Thieme

Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) – Part 2 with Recommendations on the Tertiary Prevention of Preterm Birth and the Management of Preterm Premature Rupture of Membranes

Prävention und Therapie der Frühgeburt. Leitlinie der DGGG, OEGGG und SGGG (S2k-Niveau, AWMF-Registernummer 015/025, Februar 2019) – Teil 2 mit Empfehlungen zur tertiären Prävention der Frühgeburt und zum Management des frühen vorzeitigen Blasensprungs

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Key words
preterm birth, preterm labor, cervical insufficiency, preterm premature rupture of membranes

Schlüsselwörter
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ABSTRACT

Aims This is an official guideline of the German Society for Gynecology and Obstetrics (DGGG), the Austrian Society for Gynecology and Obstetrics (ÖGGG) and the Swiss Society for Gynecology and Obstetrics (SGGG). The aim of this guideline is to improve the prediction, prevention and management of preterm birth based on evidence obtained from recently published scientific literature, the experience of the members of the guideline commission and the views of self-help groups.
Methods The members of the participating medical societies and organizations developed Recommendations and Statements based on the international literature. The Recommendations and Statements were adopted following a formal consensus process (structured consensus conference with neutral moderation, voting done in writing using the Delphi method to achieve consensus).
Recommendations Part 2 of this short version of the guideline presents Statements and Recommendations on the tertiary prevention of preterm birth and the management of preterm premature rupture of membranes.

ZUSAMMENFASSUNG

Ziel Offizielle Leitlinie der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (ÖGGG) und der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe (SGGG). Ziel der Leitlinie ist es, die Prädiktion, die Prävention und das Management der Frühgeburt anhand der aktuellen Literatur, der Erfahrung der Mitglieder der Leitlinienkommission einschließlich der Sicht der Selbsthilfe evidenzbasiert zu verbessern.
Methoden Anhand der internationalen Literatur entwickelten die Mitglieder der beteiligten Fachgesellschaften und Organisationen Empfehlungen und Statements. Diese wurden in einem formalen Prozess (strukturierte Konsensuskonferenzen mit neutraler Moderation, schriftliche Delphi-Abstimmung) verabschiedet.
Empfehlungen Der Teil 2 dieser Kurzversion der Leitlinie zeigt Statements und Empfehlungen zur tertiären Prävention der Frühgeburt sowie zum Management des frühen vorzeitigen Blasensprungs.

I Guideline Information

Guidelines program

For information on the guidelines program, please refer to the end of the guideline.

Citation format

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Guideline documents

The complete long version, a slide version of this guideline, a list of the conflicts of interest of all authors, and a guideline report on the methodological approach used, including the management of conflicts of interest, are available in German on the homepage of the AWMF: http://www.awmf.org/leitlinien/detail/ll/015-025.html

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Guideline authors (▸ Table 1)

▸ **Table 1** The following medical societies/working groups/organizations/associations were interested in participating in the compilation of the text of the guideline and in the consensus conference, and they nominated representatives to attend the consensus conference.

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Abbreviations

AFP	alpha-fetoprotein
AUC	area under the curve
CI	confidence interval
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CTG	cardiotocography
fFN	fetal fibronectin
FIRS	fetal inflammatory response syndrome
GBS	group B streptococcus
GW	week of gestation
IGFBP-1	insulin-like growth factor-binding protein-1
IL-6	interleukin-6
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
NNH	number needed to harm
NNT	number needed to treat

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OR	odds ratio
17-OHPC	17α-hydroxyprogesterone caproate
PAMG-1	placental alpha microgobulin-1
phIGFBP-1	phosphorylated insulin-like growth factor-binding protein-1
PIVH	periventricular/intraventricular hemorrhage
PPROM	preterm premature rupture of membranes
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
RR	relative risk
s/p	status post
TCO	total cervical occlusion
TNF-α	tumor necrosis factor alpha
Triple I	intrauterine inflammation or infection or both

II Guideline Application

Purpose and objectives

This guideline aims to improve both the outpatient and the inpatient care of patients at imminent risk of preterm birth in order to reduce the rate of preterm births. If preterm birth cannot be prevented, the aim is to reduce perinatal and neonatal morbidity and mortality. This should lead to improvements in the psychomotor and cognitive development of children born preterm.

Targeted areas of patient care

Outpatient and/or inpatient care

Target user groups/target audience

The recommendations of this guideline are aimed at gynecologists in private practice, gynecologists in hospitals, pediatricians in hospitals, midwives in private practice and midwives in hospitals. Other target user groups include advocacy groups for affected women and children, nursing staff (obstetrics/postnatal care, pediatric intensive care), medical and scientific societies and professional associations, institutions for quality assurance (e.g. IQTIG), healthcare policy institutions and decision-makers at the federal and state level, funding agencies and payers.

Adoption and period of validity

The validity of this guideline was confirmed by the executive boards of the participating medical societies, working groups, organizations and associations as well as by the executive boards of the DGGG, the SGGG and the OEGGG and the DGGG/OEGGG/SGGG guidelines commission in February 2019 and was thus confirmed in its entirety. This guideline is valid from 1 February 2019 through to 31 January 2022. Because of the contents of this guideline, this period of validity is only an estimate. The guideline may need to be updated earlier in urgent cases. If the guideline continues to mirror current knowledge, its period of validity may also be extended.

III Method

Basic principle

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and requirements for different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest (S3) class. The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was divided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest S3 class combines both approaches. This guideline is classified as: **S2k**

Grading of recommendations

Grading of evidence and grading of recommendations is not envisaged for S2k-level guidelines. The individual Statements and Recommendations are differentiated by syntax, not by symbols (▶ **Table 2**).

▶ **Table 2** Grading of recommendations.

Level of recommendation	Syntax
Strong recommendation, highly binding	must/must not
Simple recommendation, moderately binding	should/should not
Open recommendation, not binding	may/may not

In addition to the level of evidence, the above listed classification of "Recommendations" also takes account of the clinical relevance of the underlying studies and the various measures/factors which were not included in the grading of evidence, such as the choice of patient cohort, intention-to-treat or per-protocol outcome analyses, medical and ethical practice when dealing with patients, country-specific applicability, etc.

Statements

Scientific statements given in this guideline which do not consist of any direct recommendations for action but are simple statements of fact are referred to as "Statements". It is *not* possible to provide any information about the grading of evidence for these Statements.

Achieving consensus and strength of consensus

As part of the structured process to achieve consensus (S2k/S3 level), authorized participants attending the session vote on draft Statements and Recommendations. This can lead to significant changes in the wording, etc. Finally, the extent of consensus is determined based on the number of participants (▶ **Table 3**).

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▶ **Table 3** Grading of strength of consensus.

Symbol	Strength of consensus	Extent of agreement in percent
+++	Strong consensus	> 95 % of participants agree
++	Consensus	> 75–95 % of participants agree
+	Majority agreement	> 50–75 % of participants agree
–	No consensus	< 51 % of participants agree

Expert consensus

As the name already implies, this term refers to consensus decisions taken with regard to specific Recommendations/Statements made without a prior systematic search of the literature (S2k) or for which evidence is lacking (S2e/S3). The term "expert consensus" (EC) used here is synonymous with terms used in other guidelines such as "good clinical practice" (GCP) or "clinical consensus point" (CCP). The strength of the recommendation is graded as previously described in the chapter "Grading of recommendations", i.e., purely semantically ("must"/"must not" or "should"/"should not" or "may"/"may not") without the use of symbols.

Addendum of the OEGGG

To 6.9.1 Mode of delivery depending on fetal presentation and position

The Austrian Society of Gynecology and Obstetrics (OEGGG) is of the opinion that there is no clinical or scientific basis for the Recommendation that cesarean section should be the preferred mode of delivery based on an assumed lower risk of perinatal cerebral hemorrhage. The OEGGG is of the opinion that the mode of delivery of infants at the limit of viability (GW 22 + 0 bis 24 + 6) must be adapted to take the individual maternal and fetal clinical situation into account. For singletons at the limit of viability and in cephalic presentation, the OEGGG recommends an individualized management of delivery, which takes the maternal and fetal clinical situation into account and where the clinical decision process also includes the option of vaginal delivery as the mode of delivery [1].

To 6.6.5 Application of antenatal steroids before late preterm delivery

Based on the results of the ALPS trial [2] and the recommendations of the Society for Maternal Fetal Medicine (SMFM), the OEGGG is of the opinion that the administration of antenatal steroids in GW 34 + 0 to GW 36 + 6 may be considered, in accordance with the specifications of the SMFM.

Addendum of the SGGG

To 6.6. Administration of antenatal steroids

The opinion of the SGGG on the issues in this chapter is presented in SGGG Expert Letter No. 56, which discusses the indications for glucocorticoid therapy to promote antenatal lung maturation and the appropriate doses when preterm birth is imminent (only available in German: "Glucocorticoidtherapie zur antenatalen Lungenreifung bei drohender Frühgeburt: Indikationen und Dosierung"). *Reasoning:* The evidence-based recommendations in Switzerland differ slightly from those given in this guideline, particularly with regard to the administration of antenatal glucocorticoids in gestational weeks 34 + 0 to 36 + 0 [3].

To 1. Definition and Epidemiology (and various other chapters: 6.9.1., 6.9.6., 6.9.7., 8.8., 8.9.)

As regards care at the limits of viability, please refer to the recommendations for Switzerland which were developed together with neonatologists. *Reasoning:* The recommendations for Switzerland diverge in many points from the recommendations for Germany. They are currently being revised [4].

To 6.2. Tocolysis

With regard to tocolytic drugs, the use of beta-mimetics for tocolysis has been approved in Switzerland and they can be used as the tocolytic drug of first choice; see also SGGG Expert Letter No. 41 on tocolysis for preterm labor (only available in German: "Tokolyse bei vorzeitiger Wehentätigkeit"). *Reasoning:* The recommendations for Switzerland differ in many points from the recommendations for Germany [5].

To 8.8 Clinical management before GW 22

The option of terminating the pregnancy should be mentioned to patients with a poor prognosis. *Reasoning:* The option of terminating the pregnancy by inducing the birth in cases where there is a serious physical or psychological risk to the mother is not mentioned in the guideline, even though it is clinically important.

IV Guideline

6 Tertiary Prevention

6.1 Bed rest

Consensus-based Statement 6.S21	
Expert consensus	**Strength of consensus ++**
There is currently no data which can confirm that bed rest reduces the rate of preterm births. However, bed rest does increase the maternal risk of thrombosis and contributes to the development of muscular atrophy and osteoporosis.	
[6 – 10]	

6.2 Tocolysis

Consensus-based Recommendation 6.E18	
Expert consensus	**Strength of consensus +++**
The aim of tocolysis must be to prolong the pregnancy by at least 48 hours. This additional period would make it possible to administer antenatal steroids and carry out an in-utero transfer to a perinatal center with a neonatal intensive care unit.	

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6.2.1 Indications

Consensus-based Recommendation 6.E19	
Expert consensus	**Strength of consensus +++**
Tocolytic therapy should be administered if the patient has spontaneous, regular, preterm contractions of ≥ 4/20 min with shortening of the functional cervical length (transvaginal measurement) and/or opening of the cervix.	

Consensus-based Statement 6.S22	
Expert consensus	**Strength of consensus +++**
If the indications are present and contra-indications have been excluded, tocolysis is indicated in the period between GW 22 + 0 and GW 33 + 6.	

Consensus-based Statement 6.S23	
Expert consensus	**Strength of consensus +++**
In cases of premature labor with cervical dilation, tocolytic therapy (beta sympathomimetics, atosiban, nifedipine, indomethacin, NO donors) can delay the birth by 48 h in 75–93 % of cases and by 7 days in 62–78 % of cases.	
[11, 12]	

6.2.2 Drugs

Consensus-based Recommendation 6.E20	
Expert consensus	**Strength of consensus ++**
Because of the significantly higher rate of maternal side effects (beta sympathomimetics) compared to other tocolytic drugs and the lack of evidence confirming its tocolytic efficacy (magnesium sulfate), beta sympathomimetics and magnesium sulfate should no longer be used for tocolysis.	

Of all the tocolytic drugs, beta sympathomimetics have the greatest rate of maternal (up to 80 % cardiovascular) and fetal side effects as well as requiring the most monitoring [12]. There is also the additional problem of lung edema which occurs in around 1/350 applications [13]. They should therefore no longer be used for tocolysis [14].

The data on the use of magnesium sulfate as a tocolytic drug is controversial. Meta-analyses [11, 12] showed that magnesium sulfate was an effective tocolytic in terms of prolonging the pregnancy by 48 hours compared to placebo (OR 2.46; 95 % CI: 1.58–4.94); however, this flies in the face of the results and statements of the 2014 Cochrane Review [15], which were generated using 37 studies with 3571 pregnant women. According to the Cochrane Review, magnesium sulfate was not more effective than placebo or even no therapy at prolonging pregnancy for more than 48 hours and does not reduce the rate of preterm births. However, the tocolytic efficacy of magnesium sulfate depends in the dose, which in turn has an impact on the incidence of maternal side effects. International guidelines no longer recommend using magnesium sulfate for tocolysis [16 – 18].

Consensus-based Recommendation 6.E21	
Expert consensus	**Strength of consensus ++**
After considering their efficacy and side effects profile, calcium antagonists (nifedipine), oxytocin-receptor antagonists (atosiban) and COX inhibitors (indomethacin) should be used preferentially for tocolysis, even though some have not yet been approved for use.	
[11, 12]	

6.2.3 Combining several tocolytics

Consensus-based Recommendation 6.E22	
Expert consensus	**Strength of consensus +++**
Based on current data, combining different tocolytics is associated with significantly increased rates of maternal side effects compared to administering a single tocolytic, and as there are no data confirming any increase in efficacy, combining different tocolytics should be avoided.	
[13, 19]	

Consensus-based Recommendation 6.E23	
Expert consensus	**Strength of consensus +++**
Tocolytics should not be administered in combination with oral/vaginal progesterone (“adjunctive tocolysis”), because data on this issue is still insufficient.	
[20]	

6.2.4 Tocolysis for extremely preterm birth, multiple pregnancy and intrauterine growth restriction

Consensus-based Statement 6.S24	
Expert consensus	**Strength of consensus +++**
Evidence from randomized controlled studies on the benefits of tocolytics for extremely preterm birth, multiple pregnancy and intrauterine growth restriction is lacking. The decision whether to administer tocolytics in such cases must be made on a case-by-case basis.	
[21]	

6.2.5 Long-term tocolysis

Consensus-based Recommendation 6.E24	
Expert consensus	**Strength of consensus +++**
According to the information currently available, long-term or maintenance tocolysis (generally defined as tocolysis for more than 48 h) should not be used to reduce the rate of preterm births or neonatal morbidity and mortality rates.	
[22 – 25]	

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6.3 Progesterone for maintenance tocolysis

Consensus-based Recommendation 6.E25	
Expert consensus	**Strength of consensus +++**
After tocolysis, pregnant women with a singleton pregnancy should not be given progesterone to maintain the pregnancy and prevent preterm birth.	

A meta-analysis carried out in 2017 which selectively included high-quality studies on this issue found that the use of progesterone for maintenance tocolysis did not significantly reduce the rate of preterm births before the 37th week of gestation (OR 1.23, 95% CI: 0.91–1.67) [26].

6.4 Cervical pessary for shortened cervical length after premature labor

Consensus-based Statement 6.S25	
Expert consensus	**Strength of consensus +++**
There is some evidence from a prospective randomized study that placement of a cervical pessary in pregnant women previously treated for premature labor who have a shortened cervical length as measured by transvaginal ultrasound (< 25 mm between GW 24 + 0 and GW 29 + 6; < 15 mm between GW 30 + 0 and GW 33 + 6) may reduce the rate of preterm births.	

Pratcorona et al. recently published a prospective randomized study which included 357 patients between GW 24 + 0 and GW 33 + 6 [27]. If patients had a shortened cervical length (≤ 25 mm between GW 24 + 0 and GW 29 + 6; ≤ 15 mm between GW 30 + 0 and GW 33 + 6) 48 hours after being treated for premature labor, they were managed either by placing a cervical pessary or by standard protocol. The primary study outcome, in this case, the preterm birth rate before the 34th week of gestation, did not differ significantly between groups (10.7 vs. 13.7%; RR 0.78 [95% CI: 0.45–1.38]). However, the preterm birth rate before the 37th week of gestation was significantly lower after placement of a cervical pessary (14.7 vs. 25.1%; RR 0.58 [95% CI: 0.38–0.90]) as was the number of patients readmitted to hospital after previously being treated for premature labor (4.5 vs. 20.0%; RR 0.23 [95% CI: 0.11–0.47]). However, these results could not be confirmed in the APOSTEL VI trial [28].

6.5 Administration of antibiotics for premature labor

Consensus-based Recommendation 6.E26	
Expert consensus	**Strength of consensus +++**
Cases of premature labor without rupture of membranes must not be treated with antibiotics with the goal of prolonging the pregnancy or reducing neonatal morbidity.	

Meta-analyses found that the administration of antibiotics to cases with premature labor and no rupture of membranes had no effect on the duration of the pregnancy, the preterm birth rate, respiratory distress syndrome or neonatal sepsis [29, 30]. Given these findings, the potential risks of administering antibiotics when their administration is not indicated need to be discussed.

6.6 Administration of antenatal steroids

6.6.1 Administration and dosage

Consensus-based Recommendation 6.E27	
Expert consensus	**Strength of consensus +++**
Antenatal steroids must be administered to women at imminent risk of preterm birth before GW 34 + 0, with treatment consisting of 2 × 12 mg betamethasone administered IM at an interval of 24 h (alternatively: dexamethasone, 4 × 6 mg every 12 h).	
[31]	

6.6.2 Starting in which week of gestation?

Consensus-based Recommendation 6.E28	
Expert consensus	**Strength of consensus +++**
Antenatal steroids should also be administered in cases at imminent risk of preterm birth < GW 24 + 0 if maximum therapy in a neonatal intensive care unit is planned.	

A recently published meta-analysis found 8 non-randomized studies on this issue [32]. The impact on neonatal mortality and morbidity of a single dose of corticosteroids administered in the period GW 22 + 0 to GW 23 + 6 is shown in ▶ **Tables 4** and **5**.

While neonatal mortality was significantly reduced after a single dose of corticosteroids, it apparently had no effect on morbidity. Given the rapid recent progress in the field of neonatal intensive care, prospective randomized studies on this issue are urgently required.

▶ **Table 4** Effects of antenatal steroids on the outcome of infants between GW 22 + 0 and GW 22 + 6 [32].

GW 22 + 0 – GW 22 + 6	OR	95% CI
Neonatal mortality	0.58	0.38–0.89
Intraventricular cerebral hemorrhage (grade III–IV) or periventricular leukomalacia	1.03	0.55–1.93
Chronic pulmonary disease	1.19	0.52–2.73
Necrotizing enterocolitis (> stage II)	0.59	0.03–12.03

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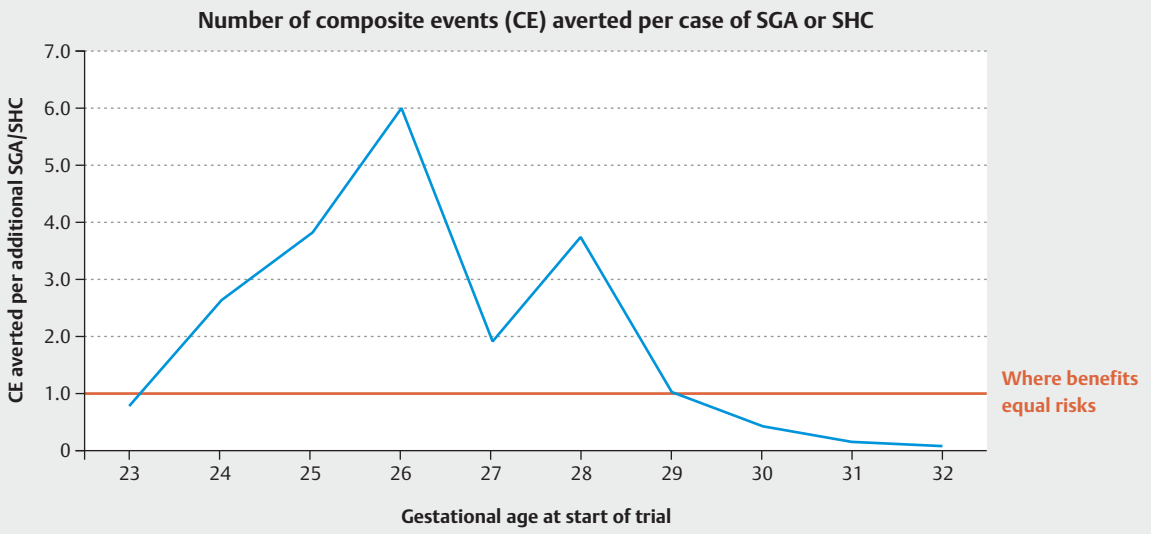

The *x-axis* shows the gestational age at entry; the *y-axis* shows the number of composite events that were averted per case of SGA/SHC. A gestational age risk benefit threshold is seen at 29 weeks' gestation, when the risk equals the benefits.

SGA: small for gestational age; SHC: small head circumference; CE: RDS, chronic lung disease (CLD), severe PIVH, PVL, bronchopulmonary dysplasia (BPD), or stillbirth

▶ **Fig. 1** Benefits of administering antenatal steroids according to gestational age [33]

▶ **Table 5** Effects of antenatal steroids on the outcome of infants between GW 23 + 0 and GW 23 + 6 [32].

GW 23 + 0 – GW 23 + 6	OR	95 % CI
Neonatal mortality	0.50	0.42–0.58
Intraventricular cerebral hemorrhage (grade III–IV) or periventricular leukomalacia	0.75	0.55–1.03
Chronic pulmonary disease	0.94	0.59–1.51
Necrotizing enterocolitis (> stage II)	0.93	0.66–1.32

6.6.3 Repeat administration of antenatal steroids

Consensus-based Recommendation 6.E29	
Expert consensus	**Strength of consensus +++**
If steroids are administered to women before the 29 + 0 week of gestation because of an imminent risk of preterm birth and steroids were administered more than 7 days previously, a further dose of steroids may be administered after the patient has been re-assessed if the imminent risk of preterm birth is increasing.	

Zephyrin and colleagues used a Markov model to investigate how to achieve the right balance between risks and benefits with repeat administration of antenatal steroids [33]. The improved neonatal outcomes after multiple glucocorticoid administrations were set against the risk of fetal growth restriction. After 29 + 0 weeks of gestation, a repeat administration of antenatal steroids was associated with increasing risks for the infant (▶ **Fig. 1**). Any repeat administration of antenatal steroids should therefore be limited to cases with a very low gestational age (< GW 29 + 0).

6.6.4 Timing of antenatal steroid administration

Consensus-based Statement 6.S26	
Expert consensus	**Strength of consensus +++**
The timing of and indication for administering antenatal steroids must be carefully weighed up, as neonatal morbidity and mortality can only be reduced in the period between 24 h and 7 days after the first administration. There is some evidence that administering antenatal steroids already has an effect before 24 h.	

There are now a number of cohort studies which show that perinatal morbidity and mortality depend significantly on the timing of lung maturity [34–36]. An example of this is shown in ▶ **Fig. 2**, which depicts the neonatal survival of infants born preterm at ≤ 26 weeks of gestation [36].

Consensus-based Recommendation 6.E30	
Expert consensus	**Strength of consensus +++**
Patients with premature contractions and a cervical length of > 30 mm or 15–30 mm as measured by transvaginal ultrasound and who additionally test negative for fibronectin, phIGFBP-1 and PAMG-1 should not be given antenatal steroids just because of the contractions, as the risk of preterm birth in the next 7 days is low (< 5 %).	
[37, 38]	

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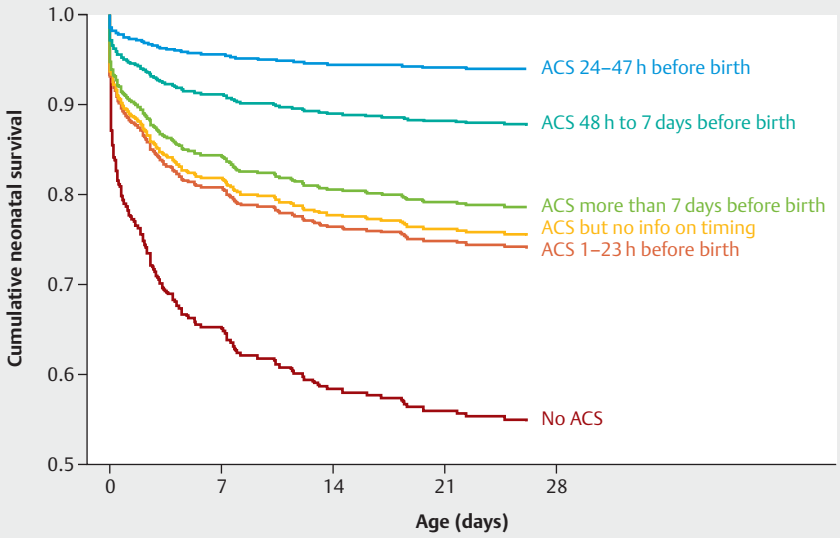

▶ **Fig. 2** Survival of very immature infants (< 26th week of gestation) according to the timing of antenatal steroid administration [36].

Consensus-based Recommendation 6.E31	
Expert consensus	**Strength of consensus +++**
So-called rapid maturation, consisting of the administration of a second dose of betamethasone after just 12 h rather than after 24 h, should be avoided as this significantly increases the risk of necrotizing enterocolitis.	
[39]	

6.6.5 Administration of antenatal steroids and late preterm birth

Consensus-based Recommendation 6.E32	
Expert consensus	**Strength of consensus ++**
Administering antenatal steroids to patients between GW 34 + 0 and GW 36 + 5 with an imminent risk of preterm birth should currently be avoided as there are still no studies on the impact this can have on the children's psychomotor development later on.	

The ALPS trial found a significant reduction in neonatal respiratory distress in children born in late preterm at GW 34 + 0 to GW 36 + 5, whose mothers were given 2 × 12 mg betamethasone IM antenatally [2]. The ASTECS trial, which studied pregnant women who underwent elective cesarean section at term, also reported a significant reduction in RDS in children born to mothers who received 2 × 12 mg betamethasone antenatally [40]. However, at a school assessment carried out by teachers 10 years later, it was found that significantly more children from the intervention group were in the lower performance quartile and fewer children were in the top performance quartile [41]. No follow-up examinations of the children in the ALPS trial have been carried out to date. Because of this, no antenatal corticoids should be administered to this group of patients for the time being.

6.7 Emergency cerclage

Consensus-based Recommendation 6.E33	
Expert consensus	**Strength of consensus +++**
An emergency cerclage may be placed in women with a singleton pregnancy and cervical dilation of more than 1 cm before GW 24 + 0 with the goal of significantly prolonging the pregnancy.	

Consensus-based Recommendation 6.E34	
Expert consensus	**Strength of consensus +++**
Women treated with emergency cerclage should receive indomethacin and antibiotics perioperatively.	

A meta-analysis published in 2015 (n = 772 women from 11 studies, n = 496 underwent emergency cerclage placement, n = 276 were managed expectantly) found a significant prolongation of pregnancy and reduction of perinatal mortality after placement of an emergency cerclage for cervical dilation (duration of pregnancy: plus 5.4 weeks, perinatal mortality reduced from 58.5% to 29.1%) [42]. The administration of indomethacin and cefazolin increased the percentage of women who did not give birth within the following 4 weeks (92.3 vs. 62.5%) [43].

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6.8 Neuroprotection

Consensus-based Statement 6.S27	
Expert consensus	**Strength of consensus +++**
Periventricular/intraventricular hemorrhage (PIVH) and periventricular leukomalacia (PVL)/diffuse cerebral white matter injury are typical forms of brain injury found in survivors of preterm birth.	
[44]	

6.8.1 Magnesium

Consensus-based Recommendation 6.E35	
Expert consensus	**Strength of consensus +++**
Magnesium may be administered intravenously for fetal neuroprotection to patients < GW 32 at imminent risk of preterm birth.	
[45, 46]	

Treatment should be started with a bolus of 4–6 g administered over 30 min, followed by a maintenance dose of 1–2 g for 12 h. The aim is to double the magnesium levels in maternal serum. If the birth does not occur within 12 h, magnesium may be administered again later on when preterm birth is once again imminent.

6.8.2 Delayed cord clamping

Consensus-based Recommendation 6.E36	
Expert consensus	**Strength of consensus +++**
Cord clamping of infants born preterm should be delayed or umbilical cord milking should be carried out.	
[47 – 49]	

6.9 Delivery

6.9.1 Delivery depends on fetal presentation

Consensus-based Recommendation 6.E37	
Expert consensus	**Strength of consensus ++**
Delivery by cesarean section may be considered after carefully weighing up the risk/benefits in each individual case if the fetus is aged < GW 30 + 0 and in cephalic presentation.	
[50 – 63]	

Consensus-based Recommendation 6.E38	
Expert consensus	**Strength of consensus ++**
Depending on the sonographically estimated fetal weight and other factors, delivery by cesarean section should be considered to reduce neonatal morbidity and mortality if the fetus is aged < GW 36 + 0 and in breech presentation.	
[64]	

6.9.2 Longitudinal uterine incision for cesarean section

Consensus-based Recommendation 6.E39	
Expert consensus	**Strength of consensus +++**
Particularly in cases of extremely preterm birth, longitudinal uterine section may be appropriate in individual cases as it may be the most beneficial form of delivery for the infant.	

Consensus-based Recommendation 6.E40	
Expert consensus	**Strength of consensus +++**
Because of the increased risk of uterine rupture, women who have had a previous longitudinal c-section must be delivered by primary repeat c-section in all subsequent births.	
[65, 66]	

6.9.3 Vaginal operative delivery

Consensus-based Recommendation 6.E41	
Expert consensus	**Strength of consensus ++**
Because of the increased risk of intraventricular hemorrhage, fetuses under the age of 34 + 0 weeks of gestation should not be delivered by vacuum extraction.	
[67]	

6.9.4 Fetal blood gas analysis

Consensus-based Recommendation 6.E42	
Expert consensus	**Strength of consensus +++**
Fetal blood gas analysis should not be carried out for fetuses under the age of 34 + 0 weeks of gestation because of the potential risk of injury.	

6.9.5 Antibiotic prophylaxis for group B streptococcus

Consensus-based Recommendation 6.E43	
Expert consensus	**Strength of consensus +++**
If the GBS status of a case of preterm birth is positive or unknown, antibiotic prophylaxis must be administered during delivery.	
[68]	

6.9.6 Cooperation with the Neonatology Department

Consensus-based Recommendation 6.E44	
Expert consensus	**Strength of consensus ++**
A pediatrician/neonatologist must be involved early on in the treatment and counselling of women with an imminent risk of preterm birth.	
[69 – 71]	

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The treating pediatrician must be given all information about the pregnant woman which may be important for the initial medical treatment and therapy of the preterm infant. Such information includes any medication taken, HBsAg status, blood group, CMV antibody status (up to the 32nd week of gestation), findings from any prenatal diagnostic workups, and results of microbiological screening of the pregnant woman at imminent risk of preterm birth for GBS, MRSA, MRGN as well as the results of any repeat screenings if pregnancy is prolonged.

Consensus-based Recommendation 6.E45	
Expert consensus	**Strength of consensus ++**
When an infant is born preterm (< GW 35 + 0), a physician with experience in neonatology must be present to directly oversee the care of the newborn infant. If there is an imminent risk of preterm birth before GW 32 + 0 and/or the estimated weight/birthweight is < 1500 g, a specialist physician with a subspecialization in neonatology must be on call.	
[72]	

6.9.7 Terminal care

Consensus-based Recommendation 6.E46	
Expert consensus	**Strength of consensus +++**
Specially trained staff must be called in to offer palliative and terminal care to deceased or dying newborns and their family in the perinatal phase. Terminal care is included in perinatology training. According to the tenets of the German Medical Association, offering terminal care with dignity is a key medical duty for physicians which they cannot delegate.	
[73 – 75]	

7 Special Aspects Relating to Twin and Multiple Pregnancies

7.1 Epidemiology and etiology

Consensus-based Statement 7.S28	
Expert consensus	**Strength of consensus +++**
Women carrying a multiple pregnancy have a significantly higher risk of preterm birth.	
[76, 77]	

7.2 Prevention

7.2.1 Progesterone

Consensus-based Recommendation 7.E47	
Expert consensus	**Strength of consensus +++**
Women must not be given progesterone to prevent preterm birth only because they are carrying twins.	
[78, 79]	

Consensus-based Recommendation 7.E48	
Expert consensus	**Strength of consensus +++**
Women carrying a twin pregnancy who have a cervical length of ≤ 25 mm before GW 24 + 0 as measured by transvaginal ultrasound should receive a daily dose of 200–400 mg progesterone applied intravaginally until GW 36 + 6.	

An individual patient data meta-analysis (IPDMA) of six studies [79 – 84] carried out by Romero et al. in 2017, which compared the application of vaginal progesterone with placebo or no treatment in 303 asymptomatic women with twin pregnancy and a cervical length of ≤ 25 mm in the second trimester, found a significant reduction in preterm births before the 33rd week of gestation (31.4 vs. 43.1 %; RR 0.69 [95 % CI: 0.51–0.93]) and improved neonatal outcomes (e.g., lower neonatal mortality rate [RR 0.53; 95 % CI 0.35–0.81], lower incidence of respiratory distress syndrome [RR 0.70; 95 % CI: 0.56–0.89], fewer neonates with a birthweight < 1500 g [RR 0.53; 95 % CI: 0.35–0.80]) [85].

7.2.2 Cerclage

Consensus-based Recommendation 7.E49	
Expert consensus	**Strength of consensus +++**
Primary or secondary cerclage should not be placed in women with twin pregnancies.	

The first meta-analysis of three prospective randomized studies found a significantly higher preterm birth rate before the 35th week of gestation for women carrying a twin pregnancy after placement of a primary or secondary cerclage (76 vs. 36 %; RR 2.15, 95 % CI: 1.15–4.01) [86 – 89]. Another meta-analysis has since been carried out which additionally took individual patient data into account [90]. This meta-analysis found that placement of a cerclage had no negative effect on the preterm birth rate or perinatal morbidity, at least for patients with a short cervix, before the 24th week of gestation.

7.2.3 Cervical pessary for shortened cervical length

Consensus-based Recommendation 7.E50	
Expert consensus	**Strength of consensus +++**
A cervical pessary can be placed in individual cases with twin pregnancy and a cervical length of ≤ 25 mm before GW 24 + 0 as measured by transvaginal sonography.	

Given the fact that prospective randomized studies have reported both positive [91 – 93] and negative [94, 95] data, the decision whether or not to carry out this procedure must be made on a case-by-case basis.

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7.2.4 Cervical pessary after preterm labor and shortened cervical length

Consensus-based Statement 7.S29	
Expert consensus	**Strength of consensus +++**
There is some evidence from a prospective randomized study that placement of a cervical pessary in cases with twin pregnancy previously treated for preterm labor and with a shortened cervical length as measured by transvaginal ultrasound (< 20 mm between GW 24 + 0 and GW 29 + 6; < 10 mm between GW 30 + 0 and GW 33 + 6) can reduce the rate of preterm births.	

In a prospective randomized study which included 132 women with twin pregnancy between GW 24 + 0 and GW 33 + 6 [96], patients who were found to have a shortened cervical length (≤ 20 mm between GW 24 + 0 and GW 29 + 6; ≤ 10 mm between GW 30 + 0 and GW 33 + 6) 48 h after treatment for preterm labor either underwent placement of a cervical pessary or received the usual standard care. The primary study outcome – i.e., the preterm rate before the 34th week of gestation – was significantly lower in the intervention goup (16.4 vs. 32.3 %; RR 0.51 [95 % CI: 0.27–0.97]) as was the number of readmitted patients after treatment for preterm labor (5.6 vs. 21.5 %; RR 0.28 [95 % CI: 0.10–0.80]). Moreover, placement of a cervical pessary significantly reduced the prevalence of necrotizing enterocolitis (0 vs. 4.6 %) and of neonatal sepsis (0 vs. 6.2 %).

7.2.5 Emergency cerclage

Consensus-based Recommendation 7.E51	
Expert consensus	**Strength of consensus +++**
If the cervix has opened more than 1 cm before GW 24 + 0, emergency cerclage may be carried out even in women with a twin pregnancy with the aim of significantly prolonging the pregnancy.	

As has already been established for women with singleton pregnancies, cohort studies have shown that a twin pregnancy can also be prolonged if an emergency cerclage is placed in women with an opened cervix before GW 24 + 0 [97 – 100].

8 Preterm Premature Rupture of Membranes (PPROM)

8.1 Prevalence and Etiology

Consensus-based Statement 8.S30	
Expert consensus	**Strength of consensus +++**
Around 3 % of all pregnant women are affected by preterm premature rupture of membranes (rupture of membranes before GW 37 + 0): 0.5 % before the 27th week of gestation, 1 % between 27 and 34 weeks of gestation and 1 % between the 34th and the 37th week of gestation.	
[101]	

8.2 Risk factors

Consensus-based Statement 8.S31	
Expert consensus	**Strength of consensus +++**
A previous history of PPROM is a significant risk factor for preterm premature rupture of membranes. The additional risk factors are similar to those for spontaneous preterm birth.	
[102, 103]	

8.3 Diagnostic workup

Consensus-based Recommendation 8.E52	
Expert consensus	**Strength of consensus +++**
In most cases, PPROM can be diagnosed by speculum examination. If there is still some uncertainty, then biochemical tests must be carried out.	
[104, 105]	

Consensus-based Recommendation 8.E53	
Expert consensus	**Strength of consensus +++**
A digital examination must be avoided in patients with PPROM.	

When examining patients with PPROM, a digital examination must be avoided where possible, because digital examinations increase the risk of ascending infection and significantly reduce the latency period to delivery [106, 107].

8.4 Latency period

Consensus-based Statement 8.S32	
Expert consensus	**Strength of consensus +++**
More than 50 % of all patients with PPROM are delivered within one week.	
[108, 109]	

8.5 Maternal and fetal risks

Consensus-based Statement 8.S33	
Expert consensus	**Strength of consensus +++**
Patients with PPROM have a risk of clinical infection. Additional risks include placental abruption and umbilical cord prolapse.	
[110 – 115]	

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8.6 Triple I (▶ **Table 6**)

Consensus-based Statement 8.S34	
Expert consensus	**Strength of consensus +++**
Internationally, the term "Triple I" has superseded the term chorioamnionitis to differentiate maternal fever from infection or inflammation or both.	

▶ **Table 6** Classification of maternal fever and Triple I*.

	Definition
Maternal fever	Maternal fever is present when the orally measured temperature exceeds 39.0 °C. If the orally measured temperature is between 38.0 and 38.9 °C, the temperature should be measured again after 30 minutes. If the temperature again exceeds 38.0 °C, then maternal fever is present.
Suspicious for Triple I	Maternal fever of unclear origin together with at least one of the following criteria: ▪ fetal tachycardia of more than 160 beats/min for > 10 min ▪ maternal leukocytes > 15 000 µl without the administration of corticosteroids ▪ purulent discharge from the cervix
Confirmed Triple I	Suspicion of Triple I and objective findings of infection, such as: positive Gram staining of amniotic fluid**, low glucose concentrations (< 14 mg/dl), increased number of leukocytes (> 30 cells/mm³), positive bacterial culture or histopathological findings*** of inflammation or infection of both of the placenta, the amniotic membranes or the umbilical cord (funisitis)

* Triple I: inflammation or infection or both; ** amniotic fluid obtained by amniocentesis; *** postpartum histopathology of the placenta [116].

8.7 Maternal and fetal risks associated with Triple I

Consensus-based Statement 8.S35	
Expert consensus	**Strength of consensus +++**
In addition to sepsis, maternal risks associated with Triple I include uterine dysfunction with the risk of failure to progress in labor and uterine atony post partum. In cases where delivery was by cesarean section, risks include wound infection, endomyometritis, thrombophlebitis and pelvic abscess formation.	
[117 – 122]	

Consensus-based Statement 8.S36	
Expert consensus	**Strength of consensus +++**
The fetus may develop inflammatory response syndrome as part of Triple I. Affected infants have a higher risk of sepsis post partum.	
[123, 124]	

8.8 Clinical management of PPROM before GW 22

Consensus-based Recommendation 8.E54	
Expert consensus	**Strength of consensus +++**
If PPROM occurs before the fetus has achieved viability, the risk of maternal sepsis, fetal pulmonary hypoplasia and fetal skeletal deformities must be discussed with the future parents.	
[125 – 127]	

Consensus-based Recommendation 8.E55	
Expert consensus	**Strength of consensus +++**
Antibiotic therapy may be considered in patients with PPROM before the fetus has achieved viability.	

As almost all studies on antibiotic therapy in cases with rupture of membranes only recruited patients after the 24 + 0 week of gestation, there are no reliable data on the administration of antibiotics before the fetus has achieved viability. But the risk that the patient may develop sepsis due to ascending infection suggests that antibiotic therapy is advisable [128]. The same regimen as the one described for PPROM between (GW 22 + 0) GW 24 + 0 and GW 33 + 6 GW can be used.

Consensus-based Recommendation 8.E56	
Expert consensus	**Strength of consensus +++**
Antenatal steroid administration, tocolysis and neuroprotection with magnesium must not be carried out in cases with PPROM before the fetus has achieved viability.	

8.9 Clinical management of PPROM between (GW 22 + 0) GW 24 + 0 and GW 33 + 6

Consensus-based Recommendation 8.E57	
Expert consensus	**Strength of consensus +++**
Recommendation: Between GW 22 + 0 and GW 23 + 6 the further course of action should be agreed upon with the parents in accordance with the German-language guideline "Frühgeborene an der Grenze der Lebensfähigkeit 024–019" [Preterm infants at the limits of viability].	

8.9.1 Expectant management

Consensus-based Recommendation 8.E58	
Expert consensus	**Strength of consensus ++**
If PPROM occurs between GW 24 + 0 and GW 33 + 6 or between GW 22 + 0 and GW 23 + 6 if maximum therapy is requested, expectant management must be considered first if there is no immediate risk to mother or child.	

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If PPROM occurs between GW 24 + 0 and GW 33 + 6 or between GW 22 + 0 and GW 23 + 6 if maximum therapy is requested, the risks of ascending infection must be weighed against the neonatal risks which can result from preterm birth (▶ **Table 7**). An ascending infection with chorioamnionitis, preterm placental abruption, pathological CTG, or umbilical cord prolapse are indications for immediate delivery of the fetus. Otherwise expectant management is currently the international standard of care [129].

▶ **Table 7** Planned delivery vs. expectant management of PPROM between the 24th and the 37th week of gestation.

Planned delivery vs. expectant management	RR	95% CI
Neonatal sepsis	0.93	0.66–1.30
Neonatal infection (positive blood culture)	1.24	0.70–2.21
RDS	1.26	1.05–1.53
Cesarean section	1.26	1.11–1.44
Perinatal mortality	1.76	0.89–3.50
Intrauterine fetal death	0.45	0.13–1.57
Neonatal mortality	2.55	1.17–5.56
Mechanical ventilation required	1.27	1.02–1.58
Transfer to neonatal intensive care unit	1.16	1.08–1.24
Chorioamnionitis	0.50	0.26–0.95
Endomyometritis	1.61	1.00–2.59
Induction of labor	2.18	2.01–2.36

[130]

8.9.2 Administration of antenatal steroids

Consensus-based Recommendation 8.E59	
Expert consensus	**Strength of consensus +++**
Patients with PPROM between GW 24 + 0 and GW 33 + 6 or between GW 22 and GW 23 + 6, if maximum therapy is requested, must be given antenatal steroids consisting of 2 × 12 mg betamethasone administered IM at an interval of 24 h (alternatively dexamethasone, 4 × 6 mg every 12 h).	

8.9.3 Administration of antibiotics

Consensus-based Recommendation 8.E60	
Expert consensus	**Strength of consensus ++**
Patients with PPROM between GW 24 + 0 and GW 33 + 6 or between GW 22 and GW 23 + 6, if maximum therapy is requested, must be given antibiotic therapy.	
[131]	

Consensus-based Recommendation 8.E61	
Expert consensus	**Strength of consensus +++**
The data are not sufficient to permit any recommendations to be made about specific therapy regimens. One option is IV administration of ampicillin over 2 days followed by 5 days of oral amoxicillin and a single oral dose of azithromycin at the start. Amoxicillin must not be combined with clavulanic acid.	
[108, 129, 131]	

8.9.4 Tocolysis

Consensus-based Statement 8.S37	
Expert consensus	**Strength of consensus +++**
Tocolysis is not associated with any significant improvement in perinatal morbidity and mortality rates in cases with PPROM.	
[132]	

8.9.5 Neuroprotection

See 6.8.1.

8.9.6 Maternal and fetal monitoring

Consensus-based Recommendation 8.E62	
Expert consensus	**Strength of consensus +++**
Patients with PPROM must be carefully monitored for Triple I. Clinical signs include maternal fever plus one of the following: fetal tachycardia (> 160 beats/min) or leukocytes > 15 000/µl or purulent discharge from the cervix.	

Pregnant women with preterm premature rupture of membranes should be routinely examined for signs of infection. In addition to the above-mentioned clinical parameters, such signs also include symptoms such as painful uterus, uterine contractions, maternal blood pressure and heart rate [116]. Blood count and CRP must additionally be monitored at least once a day. However, the benefit of daily laboratory tests is disputed [133]. Kunze et al. reported an AUC of just 0.66 for a combination of maternal fever, CRP and leukocytes to predict FIRS [134]. Musilova et al. reported a sensitivity of 47%, specificity of 96%, positive predictive value of 42% and negative predictive value of 96% for a CRP value of 17.5 mg/l in maternal serum to predict intraamniotic infection or inflammation [135].

Daily CTG monitoring of patients with PPROM is standard clinical practice. But currently there is no fetal monitoring method which can reliably detect intrauterine inflammation or infection. Neither CTG nor the use of a biophysical profile (CTG plus fetal breathing movements and other fetal movements, fetal tone and amniotic fluid volume assessment) are suitable predictors for intrauterine infection (CTG: sensitivity 39%; biophysical profile: 25%) [115].

Regular monitoring of amniotic fluid volumes is similarly of little benefit. While a reduction in amniotic fluid volume increases

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the risk of umbilical cord compression and demonstrably reduces the time to the start of labor, its predictive value for a negative outcome is low [136]. The use of Doppler sonography has no proven benefits for premature rupture of membranes [137].

Consensus-based Statement 8.S38	
Expert consensus	**Strength of consensus ++**
The use of amniocentesis to diagnose Triple I is only useful in exceptional cases, e.g. when the source of maternal infection is not clear.	
[138]	

Consensus-based Statement 8.S39	
Expert consensus	**Strength of consensus +++**
The prediction of Triple I based on biochemical parameters measured in vaginal secretions is not useful according to current knowledge.	
[134, 139]	

8.9.7 Amniotic infusion

Consensus-based Statement 8.S40	
Expert consensus	**Strength of consensus +++**
The value of amniotic infusion in cases of PPROM cannot be sufficiently evaluated based on the data currently available.	
[140]	

8.9.8 Antibiotic prophylaxis for Group B streptococcus

See the recommendations on GBS prophylaxis.

8.9.9 Delivery

Consensus-based Recommendation 8.E63	
Expert consensus	**Strength of consensus +++**
Patients with PPROM between GW 24 + 0 and GW 33 + 6 or between GW 22 and GW 23 + 6, if maximum therapy is requested, can be delivered from GW 34 + 0 onwards. Indications for immediate delivery are Triple I (suspicion of Triple I or confirmed), premature placental abruption, pathological CTG or high risk, or umbilical cord prolapse.	
[129, 130]	

Consensus-based Recommendation 8.E64	
Expert consensus	**Strength of consensus +++**
Patients with Triple I (suspicion or confirmed) must be given antibiotics and their infant must be delivered.	

8.10 Clinical Management of PPROM between GW 34 + 0 and GW 36 + 6

Consensus-based Recommendation 6.E65	
Expert consensus	**Strength of consensus +++**
If preterm premature rupture of membranes occurs between GW 34 + 0 and GW 36 + 6, expectant management may be considered as an alternative to prompt delivery, with the aim of prolonging the pregnancy until GW 37 + 0. This does not apply if Group B streptococcus is detected in vaginal secretions.	

A total of 1839 women between GW 34 + 0 and GW 36 + 6 who had preterm premature rupture of membranes (PPROM) were recruited into the PPROMT trial between 2004 and 2013 [141]. Immediate induction of labor was compared with expectant management. In the study group, 21 % of infants were born after the 37th week of gestation to women managed expectantly compared to only 3 % in the control group. The prevalence of neonatal sepsis was the same for both groups, however respiratory distress syndrome (RDS) occurred significantly less often after expectant management. In this group, the birthweight of the children was also significantly higher and the stay in the neonatal intensive care unit or in hospital was shorter. However, as expected, uterine bleeding before or during birth occurred more often in the mothers of these children as did peripartum fever. The c-section rate was significantly lower compared to the group who had induction of labor [141].

The results of the PPROMT trial were supported by the findings of the PPROMEXIL and PPROMEXIL-2 trials [142, 143]. But if Group B streptococcus colonization was diagnosed, the prevalence of early onset sepsis was significantly higher among affected neonates (15.2 vs. 1.8 %; p = 0.04) [144].

According to a meta-analysis of this issue which included 12 studies, expectant management was still not found to be associated with an increased prevalence of neonatal sepsis. Following immediate induction of labor, the rates for RDS, neonatal mortality, required ventilation, endomyometritis and cesarean section were significantly higher while the incidence of chorioamnionitis was lower [130]. A patient-level meta-analysis came to similar conclusions [145].

Consensus-based Recommendation 8.E66	
Expert consensus	**Strength of consensus +++**
Clinical monitoring and antibiotic therapy in cases with PPROM between GW 34 + 0 and GW 36 + 6 must follow the recommendations for (GW 22 + 0) GW 24 + 0 – GW 33 + 6. Antenatal steroids, tocolysis or neuroprotection with magnesium must not be administered.	

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9 Psychosomatic Care and Supportive Therapy

Consensus-based Recommendation 9.E67	
Expert consensus	**Strength of consensus ++**
Pregnant women admitted to hospital for premature labor and women who had a preterm birth should be offered psychosomatic care and supportive therapy.	

In addition to worries about the health consequences of a preterm birth (which are difficult to estimate), therapeutic measures, which can include immobilization, medication to stop contractions and the administration of corticosteroids, may be experienced as stressful. If there are additional stresses (a previous experience of loss, prior mental health problems, partnership difficulties, etc.), then the incidence of anxiety and depression is higher [146 – 148]. Particularly for large families, admission of the mother to hospital represents substantial organizational pressures for the family.

There are a number of psychometric tests which are used to detect psychological and social stress factors, such as HADS, the Babylotse Plus screening questionnaires, etc. [149].

Affected couples should be offered acute psychological crisis intervention, followed by offers of supportive talks and psychotherapy where necessary. This also supports parent-child bonding.

The support offered by self-help groups such as the German federal association “Das Frühgeborene Kind” [The Preterm Infant] [150] can help affected parents, and parents should be informed about such options.

Affected families should be actively offered options in the context of the Frühe Hilfe network. This is a German network that creates local and regional support systems offering coordinated services to parents and children, which aims to improve familial and social development opportunities for children and parents, both in the early stages and over the long term [151].

The “Babylotse” program, which arranges the transfer of families from the regular healthcare system to the Frühe Hilfe network and other social care systems has proven to be particularly useful. The core aspect of this program is the role it plays in guiding parents to find and use the most suitable options from among the numerous local choices available.

All of these measures are services which provide compassionate support to the patient and her family and which are offered in addition to the care provided by the attending midwife.

Conflict of Interest

The conflict of interest statements of all the authors are available in the long version of the guideline.

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