Preterm Premature Rupture of Membranes – Inpatient Versus Outpatient Management: an Evidence-Based Review

Häusliches versus stationäres Vorgehen bei frühem vorzeitigem Blasensprung: eine evidenzbasierte Übersicht

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ABSTRACT

According to current guidelines, inpatient management until birth is considered standard in pregnant women with preterm premature rupture of membranes (PPROM). With the increasing burden on obstetric departments and the growing importance of satisfaction and right to self-determination in pregnant women, outpatient management in PPROM is a possible alternative to inpatient monitoring. The most important criterion for this approach is to ensure the safety of both the mother and the child. Due to the small number of cases (n = 116), two randomised controlled trials (RCTs) comparing inpatient and outpatient management were unable to draw any conclusions. By 2020, eight retrospective comparative studies (cohort/observational studies) yielded the following outcomes: no significant differences in the rate of maternal complications (e.g., chorioamnionitis, premature placental abruption, umbilical cord prolapse) and in neonatal morbidity, significantly prolonged latency period with higher gestational age at birth, higher birth weight of neonates, and significantly shorter length of stay of preterm infants in neonatal intensive care, shorter hospital stay of pregnant women, and lower treatment costs with outpatient management. Concerns regarding this approach are mainly related to unpredictable complications with the need for rapid obstetric interventions, which cannot be performed in time in an outpatient setting. Prerequisites for outpatient management are the compliance of the expectant mother, the adherence to strict selection criteria and the assurance of adequate monitoring at home. Future research should aim at more accurate risk as-

sessment of obstetric complications through studies with higher case numbers and standardisation of outpatient management under evidence-based criteria.

ZUSAMMENFASSUNG

Nach aktuellen Leitlinien gilt bei Schwangeren mit frühem vorzeitigem Blasensprung (PPROM) die stationäre Überwachung bis zur Geburt als Standard. Mit der steigenden Belastung geburtshilflicher Kliniken und der zunehmenden Bedeutung der Zufriedenheit und des Selbstbestimmungsrechts der Schwangeren stellt die häusliche Betreuung bei PPROM eine mögliche Alternative zur stationären Überwachung dar. Die wichtigste Voraussetzung für dieses Vorgehen ist die Gewährleistung der Sicherheit für Mutter und Kind. Aus 2 randomisierten kontrollierten Studien (RCT), die ein häusliches mit einem stationären Management verglichen, ließen sich aufgrund der geringen Fallzahl (n = 116) keine diesbezüglichen Rückschlüsse ziehen. Bis zum Jahr 2020 liegen aus 8 retrospektiven Vergleichsstudien (Kohorten-/Beobachtungsstudien) folgende Ergebnisse vor: keine signifikanten Unterschiede in der Rate mütterlicher Komplikationen (z. B. Chorioamnionitis, vorzeitige Plazentalösung, Nabelschnurvorfall) und in der neonatalen Morbidität, signifikant verlängerte Latenzperiode mit höherem Gestationsalter bei Geburt, höherem Geburtsgewicht der Kinder und signifikant kürzerer Verweildauer der Frühgeborenen auf der neonatalen Intensivstation, kürzerer stationärer Aufenthalt der Schwangeren sowie geringere Behandlungskosten bei häuslichem Management. Bedenken gegen dieses Vorgehen bestehen vor allem hinsichtlich unvorhersehbar auftretender Komplikationen mit Notwendigkeit zu raschen geburtshilflichen Interventionen, die dann nicht zeitgerecht durchführbar sind, wenn die Schwangere zu Hause ist. Voraussetzungen für ein häusliches Management sind die Compliance der Schwangeren, die Beachtung strikter Selektionskriterien und die Gewährleistung einer adäquaten häuslichen Überwachung. Ziel künftiger Forschung sollte eine genauere Risikoeinschätzung für geburtshilfliche Komplikationen durch Studien mit höheren Fallzahlen und die Standardisierung einer häuslichen Vorgehensweise unter evidenzbasierten Kriterien sein.

Introduction

Preterm premature rupture of membranes (PPROM) is defined as spontaneous rupture of the membranes before the onset of labour before 37 + 0 weeks [1]. The incidence is reported to be 3% overall [1], including 0.5% before 27 weeks' gestation, 1% between 27 + 0 and 33 + 6 weeks' gestation and 1.5% between 34 + 0 and 36 + 6 weeks' gestation [2].

PPROM accounts for 25–30% of all preterm births and is implicated in 18–20% of perinatal mortality [1].

Severe obstetric complications and neonatal morbidity (e.g., respiratory distress syndrome, necrotising enterocolitis, intraventricular cerebral haemorrhage, neonatal sepsis) correlate inversely with gestational age at the time of PPROM [3, 4].

Depending on the gestational age, chorioamnionitis following PPROM is seen in 15–30% of cases [3, 5], premature placental abruption in 4–12% [2, 6, 7], IUFD due to infection/umbilical cord prolapse in up to 2% of pregnant women [3, 4], and postpartum infections in 15–20% of those affected [4]. In 32–76% of cases, depending on the amount of amniotic fluid, umbilical cord compression and consecutive "foetal distress" must be expected [2, 3].

According to a retrospective cohort study (n = 234, PPROM between 22–33 weeks' gestation), a rate of obstetric complications before 28 weeks' gestation was found in 64% and ≥ 28 weeks' gestation in 11% of cases, manifesting within the first 3 days in 45% of patients and ≥ 12 days post PPROM in 25% [8].

The clinical course following PPROM also depends to a large extent on the latency period (interval between PPROM and delivery), which is inversely correlated with gestational age [7] and whose duration depends not only on gestational age at manifestation and parity [7] but above all on the presence of antepartum haemorrhage [4], the amount of amniotic fluid [7, 9 – 11], the clinical and laboratory evidence of chorioamnionitis [12], and the degree of clinical cervical opening (shorter latency period with cervical opening > 2 cm than with ≤ 2 cm) or the shortening of the cervix (shorter latency period for < 2 cm than for ≥ 2 cm) as measured by ultrasound [11, 13 – 15].

The median latency period ranges from 9 days at 24 + 0 weeks to 5 days at 31 + 6 weeks [16] and from 32 + 0 to 36 + 6 weeks at a median of 3.3 to 4 days [17].

According to Mercer et al. [18], between 24 + 0 to 33 + 6 weeks' gestation, 27% of pregnant women with PPROM give birth within 48 hours, 56% within 7 days, 76% within 14 days and 86% within 21 days.

Based on a 2017 Cochrane review [19], current guidelines [4, 20 – 22] recommend an expectative approach in PPROM management unless there are contraindications to prolong pregnancy.

The standard in guidelines is inpatient management of the pregnant woman until birth/initiation of labour from 37 + 0 weeks' gestation [4, 20].

In view of an increasing burden on departments of obstetrics, due a. o. to the increasing number of births and a rising percentage of high-risk pregnant women, as well as scarce staff and financial resources, the shift from traditionally inpatient obstetric measures to outpatient/home care is becoming more and more important [23]. The current COVID 19 pandemic has exacerbated this situation.

Against this background, the question arises whether outpatient management is also justified in PPROM without endangering the safety of mother and child.

This procedure has been the subject of case series [24 – 26] with different recommendations [27, 28] since 1942, and the outcomes of new trials have returned it to the focus of clinical interest.

The aim of this systematic review covering the period from 1993 to December 2020 (PubMed) was to evaluate the data on

inpatient versus outpatient management of PPROM < 37 weeks' gestation based on evidence criteria.

Results from Randomised Controlled Trials (RCT)

There are only two RCTs with a total of 116 pregnant women from 1993 [29] and 1999 ([30], only abstract available) comparing inpatient with outpatient management in preterm premature rupture of membranes (PPROM) before 37 + 0 weeks' gestation. The results were summarised and evaluated in a Cochrane Review [31] in 2014. With comparable inclusion criteria (▶ **Table 1**), these were fulfilled by only 18 % [29] and 11 % [30] of the pregnant participants, respectively. Significant differences between both approaches were only seen in inpatient length of stay and hospital costs, which were 1.8 times higher with inpatient management (▶ **Table 1**).

However, according to the Cochrane Review [31], due to the small number of cases and the associated lack of statistical power, it was not possible to draw clinically significant conclusions regarding the safety of outpatient management.

Outcomes from Retrospective Studies

The inclusion criteria of Carlan et al. [29] for outpatient management in PPROM (▶ **Table 1**) were reviewed in 2007 in a retrospective analysis of pregnant women with PPROM in 24–34 weeks' gestation (n = 138) with regard to their clinical usefulness [32]. According to this, only 32 pregnant women (23 %) were eligible for this approach, 12 had to be delivered within 2 h due to severe complications (e.g., acute clinical chorioamnionitis, umbilical cord prolapse, premature placental abruption), so that even taking into account strict inclusion criteria, the authors argued against outpatient management.

A retrospective cohort study from Australia in 2013 [33] included a total of 144 pregnant women with PPROM in 24 + 0 to 32 + 0 weeks' gestation who did not deliver within 72 h; 53 were cared for at home while 91 were hospitalised (inclusion criteria see ▶ **Table 1**). The study also included multiple pregnancies, breech presentations and pregnant women with diabetes and hypertensive pregnancy disorders. On admission, all patients received betamethasone for foetal lung maturation, oral nifedipine for tocolysis until 12 h after completion of lung maturation induction, and oral erythromycin for 10 days. After 72 hours of inpatient monitoring, the decision to proceed as an outpatient or inpatient was made by the obstetrician in charge.

The modalities of outpatient monitoring corresponded with the criteria of the study by Dussaux et al. [34]. Primary outcome measures of the study were maternal morbidity and perinatal/neonatal morbidity and mortality.

The study groups did not differ significantly with regard to these outcome measures, but they did differ significantly with regard to mean latency period, gestational age at birth, birth weight, and the length of stay of the preterm infants on the neonatal intensive care unit (see ▶ **Table 1**).

Multivariate regression analysis found no differences between the study groups in perinatal morbidity/mortality (56.6 vs. 68.1 %, aOR 1.37; 95 % CI 0.55–3.47) and overall maternal morbidity (26.4 vs. 23.1 %; aOR 1.62; 95 % CI 0.67–3.89).

The authors did not provide a convincing explanation as to why the gestational age at birth was lower and the latency period shorter in the inpatient pregnant women, nor did they provide any clinical recommendations for one or the other approach.

This study is limited by the fact that it is a retrospective observational study based on electronic data analysis. This implies the problem of data entry errors and the inaccurate documentation of rare clinical outcome parameters. The criteria as to why which pregnant women were cared for as outpatients versus inpatients were not defined (possible selection bias). Moreover, no data were provided on the overall number of pregnant women recruited for the outpatient procedure and how many were then actually included in the study, as well as information on anamnestic risk factors for preterm birth (e.g. previous spontaneous preterm birth, previous PPROM). Due to the small number of cases, the statistical power for severe complications (e.g. umbilical cord prolapse, premature placental abruption) was inadequate.

The aim of two retrospective cohort studies [35, 36] published in French was to compare inpatient versus outpatient management in pregnant women with PPROM in terms of the rate of maternal complications (e.g. chorioamnionitis, premature rupture of membranes, intrauterine foetal death) and in perinatal/neonatal outcome. ▶ **Table 1** lists the inclusion criteria for these studies. The study groups did not differ significantly in maternal and neonatal morbidity, the median latency period was significantly longer with outpatient management, and the median length of stay of preterm infants on the neonatal intensive care unit was significantly shorter than with inpatient management ([36], ▶ **Table 1**). The authors of both studies concluded that with strict selection criteria, outpatient management in PPROM is a promising alternative to continuous inpatient care.

A retrospective cohort study from Australia [37] compared 133 pregnant women with PPROM at 20–34 weeks' gestation who received outpatient care with 122 pregnant women of comparable gestational age with inpatient management. Antibiotic treatment with erythromycin/ampicillin (duration and dosage not specified) and foetal lung maturation with betamethasone were mandatory in both groups. The inclusion criteria are shown in ▶ **Table 1**. The primary outcome measure of the study was the latency period (interval between PPROM and birth). The mean gestational age at the time of PPROM was 28.3 and 28.6 weeks, respectively. At 18 (7–77) days, the median latency period in the outpatient group was significantly longer than the 11 days (7–71 days, p < 0.001) in the inpatient group. ▶ **Table 1** presents other significant outcomes of this study. No significant differences were found in the rate of clinical chorioamnionitis (5 vs. 11 %), umbilical cord prolapse (1 vs. 4 %) and premature placental abruption (3 vs. 6 %). However, the rate of chorioamnionitis confirmed by histology was significantly lower in the outpatient group than in the inpatients (47 vs. 64 %, p = 0.008).

The authors concluded that both approaches offer comparable safety, provided that careful risk assessment is performed and strict selection criteria are taken into account. However, the retro-

▶ **Table 1** Inpatient versus outpatient management of preterm premature rupture of membranes (PPROM): Literature review.

Author/year	Trial (EL)	n: outpatient/ inpatient	Inclusion criteria	Primary outcome measures	Outcomes
Carlan 1993	RCT (EL Ib)	28/27	PPROM < 37 weeks Inpatient 72 h Singleton pregnancy, CP No contractions, no signs of infection, cervical dilation < 4 cm AFI > 2 cm	Latency period Gestational age at birth	**prim. outcome measures: no significant differences:** **s:** mean hospital stay: 7.7 vs. 14.6 days Mean hospital costs: 5388 vs. 10 395 US $
Ryan 1999	RCT (EL Ib)	31/30	See Carlan 1993	Not specified	**s:** mean hospital stay: 142 vs. 256 h Costs/patient: 5366 vs. 8342 Can $
Ayres 2002	Retrospective case series (EL IIIb)	10/8	PPROM 24–34 weeks Oral temperature < 38 °C CP, clear amniotic fluid AFI > 3 cm	Not specified	**s:** mean hospital stay: 9.4 vs. 22.3 days
Beckmann 2013	Retrospective observational study (EL IIIb)	53/91	PPROM 24 + 0 to 32 + 0 weeks inpatient: 72 h No labour No clin. sign of CA	Overall maternal and perinatal/neonatal morbidity	**prim. outcome measures: no significant differences** **s:** mean latency period: 32.6 vs. 12.4 days Mean gestational age at birth: 32.7 vs. 30.4 weeks Mean birth weight: 2131 vs. 1602 g Mean LOS on NICU: 20.2 vs. 32.8 days
Huret 2014[+]	Retrospective cohort (EL IIb)	82/149	PPROM: 32 + 0 to 36 + 6 weeks inpatient: 5–7 days No clin. sign of CA, CP	Maternal and neonatal morbidity	**prim. outcome measures: no significant differences**
Garabedian 2015	retrospective cohort (EL IIb)	24/32	PPROM: 24–35 weeks inpatient: 7 days Singleton pregnancy No clin. sign of CA Cervical dilation < 3 cm	Maternal and neonatal morbidity	**prim. outcome measures: no significant differences** **s:** median latency period: 27.5 vs. 16.5 days Median LOS on NICU: 12.5 vs. 43 days
Catt 2016	Retrospective cohort (EL IIb)	133/122	PPROM: 20–34 weeks Latency period at least 72 h No clin. sign of CA Cephalic/breech presentation	Latency period	**Primary outcome measures 18 vs. 11 days (s):** **s:** histol. CA: 47 vs. 64 % Mean gestational age at birth: 32.3 vs. 30.6 weeks Mean birth weight: 1887 vs. 1599 g
Palmer 2017	retrospective observational study (EL IIIb)	87/89	PPROM: 23 + 0 to 34 + 0 weeks inpatient: 72 h No clin. sign of CA Cephalic/breech presentation, no vaginal bleeding, no cervical opening	Maternal and neonatal morbidity/ mortality	**prim. outcome measures: no significant differences** **s:** median latency period: 17 vs. 12 days Median hospital stay: 7 vs. 14 days Gestational age at birth: 238 vs. 224 days Median birth weight: 2134 vs. 1807 g Mean LOS on NICU: 13 vs. 20 days
Dussaux 2018	Retrospective cohort (EL IIb)	90/324	PPROM: 24 + 0 to 34 + 0 weeks inpatient: 72 h No labour No signs of infection	Maternal and neonatal morbidity/ mortality	**prim. outcome measures: no significant differences** **s:** Latency period: 29.9 vs. 11.5 days Gestational age at birth: 33.6 vs. 32 weeks Birth weight: 1970 vs. 1676 g LOS on NICU: 17.8 vs. 27.3 days

Continued next page

▶ **Table 1** Inpatient versus outpatient management of preterm premature rupture of membranes (PPROM): Literature review. *(Continued)*

Author/year	Trial (EL)	n: outpatient/ inpatient	Inclusion criteria	Primary outcome measures	Outcomes
Bouchghoul 2019	retrospective observational study (EL IIIb)	341/246	PPROM: 24 + 0 to 33 + 6 weeks inpatient: 48 h No clin. sign of CA, Cervical dilation < 3 cm	Perinatal and neonatal morbidity	**prim. outcome measures: no significant differences** **s:** Median birth weight: 1790 vs. 1632 g
Guckert 2020	retrospective Comparison of 2 periods: 2002–2009: inpatient 2010–2015: outpatient (EL IIIb)	191/204	PPROM: 24 + 0 to 35 + 6 weeks inpatient: 5 days No clin. sign of CA, singleton pregnancy, cervical dilation < 3 cm	Latency period	**Median latency period: 39 vs. 21 days (s)** **s:** Mean gestational age at birth: 35.6 vs. 32.4 weeks Rate clin. CA: 15.7 vs. 24.0 % Median birth weight: 2310 vs. 1860 g Median LOS on NICU: 9 vs. 21 days

Inclusion criteria in all trials: outpatient distance from hospital (e.g. < 30 min, < 50 km).

[+] = Trial in French language only

Abbreviations: **s:** significant results, RCT: randomised controlled trial, AFI: amniotic fluid index, CA: chorioamnionitis, CP: cephalic presentation, NICU: neonatal intensive care unit, EL: level of evidence, LOS: length of stay

spective design limits the validity of this study, as does a selection bias, since no randomisation took place and the women were assigned to the study groups subjectively by their respective obstetrician. In addition, no detailed information was available on the mode of delivery, comorbidities of the pregnant women, and neonatal morbidity.

In another retrospective ICD-based data analysis from Canada [38], 87 pregnant women with PPROM at 23 + 0 to 34 + 0 weeks' gestation were managed at home and 89 as inpatients (see ▶ **Table 1** for inclusion criteria). After hospital admission, all pregnant women received antibiotics and betamethasone for foetal lung maturation induction for 3 days and then were assigned to either of the two study groups. The modalities of outpatient management are summarised in ▶ **Table 2**. Primary outcome measures of the study were maternal morbidity and neonatal morbidity/mortality. There were no significant differences in overall maternal morbidity (aOR 0.64; 95 % CI 0.35–1.17), including the rate of clinical (11.5 vs. 20.2 %) and histologically confirmed chorioamnionitis (29.1 vs. 39.3 %). Other significant differences between both study groups (latency period, gestational age at birth, birth weight, length of stay in hospital, stay on neonatal intensive care) are presented in ▶ **Table 1**. There were also no significant differences in overall neonatal morbidity/mortality (aOR 0.63; 95 % CI 0.31–1.30).

Logistic regression analysis did not find any significant differences with regard to the primary outcome measures.

The authors regard outpatient management of pregnant women with PPROM as a possible alternative to continuous inpatient monitoring.

However, the study has numerous limitations: retrospective data analysis with low evidence level (IIIb), potential selection bias due to lack of randomisation, different obstetric practices in the two participating hospitals, lack of information on risk factors for preterm birth, duration of antibiotic administration and obstetric complications such as premature placental abruption, IUFD and umbilical cord prolapse.

A retrospective cohort study at 3 French perinatal centres included 90 pregnant women with outpatient and 324 with inpatient management of PPROM at 24 + 0 to 34 + 0 weeks' gestation [34], who did not deliver within 24 hours after rupture of the membranes. Initial treatment included antibiotics (amoxicillin 1 g every 8 h for 2–5 days) and betamethasone for induction of foetal lung maturation. Taking into account the inclusion criteria (▶ **Table 1**), outpatient monitoring (see ▶ **Table 2**) was possible after an inpatient observation period of 72 h.

In uncomplicated cases, labour was induced at 36/37 weeks' gestation. The median gestational age at the time of PPROM in the inpatient group was significantly higher (30.3 vs. 28.8 weeks, $p < 0.01$) and the ultrasound measurement of cervical length was significantly shorter (24.3 mm vs. 31.7 mm, $p = 0.01$) than in the outpatient group. 14.4 % of outpatients and 31.8 % of inpatients presented with additional risks of pregnancy (e.g. hypertension, diabetes) ($p < 0.01$).

Outcome measures were gestational age at birth, maternal morbidity, obstetric complication rate, and perinatal/neonatal outcome.

None of the outpatient pregnant women gave birth outside the hospital.

▶ **Table 1** summarises the significant differences between both groups (inpatient versus outpatient care). There were no significant differences in the rate of clinical chorioamnionitis (8.9 vs. 9.6 %) and obstetric complications such as IUFD (0 vs. 0.3 %), premature placental abruption (2.2 vs. 2.2 %), umbilical cord prolapse (1.1 vs. 1.9 %), and perinatal outcome.

Multivariate regression analysis did not find significant differences in neonatal morbidity and mortality.

The authors attributed the younger gestational age at birth in the inpatient group to the higher risk of preterm birth in this

▶ **Table 2** *(Outpatient)* Management following preterm premature rupture (from studies)*.

Author/Year	Management
Carlan 1993	Body temperature and pulse every 6 h, foetal movements = 1×/day CTG and blood count = 2×/week, ultrasonography and speculum examination = 1 ×/week
Beckmann 2013	Clinical symptoms, abdominal palpation, pulse/BP, foetal HR = 2×/week. Blood count/CRP = 2 ×/week, ultrasonography (foetal growth, amount of amniotic fluid) = every 2 weeks.
Palmer 2017	Clinical follow-up by midwife *(symptoms, temperature, pulse, abdominal palpation)* = 1 ×/day Auscultation of the foetal HR in turn with CTG = 3 ×/week
Dussaux 2018	Clinical follow-up by midwife = 1 ×/day, foetal HR Blood count/CRP and vaginal smear *(microbiology)* = once or twice/week, ultrasonography = 1 ×/week
Petit 2018	Clinical follow-up by midwife *(symptoms, abdominal palpation, foetal HR)* = 3 ×/week Blood count/CRP = 2 ×/week, microbiology (*vagina, urine*) = 1 ×/week Ultrasonography *(foetal growth, amount of amniotic fluid)* = every 15 days
Bouchghoul 2019	CTG = 1 ×/day, blood count/CRP = 2 ×/week Clinical examination and ultrasonography = 1 ×/week
Guckert 2020	For monitoring modalities see Petit et al. 2018

* if specified in study, only English-language literature

group and to the risk of potential nosocomial infections, notwithstanding a comparable rate of chorioamnionitis. In selected pregnant women, they regarded outpatient management of PPROM at 24 to 34 weeks' gestation as an option to inpatient care.

The main criticism of this study includes the retrospective design and the potential selection bias with different entry criteria (see above) as well as the inadequate statistical power for rare obstetric and neonatal complications in the outpatient study group. In addition, only the neonatal, but not the obstetric outcome parameters were subjected to multivariate regression analysis. No analysis of satisfaction and cost-effectiveness was carried out.

The aim of a retrospective cohort study [39] was to evaluate predictive factors for complications in outpatient management of pregnant women with PPROM at 24 + 0 to 35 + 0 weeks' gestation. Complications were defined as intrauterine foetal death premature placental abruption, umbilical cord prolapse, out-of-hospital birth, and neonatal death. The inclusion criteria for outpatient management were: singleton pregnancy, no evidence of chorioamnionitis, stable maternal condition until day 5 post rupture of membranes, cervical dilation < 3 cm, and distance from hospital < 30 minutes. The patients were discharged after an initial inpatient stay of 5–7 days with induction of foetal lung maturation and prophylactic antibiotics for 7 days. ▶ **Table 2** summarises the outpatient management modalities of this study. Labour was induced starting at 36 week's gestation.

The study groups were divided into pregnant women with and without complications (see above).

Both groups reported similar demographic details, with 12 (6.4%) of 187 pregnant women experiencing the following complications (some with multiple responses): 2 cases with IUFD (premature placental abruption, chorioamnionitis), 4 with neonatal death (chorioamnionitis, twice umbilical cord prolapse, birth outside the hospital) and pregnant women with premature placental abruption (n = 4), birth outside the hospital (n = 1) and umbilical cord prolapse (n = 1). In this "complication group", the median gestational age at PPROM and at birth was significantly earlier and the rate of neonatal complications significantly higher than in the comparison group without complications. Gestational age at rupture of membranes < 26 weeks, non-cephalic presentation and oligohydramnios (amniotic fluid index < 2 cm) at discharge were found to be significant risk factors ($p < 0.05$) for the presence of complications, with ORs ranging from 4.3 to 6.2. According to logistic regression analysis, the risk increased 1.6-fold for one of these criteria, 6.9-fold for two criteria, and 32.8-fold for all three criteria. The authors therefore recommend hospitalisation of pregnant women if a combination of these risk factors are present, but otherwise consider outpatient management of PPROM < 36 weeks' gestation a suitable alternative to inpatient care.

This analysis was limited by the retrospective design of the study and the inadequate statistical power with regard to overall rare severe complications; due to the small number of cases, a multivariate regression analysis was not possible.

A French retrospective multicentre study from 2019 [40] included a total of 587 pregnant women with PPROM at 24 + 0 to 33 + 6 weeks' gestation and a latency period of ≥ 48 h; 246 patients were managed as inpatients and 341 as outpatients. The inclusion criteria of the study are presented in ▶ **Table 1**, the monitoring modalities for outpatient management in ▶ **Table 2**.

All patients received betamethasone for induction of foetal lung maturation, antibiotics (ampicillin, cefuroxime) according to local protocol, and tocolysis for 48 h as determined by the obstetrician. The approach was expectative until the onset of spontaneous labour or the manifestation of complications (e.g. pathological CTG), and induction of labour or caesarean section was performed from 37 + 0 weeks' gestation.

Primary outcome measures of the study were overall perinatal/neonatal morbidity; secondary outcome measures included latency period, rates of chorioamnionitis, premature placental abruption, umbilical cord prolapse, and mode of delivery. Taking

into account the inclusion criteria, outpatient management was possible for a total of 19.4% of all patients. The following parameters did not reveal any significant differences: latency period, gestational age at birth, mode of delivery, overall neonatal morbidity (14.6 vs. 15.5%), rate of chorioamnionitis (12.0 vs. 9.8%), and in the rate of intrauterine foetal death, premature placental abruption, maternal sepsis, or endometritis. The rate of umbilical cord prolapse was significantly higher in the inpatient group compared to the outpatient group, 4.5 vs. 1.8% (p = 0.03).

The rate of births after the 32nd week of gestation was significantly lower in pregnant inpatients than in the comparison group (47.3 vs. 55.4%, p = 0.05) and the rate of births < 28th week of gestation was significantly higher (18.0 vs. 12.9%, p = 0.01).

Taking into account the propensity score matching to reduce a possible selection bias due to confounder variables, no significant differences were found in both groups with regard to all outcome criteria. According to the authors, following extensive informed consent outpatient management is a possible alternative to standard inpatient care for pregnant women with uncomplicated PPROM < 34 + 0 weeks' gestation, despite inadequate evidence to date.

This retrospective observational study was limited by the fact that its level of evidence was low (IIIb). The decision to proceed was taken subjectively by the obstetrician; there was no randomisation (selection bias). In addition, the three centres had different obstetric approaches with outpatients (e.g. tocolysis, antibiotics). Ultimately, only 66 of 341 pregnant women (19.4%) were included in the study, and neither satisfaction nor cost-effectiveness was analysed. With regard to obstetric complications and neonatal morbidity, the study had inadequate statistical power.

A retrospective monocentric study from France in 2020 [41] compared two observation periods in pregnant women with PPROM at 24 + 0 to 35 + 6 weeks' gestation: in the years 2002–2009, treatment was exclusively provided under inpatient conditions until birth (n = 204); in the following observation period until 2015, care was provided on an outpatient basis (n = 191). The inclusion criteria are shown in ▶ **Table 1**, the outpatient care modalities in ▶ **Table 2**. All pregnant women initially received steroids for induction of lung maturation and antibiotic treatment. On day 5 after admission, the obstetrician decided on the further management. Labour was induced in both groups starting at 36 + 0 weeks' gestation.

The primary outcome measure of the study was the duration of the latency period, while secondary outcome measures were maternal morbidity and perinatal morbidity and mortality. Both study groups were comparable in terms of demographic details. The latency period was significantly longer for the pregnant outpatients, with a median of 39 days (20–66 days) compared with 21 days (13–42 days; p < 0.01) for the inpatient group. Significant differences were found between the study groups with regard to gestational age at birth, birth weight, the rate of clinical chorioamnionitis, and the length of stay of the preterm infants in the neonatal intensive care unit (see ▶ **Table 1**). Significant differences favouring the outpatient approach were also found in the median RDS rate (29.4 vs. 47.5%; p < 0.001), neonatal sepsis rate (13.9 vs. 22.1%; p = 0.037) and intracerebral haemorrhage rate (1.6 vs. 4.9%, p = 0.04).

The rates of intrauterine foetal death (1 vs. 0%), premature placental abruption (2.0 vs. 1.5%) and umbilical cord prolapse (0.5 vs. 1.5%) did not differ significantly between both study groups.

The prolongation of the latency period in the pregnant outpatients correlated with the comparably lower neonatal morbidity. The authors explain the shortened latency period in the pregnant inpatients by the need for earlier delivery by the significantly higher rate of chorioamnionitis with its increased risk of nosocomial infections. Other reasons given are the increased stress caused by long antenatal hospitalisation and the higher rate of iatrogenic interventions (e.g. vaginal examinations, induction of labour, elective caesarean section). Despite promising results from this largest study to date comparing outpatient and inpatient management of PPROM, the authors call for confirmation of their findings by randomised controlled trials before routine outpatient management can be recommended.

The validity of this study is limited by the following critical aspects including: retrospective observational study with low evidence level, potential selection bias (no randomisation, no exclusion of confounders by multivariate regression analysis), failure to take into account advances in neonatology over an observation period of 15 years, lack of information on anamnestic risk factors for preterm birth.

Discussion

Against the background of increasing staffing and financial burdens on obstetric departments, outpatient/home management is also becoming increasingly important in high-risk pregnancies (e.g. induction of labour, monitoring of hypertensive pregnant women) [23, 42], a development that is being accelerated by steady advances in telemedicine (telemonitoring) [43]. Whether pregnant women with PPROM might also be eligible for this approach without endangering the safety of mother and child is the focus of our data analysis. According to IQTIG (Institute for Quality Assurance and Transparency in Health Care) statistics 2019 [44], there were 750 996 births in Germany, but the number of pregnancies was not specified. Assuming a mean value of 3% with PPROM, this would be around 22 530 cases. According to studies [29, 30, 32, 40], 20% of these could be considered for outpatient management. This would mean around 4500 pregnant women a year in Germany who might be eligible for outpatient treatment.

The risks of outpatient management are the unexpected birth outside the hospital [34, 39] and the unpredictable presence of complications (IUFD, premature placental abruption, umbilical cord prolapse, chorioamnionitis) requiring prompt obstetric intervention [32, 45]. In PPROM, the clinical course largely depends on the latency period and gestational age [7]; in about 30% of such pregnant women, birth occurs within 48 h [3]. This must be taken into account when managing pregnant outpatients and is a guideline for the duration of initial inpatient monitoring, which in previous studies varied between 48 h [40] and 7 days [35, 36], with the majority at 72 hours. This length of initial hospitalisation is not evidence-based but rather on clinical-empirical recommendations [46]. According to Bendix et al. [8], in 45% of cases severe obstetric complications occur within the first 3 days post PPROM.

A particular challenge for the obstetrician is the selection of pregnant women with PPROM who might qualify for outpatient management (see ▶ **Tables 1** and **3**).

Taking these selection criteria into account, only 11% [30], 18% [29], 19.4% [40] and 23% [32], respectively, were eligible for outpatient management in studies.

Above all, management (at home or as an inpatient) aims to diagnose chorioamnionitis as early as possible (see ▶ **Table 2**). One problem in this context is the lack of sensitivity of clinical, laboratory and instrument-based (CTG) diagnostic procedures [21].

To date, the evidence on management modalities in PPROM is inadequate [47]; inpatient management is based on clinical empirical studies or on individual decisions of the obstetrician [29, 46].

When comparing inpatient and outpatient management of PPROM, the evidence regarding the safety of mother and child is still low.

Two RCTs with small case numbers [29, 30] did not allow clinically significant conclusions to be drawn in this regard [31]. There is considerable heterogeneity between the retrospective studies in terms of study design (cohort/observational studies, case series, etc.: evidence level IIb–IIIb), selection criteria, outpatient care modalities, obstetric criteria at enrolment (e.g. inclusion of high-risk pregnancies, risk factors for preterm birth, cervical status), primary outcome measures, and the obstetric approach in the department. In addition, there is selection bias due to the lack of randomisation (assignment to study groups at the discretion of the obstetrician in charge) with the likelihood that pregnant women with a high risk profile are more likely to be managed as inpatients [33, 34] as well as inadequate statistical power due to low case numbers of severe complications and neonatal morbidity/mortality.

Regardless of this, previous studies did not find any statistically significant differences in maternal and perinatal/neonatal morbidity between both approaches (see ▶ **Table 1**).

Studies have almost uniformly reported a significant prolongation of the latency period with outpatient care compared to inpatient management, associated with a significantly higher gestational age at birth, higher birth weight and a shorter length of stay of preterm infants on the neonatal intensive care unit (▶ **Table 1**).

The avoidance of nosocomial infections potentially necessitating premature delivery, the lessening of stress and the reduction in obstetric interventions compared to prolonged hospitalisation have been suggested as possible reasons for this prolonged latency period [34, 41].

The EPIPAGE II trial demonstrated that a prolonged latency period in PPROM does not worsen neonatal prognosis. The higher gestational age at birth led to an increase in the survival rate/survival without severe neonatal morbidity [48, 49].

Arguments against outpatient management and in favour of inpatient care include the risk of severe complications, which may in principle occur with either approach, but can be treated more quickly if the pregnant women are hospitalised. In the trial by Ellestad et al. [32], 18% (12 of 65) of pregnant women had to be delivered within 2 h after manifestation of a complication.

Details on readmission to the department after discharge at home due to "symptoms or complications" are scarce. Only Catt et al. [37] reported a rate of 22% of pregnant outpatients who required readmission to hospital (no reason given).

▶ **Table 3** Conditions and selection criteria for outpatient (*home*) management in preterm premature rupture of the membranes – summary from studies.

- Initial inpatient management for 3–5 days: Antibiotics, induction of foetal lung maturation
- Informed consent: Preferences/compliance of the pregnant woman, risks, instructions for rapid readmission to hospital, phone contact with the hospital
- Attention to the selection criteria before discharge:
  - Unremarkable CTG, no foetal tachycardia, no contractions
  - No clinical signs of chorioamnionitis *(symptoms, body temperature, lab panel)*
  - No vaginal bleeding
  - Cervical opening < 2 (3) cm
  - Singleton pregnancy
  - No PPROM < 26 weeks' gestation (Petit et al. 2018)
  - Optional: Cephalic presentation, AFI > 2 cm, no additional risks of pregnancy
  - Short distance to the hospital (e.g. 30 min, < 50 km)
- Ensuring adequate outpatient management

Overall, comparative studies found no significant differences in the rate of major complications, including chorioamnionitis, between the study groups [33, 34, 37, 38, 40, 41].

According to Petit et al. [39], gestational age < 26 weeks, non-cephalic presentation and oligohydramnios at discharge (AFI < 2 cm) were significant risk factors for the presence of obstetric complications (OR 4.3–6.4).

The clear benefit of outpatient management compared to inpatient care is the significantly shorter hospital stay [30, 34, 38, 40, 50], which in combination with a significantly shorter length of stay of preterm infants on the neonatal intensive care unit results in considerable savings in treatment (hospital) costs [29, 30, 51].

Structured analyses comparing both approaches in terms of satisfaction of the pregnant women are not yet available; there is clearly a need to address this issue. However, pregnant women are less likely to be stressed if care is provided at home [52 – 54].

It must also be determined on a case by case basis whether it is possible to care for the pregnant woman at home in terms of ensuring adequate monitoring, while also taking into account the domestic circumstances (e.g. support from partner/family).

Good communication skills and and sufficient patient's compliance are also indispensable, especially with regard to understanding possible risks/complications and understanding the reasons when rapid readmission to the hospital is mandatory.

Outpatient management can be provided by trained midwives in close cooperation with a obstetrician's office and there should be the possibility of 24/7 visits to a perinatal centre.

For pregnant women with PPROM, outpatient care is a possible alternative to inpatient management in the context of family-oriented obstetrics. After all, in a US nationwide survey, 43% of obstetricians favoured outpatient management of PPROM [55].

However, such an individual decision must always be reached by consensus between the obstetrician and the pregnant woman.

Since the rates for severe maternal and neonatal complications are low, further studies (multicentre studies) with large numbers of cases are needed to assess the safety of outpatient management for mother and child.

The call for RCTs in published studies is also likely to be problematic with regard to the question of whether pregnant women will accept randomisation in this stressful situation for them.

In current guidelines, outpatient management is either not recommended for pregnant women with PPROM due to insufficient data [4] or may be offered to pregnant women with low evidence level (III), taking into account the latency period and individual risk profile [21].

Conclusion

Against the background of increasing pressure on departments of obstetrics, outpatient management of pregnant women with PPROM at 24 + 0 to 36 + 6 weeks' gestation is a potential alternative to inpatient care. According to low-evidence retrospective studies, this approach does not increase the rate of maternal complications and neonatal morbidity, shortens the length of stay in hospital and saves treatment costs.

However, evidence-based selection criteria for outpatient management are still lacking, as are uniform monitoring modalities for these pregnant women. Therefore, more studies with higher case numbers are needed to prove beyond any doubt the safety of this procedure for mother and child and to be able to recommend it for clinical practice. Until then, home management of pregnant women with PPROM remains a case-by-case decision, taking into account patient-specific risk factors. For forensic reasons, possible risks should be carefully explained, documented and countersigned by the pregnant woman. Even if no evidence-based guidelines for patient's surveillance can be given, it is advisable to provide the pregnant woman with detailed written instructions on how to proceed in her individual situation (temperature measurement, abnormalities in the smell and colour of amniotic fluid, contractions, pressure sensations, CTG checks).

In cases where non-compliance is to be expected (e.g. communication difficulties), outpatient management should generally be avoided.

Conflict of Interest

The authors declare that they have no conflict of interest.

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