

Antibiotic Therapy for Premature Rupture of Membranes and Preterm Labor and Effect on Fetal Outcome

Antiinfektiöse Therapie bei vorzeitigem Blasensprung und Wehentätigkeit und Fetal Outcome

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- ◉ impending preterm birth
- ◉ premature uterine contractions
- ◉ antibiotics for impending preterm birth

Schlüsselwörter

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- ◉ drohende Frühgeburt
- ◉ vorzeitige Wehen
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Abstract

In Germany almost 10% of children are born before the end of 37th week of gestation. In at least one quarter of these cases, ascending infection of the vagina plays a causative role, particularly during the early weeks of gestation. If, in addition to the decidua, the amniotic membrane, amniotic fluid and the umbilical cord are also affected, infection not only triggers uterine contractions and premature rupture of membranes but also initiates a systemic inflammatory reaction on the part of the fetus, which can increase neonatal morbidity. Numerous studies and meta-analyses have found that antibiotic therapy prolongs pregnancy and reduces neonatal morbidity. No general benefit of antibiotic treatment was found for premature uterine contractions. But it is conceivable that a subgroup of pregnant women would benefit from antibiotic treatment. It is important to identify this subgroup of women and offer them targeted treatment. This overview summarizes the current body of evidence on antibiotic treatment for impending preterm birth and the effect on neonatal outcomes.

Introduction

According to Goldenberg et al. [1], the rate of premature births in Europe is between 5 and 7%. With almost 500 000 premature births annually, the rate in the United States is 12–13%, almost twice that of Europe. In Germany, the rate of premature births is approximately 9%, making Germany one of the European countries with the highest rates of neonates delivered at less than 37 weeks' gestational age [2]. Between 2001 and

Zusammenfassung

In Deutschland kommen fast 10% aller Kinder vor Vollendung der 37. Schwangerschaftswoche zur Welt. In mindestens einem Viertel davon spielt eine aufsteigende Infektion aus der Vagina eine kausale Rolle, insbesondere in einem niedrigen Gestationsalter. Sind neben der Dezipua die Eihäute, das Fruchtwasser und die Nabelschnur davon betroffen, werden durch entzündliche Prozesse nicht nur Wehen oder ein vorzeitiger Blasensprung ausgelöst, sondern auch eine systemische inflammatorische Reaktion des Fetus selbst in Gang gesetzt, welche die neonatale Morbidität negativ beeinflussen kann. Als Therapiemaßnahme bei vorzeitigem Blasensprung hat sich in zahlreichen Studien und Metaanalysen eine antibiotische Behandlung bewährt, indem die Schwangerschaft prolongiert und die neonatale Morbidität reduziert werden konnte. Bei vorzeitiger Wehentätigkeit hat sich dagegen ein Benefit generell nicht nachweisen lassen. Es ist aber anzunehmen, dass es eine Subgruppe von Schwangeren gibt, die dennoch davon profitieren könnte. Es gilt diese zu identifizieren und gezielt zu behandeln. Die vorliegende Übersicht umreißt die derzeitige Evidenzlage zur antibiotischen Behandlung bei drohender Frühgeburt und zum neonatalen Outcome.

2010, the rates of extremely premature babies (delivered before the 28th week of gestation [GW]) and preterm neonates (born between the 28th and 32nd GW) increased most (<28 GW: from 0.35% to 0.6%; 28–32 GW: from 0.7% to 1%). Around one third of premature deliveries are due to premature rupture of membranes, approximately 45% to premature uterine contractions and the rest to delivery for maternal or fetal indication, e.g. pre-eclampsia or fetal growth restriction.

Role of Intrauterine Infection

It is currently assumed that at least every fourth preterm birth is caused by intrauterine infection [3], which develops most commonly through ascension from the vagina or, rarely, via hematogenous routes or per continuitatem (from another focus). Amniocentesis after premature rupture of membranes results in bacterial contamination of amniotic fluid in 30–50% of cases [4]. Decreasing rates of bacterial colonization ranging from 79% in the 23rd week of gestation (GW) to 43% in the 27th GW were found in preterm placentas [5].

Infection and inflammation resulting from bacterial ascension to fetomaternal membranes triggers prostaglandin synthesis through elevation of local proinflammatory cytokines and can lead to maternal uterine contractions, a process that also plays a key role in term births. Inflammation of the amnion and chorion is referred to as chorioamnionitis. It is present as a complication in 1–4% of births; the prevalence of chorioamnionitis is 20–70% in all preterm births, decreasing to 1–13% in births at term. While half of all preterm births with a gestational age of 23–24 weeks are associated with chorioamnionitis, it is only present in 5% of births delivered at a gestational age of more than 37 weeks [6]. Chorioamnionitis is associated with complications in the postnatal period, particularly when diagnosis is based on clinical symptoms (maternal fever $> 38^{\circ}\text{C}$ + leukocytosis and/or maternal/fetal tachycardia, uterine tenderness, fetid amniotic fluid) and not only on histological examination of inflammatory changes, e.g. confirmation of infiltration of polymorphonuclear leukocytes and other immune cells such as macrophages and T-cells. Neonatal intraventricular bleeding (IVH), white brain matter injury, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and sepsis have all been associated with histological chorioamnionitis [7–22].

Meta-analyses of clinical case-control and cohort studies have indicated that long-term effects include an increased risk of cerebral palsy [23], with clinical and histological chorioamnionitis associated with periventricular cystic leukomalacia (PVL) [24]. The ELGAN study of 1200 preterm babies born before the 28th week of gestation published in 2010 showed that both histological chorioamnionitis and the detection of microorganisms in the placenta were predictive for ventriculomegaly on neonatal cranial ultrasound and for diparetic cerebral palsy at follow-up after 2 years [25]. However, a recent Canadian study [26] reported that clinical and histological chorioamnionitis were not predictive of neonatal mortality, periventricular leukomalacia or cerebral palsy. Sepsis, bronchopulmonary dysplasia, severe intracranial hemorrhage and retinopathy of prematurity could not be predicted based on the presence or absence of chorioamnionitis.

Evidence would appear to indicate the importance of fetal involvement in the inflammatory process as a pre-condition for neonatal morbidity.

Fetal infection through the umbilical cord or the amniotic fluid triggers an inflammatory immune response (FIRS = fetal inflammatory response syndrome), which is reflected in higher concentrations of interleukin-6 and other proinflammatory cytokines such as $\text{IL}\beta$ and $\text{TNF}\alpha$ as well as higher CRP levels and increased leukocyte counts in cord blood [27]. The histological correlates are funisitis and chorial vasculitis.

FIRS is associated with higher neonatal morbidity which can take the form of RDS (respiratory distress syndrome), sepsis, IVH, PVL or NEC [28]. According to a Dutch study of 301 preterm neonates born before 32 weeks of gestation, fetal inflammation (i.e. histo-

pathological confirmation of chorial vasculitis, umbilical phlebitis or vasculitis, necrotizing funisitis or concentric umbilical perivasculitis) associated with histologically diagnosed chorioamnionitis had a significant impact on the prevalence of NEC (9 vs. 2%; $p < 0.05$), IVH (25 vs. 12%; $p < 0.05$) and neonatal mortality (19 vs. 9%; $p < 0.05$) compared to fetuses without fetal inflammation [29]. A close association between high cytokine levels in amniotic fluid [21,30] and cord blood [31,32] and subsequent cerebral palsy has been reported in several studies.

In a report in the New England Journal published in 2000, Goldenberg et al. [33] provided a comprehensive summary describing ascending infection as a trigger for preterm births and fetal infection. Their representation of bacterial dissemination across fetomaternal membranes has been used ever since to illustrate the pathways of ascending infection.

Numerous unspecific gram-negative and gram-positive microorganisms such as *Bacteroides*, *Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, *Propionibacterium*, *Pseudomonas*, *Staphylococcus* and *Streptococcus* and specific organisms from the urogenital tract such as *E. coli*, *Enterobacter*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, Group B *Streptococcus* (GBS), *Ureaplasma*, *Mycoplasma hominis*, and *Neisseria gonorrhoeae* have been identified [4].

In an analysis of placental samples from extremely preterm births between the 23rd and 27th GW, positive bacteria cultures were found in 68% of vaginal births and 41% of cesarean sections; of these, 30% of samples had only aerobic bacteria, 21% had only anaerobic bacteria and 9% of the culture-positive samples had only *Ureaplasma/Mycoplasma* [34].

Interest in *Ureaplasma urealyticum* and *Mycoplasma hominis* has increased since the 1990s, as they are the most common organisms detected in the amniotic fluid of women with premature rupture of membranes, premature uterine contractions and cervical insufficiency [35–40]. *U. urealyticum* or *M. hominis* was detected in cordal blood of 9/84 preterm neonates; funisitis was identified in all of these 9 but only in 13% of neonates without *U. urealyticum* or *M. hominis* ($p < 0.001$) [41]. Based on the leukocyte count in amniotic fluid, the maternal leukocyte count and CRP, intraamniotic infection with genital *Mycoplasma* organisms appears to trigger a more intense inflammatory reaction compared to other bacteria [42].

In 351 preterm infants born between the 23rd and 32nd GW, the Alabama Preterm Birth Study identified *U. urealyticum* or *M. hominis* in 23% samples cultured from umbilical cord blood; this figure increased to 34.7% for spontaneous preterm deliveries compared to only 3.2% in indicated preterm deliveries [43].

Infants with cord blood cultures positive for *U. urealyticum* or *M. hominis* had significantly higher rates of neonatal systemic inflammatory response syndrome (41.3 vs. 25.7%; $p = 0.007$) and bronchopulmonary dysplasia (26.8 vs. 10.1%; $p = 0.0001$) compared to infants with negative blood cultures. Neonatal mortality, rates of intraventricular hemorrhage grade 3 and 4, RDS, PVL and NEC did not differ significantly.

In a recent analysis of 126 women with premature uterine contractions, *U. urealyticum* was identified in 62.7% and *M. hominis* in 12.7% of vaginal swab specimens. In women who had preterm deliveries, vaginal swab specimens were positive for *M. hominis* in 17.3% and positive for *Ureaplasma* in 60.9% of cases. However in women without premature delivery, specimens were positive for *M. hominis* in only 3.7% but positive for *Ureaplasma* in 53.8% of cases [44]. Thus the significance of these

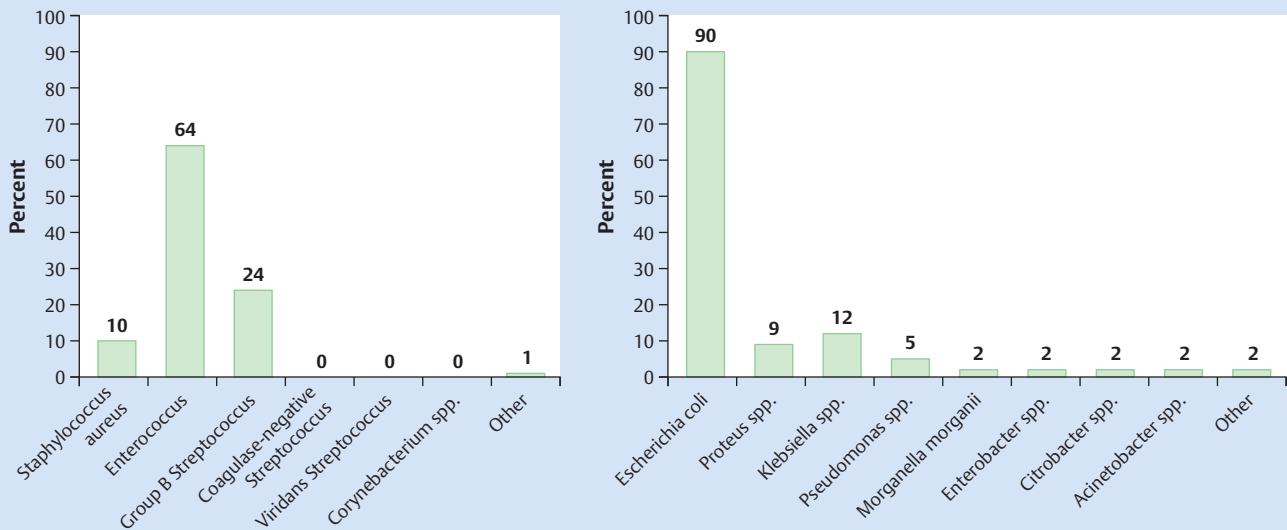


Fig. 1 Percentages for different gram-positive and gram-negative bacteria in vaginal swab cultures obtained from pregnant women with impending

preterm birth examined at the University Clinic for Obstetrics and Gynecology St. Hedwig, Regensburg.

bacteria as a cause of preterm birth must be qualified. The intra-vaginal presence of *Mycoplasma* species and *U. urealyticum* alone is therefore not sufficient to induce premature birth [45]. Despite the assumed association between *Mycoplasma* and preterm birth, a randomized American multicenter study showed quite early on that targeted antibiotic therapy with erythromycin vs. placebo in 1181 women with *U. urealyticum* detected in cultured vaginal specimens offered no benefits with regard to gestational age at delivery, birth weight, Apgar scores and neonatal mortality. Maternal side-effects, nausea and diarrhea occurred significantly more often in the erythromycin-treated group [46]. The Cochrane Review of 2011 came to the conclusion that the current body of evidence does not support antibiotic therapy to prevent preterm birth in pregnant women with vaginal *Ureaplasma* colonization [47].

Using specially designed DNA probes, organisms were detected in 70% of amnion or chorion of infants delivered at term by cesarean section [48]. This indicates that the presence of bacteria alone may not always be sufficient to trigger maternal or fetal inflammation [27].

In our own patient cohort of women with impending preterm birth, the most common gram-positive organisms identified in vaginal swabs were Enterococci with a prevalence of 64%, followed by Streptococci B with prevalence of 24%. *E. coli* was the most commonly found gram-negative species with a prevalence of 90% (● Fig. 1). *Mycoplasma* were rarely detected.

The association between intrauterine infection and premature rupture of membranes, premature uterine contractions and neonatal morbidity is the rationale for initiating antibiotic therapy when preterm birth is impending.

The goal of treatment is

1. to prolong the pregnancy to reduce neonatal mortality and morbidity associated with lower gestational age,
2. to prevent infection and inflammation-related neonatal morbidity as a result of (sub)clinical infection of the fetus, and
3. last but not least, to protect the mother from uterine or pelvic infection.

Antibiotics and Premature Rupture of Membranes

▼ In the last three decades, more than two dozen studies have investigated the efficacy of antibiotic therapy after premature rupture of membranes, and the question has been discussed in structural reviews and meta-analyses since 20 years [4]. The most recent review was published in 2010 and included 22 studies with 6800 women and their infants [49]. The studies included in the review investigated the impact of different antibiotic regimens (penicillins, β -lactam antibiotics including amoxicillin/clavulanic acid and macrolide antibiotics) administered in different forms and over varying periods in women with premature rupture of membranes between week 20 and week 37; some studies also included multiple pregnancies. The studies also differed with regard to the use of tocolysis and RDS prophylaxis. An overall comparison of all antibiotics used in the studies showed a significantly lower risk for chorioamnionitis compared to placebo (RR 0.66; 95% CI: 0.46–0.96), a lower risk of delivery within 48 h and 7 days (RR 0.71; 95% CI: 0.58–0.8 and 0.79; 95% CI: 0.71–0.89, respectively). Neonatal morbidity was also significantly lower in the group which received antibiotic therapy; administration of antibiotics was associated with a reduced risk of neonatal infection (RR 0.67; 95% CI: 0.52–0.85), lower surfactant use and lower rates of oxygen therapy (RR 0.083; 95% CI: 0.72–0.96 and RR 0.88; 95% CI: 0.81–0.96) and lower rates of abnormal cranial ultrasound at discharge (RR 0.81; 95% CI: 0.68–0.98). However, a sub-analysis showed that the administration of amoxicillin/clavulanic acid was associated with a more than fourfold higher risk of neonatal necrotizing enterocolitis (NEC) (RR 4.72; 95% CI: 1.57–14.23).

The Cochrane Systematic Reviews have been dominated since 2002 by the British Oracle I Trial [50], which investigated a total of 4826 women and had by far the greatest impact on the results of the meta-analyses, followed by the 1997 study by Mercer et al. [51] with 614 randomized pregnant women.

The Oracle I Trial was carried out between 1994 and 2000 in 161 participating centers located predominantly in the UK. Pregnant

Table 1 Comparison of the most significant results of the ORACLE I and II Trials.

	Oracle I (n = 4826)				Oracle II (n = 6295)			
	Erythro- myin 1 190	Co- amoxi- clav 1 205	Erythromycin + co-amoxi- clav 1 189	Placebo 1 225	Erythro- myin 1 600	Co- amoxi- clav 1 534	Erythromycin + co-amoxi- clav 1 551	Placebo 1 556
Delivery								
E < 48 h (%)	34.9	30.5	31.3	40.7	10.4	9.9	10.7	9.8
E < 7 d (%)	60.9	51.7	54.4	63.3	15.8	15.4	15.1	15.2
Maternal antibiotic regimen (%)	24.6	25.7	24.6	26.9	9.8	9.2	8.8	11.8
Gestational age at delivery (d)	236	236	237	236	267	267	267	266
Birth weight (g)	2 102	2 083	2 123	2 072	2 823	2 842	2 851	2 857
Early morbidity								
RDS (%)	19.8	20.0	20.4	21.7	8.3	8.3	9.0	8.9
Oxygen therapy (> 21% O ₂) (%)	31.1	30.1	31.1	35.6	13.6	13.2	13.5	13.3
Use of surfactant (%)	14.8	15.1	14.1	17.7	5.6	5.3	5.8	5.7
Positive blood culture (%)	5.7	6.8	7.0	8.2	2.1	1.8	2.2	2.0
NEC (%)	0.9	1.9	1.7	0.5	0.4	0.6	0.7	0.3
Total morbidity (%)	12.7	13.5	14.0	15.2	5.6	5.0	5.9	5.0
Abnormal cerebral ultrasound (%)	4.2	3.8	3.9	5.0	1.6	1.8	2.2	1.9
Mortality (%)	5.9	6.6	6.5	6.7	2.7	2.5	3.0	2.5

Co-amoxiclav = amoxicillin/clavulanic acid. Figures in **Bold** indicate significant differences.

Table 2 The most important results of a meta-analysis of 7 randomized controlled trials (RCTs) with i. v. antibiotics administered to women with premature rupture of membranes fewer GW 34 (Mercer 2012): pregnancy outcomes.

Pregnancy outcome	i. v. Antibiosis n = 527	Control n = 537	Significance
Prolongation of pregnancy ≥ 7 d	46.0%	25.9%	p < 0.00001
Amnionitis	20.5%	31.3%	p < 0.0001
Cesarean section	27.5%	28.5%	p = 0.63
Endometritis postpartum	10.5%	13.0%	p = 0.21

Based on Mercer 2012: Antibiotics in the management of PROM [4]

women with premature rupture of membranes were randomized into groups to receive either erythromycin 4×/day orally or amoxicillin/clavulanic acid 325 mg 4×/day orally or erythromycin 250 mg + amoxicillin/clavulanic acid 325 mg, 4×/day orally or placebo 4×/day orally for 10 days or until delivery. Administration of all three antibiotic regimens was associated with a significantly lower rate of deliveries within 48 hours compared to placebo; the administration of amoxicillin/clavulanic acid alone and in combination with erythromycin was additionally associated with a significantly lower rate of deliveries within 7 days. Mean age of gestation and neonatal birth weight were approximately similar for all groups; the prevalence of respiratory distress syndrome, total morbidity and neonatal mortality did not differ significantly between groups. Antibiotic therapy significantly reduced the rates of infants dependent on oxygen, irrespective of the regimen. A significant reduction in positive neonatal blood cultures was only found after administration of erythromycin. A fourfold higher rate of NEC was found in both groups treated with amoxicillin/clavulanic acid (● **Table 1**).

Because of heterogeneity of previous reviews, in his meta-analysis published in 2012 Mercer [4] only analyzed studies which had exclusively recruited women with premature rupture of mem-

branes before GW 34 and which compared broad spectrum antibiotics administered i. v. with controls or placebo [51–57]. With the exception of the study by Mercer et al. in 1997 [51] with 299 and 312 pregnant women, the other studies had only limited case numbers with fewer than 50 patients in the study or control group. The Oracle I Trial was excluded because administration was exclusively oral.

Meta-analysis of the 7 studies showed a higher rate of pregnancy prolongation by more than 7 days (46.0 vs. 25.9% [RR 1.8; 95% CI: 1.52–2.13]) in the group treated with antibiotics, fewer clinical cases of amnionitis (20.5 vs. 31.3%; RR 0.67; 95% CI: 0.67 [0.54–0.87]), but no changes in the rates of cesarean sections (27.5 vs. 28.5%) or endometritis postpartum (● **Table 2**).

In addition, they found a significant positive effect on neonatal morbidity. Significantly lower rates of sepsis, RDS and IVH were recorded for infants born to mothers treated with broad-spectrum i. v. antibiotics.

Although the prevalence of pneumonia was also half that of the control group, this difference did not reach statistical significance. Rates of NEC, intrauterine fetal death (IUFD) and total survival till discharge were approximately the same for both groups (● **Table 3**).

Table 3 The most important results of a meta-analysis of 7 randomized controlled trials (RCTs) with antibiotics administered i.v. to women with premature rupture of membranes before GW 34 (Mercer 2012): neonatal morbidity.

Neonatal morbidity	i. v. Antibiosis group n = 527	Controls n = 537	Significance
Sepsis	10.9%	16.8%	p = 0.01
Respiratory distress syndrome (RDS)	37.9%	46.2%	p = 0.002
Intraventricular bleeding (IVH)	12.9%	17.8%	p = 0.02
Pneumonia	3.6%	6.3%	p = 0.09
Necrotizing enterocolitis (NEC)	8.2%	6.9%	p = 0.45
Intrauterine fetal death (IUFD)	0.9%	2.7%	p = 0.2
Survival rate	93.7%	92.4%	p = 0.37

It is still not clear how long antibiotics should be administered. Mercer et al. [51] preferred the administration of amoxicillin 2 g + erythromycin 250 mg every 6 hours for two days. Subsequently, the pregnant women additionally received 250 mg ampicillin + erythromycin 333 mg orally every 8 hours for 5 days. This regimen was used in a randomized double-blind study undertaken in 11 centers which recruited 614 patients with premature rupture of membranes between GW 24 and GW 32; with this regimen, pregnancy was significantly prolonged compared to placebo (placebo: 2.9 days, antibiotics 6.1 days; $p < 0.001$) and the number of births within 48 hours reduced from 36.6 to 27.3% ($p < 0.03$); the number of births within 7 days also dropped from 73.5 to 55.5% ($p < 0.001$). The number of women who did not give birth within 14 days increased from 12.1% without administration of antibiotics to 24.4% with administration of antibiotics, and the number of women who did not give birth within 21 days increased from 7 to 14.3%.

Total neonatal morbidity was significantly lower, with 44.1% compared to 52.9% ($p = 0.04$). The same applied to rates for sepsis (8.4 vs. 15.6%; $p = 0.01$), RDS (40.5 vs. 48.7%; $p = 0.04$), BPD (13.0 vs. 20.5%; $p = 0.01$), pneumonia (2.9 vs. 7%; $p = 0.04$) and NEC levels 2 and 3 (2.3 vs. 5.8%; $p = 0.03$). It should also be noted that in this study 116 women who tested positive for Group B Streptococcus infection received 500 mg ampicillin orally for one week and ampicillin i.v. 2 g every 6 hours intrapartum in addition to the above regimen which was administered after randomization. No significant benefit was found for additional administration of ampicillin.

Shorter administration times for antibiotics were trialed in two smaller studies of women with premature rupture of membranes. The first study with 84 pregnant women compared 3-day i.v. administration of ampicillin/sulbactam 3 g every 6 hours with 7-day administration. No statistical differences were found with regard to duration of pregnancy prolongation (mean for 3-day treatment: 137 hours vs. mean for 7-day treatment: 146 hours) or rates of neonatal mortality and morbidity as measured by rates of transfer to the neonatal intensive care unit, RDS, NEC, and IVH level 3 and 4 [58]. The second study with only 48 patients compared 1-day treatment with 5-day treatment consisting of oral ampicillin 500 mg every 6 hours, after prior 2-day i.v. administration of ampicillin 2 g, 4×/day. Here too, no significant differences were found in duration of pregnancy prolongation (8 vs. 8.5 days), prevalence of endometritis and chorioamnionitis and neonatal mortality and morbidity rates [59].

The Canadian Guideline [60] recommends penicillins or macrolide antibiotics as the antibiotic of choice, administered intravenously, orally or in combination: either ampicillin 2 g + erythromycin 250 mg every 6 hours for two days i.v., followed by amoxicil-

lin 250 mg + 333 mg erythromycin orally every 6 hours for 5 days or erythromycin 250 mg orally every 6 hours for 10 days.

The German AWMF Guideline 015/029 [61] recommends mezlocillin, piperacillin, clindamycin, ampicillin and erythromycin as suitable antibiotics to treat women with premature rupture of membranes. The Guideline offers no recommendations with regard to the duration of antibiotic treatment. The Guideline is currently being revised.

Antibiotics and Preterm Uterine Contractions

The clear benefits of antibiotic therapy to treat women with premature rupture of membranes were not mirrored in the existing studies and meta-analyses of women with preterm uterine contractions without rupture of membranes. A few smaller studies from the late 1980s and 1990s reported a significant prolongation of pregnancy after administration of antibiotics to women with preterm uterine contractions [62–67] and a reduction in the number of infants born within 7 days. The prospective randomized placebo-controlled double-blind study of McGregor et al. published in 1986 [62] found a significant prolongation of pregnancy (32.5 vs. 22.4 days; $p = 0.027$) in 58 pregnant women with preterm uterine contractions before GW 34 after administration of erythromycin 333 mg orally 3×/day for 7 days. The same study group also reported a mean prolongation of pregnancy (35 vs. 25 days; $p = 0.02$) in 117 randomized pregnant women compared to placebo after administration of clindamycin for 3 days i.v. followed by 4 days' oral administration [63]. Moreover, in a subgroup of women positive for bacterial vaginosis, the gestational age at delivery (35 vs. 34 GW) and the birth weight of the infants were higher (2634 vs. 2256 g) in the clindamycin group.

A study in Florida randomized 150 women with cervical dilation of 1 cm or more and preterm uterine contractions into one of three groups to receive either 500 mg ampicillin orally 4×/day, 500 mg erythromycin orally 4×/day or placebo for 10 days. Morales et al. reported a significant delay between admission and delivery after administration of antibiotics (antibiosis: 30 days vs. placebo: 17 days) [64].

In a South African multicenter study [65] 43 patients with preterm uterine contractions between GW 26 and GW 34 were given 1 g ampicillin i.v. + 1 g metronidazole as a suppository every 6 hours for 1 day, followed by 3×500 mg amoxicillin per day + 3×400 mg metronidazole per day orally for 5 days. 38 women in the control group received placebo [65].

All women received the tocolytics hexoprenaline and indomethacin together with betamethasone for fetal lung maturation for 24 hours. In patients receiving antibiotics, the pregnancy was sig-

nificantly prolonged (mean: 15 days vs. 2.5 days, $p=0.04$), and significantly more women were still pregnant at 7 days after admission (63 vs. 37%; $p=0.04$; OR 0.34; 95% CI: 0.13–0.94). Total infant morbidity (hyaline membrane disease, pneumonia, septicemia, PDA [persistent ductus arteriosus] and NEC) was lower in the group receiving antibiotics (24 vs. 39%) compared to the placebo group, but the difference was not statistically significant. Five infants in the placebo group and none in the antibiotics group developed NEC ($p=0.02$).

In a Baltic-Scandinavian randomized controlled trial, 59 and 52 pregnant women with preterm uterine contractions between GW 22 and GW 34 were randomized either into an antibiotics group to receive 1 g ampicillin every 8 hours for 7 days or a placebo group. The mean gestational age at birth in the group receiving antibiotics was significantly higher (36.6 weeks) compared to the placebo group (33.8 weeks; $p<0.05$), and the mean birth weight was also significantly higher (2885 vs. 2336 g; $p<0.05$). Neonatal infections, intrauterine growth retardation, histological chorioamnionitis and puerperal endometritis-myometritis occurred significantly less frequently in the ampicillin-treated group [66].

In a Danish multicenter trial [67], 112 pregnant women with preterm uterine contractions between GW 26 and GW 34 were randomized either into a group treated with 2 g ampicillin i.v. 4× daily and 500 mg metronidazole 3×/day for 24 hours, followed by 500 mg pivampicillin and 400 mg metronidazole for 7 days or into a placebo group. Treatment with antibiotics was associated with a significant prolongation of pregnancy (mean: 47.5 vs. 27 days; $p<0.05$), a higher gestational age at delivery (37 vs. 34 weeks; $p<0.05$) and a lower rate of infants admitted to the neonatal intensive care unit (40 vs. 63%; $p=0.03$). No statistically significant differences were found in neonatal mortality (no deaths in either group) or morbidity with regard to meningitis, sepsis and pneumonia (10 vs. 22%).

In the years that followed, with the exception of a Chilean randomized controlled trial [68], no study on antibiotic treatment for preterm uterine contractions found a significant benefit with regard to prolonged pregnancy and neonatal outcomes, neither with β -lactam antibiotics, macrolide antibiotics or cephalosporins nor combinations of these drugs [69–74]. Since 2002, meta-analyses have been numerically dominated by the ORACLE II Trial [74]. In analogy to the ORACLE I Trial, 6295 pregnant women with preterm uterine contractions before GW 37 but without rupture of membranes were randomized into 4 groups and received either erythromycin 250 mg 4× daily or 325 mg amoxicillin/clavulanic acid 4×/day or 250 mg erythromycin + 325 mg amoxicillin/clavulanic acid 4×/day or placebo 4×/day for 10 days. With the exception of lower rates of maternal infection and a significantly higher rate of NEC in the erythromycin + amoxicillin/clavulanic acid group, no significant differences were found between groups (Table 1). The most recent update of the Cochrane Systematic Review of 2011 analyzed 11 studies based on 7428 datasets and reported no important new volume of information obtained compared to the meta-analysis of 2002 [75]. In this latest meta-analysis, the ORACLE II Trial dominated as it contributed 6 times as many patients as all other randomized controlled studies combined. In consequence, the authors drew the conclusion that with the exception of reducing maternal infection (RR 0.74; 95% CI: 0.64–0.87) no benefit could be demonstrated from prophylactic antibiotic treatment for preterm labor without rupture of membranes. However, the large ORACLE II Trial does give some cause for criticism for the following reasons:

there is some doubt whether the investigated cohort was even suitable to detect differences between differing forms of treatment.

1. The inclusion of pregnant women in the study depended on the subjective assessment of obstetrician whether uterine contractions were actually preterm labor.
2. On admission, more than half of all women in all randomized groups had cervical dilation of 1 cm or less. This could be an indication that uterine contractions with cervical dilation were not present and not likely to result in spontaneous birth.
3. Analyses of vaginal swabs and inflammatory parameters were either not carried out or not included in the Oracle II Trial.
4. The mean gestational age at delivery in all groups was around 266 days, i.e. GW 38, a gestational age at which the investigated neonatal morbidities normally only rarely occur.

It is therefore understandable that the Cochrane team limited the core statement of the trial, suggesting that there might be a subgroup of women who would benefit from antibiotic therapy due to the presence of latent infection. The assumption is supported by a study by Ovalle et al. published in 2006 [76], which reported a significantly lower total neonatal morbidity for the group treated with antibiotics compared to the placebo group in a subgroup analysis of women with preterm labor and endocervical inflammation (4% [1/24] vs. 28% [7/25]; $p<0.05$).

Identifying those women with preterm uterine contractions who have a high risk of preterm delivery is important as this will permit obstetricians to select those pregnant women who would benefit from antibiotic treatment. Vaginal ultrasound to measure cervical length, fetal fibronectin (fFN) test [77], n-ph IGFBP-1 and PAMG-1 tests or combinations of the above are all tools which have a high negative predictive value for preterm delivery within 7 and 14 days. In a recent study from Thailand, the mean test-to-delivery time was significantly shorter in women with preterm uterine contractions and a positive PAMG-1 test compared to women with a negative test (20 vs. 720 hours; $p=0.025$) [78]. At present, there are no cohort studies of women with preterm uterine contractions given antibiotic therapy selected using one of these tests. A few randomized controlled trials have investigated the efficacy of treatment with erythromycin and metronidazole compared to placebo in women with positive fFN test after fetal fibronectin screening late in the 2nd trimester. However, these studies only investigated pregnant women who were asymptomatic.

An American multicenter study [79] carried out screening for vaginal and cervical fetal fibronectin in 16317 pregnant women between the 21st and 25th week of gestation; 6.6% of them tested positive. The study group ($n=347$) received oral antibiotic therapy with metronidazole 250 mg 3× daily + erythromycin 250 mg 4× daily for 10 days, and the control group ($n=356$) received placebo for 10 days. The rate of preterm births was 14.4% before GW 37, 6.9% before GW 35 and 4.3% before GW 32 in the group treated with antibiotics; in the control group the rates were 12.4% < GW 37 (RR 1.17; 95% CI: 0.80–1.70), 7.5% < GW 35 (RR 0.92; 95% CI: 0.54–1.56) and 2.2% < GW 32 (RR 1.92; 95% CI: 0.83–4.52). Neonatal morbidity also did not differ between groups. Among women with prior spontaneous preterm delivery, the rate of repeat spontaneous preterm delivery was significantly higher in the group treated with antibiotics compared to the placebo group (46.7 vs. 23.9%; $p=0.03$). The PREMETS study reached a similar result [80]. Women with a history of previous spontaneous preterm delivery who had a positive fFN test gave birth more often before GW 30 if they had received prior treat-

ment with oral metronidazole compared to placebo (21 vs. 11%) and significantly more often before GW 37 (62 vs. 39%; RR 1.6; 95% CI: 1.05–2.4). After approximately 100 women had been recruited, the study was stopped early. In another study, 215 asymptomatic pregnant women between 22 and 26 weeks of gestation who tested positive for bacterial vaginosis (BV) and fetal fibronectin were treated either with 250 mg erythromycin + 250 mg metronidazole 3 × daily for 10 days or placebo. In 77% of the group treated with antibiotics no bacterial vaginosis was subsequently detected compared to 28.7% in the placebo group ($p < 0.0001$). The rate of preterm deliveries < GW 34 in the BV-negative group was significantly lower compared to the group which still tested positive for BV (0 vs. 5.7%) [81].

Long-Term Outcomes

Only infants from the ORACLE I and II Trials have been followed up. The parents of 4148 children from the ORACLE I Trial and of 4221 children from the ORACLE II Trial were interviewed using a standardized questionnaire based on the Multi-Attribute Health Status classification system. Children resident in England were additionally assessed using the results of national curriculum tests done at the age of 7 years. A comparison of the individual regimens of the children in the original ORACLE I Trial showed no significant differences between children of mothers who received antibiotics for preterm rupture of membranes compared to children of mothers who had received placebo with regard to behavioral difficulties, specific medical conditions and educational outcomes [82]. In contrast, children whose mothers with preterm uterine contractions had received erythromycin alone or in combination with amoxicillin/clavulanic acid in the original ORACLE II Trial had more functional impairments than children whose mothers had not received erythromycin (42.3 vs. 38.3%; OR 1.18; 95% CI: 1.02–1.37) [83]. This was not the case for amoxicillin/clavulanic acid. Surprisingly, there were more cases with cerebral palsy among the children of mothers who had been given erythromycin or amoxicillin/clavulanic acid compared to the children of mothers who had not received these antibiotics (erythromycin: 53/1611 [3.3%] vs. 27/1561 [1.7%], OR 1.93, 95% CI: 1.21–3.09; amoxicillin/clavulanic acid: 50/1587 [3.2%] vs. 30/1586 [1.9%], OR 1.69, 95% CI: 1.07–2.67). No significant differences in rates of cerebral palsy were noted for the children of the ORACLE I Trial, neither for erythromycin nor for amoxicillin/clavulanic acid (erythromycin 2.9 vs. 2.5%, OR 1.18 [0.77–1.81]; co-amoxiclav: 2.4 vs. 2.9%, OR 0.81 [0.53–1.24]) [82]. An analysis of the group with cerebral palsy [84] showed that the majority of cerebral palsy (CP) cases in the ORACLE II Trial (57/80 [71%]) were children who had been born at more than 32 weeks of gestation, while the majority of CP cases in the ORACLE I Trial (61/87 [60%]) were children born before 32 weeks of gestation. This surprising result prompted the authors to make the bold suggestion that antibiotic treatment had led to suppression of the infection but not of the inflammation and that the children with cerebral palsy in the ORACLE II Trial might have been exposed to an inflammatory milieu for a longer period of time. Unfortunately the analysis does not show whether other perinatal factors such as perinatal asphyxia could have played a role in the causation of CP. Two analyses investigated the impact of publishing the Oracle I and II Trials in the Lancet in 2001 and of the follow-up study in 2007. Before and after the publication of each study, questionnaires investigating the antibiotic therapy prescribed to women

with PROM (preterm premature rupture of membranes) and preterm labor were sent to all obstetric units in the UK. After publication of the ORACLE I and II Trials in the Lancet 2001, almost 50% of departments changed their antibiotic management: the percentage of patients with PROM who did not receive routine antibiotic treatment dropped from 77 to 41%, the percentage of patients with preterm labor receiving antibiotic treatment rose from 85 to 92%. Erythromycin was prescribed 46% more often, amoxicillin/clavulanic acid was prescribed 8% less often [85]. Almost no changes were reported after publication of the follow-up studies in 2007: prior to publication, 2% did not prescribe antibiotics for premature rupture of membranes, a figure that rose to 4% after publication; 79% prescribed antibiotics for preterm labor before publication, rising to 84% after publication. The majority of clinics (98%) reported that their antibiotic of choice was erythromycin [86].

The need for caution in the routine prescription of antibiotics for pregnant women with impending preterm birth is supported by reports of increasing rates of *E. coli* early-onset sepsis in very low birth weight (< 1500 g) premature neonates and late-onset sepsis in preterm and term infants. The administration of ampicillin, which is recommended intrapartum for verified GBS infection, was found to be an independent risk factor for ampicillin-resistant *E. coli* early-onset sepsis in preterm infants [87].

A retrospective Canadian analysis showed that antibiotic resistance in children with early-onset sepsis was associated with maternal exposure to antibiotics, irrespective of whether administration was intrapartum or antepartum [88].

In the last 15 years, prevention of fetal infection has been a dominant goal of obstetrical management. Neonatologists dread sepsis and severe cranial hemorrhage as serious infection-related complications for preterm infants and prefer to deliver infants at a younger gestational age but without infection than at a later age with infection. The literature on the association of neonatal morbidity and intrauterine infection and low gestational age is currently being re-examined [89]. Thus, discussion of the originally postulated causative role of intrauterine infection for chronic lung disease [90] and neonatal white matter disease has now become more nuanced. In a study by Chau et al. published in 2009 [91], histologically verified chorioamnionitis was not considered the primary cause of noncystic white matter injury detected on magnetic resonance imaging of preterm neonates. Rather, postnatal infections and hypotension were associated with a higher risk of white matter injury [91].

Actuated by a fear of fetal infection, we obstetricians do everything in our power to prevent such infections and remove the fetus from the inflammatory environment at the earliest indication.

Unfortunately we have no reliable clinical parameters for fetal involvement which could serve as an indication for preterm artificial induction of labor.

In women with premature rupture of membranes between GW 24 and GW 33, maternal CRP > 20 µg/ml was identified as a simple predictive parameter for funisitis [92]. However, because the body of evidence is insufficient, even the AWMF Guideline does not provide an absolute cut-off for maternal CRP levels and recommends serial controls and delivery of the infant if values continue to rise despite antibiotic treatment.

Persistent inflammation despite antibiotic therapy is reflected in persistently increased maternal interleukin-6 levels, which have an 86.7% sensitivity and a negative predictive value of 77.8% for funisitis at a cut-off von 1.98 pg/ml (specificity: 46.7%, positive

predictive value 61.9%) [93]. However in a study published in 2012, Mercer et al. [94] found that in conservatively managed women with preterm premature rupture of membranes (between GW 24 and GW 32), interleukin-6, interleukin-10, G-CSF and ICAM-1 levels in maternal blood were not adequately predictive for neonatal sepsis, IVH level 3–4, NEC level 2–3, RDS, IUFD or neonatal mortality. Only maternal TNF α at delivery was significantly associated with neonatal sepsis prior to discharge. However, significantly higher maternal and umbilical cord blood levels of G-CSF, IL-6 and IL-10 and TNF α were associated with clinical chorioamnionitis. Umbilical cord blood levels of G-CSF and IL-6 were significantly increased in neonates who presented with sepsis or another of the above neonatal morbidities within 72 hours of birth. Routine use of cordocentesis to measure these parameters has not become an accepted procedure. Detection of increased levels of these parameters could already be an indication of acute FIRS.

In addition to anti-infectious therapies with antibiotics, another approach, still in its experimental stages, consist in the containment of the fetal inflammatory processes (FIRS) to prevent or reduce typical short and long-term morbidities (sepsis, NEC, BPD, white matter injury, CP). Interleukin-10 has a high anti-inflammatory potential and appears to play a role in reducing the inflammatory reaction in women with preterm labor [27,95]. A nonhuman primate study in rhesus monkeys demonstrated that the intra-amniotic administration of interleukin-10 significantly reduced IL- β -induced uterine contractility [96]. Another study found that i.v. maternal administration of interleukin-10 had a protective effect against white matter injury in new born rat pups [97]. A mouse model also demonstrated that exogenous interleukin-10 can provide neuroprotection against interleukin- β -induced inflammation [98]. In premature newborns delivered before 28 weeks of gestation, prolonged therapy with the non-steroidal anti-inflammatory agent indomethacin was associated with less white matter injury on MRI [99].

Our vision for the future is the prolongation of pregnancies with an effective anti-infective *and* anti-inflammatory therapy which will also reduce neonatal morbidity.

Conclusion

Despite a number of initially promising studies on the prevention of preterm births through screening for bacterial vaginosis and antibiotic therapy, some also done in Germany [100], the most recent meta-analysis [101] found that antibiotic therapy of asymptomatic pregnant women was not always associated with a significant decrease in preterm delivery. The necessity of a therapeutic regimen for acute impending preterm delivery due to preterm rupture of membranes or preterm uterine contractions remains.

Based on the current body of evidence, treatment with broad-spectrum antibiotics and initial intravenous administration is recommended in women with preterm rupture of membranes. Administration until delivery or for a period of 7 days has been found to be effective. The literature to date militates against the routine administration of antibiotics in women with preterm uterine contractions. Nevertheless, a subgroup with subclinical infection/inflammation could benefit from antibiotic therapy. Vaginal swabs for bacterial infection and clinical markers such as maternal CRP and/or interleukin-6 could be included in the decision whether or not to prescribe antibiotics. The identification of

particularly high-risk pregnancies may be possible using the fFN test, the PAMG-1 test or n-pH IgFBP-1 test. In future, particularly high-risk groups could be selected through the detection of cytokines and other predisposing genetic polymorphisms.

Conflict of Interest

None.

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