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POSITION STATEMENTS AND GUIDELINES

Tocolysis for preterm labor: Expert opinion

Irène Hösli · Christiane Sperschneider · Gero Drack · Roland Zimmermann · Daniel Surbek · Olivier Irion

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Abstract Tocolysis is an important treatment in the improvement of outcome in preterm labor and preterm birth, provided that its use follows clear evidence-based recommendations. In this expert opinion, the most recent evidence about efficacy and side effects of different tocolytics is being reviewed and evidence-based recommendation about diagnosis and treatment of preterm labor is given. Further aspects such as progesterone administration or antibiotic treatment for the prevention of preterm birth are included. Our review demonstrates that an individualized choice of different tocolytics and additional treatments is necessary to improve short- and long-term neonatal outcome in preterm labor and preterm birth.

Keywords Tocolysis · Preterm labor · Preterm birth

Introduction

This Expert Opinion Letter gives current evidence-based recommendations on indication and selection of tocolytics.

The incidence of preterm birth, i.e., delivery before 37 weeks of gestation, in Switzerland lies around 7.5 %, with 1 % occurring before 32 weeks of gestation [1]. This puts Switzerland in the middle of the pack compared with the rate of prematurity in Europe as a whole (5.5–11.4 %). Prematurity accounts for about 75 % of perinatal mortality and for about 50 % of long-term morbidity [2].

It is often difficult to identify the pregnant women at high risk for preterm birth in time to prevent it. Approximately 90 % of women presenting with contractions will not deliver within the next 7 days and about 75 % of them will reach term without tocolysis or any other therapies [3].

Many pregnant women with preterm contractions are thus "over-treated". The goal must therefore be the identification of the women who are truly at risk of going on to preterm birth to prevent unnecessary and costly interventions.

Only the timely recognition of an impending preterm birth allows for a risk-specific management with stabilization of the pregnant woman and transfer to a specialized perinatology unit. About a third of all preterm births are medically indicated (preeclampsia, intrauterine growth retardation, etc.). Approximately 40–50 % are the results of preterm labor and a further 30 % occur after preterm rupture of membranes before 37 weeks of gestation. The recommendations presented concern predominantly the latter two groups.

The management of threatened preterm birth consists of:

- Diagnostic procedures to evaluate the risk and plan appropriate therapy.
- Initiation of tocolysis.
- Administration of corticosteroids to promote fetal lung maturity [4].
- Possible administration of antibiotics.
- Transfer to a specialized perinatal center.

Diagnosis

The following diagnostic procedures are mandatory:

Committee for Quality Assurance of the Swiss Society of Obstetrics and Gynecology.

I. Hösli · C. Sperschneider · G. Drack · R. Zimmermann · D. Surbek (✉) · O. Irion
Committee for Quality Assurance, Swiss Society of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, University Hospital Inselspital, Effingerstrasse 102, 3010 Bern, Switzerland
e-mail: daniel.surbek@insel.ch

1. Medical history: Identification of women at high risk, i.e., with multiple gestations, uterine malformations, fibroids, or a history of previous preterm birth, second trimester pregnancy loss, induced abortions, and repeated uterine curettage, conization, or other cervical procedures. Careful documentation of complications in the current pregnancy as well as the actual complaints at presentation such as lower abdominal cramping, back pain, and vaginal discharge [5, 6].
2. CTG: Assessment of fetal wellbeing and uterine activity.
3. Abdominal ultrasound examination: Position, weight, morphology of the fetus, position and morphology of the placenta, amount of amniotic fluid, Doppler evaluation of placental and fetal circulation.
4. Speculum Exam: Evaluation of possible bleeding, amniotic fluid leak, prolapse of fetal membranes. To obtain material for cultures. Fetal fibronectin test and tests for presence of amniotic fluid are optional (see below).
5. Endovaginal Sonography: Evaluation of cervical length, evaluation/exclusion of placenta previa, and vasa previa.
6. Blood tests: CRP and leucocytes for exclusion of amniotic fluid infection syndrome.

Transvaginal ultrasound is superior to digital examination in the detection of impending premature birth [7–9]. In the presence of preterm rupture of membranes, all vaginal examinations (speculum or sonography) should be restricted as much as possible and only conducted under strictly sterile conditions [10, 11]. Digital examination should be avoided before delivery is under way. If after history, speculum exam and sonography there is still uncertainty as to the presence of preterm rupture of membranes, immune-chromatological tests (AmniSure®, Actim Prom test®) are recommended [12].

Indications for tocolysis (24 + 0–33 + 6 weeks of gestation)

The use of tocolytics before 24 weeks of gestation can be justified in individual cases (i.e., preoperatively with cervical cerclage). The use of tocolytics during external version for breech position, for the intrauterine reanimation or for the delivery of the baby during cesarian section will not be addressed in this Expert Opinion Letter.

For initiation of tocolysis one or more of the following criteria must be met:

- Preterm spontaneous labor (CTG >4 uterine contractions in 20 min, or 6 in 60 min) and one of the following:
  - Shortening of the functional length of the cervix to ≤25 mm, or shortening of the cervix by >5 mm (by transvaginal sonography) over the course of 2 h.
  - Positive fibronectin test (optional).
  - Symptomatic placenta previa/low lying placenta with vaginal bleeding.
  - Cervical dilatation of >2 cm and <5 cm.
- Preterm spontaneous rupture of membranes prior to 34 weeks of gestation without signs of chorioamnionitis (optional indication, no general recommendation).

In unclear situations, the measuring of fetal fibronectin may provide further guidance on how to proceed. The risk of preterm birth rises to 50 % with gestational age of ≤32 weeks, cervical length of ≤15 mm, and a positive fibronectin test. If the fibronectin test is negative and cervical length is 15 mm, the risk of delivery within the next 7 days drops to ≤1 % [13–15]. With a cervical length of ≥25 mm and a negative fibronectin test at 24 weeks of gestation, the risk of preterm birth is minimal based on a negative predictive value of >95 % [16]. Other biochemical tests including IGFBP-1 (insulin growth factor binding protein-1) and PAMG-1 (placental alpha microglobulin-1) have similar predictive values in the diagnosis of "true" preterm labor, and can be used clinically.

Goal of tocolysis

The primary goal of a tocolysis is the prevention of a preterm delivery before the end of the 37th week of gestation. As this goal is often not obtainable, tocolysis should aim for prolonging the pregnancy to 34 weeks of gestation, or at the very least by 48 h to allow for one-time administration of Betamethasone (Celestone®), 2 × 12 mg i.m. 24 h apart, which can reduce perinatal mortality and morbidity by as much as 50 % [17]. A further goal of tocolysis is making it possible to transfer the fetus in utero to a specialized perinatal center which further significantly reduces perinatal mortality and morbidity. Conversely, the fetus should not sustain any damage from remaining in a hostile intrauterine environment (i.e., due to infection!); under these circumstances, a prolongation of the pregnancy through tocolysis would not be appropriate.

Contraindications to tocolysis [18]

Maternal indications for ending the pregnancy	Fetal indications for ending the pregnancy
Sepsis	Pathological CTG
Severe preeclampsia	Premature placental separation (relative contraindication)
Maternal hemodynamic instability	Chorioamnionitis
Pulmonary edema	Intrauterine fetal demise or fetal malformations not compatible with life

Acute tocolysis

Tocolytics manage to delay delivery by 24 to max. 7 days. However, so far no reduction of the rate of preterm birth before 32, resp., 37 weeks of gestation, or of neonatal morbidity (respiratory distress syndrome or intraventricular hemorrhage) and/or perinatal mortality could be documented in randomized placebo-controlled trials for the various beta-sympathomimetics, oxytocin receptor agonists or prostaglandin synthesis inhibitors [19]. This lack of demonstrable benefit for the neonate can be explained though by methodological weaknesses in the RCTs published thus far [20]. The positive effect on morbidity and mortality of the transfer to a specialized perinatal center made possible by tocolysis and the induction of lung maturity is not taken into account either. According to the current state of knowledge, all the listed tocolytics are equally efficacious in regards to suppression of labor and their selection should be on the basis of absolute and relative contraindications for their use is a given patient. Calcium antagonists appear to have a better neonatal outcome than beta-sympathomimetics, though long-term outcome data are lacking [21]. Beta-sympathomimetics and oxytocin receptor antagonists are approved in Switzerland for tocolysis, whereas the use of calcium antagonists for tocolysis is an off-label indication, which has to be disclosed and explained to the patient before starting them.

The need for a change in treatment (rescue therapy, non-response to a tocolytics), the general attitude in a specific institution, or economic criteria may all influence the choice of tocolytic [22]. The lack of evidence justifies a restricted use of tocolytics. A combination of different tocolytics should generally be avoided because such combination may potentiate severe adverse effects [22, 23].

Tocolytics with promising data

Beta-Sympathomimetics

Intravenously administered beta-sympathomimetics (hexoprenaline, fenoterole) have a documented tocolytic effect, though when compared to placebo or oxytocin receptor antagonists, they clearly have a higher rate of maternal adverse effects based on their mechanism of action (palpitations in 48 %, tremor in 39 %, headache in 23 %, chest pain in 10 % of patients). In combination with corticosteroids and excessive i.v. fluid administration (especially in the presence of infection) they also have a higher risk (1:425) of pulmonary edema [19, 20]. By administering tocolysis in bolus form or through fluid restriction, the rate of maternal adverse effects can be reduced [24]. Fetal adverse effects include transient tachycardia or hypoglycemia when beta-sympathomimetics were administered within 2 days of delivery [22]. It is therefore recommended to use them for a restricted duration and dosage under strict volume control [25]. There is no documented efficacy of beta-sympathomimetics when given orally.

Specific contraindications for beta-sympathomimetics are:

- Cardiac disease including arrhythmias.
- Thyrotoxicosis.
- Severe preeclampsia.
- Uncontrolled diabetes mellitus (cave; exacerbation of hyperglycemia).
- Pulmonary edema.
- Multiple gestation (relative contraindication).
- Severe anemia.

Oxytocin receptor antagonists

Oxytocin receptor antagonists have comparable tocolytic efficacy to beta-sympathomimetics, but with markedly fewer maternal adverse effects [26, 27, 28] and have an optimal risk–benefit profile. Palpitations occur in 2 %, tachycardia in 6 %, and headache in 10 % of patients. Severe adverse effects have not been reported for use of oxytocin receptor antagonists alone [22]. For this reason they are considered, together with calcium antagonists, the first line tocolytic by many international specialty societies. In high-risk situations (elevated risk for pulmonary edema, in multiple gestations, with polyhydramnios, cardiac or pulmonary disease, diabetes mellitus I, persistent contractions, and/or tachycardia with hexoprenaline) atosiban should be the first line tocolytic. Atosiban is administered i.v. in a loading dose of 6.75 µg over 1 min, followed by 3 h of 18 mg per hour and thereafter as a maintenance dose of 6 mg/h for 45 h. The total treatment time should not exceed 48 h. The maximal dose for a single course should not exceed 330 mg. The price is significantly higher than for other tocolytics.

Calcium antagonists

Calcium antagonists have, compared to beta-sympathomimetics, a better risk–benefit profile, i.e., equal efficacy in regards to prolongation of pregnancy with a low rate of maternal and fetal adverse effects. For this reason they are recommended by various international specialty societies, together with oxytocin receptor antagonists, as first line tocolytics [20, 29, 30]. It is also important to notice that calcium antagonists are the only tocolytic that can be given orally. This, however, has only been

documented with nifedipin (but not for other calcium antagonists) in comparison with other tocolytics [31]. Compared to beta-sympathomimetics, nifedipin improves neonatal morbidity (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis) and has fewer maternal adverse effects [32]. Based on the lack of long-term outcome data and because of the question regarding the optimal dosage there is still a need for further and larger scale studies. Adverse effects include lowering of blood pressure (cave: orthostatic vertigo) and headaches. Severe adverse reactions in the form of pulmonary edema have been observed, especially in twin pregnancies.

Current recommendations call for nifedipin slow release (Adalat CR®) with a loading dose of 30–40 mg p.o. (10 mg every 10–15 min) during the first hour, then 60 mg a day up to a maximal dose of 120–150 mg per day [33]. An alternative regimen consists of nifedipin 10 mg to chew, combined with 20 mg nifedipin slow release (Adalat CR®) for a rapid saturation; after 60 min a maintenance dose of 60 mg nifedipin low release is given and 30 mg nifedipin slow release kept in reserve [34]. A maintenance dose of 90 mg nifedipin slow release (alternating 30 mg and 60 mg every 12 h) also was well tolerated [35, 36]. Nifedipin can be combined with high dose magnesium sulfate (i.e., with preeclampsia) [37].

Specific contraindications for calcium antagonists are [38]:

- Cardiac disease including arrhythmias.
- Arterial hypertension.
- Pulmonary edema.
- Multiple gestation (relative contraindication).
- Intrauterine growth retardation (<5th percentile).

Tocolytics with limited data, despite documentation of tocolytic effect

Prostaglandin synthesis inhibitors

Prostaglandin synthesis inhibitors (especially indomethacin) have been used for tocolysis. In randomized studies a significantly better tocolytic effect compared to placebo and at least comparable with that of other tocolytics was documented. However, the subject numbers are too small to give a clear recommendation [39, 40]. Possible fetal adverse effects include impaired renal function (with subsequent oligohydramnios) and the constriction of the ductus arteriosus; they should therefore not be used for longer than 48 h. Recommended are 100 mg as a loading dose followed by 50 mg every 6–8 h.

Specific contraindications to indomethacin are:

- Gestational age >32 weeks.
- Current or past gastric ulcer.
- Hypertension.
- Allergy to NSAIDs.
- Severe intrauterine growth retardation.
- Oligohydramnios.

Nitric oxide donor drugs

Even though NO-donors (transdermal with NitroTTS patch) were able to show in an RTC a significant reduction in neonatal morbidity with preterm birth before 28 weeks of gestation, there is not yet sufficient evidence of the efficacy of using them as tocolytics outside of a study setting [41]. The most common adverse effect is therapy resistant headache.

Tocolytics without demonstrated tocolytic effect

Magnesium sulfate

There is no definitively proven effect of magnesium sulfate as a tocolytic. The effects of magnesium on tocolysis have yielded contradictory results in clinical studies [42, 43]. Nevertheless, magnesium is, unlike in Europe, the most commonly used tocolytic in the USA. The usual initial dose of 6 g i.v. over 20 min is generally followed by a maintenance dose of 3–4 g/h, a dose somewhat higher than the one commonly used for preeclampsia [44]. If used at all, $MgSO_4$ should be limited to 48 h. The neuroprotective effect for the child, long suspected based on epidemiological data, is now also documented in a randomized study [45]. Due to remaining open questions, the use of magnesium sulfate as a neuroprotective agent can at this point not be recommended generally. If used, it should be administered during the last 24 h before delivery. The only well-documented indication for intravenous magnesium sulfate administration to pregnant women remains the prophylaxis and treatment of seizures in preeclampsia and eclampsia.

Regulatory approval of tocolytics

In Switzerland, the beta-sympathomimetic hexoprenaline (Gynipral®) and the oxytocin antagonist atosiban (Tractocile®) are approved for the treatment of preterm labor, while this is not the case for calcium antagonists, prostaglandin synthesis inhibitors, and nitrous oxide donors. If these are to be used, the patient has to be fully informed about their "off-label" use and possible alternative treatments [46].

Long-term tocolysis

So far there is no clear evidence for the benefits of an oral long-term tocolysis with beta-sympathomimetics, oxytocin receptor agonists or calcium antagonists [47–50]. Routine long-term tocolysis can therefore not be recommended and should only be used in selected individual cases (i.e., with symptomatic placenta previa and early gestational age). In general practice, we frequently encounter individual cases where a continuation of tocolysis appears to have resulted in the prevention of preterm delivery. It is likely that the assumed benefits for the newborn in those instances cannot be statistically captured due to the small number of cases.

Further measures

Bed rest

A randomized study published in 1994 showed no effect of strict bed rest on the rate of preterm birth [51]. Because of the documented adverse effects associated with strict bed rest, such as an increased risk of thrombo-embolic events, more frequent depression or a feeling of isolation, there is generally no indication for ordering strict bed rest [52, 53]. Prescription of modified bed rest and sick leave is acceptable.

Bryophyllum

A tocolytic effect of Bryophyllum pinnatum has been shown in vitro and in several observational reports or retrospective studies. Data from two prospective controlled studies (RCT) conducted according to the requirements of the regulatory agencies are pending. Further studies will be necessary to increase the evidence for its use as a tocolytic [54–56].

Antibiotics

There is no evidence that the administration of antibiotics to women with preterm labor and intact membranes lowers the rate of preterm birth [57]. Follow-up studies at 7 years have shown an increased risk of cerebral palsy in the same patient collective [58]. In selected cases, such as with preterm labor in the presence of a smear positive for group B streptococci, antibiotic is indicated even with intact membranes [59]. In women with preterm rupture of membranes before 34 weeks gestation, on the other hand, the administration of antibiotics (erythromycin, amoxicillin, clindamycin) results in a prolongation of the pregnancy and a reduction of neonatal morbidity [60].

Progesterone

According to a meta-analysis in 2012, the prophylactic administration of vaginal progesterone (100–200 mg per day) to asymptomatic women with a singleton pregnancy and a cervical length of <25 mm, as well as to women with a prior preterm birth, reduced the rate of preterm delivery by 50 % and favorably influenced perinatal morbidity and mortality (less RDS, less LBW). Progesterone did not work in twin or higher grade multiple gestations [61–66]. About the use of progesterone for the treatment of preterm labor, there is so far insufficient evidence-based information.

Conflict of interest The authors report no conflict of interest.

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