures included the induction-to-delivery interval, the number of vaginal births within 24 and 48 hours, the number of unsuccessful inductions of labor (defined as no birth within 72 hours), the total dose of misoprostol, umbilical cord blood pH and base excess (BE), and Apgar score at five minutes. The number of neonatal infections and of transfers of neonates to children’s hospitals and the incidence of puerperal endometritis were also reviewed.

Statistical analysis

All statistical calculations and analyses were done with the statistical software package SAS, Release 9.3 (SAS Institute Inc., Cary, North Carolina, USA). Absolute and relative frequencies are shown for nominally scaled variables; nearly normally distributed quanti-
tative variables are presented as means and standard deviation. The median and the two min/max values are given for ordinally scaled and quantitatively discrete variables, instead of the mean. χ²-test or (if the necessary conditions were not fulfilled) Fisher’s exact test were used to compare nominally scaled variables between the two groups. Comparisons of the means of two groups were done using t-test for two unpaired samples. Mann-Whitney U-test was used for ordinally scaled or discrete quantitative variables. All tests were 2-tailed. The results were considered significant if the p-value was less than 0.05.

For the primary outcome measure “cesarean section”, the odds ratios and associated p-values of every potential moderating factor were determined by logistic regression analysis. Similarly, the secondary outcome measure “induction-to-delivery interval” was analyzed using linear regression, and the regression coefficient and p-value of every moderating variable were calculated. Multivariate regression analysis was done to analyze several moderating factors simultaneously. Parameters were integrated into the respective statistical model up to a significance level of 0.05 using the option “Selection = Forward”.

Results

A total of 17,649 births occurred in the study period; 4381 of them were induced (24.8%). After taking the inclusion and exclusion criteria into account, 1861 cases were included in this study (▶ Fig. 1). Misoprostol was administered to 816 women to induce labor for PROM (PROM group) and administered to 1045 women to induce labor for other indications (no-PROM group).

Demographic data

Demographic data are presented in ▶ Table 1. There were significant differences relating to various parameters between the two groups: the women in the PROM group were older (30.7 ± 5.2 years vs. 30.1 ± 5.6, p = 0.0196) and had a lower BMI (29.0 ± 5.3 vs. 30.5 ± 5.4, p < 0.0001). Gestational age and infant birth weight were lower in the PROM group at delivery (276.4 ± 7.4 vs. 283.3 ± 7.4, p < 0.0001; 3350.6 ± 417.8 vs. 3507 ± 473.2, p < 0.0001). Rates of gestational diabetes (9.6 vs. 15.9%, p < 0.0001), hypertensive disorders of pregnancy (1.7 vs. 7.7%, p < 0.0001) and intrauterine growth retardation/placental insufficiency (1.7 vs. 4.6%, p = 0.0006) were lower for the women in the PROM group.

| Table 1 | Demographic data of the study group with premature rupture of membranes (PROM) and the study group without premature rupture of membranes (no PROM). |
|-----------------|-----------------|-----------------|-----------------|
| PROM (n = 816)  | no PROM (n = 1045) | p-value         |
| Age (years)     | 30.7 ± 5.2       | 30.1 ± 5.6       | 0.0196          |
| Maternal height (cm) | 166.6 ± 6.7     | 166.4 ± 6.6     | 0.5986          |
| Maternal weight (kg) | 82.3 ± 15.0      | 85.0 ± 16.0      | 0.0002          |
| Body mass index | 29.0 ± 5.3       | 30.5 ± 5.4       | < 0.0001        |
| Gravidity       | 1 (1–7)          | 2 (1–14)         | < 0.0001        |
| Parity          | 0 (0–4)          | 0 (0–9)          | < 0.0001        |
| Gestational age (days) | 276.4 ± 7.4     | 283.3 ± 7.4     | < 0.0001        |
| Birth weight (g) | 3350.6 ± 417.8  | 3507.5 ± 473.2  | < 0.0001        |
| Bishop score    | 2 (0–6)          | 2 (0–6)          | 0.0095          |
| Gestational diabetes | 78 (9.6%)       | 166 (15.9%)     | < 0.0001        |
| Hypertensive disorders of pregnancy | 14 (1.7%) | 80 (7.7%) | < 0.0001 |
| Intrauterine growth retardation. placental insufficiency | 14 (1.7%) | 48 (4.6%) | 0.0006 |

p < 0.05 is considered statistically significant
Indications for the induction of labor

Table 2 lists the indications for the induction of labor for the women in the no-PROM group. The most common indications were overdue pregnancy (53.2%), gestational diabetes (10.4%), and patient’s request with no medical reason (8.4%).

Outcome measures

The outcome parameters for both groups are shown in Table 3. The cesarean section rate, i.e. the primary outcome measure, was significantly lower for the PROM group (21.9 vs. 26.3%, p = 0.0391). Likewise, the induction-to-delivery interval for the PROM group was shorter (972 ± 726.5 vs. 1741 ± 1335 [97–10834] min, p < 0.0001) and the rate of vaginal births within 24 hours (80.9 vs. 52.0%, p = 0.0001) and 48 hours (98.4 vs. 85.3%, p = 0.0001) was higher. There were fewer unsuccessful inductions when labor was induced because of PROM (0.5 vs. 5.6%, p = 0.0001). Fewer doses of misoprostol were required in the PROM group (1 [1–10] vs. 3 [1–10], p < 0.0001) and the total dose of misoprostol was lower (50 [50–750] vs. 150 µg [50–250], p < 0.0001).

Table 2: Indications for the induction of pregnancy if there was no premature rupture of membranes.

| Indications                        | no PROM |
|-----------------------------------|---------|
| Overdue pregnancy                 | 556 (53.2%) |
| Gestational diabetes              | 109 (10.4%) |
| Patient’s request with no medical reason | 88 (8.4%) |
| Anhydramnios, oligohydramnios     | 58 (5.6%) |
| Suspicion of fetal macrosomia     | 39 (3.7%) |
| Decreased fetal movement          | 20 (1.9%) |
| Intrauterine growth retardation, placental insufficiency, pathological Doppler sonography | 36 (3.4%) |
| Hypertensive disorders of pregnancy (HDP) | 61 (5.8%) |
| Suspicious/pathological CTG        | 28 (2.7%) |
| Cholestasis of pregnancy (ICP)    | 11 (1.1%) |
| Other                             | 39 (3.7%) |
| CTG: cardiotocography             |         |

Table 3: Outcome measures for the two study groups (PROM und and no PROM).

| Outcome measures                                      | PROM (n = 816) | no PROM (n = 1045) | p-value |
|-------------------------------------------------------|----------------|-------------------|---------|
| Mode of delivery (n, %)                               |                |                   |         |
| ▪ spontaneous delivery                                | 529 (64.8%)    | 659 (63.1%)       | 0.4314  |
| ▪ surgical vaginal delivery                           | 108 (13.2%)    | 111 (10.6%)       | 0.0826  |
| ▪ cesarean section                                    | 179 (21.9%)    | 275 (26.3%)       | 0.0290  |
| Induction-to-delivery interval (min) *                 | 972 ± 726.5    | 1741 ± 1335.0     | < 0.0001|
| Vaginal birth within 24 h (n, %) **                    | 515 (80.9%)    | 400 (52.0%)       | < 0.0001|
| Vaginal birth within 48 h (n, %) **                    | 627 (98.4%)    | 657 (85.3%)       | < 0.0001|
| Unsuccessful induction of labor = no vaginal birth within 72 h (n, %) ** | 3 (0.5%) | 43 (5.6%) | < 0.0001 |
| Number of misoprostol doses administered (median, range) * | 1 (1–10) | 3 (1–100) | < 0.0001 |
| Total dose of misoprostol (µg; median, range) *       | 50 (50–750)    | 150 (50–2500)     | < 0.0001|
| Arterial cord blood pH < 7.05 (n, %)                  | 5 (0.6%)       | 8 (0.8%)          | 0.6936  |
| Arterial cord blood pH < 7.10 (n, %)                  | 21 (2.6%)      | 24 (2.3%)         | 0.7013  |
| BE < −12 (n, %)                                       | 4 (0.5%)       | 13 (1.3%)         | 0.0872  |
| Apgar score after 5 min (median, range)               | 10 (5–10)      | 10 (4–10)         | 0.1756  |
| Apgar score after 5 min < 7 (n, %)                    | 7 (0.9%)       | 8 (0.6%)          | 0.4689  |
| BE < −12 and Apgar score after 5 min < 7 (n, %)       | 0              | 1 (0.1%)          | 1.0000  |
| Pathological CTG (n, %)                               | 167 (20.5%)    | 258 (24.7%)       | 0.0313  |
| Pathological fetal blood sampling results (n, %)      | 3 (0.4%)       | 5 (0.5%)          | 1.0000  |
| Epidural analgesia (n, %)                             | 388 (47.1%)    | 382 (38.0%)       | < 0.0001|
| Oxytocin (n, %)                                       | 393 (49.0%)    | 443 (43.0%)       | 0.0106  |
| Green amniotic fluid (n, %)                           | 100 (12.3%)    | 172 (16.5%)       | 0.0108  |
| Amniotic infection syndrome                           | 7 (0.9%)       | 6 (0.6%)          | 0.4659  |
| Postpartum transfer of infant to a children’s hospital (n, %) | 90 (13.2%) | 139 (18.4%) | 0.0075  |
| Neonatal infection (n, %)                             | 21 (2.6%)      | 29 (2.8%)         | 0.7896  |
| Puerperal endometritis (n, %)                         | 2 (0.3%)       | 2 (0.2%)          | 1.0000  |

BE: base excess
* without cesarean section and unsuccessful induction of labor
** without cesarean section
p < 0.0001). There were significantly fewer pathological CTG patterns (20.5 vs. 24.7%, p = 0.0313), cases of green amniotic fluid (12.3 vs. 18.4%, p = 0.0075) in the PROM group; however, the rates of oxytocin administration (49.0 vs. 43.0%, p = 0.0106) and epidural analgesia (47.1 vs. 38.0%, p < 0.0001) were higher.

**Outcome measures according to parity**

Table 4 shows the outcome measures broken down according to parity. The cesarean section rate was lower in the PROM group for both primiparae (28.5 vs. 37.1%, p = 0.0056) and multiparae (4.1 vs. 10.8%, p = 0.0158). The frequencies for cesarean section, spontaneous delivery, and surgical vaginal delivery in the PROM group differed significantly from those of the no PROM group for both primiparae and multiparae (Table 4). Similarly, the induction-to-delivery interval was shorter (1114 ± 734 vs. 1977 ± 1379 min, p < 0.0001; 684 ± 618 vs. 1501 ± 1245 min, p < 0.0001), the rate of vaginal deliveries within 24 hours (75.2 vs. 42.4%, p < 0.0001; 92.4 vs. 61.7%, p < 0.0001) and 48 hours (97.9 vs. 82.8%, p < 0.0001; 99.5 vs. 87.9%, p < 0.0001) was higher, and the percentage of successful inductions of labor was lower (0.5 vs. 8.0%, p < 0.0001; 0.5 vs. 3.1%, p = 0.0390). Misoprostol was administered less often (1 [1–9] vs. 3 [1–10], p < 0.0001; 1 [1–10] vs. 3 [1–16], p < 0.0001) and the total dose of administered misopros-
tol was lower (50 [50–750] vs. 150 µg [50–1350], p < 0.0001; (50 [50–750] vs. 150 µg [50–1350], p < 0.0001). Pathological CTG patterns (25.0 vs. 33.0%, p = 0.0020) and green amniotic fluid (12.7 vs. 20.4%, p = 0.0003) were only lower for primiparae in the PROM group. The epidural analgesia rate was also only significantly higher for the primiparae in the PROM group (55.8 vs. 50.0%, p = 0.0455). The percentage of infants transferred to a children’s hospital post partum was lower for both primiparae and multiparae (15.4 vs. 22.0%, p = 0.0085; 6.9 vs. 13.2%, p = 0.0333).

Multivariate analysis

The results of multivariate analysis for the outcome measures “cesarean section” and “induction-to-delivery interval” are shown in ▶ Tables 5 and 6. As regards the cesarean section rate, it is clear that some factors which were shown to be significant moderating factors included in the final statistical model. The binary factors PROM, gestational diabetes, and hypertensive disorders of pregnancy had a value of 0 (no) or 1 (yes).

### Table 5 Univariate and multiple logistic regression analysis for the primary outcome measure “cesarean section”. Parameters with a significance level of up to α = 0.05 were included in the final statistical model.

| Moderating factor | Univariate analysis | Multiple logistic regression |
|-------------------|---------------------|----------------------------|
|                   | odds ratio | p-value | odds ratio | p-value |
| Age (years)       | 1.0000     | 0.9646  | –          | –       |
| Maternal height (cm) | 0.966    | <0.0001 | 0.959      | <0.0001 |
| Maternal weight (kg) | 1.012    | 0.0003  | –          | –       |
| Body mass index   | 1.061      | <0.0001 | 1.060      | <0.0001 |
| Gestational age (days) | 0.998    | 0.7432  | –          | –       |
| Birth weight (g)  | 1.000      | 0.8639  | –          | –       |
| Gravidity         | 0.653      | <0.0001 | 0.633      | <0.0001 |
| Parity            | 0.413      | <0.0001 | –          | –       |
| Bishop score      | 0.818      | <0.0001 | 0.852      | <0.0001 |
| PROM              | 0.787 (yes vs. no) | 0.0292 | –          | –       |
| Gestational diabetes | 1.262 (yes vs. no) | 0.1303 | –          | –       |
| Hypertensive disorders of pregnancy | 2.783 (yes vs. no) | <0.0001 | 2.063 (yes vs. no) | 0.0030 |
| Intrauterine growth retardation, placental insufficiency | 2.158 (yes vs. no) | 0.0037 | –          | –       |

### Table 6 Univariate and multiple linear regression analysis for the secondary outcome measure “induction-to-delivery interval”. Parameters with a significance level of up to α = 0.05 were included in the final statistical model. The binary factors PROM, gestational diabetes, and hypertensive disorders of pregnancy had a value of 0 (no) or 1 (yes).

| Moderating factor                      | Univariate analysis         | Multiple linear regression |
|----------------------------------------|-----------------------------|----------------------------|
|                                        | regression coefficient | p-value | regression coefficient | p-value |
| Age (years)                            | − 6.804                   | 0.2513  | –                      | –       |
| Maternal height (cm)                   | 3.797                     | 0.4224  | –                      | –       |
| Maternal weight (kg)                   | 12.147                    | <0.0001 | –                      | –       |
| Body mass index                        | 39.603                    | <0.0001 | 21.391                 | <0.0001 |
| Gestational age (days)                 | 23.345                    | <0.0001 | –                      | –       |
| Birth weight (g)                       | 0.333                     | <0.0001 | 0.225                  | 0.0012  |
| Gravidity                              | − 90.404                  | 0.0003  | –                      | –       |
| Parity                                 | − 143.724                 | <0.0001 | − 213.596              | <0.0001 |
| Bishop score                           | − 136.677                 | <0.0001 | − 111.166              | <0.0001 |
| PROM                                   | − 768.939                 | <0.0001 | − 710.722              | <0.0001 |
| Gestational diabetes                   | 337.895                   | 0.0003  | 243.398                | 0.0070  |
| Hypertensive disorders of pregnancy    | 842.171                   | 0.0002  | 417.867                | 0.0102  |
| Intrauterine growth retardation, placental insufficiency | 424.003 | 0.0290 | –                      | –       |

Amniotic infection syndrome (primiparae/multiparae: < 0.5%) and puerperal endometritis (primiparae/multiparae: approx. 0.2%) were very rare events. Neonatal infections were more common for primiparae compared to multiparae (40 [3.3%] vs. 10 [1.5%], p = 0.0270).
Discussion

This historical cohort study showed that induction of labor for PROM is associated with lower cesarean section rates, a shorter induction-to-delivery interval, and a higher number of births within 24 and 48 hours compared to other indications for the induction of labor. This finding applied to both primiparae and multiparae. In multivariate analysis the effect of PROM was only significant for the induction-to-delivery interval.

This study used oral misoprostol. Misoprostol is the most effective medication for inducing labor; the rate of cesarean sections after misoprostol administration is significantly lower than, for example, after the administration of dinoprostone [4]. A Cochrane analysis done in 2014 found that oral misoprostol was more effective than placebo to induce labor and resulted in fewer cesarean sections, irrespective of whether women had PROM or not [4]. Park et al. reported that primiparae who received dinoprostone or oxytocin to induce labor for PROM had higher cesarean section rates compared to women who did not have PROM [17]. In their meta-analysis Wood et al. investigated whether the induction of labor without PROM led to a higher rate of deliveries by cesarean section. In contrast to the findings in our study presented here, they came to the conclusion that inducing labor when membranes were intact resulted in fewer cesarean sections [18].

In our current study, the induction-to-delivery interval in the PROM group was significantly shorter, even in multivariate analysis, and the rate of unsuccessful inductions (no vaginal birth within 72 hours) was lower. This shorter interval to delivery has already been reported in a number of earlier previous studies [2, 5, 19–21]. The rupture of membranes itself is a trigger for the start of childbirth [22], even if contractions only start more than 24 hours later in around 40% of women [2].

Misoprostol can safely be used to induce labor after PROM. The rate of pathological CTGs in the PROM group was lower, and there was no difference in the rate of invasive procedures to investigate possible issues (e.g., fetal blood analysis). In their study, Crane et al. also found no difference with regard to the number of fetal blood analyses performed when misoprostol was administered for premature rupture of membranes at term compared to the use of oxytocin [8].

Our study found no difference in the frequency of infant and maternal infections. Amniotic infection syndrome and puerperal endometritis were extremely rare. There was no difference in the rates of neonatal infection between the two groups, but neonatal infection occurred more frequently with primiparae than multiparae. But this could be due to the longer interval until the infant was delivered, as previous studies have reported that a longer interval after PROM is associated with a higher risk of maternal infection [23]. Moreover, vaginal administration also appears to be associated with an increased risk of infection [24], and on the third day of inducing labor, misoprostol was administered vaginally.

The limitation of this study is its retrospective nature. The two comparison groups also differed significantly from one another with regard to certain factors. But, given the differences, these factors did not always appear to be clinically relevant. The strengths of this study are the large number of cases, the study’s multicentricity, and the uniform procedure used to induce labor with misoprostol.

This study was able to show that PROM at term has a beneficial effect on inducing labor and results in a shorter induction-to-labor interval. When studies are carried out to assess the efficacy of inducing labor, the information from our study should lead to PROM being taken into account and cases with PROM excluded from the analysis.

Conclusion for Clinical Practice

In summary, the induction of labor with misoprostol in women with premature rupture of membranes leads to a shorter induction-to-delivery interval compared to the induction of labor for other indications. This impact of PROM should be taken into account when studies are carried out to assess the efficacy of methods used to induce labor. The use of misoprostol to induce labor for PROM is safe as it results in fewer pathological CTGs and fewer postpartum transfers of neonates to children’s hospitals, and there is no increase in the rates of infant and maternal infection.

Conflict of Interest

The authors declare that they have no conflict of interest.

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