

PREVENTION OF PRETERM DELIVERY OF TWINS



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Abstract

The incidence of twin gestation has increased over the past decades and contributes to an increased rate of spontaneous preterm birth and increased mortality and morbidity up to adult age. Prevention of spontaneous preterm birth in twin pregnancies differs from interventions in singleton pregnancies.

Up to now, many treatment modalities have been investigated such as bed rest, tocolytics, antibiotics, cerclage or progestagens, but have failed to prevent prematurity rates in twin gestations or were even combined with harmful effects. Cervical pessaries might be a non-invasive cost-effective option, but it is mandatory to evaluate vaginal progesterone and cervical pessaries in twin gestations with a short cervix in further randomized trials.

Key words: *twin pregnancy, prevention of spontaneous preterm birth, cervical assessment*

The high rate of perinatal mortality and morbidity associated with twin pregnancy is mainly due to prematurity. Multiple gestations account for 2–3% of all pregnancies but constitute at least 10% of cases of preterm delivery. Many strategies have been suggested but up till present, failed to prevent spontaneous preterm birth (SPB) in a population-based approach.

PATHOPHYSIOLOGY

Precocious cervical ripening is characterized by collagenolytic activity, a decrease of total collagen content and an influx of inflammatory cells with increasing levels of cytokines and prostaglandins ¹. Premature cervical ripening with a loss of cervical integrity may be the result of a congenital disposition of the connective tissue, traumatic damage, uterine overdistension, vascular lesions in the placenta inducing membrane destabilization and local or ascending intrauterine infections ². Cervical shortening and opening of the internal os may facilitate the ascension of microorganisms, injuries to the decidua-chorioamnion interface and of membrane activation and amnionitis. Sonographic findings of the cervix were compared with placental lesions and demonstrated a greater frequency of acute inflammatory lesions in patients in whom cervical shortening developed during the second trimester also in twin gestations ³.

However, compared to singleton pregnancy microbial invasion of the amniotic cavity in twin gestations presenting with SPB is rare and only found in 11.9% of pregnancies

with symptoms of SPB ⁴ suggesting that intra-amniotic infection is not responsible for the excessive rate of SPB in twin pregnancies. Uterine overdistension and pressure to the cervix may be leading pathogenetic factors in twin gestations.

CERVICAL ASSESSMENT

Early diagnosis of twin pregnancy and the membrane status by ultrasound is mandatory for appropriate planning of antenatal visits and for providing information to the parents.

Digital examination was performed in twin gestations at weekly intervals in 86 twin gestations. Intervals to delivery decreased significantly with lower a short and/or dilated cervix ⁵.

Transvaginal sonography (TVS) can visualize more objectively the internal os and cervical shortening allowing the comparison of successive examinations by different examiners and during the course of pregnancy. The two-dimensional transvaginal approach with probes of 5-8.5 Mhz is regarded as the most feasible imaging modality for routine detection or exclusion of patients at risk for SPB. Before TVS, women are asked to empty their bladders. The closed endocervical canal should be visualized. The ratio of a curved/ straight cervix decreases with decreasing length, and, therefore, the disparity does not have essential implications. After serial measurements, the shortest result should be considered. Cervical length (CL), funneling width (Y, V or U-shaped) and length, the

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area of the internal opening, the position of the cervix and the thickness of the endocervical mucus all can be determined. Most examiners perform their examinations with the women in a supine position. In a pilot study of twin pregnancies we demonstrated that the closed cervix may shorten in the upright position due to an increasing opening of the internal os. ⁶ These changes significantly reflect a risk for SPB ⁷. The shorter the CL ⁸ in a recumbent position, the greater is the difference between recumbent and upright position. The findings clarify the risk of postural stress and may be useful for maternal lifestyle changes.

In early pregnancy, the cervical glands can be identified by high resolution sonography ⁹. The endocervical canal is bordered by mucosa, which is of decreased but occasionally of increased echogenicity. Between 11 and 13 weeks, Greco et al. measured the linear distance of the glandular area of the endocervical canal and the isthmus separately but only in singleton pregnancies.¹⁰ No investigations have been performed as early in twin gestations. There are still discrepant views how to measure the CL. Opposite to the group of Nicolaides most investigators use the "standard technique" described by Iams et al.¹¹ Vayssiere et al. used this technique in twin gestations¹², according to his opinion the inter-operator variance is less compared to the technique of the Fetal Medicine Foundation. Normal values measuring the CL from external to internal os demonstrate higher CL values compared to measurements obtained from the glandular area alone.

We collected data of the CL and funneling width for normal singleton, twin and triplet pregnancies in the supine and upright positions using the standard technique. ⁷ The CL decreases significantly from 15 weeks to term in both positions ($p < 0.001$) and values between both positions are significantly different from 20 weeks onwards ($p < 0.001$). In normal twin pregnancies, a width of the internal os of $> 5\text{mm}$ was observed in an upright position at > 30 gestational weeks and funneling between the positions was significantly different from 25 weeks onwards ($p = 0.005$). These observations suggest a correlation with epidemiological data demonstrating that workload and physical activity have an adverse effect on the cervix. ¹³

Reference values should be integrated in daily practice. We recommend a reduction of physical stress and workload or even a pessary in multiple gestation when values are outside of the 50% -box, e.g. below the 25th centile for CL (see below). Few others describe dynamic cervical changes with advancing twin gestation ¹⁴. The normal CL values of this study are comparable with our data where the mean values of CL decrease from 44 to 30 mm between 18 and 36 weeks. In the study of Bergelin and Valentin the values of CL decreased from 41 mm to 31 mm between 24 and 32 gestational weeks ¹⁴. The same authors describe a higher shortening rate in women delivering preterm. In agreement with our results, three studies found that the cervix widened with advancing gestation ^{14, 15}, a finding which had not yet been confirmed by other authors.

Three-dimensional multiplanar sonography of the cervix has been proposed to improve our understanding of cervical morphology ¹⁶.

PREDICTION OF SPB

Variations exist with respect to gestational age at testing, definition of abnormality thresholds and of the outcome reference in twin pregnancies ^{12 17-33}. Published studies were stratified according to singleton or twin pregnancy, gestational age at testing, CL and funneling width thresholds or reference standards to produce summary estimates of likelihood ratios ³⁴. The given thresholds to predict SPB vary, even if symptomatic and asymptomatic patients are analyzed separately. Both CL measurement and funneling, whether alone or in combination, appeared to be useful in predicting SPB in twin pregnancies, whereas CL appeared to be the predictor of choice at 27 weeks of gestation, at 22 weeks the diagnostic values of both parameters were comparable ¹². In our longitudinal data set of twin pregnancies, we observed that $CL < 25\text{ mm}$ and funneling width $> 10\text{mm}$ between 20 and 28 weeks in both positions predict a risk of SPB.

In a study of asymptomatic twin pregnancies, a CL of $\leq 2.0\text{ cm}$ measured between 15 and 28 weeks' gestation appeared to be a reasonable parameter at predicting SPB in twin gestations ²⁶. The high specificities indicate that CL is better at predicting the absence than the presence of threatening SPB ²⁶. Both a $CL \leq 30\text{ mm}$ and cervical funneling in twin pregnancies under 26 weeks' gestation are independently associated with a risk for SPB ²⁶. Because a long cervix, of $> 35\text{ mm}$, is associated with very low risk (4%) for preterm birth, pregnant women can be reassured ²⁵. After 30 weeks, CL was shown to be not predictive of SPB ²⁹. A simple equation using the CL (in mm) divided by 3 can predict mid gestation scan-to-delivery interval in twin gestation ³³.

The most recent systematic review and meta-analysis showed that among asymptomatic women with twin pregnancies, a $CL < 20\text{ mm}$ at 20-24 weeks of gestation had pooled positive and negative likelihood ratios of 10.1 and 0.64, and 9.0 and 0.64, respectively, to predict preterm birth at < 32 and < 34 weeks of gestation, respectively. ³⁵

In symptomatic twin pregnancies TVS can identify impending SPB before advanced cervical dilatation and may therefore help to indicate maternal in-utero transfer. The high specificities underline that current use of CL and fetal fibronectin are of importance in situations where negative results can avoid unnecessary interventions ³⁶. However, also in the most comprehensive systematic review of TVS in twin gestations, the predictive accuracy of CL for SPB was low in symptomatic women ³⁵.

As reported by the first study of the National Institute of Child Health and Human Development -Maternal-Fetal Medicine Network Preterm Prediction Study dealing with twin pregnancies, most widely known risk factors for SPB were not significantly associated with SPB of twins. At 24

weeks, a CL \leq 25 mm was the best predictor of SPB. Of all other risk factors evaluated at 28 weeks, fetal fibronectin was the only statistically significant predictor of SPB¹⁷.

Interventions and expectant management

Although studies have demonstrated that TVS of CL is predictive of SPB in women with twin pregnancies, it is unclear if antenatal management can prevent preterm birth.

125 women with twin pregnancies were randomly assigned to undergo a TVS measurement of the CL and a cervical digital examination every 4 weeks from t 16-20 weeks until 28 weeks or to a digital cervical examination alone at the same intervals. Women who underwent TVS were treated with a predetermined algorithm for cerclage and bed rest. Treatment decisions in the control group were not based upon a predetermined algorithm. There was no significant difference between groups in mean length of gestation, but life table analysis revealed that SPB < 35 weeks in the TVS group was significantly reduced ($P < .02$).³⁷ Otherwise, neither bed rest, oral betamimetics, cervical cerclage nor progesterone have been successful to reduce SPB in twin gestations. Most of these procedures lack any evidence at all whether they contribute to improved outcome but may even add unnecessary costs and risks for both mother and fetus. The lack of well-designed randomized controlled trials (RCT's) for twin pregnancies has led to a policy where management decisions are based on indirect conclusions from RCT's from singleton pregnancies, although results could be different. Cervical assessment and the described thresholds is therefore an essential tool to exclude patients from unnecessary and possibly even harmful therapies.

A recent review summarizes all treatment modalities to prevent SPT in twin gestations.³⁸

Routine hospitalization and bed rest

Hospitalization was a stressful experience for twin mothers and their families, as well as costly for the health care system³⁹. No observational study describes cervical changes during hospitalization. The results from RCT's suggest that bed rest may even increase the rate of SPB in uncomplicated twin pregnancies and that hospitalization did not reduce the rate of SPB nor any outcome parameter in twin pregnancies with cervical effacement and dilatation³⁹. Nevertheless, based on studies of Papiernik¹³, a reduction of physical stress for women with multiple pregnancies in an outpatient setting is recommendable.

Tocolytic treatment

Tocolytics have not been shown to improve perinatal and neonatal outcomes. Moreover, they cause adverse effects on women in preterm labor⁴⁰. Premature labor occurs frequently in twin gestations, but no RCT's have been designed for twin pregnancies. Intravenous magnesium sulfate and β -mimetics have been commonly prescribed and have been compared in twin versus sin-

gleton pregnancies. For magnesium sulphate, frequencies of side effects, durations of therapy, the number of days until delivery and delays in delivery during the first 72 hours were the same, and the therapy was deemed equally safe in both groups³⁹. However, when β -mimetics were used, multiple pregnancies were associated with a marked increase in the duration of therapy, incidence of delivery before 37 weeks, and of the incidence of maternal cardiovascular complications. There was no effect on the neonatal outcome⁴¹. A further study confirmed that pulmonary capillary pressure, cardiac index and the ratio of preejection period to left ventricular ejection time significantly increased during the infusion period with β -mimetics in twin gestations⁴².

Oxytocin antagonists and calcium channel blockers have been used, but no data in twin gestations are available.

Corticosteroids

Antenatal treatment with corticosteroids is indicated for pregnant women at risk for SPB delivering more than 24 hours and less than 7 days after start of treatment, as it results in a substantial decrease of neonatal mortality and morbidity, as well as in savings of health care costs⁴³. The use of repeated doses in women whose risk of SPB persists for more than a week may reduce the incidence of respiratory distress syndrome but may cause harmful effects on mother and fetus⁴³. Antenatal corticosteroid therapy appears to be less beneficial in multiple compared to singleton pregnancies possibly due to the shorter half-life of betamethasone in mothers with twin pregnancies⁴⁴. A study with the largest series of retrospectively evaluated nonrandomized antenatal glucocorticoid responses in twins concluded that corticosteroids have no beneficial effect on the risk of respiratory distress syndrome in preterm twin babies, but exposed a large number of infants to unnecessary treatment that might adversely affects growth⁴⁵. The Cochrane database states that studies show no benefit of antenatal standard doses of glucocorticoids in twin pregnancies⁴³, possibly because the causes of SPB in singletons differ from twins.

As the risks and benefits of repetitive application are still controversial in singleton pregnancies, multiple doses should not be encouraged in twin pregnancies in the absence of well-designed RCT's.

ANTIBIOTICS

Antibiotics are recommended during pregnancy for the prevention of SPB in patients with recurrent symptomatic bacterial vaginosis and a history of SPB⁴⁶, as they reduce the incidence of pyelonephritis during pregnancy and possibly of SPB⁴⁷. There is no proven evidence that antibiotics improve the outcome in pregnancies with intact membranes and threatening SPB, but there is concern about increased neonatal morbidity⁴⁸. Although no specific studies exist for twin pregnancies, it seems probable that the results from singleton pregnancies also

hold true for twins. Antibiotic administration following PROM is associated with a delay of preterm birth and with an improvement of the major indicators of neonatal outcome ⁴⁹. In a study considering twin pregnancies after PROM it was shown that the latency period was significantly shorter in twins, and more twins were born within 48 hours compared to singletons ⁵⁰. The role of cervical assessment in pregnancies with PROM has only been evaluated in singleton pregnancies ⁵¹.

The results of the ORACLE trial stress the importance of carrying out long-term follow up of infants after interventions aimed at prolonging gestational age at delivery and reducing short-term risks of infection. Pathological processes associated with increased risk of preterm delivery, such as infection, may affect infant outcome, and may potentially even increase risk of neonatal complications in relation to pregnancy prolonging treatments ⁵².

CERCLAGE

Soon after the introduction of a cervical cerclage by Mc Donald and Shirodkar, or anatomic cervical incompetence, "prophylactic" cerclages in twin pregnancies were embraced with enthusiasm but questionable indications. In a prospectively conducted randomized trial of the Royal College of Obstetricians and Gynaecologists, no significant differences in perinatal or neonatal mortality were found in spite of a reduced rate of SPB <33 weeks in the study compared to the control group ⁵³. Moreover, the risk of long hospital stay, further interventions and maternal complications was increased in the study group. After the introduction of TVS it could be visualized that the internal os can weaken and the membranes descend to the level of the suture. These findings were associated with earlier preterm delivery in the study group of 44 singleton, 6 twin and 3 triplet gestations who had undergone cervical cerclage, and all births occurred before 28 weeks ⁵⁴.

Currently, results from studies in women with twin gestations who may benefit from a cerclage based on TVS results are rare. In one observational study, cases with multiple pregnancy and „prophylactic“ cerclage were compared to cases with a cerclage based on TVS findings ⁵⁵, the duration of pregnancy did not differ between both groups. In patients without prophylactic cerclage, the frequency of preterm contractions was lower. However, the frequency of PROM was higher, and it was concluded that prophylactic cerclage did not improve the outcome of twin pregnancies. In a more recent prospective (non-randomized) cohort study of 147 twin pregnancies who underwent TVS measurement between 18 and 26 weeks' gestation, cerclage was offered to 21 women with a CL < or = 25 mm. The results were compared to the data of 13 twin pregnancies with the same TVS results who received no cerclage ⁵⁶. Decreasing CL was significantly associated with a shorter length of gestation, delivery at ≤ 34 weeks and PROM, however, none of these outcomes was altered by cerclage placement. Only one pilot study using historic controls compared cervical cerclage in patients with twin-to-twin perfusion syndrome when CL was < 15 mm and found that cerclage might reduce SPB. ⁵⁷In a meta-analysis of four RCTs Berghella et al. found a significant increase in SPB at less than 35 weeks in twin gestations (RR 2.15, 95% CI 1.15-4.01).⁵⁸ This is why it is nowadays not any longer recommended to perform a cerclage in twin gestations.

In exceptional patients with a history of trachelotomy abdominal cerclage might be an option even in twin pregnancies to prevent pregnancy loss or early SPB ⁵⁹.

Cervical (Arabin) pessary

Vaginal pessaries have been used in pregnant women to direct the cervix posteriorly. It is postulated that they might prevent further opening of the internal os or even premature rupture of membranes. Compared with operative cerclage, pessaries have the advantage of being cost-effective and operator-independent.

In 2003 we published a matched control analysis of 46 pairs with twin pregnancies. ⁶⁰. All had a short cervix of < the 10th centile before 28 weeks; 23 pregnant women were treated with vaginal pessaries, and 23 had expectant management. The interval from treatment to delivery was 85 (43-129) days in the treatment and 67 (21-100) days in the control group (p=0.001), gestational age at delivery was 35+6 and 33+2 respectively (p=0.02). Within the pessary group, there were 8/23 cases with SPB <36 weeks but none with SPB <32 weeks, compared to 12/23 cases with SPB <36 weeks and 7/23 with SPB <32 weeks in the control group (p<0.001). Another pilot study in monozygotic twin pregnancies with twin-to-twin transfusion

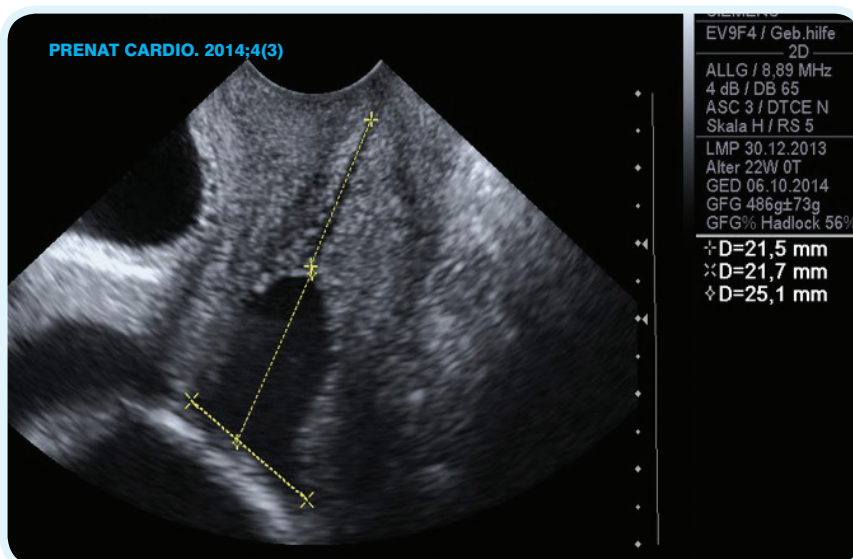


Figure 1. Transvaginal sonography in a twin pregnancy demonstrating with a short cervix and funneling at 22 weeks

syndrome and laser coagulation where patients with a pessary were compared to historic controls without pessary both with a CL < 25 mm found a significant reduction of SPB by 4 weeks in the treatment group.⁶¹

The so-called Pro-Twin trial was a multicentre, open-label randomised controlled trial in 40 hospitals in the Netherlands, whereby women with a multiple pregnancy between 12 and 20 weeks' gestation were randomly assigned (1:1) to pessary or control groups using a web-based application with random block sizes stratified by hospital. 813 women underwent randomisation, of whom 808 were analysed (401 in the pessary group; 407 in the control group). At least one child of 53 women (13%) in the pessary group had poor perinatal outcome, compared with 55 (14%) in the control group (relative risk 0.98, 95% CI 0.69–1.39). However, in the prespecified subgroup of women with a CL < 25th percentile (38 mm), the pessary group (n=78) had a lower adverse neonatal outcome rate as compared the non-intervention group (n=65) (10% vs 25%, RR 0.41; 0.19-0.90). This was accompanied by a significantly reduced preterm delivery rate < 32 weeks (12% vs 28%, RR 0.43; 0.21-0.89), but not < 37 weeks (61% vs 75%, RR 0.80; 0.54-1.2).⁶²

The most recent RCT from Spain compared twin gestations whereby women were randomized with a CL < 25mm to either pessary or expectant management. Patients in the pessary group showed a significant reduction of SPB before 34 weeks (Carreras, personal communication and contribution of the FMF World Congress, Nizza, 2014). Several randomised trials in multiple pregnancies are registered with www.clinicaltrials.gov and will be conducted in France, the Netherlands, the US and England. The history and state of the art related to the treatment with pessaries to prevent SPB was recently summarized⁶³ and the cervical changes reflected by a MRI study⁶⁴. In this study it could be suggested that the angle between cervix and lower uterine segment is changed by

the pessary and in some patients funnelling during the course of treatment even disappears. Similarly, we could demonstrate that in some twin pregnancies, funnelling as shown by TVS disappears during the course of pessary treatment (Figure 1 a and b).

Progesterone

Progesterone plays an important role in the prevention of SPB in singleton pregnancies.

"Natural" progesterone is administered vaginally as gel or tablets containing micronised progesterone. The synthetic compound 17-alpha-hydroxyprogesterone caproate (17-OHPC) is administered intramuscularly, has a longer half life and has been shown to be effective in patients with previous SPB. Romero et al. published an individual patient data meta-analysis of cases with vaginal progesterone.⁶⁵ This study yielded a non-significant relative risk of 0.7 (95% CI 0.3 to 1.4) for SPB before 33 weeks. When evaluating composite neonatal morbidity and mortality, the effect of progesterone was statistically significant (RR 0.5, 95% CI 0.3 to 0.9) in a sub-population of 52 twin pregnancies. These findings should be confirmed in trials aimed at investigating the effect of progesterone in women with twin pregnancies and a short CL. Several placebo-controlled trials have been published examining the effect of progesterone in women with twin pregnancies varying in size from 24 to 675 included twin pregnancies. Some studies have used vaginal progesterone (90–400 mg/day)⁶⁶⁻⁷¹ and others 17-OHPC (200–250 mg/day)⁷²⁻⁷⁶.

Despite the differences, none of the published trials have shown a significant effect of progesterone in twin pregnancies. One RCT with twin pregnancies using 200 mg or 400 mg progesterone found no advantages of 400 mg over 200 mg.⁷⁰ A collaboration between all published and ongoing RCTs including twin pregnant women, has been initiated in the Netherlands.⁷⁷ This individual patient data meta-analysis will include data from

13 studies randomising more than 3500 women with twin pregnancies and perform subgroup analyses to compare effects of vaginal progesterone treatment with 17-OHPC treatment. A recent meta-analysis suggested that progesterone may have adverse effects in multiple pregnancies.⁷⁸ The risk for perinatal death was 1.6 (95% CI 1.01 to 2.4), and the risk ratio for composite adverse outcome was 1.2 (95% CI 1.03 to 1.4). A safety signal has been proposed for 17-OHPC⁷⁹, but not for vaginal progesterone, because a triplet study comparing 17-OHPC with placebo showed significantly increased risk of midtrimester fetal loss ($P < 0.02$)⁸⁰. In addition Caritis et al. observed higher levels of CRP and even of SPB in twin pregnancies.⁷⁶

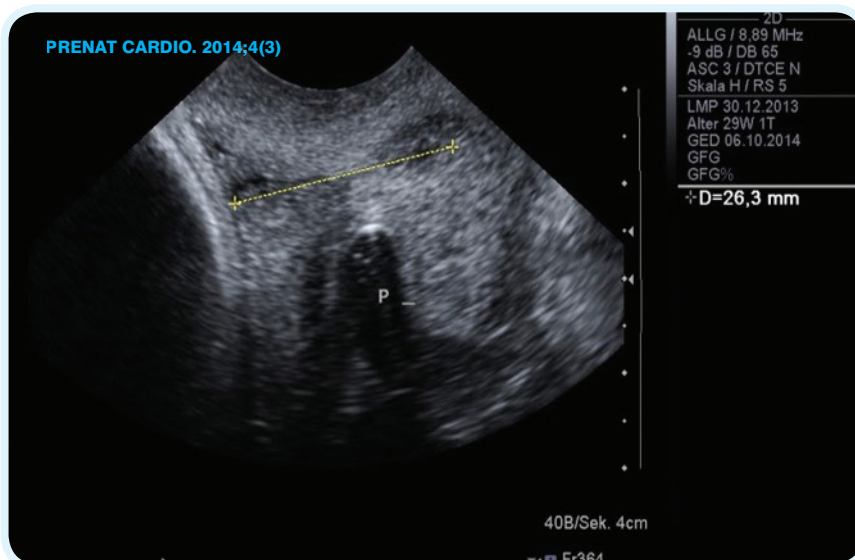


Figure 2. Transvaginal sonography in a twin pregnancy demonstrating elongation of the cervical length without funnelling during the course of pessary treatment (shadow evoked by the pessary) at 28 gestational weeks

Cervical surveillance in cases with progressive dilatation

Cervical assessment has not yet been integrated into the population-based routine surveillance of twin pregnancies. Unfortunately, it is still common practice to wait until clinical symptoms such as uterine contractility, bulging membranes or PROM are „unpredictably“ present although the condition might have been apparent earlier or even been preventable. One of the most frequent indications for in-utero transfer of a multifetal pregnancy to level III facilities is threatened preterm delivery with progressive dilatation when the first symptoms have been missed or unsuccessfully treated. In twin pregnancies with a cervical dilatation of >4 cm we have successfully postponed pregnancy for up to 4 weeks.⁸¹ In these patients, TVS is useful to detect the degree of protrusion (“ballooning”), the position of the first or even both twins, as well as the umbilical cord, and whether there is a dissociation of membranes. In our first 30 patients (20 pregnancies with twin gestations) with progressive dilatation and ballooning < 28 weeks at admission, we could prolong the interval to delivery for two weeks (mean) and a maximum of up to 4 weeks. In those patients longitudinal TVS is a non-invasive procedure used in the surveillance of progression.

Delayed interval delivery

Delayed interval delivery of twin pregnancies, is the last option to help at least one twin to survive if delivery of the first twin before viability cannot be prevented. TVS is used for cervical assessment before and even more after the delivery of the first twin⁸² and helps to predict the success of the procedure. In the twin pregnancy with the longest interval between the delivery of the first and the second twin (106 days), we observed that the umbilical cord of the first twin had completely disappeared above the internal os and that the cervix restored to a length of more than 3 cm. The survival chance of the second twin was approximately 50%.

CONCLUSIONS

Very few interventions have been shown to be effective in twin gestations to prevent SPB, some might even do more harm than good. Progesterone does not reduce the rate of SPB in twins in general, subgroup analysis might evaluate the impact in twin gestations with a short CL. Tocolytics are not indicated as long-term treatment and a cerclage does not reduce but possibly increases SPB.

The cervical pessary is still further evaluated but has shown some benefit in published and non-published trials. Cervical assessment should be incorporated in the routine care of twin pregnancies from 15 weeks onwards to recognize first symptoms of SPB, to reduce physical stress and possibly apply a pessary or take part in further studies. Specially trained staff and twin clinics are desirable. Collaborative studies are needed with a definition of dynamic thresholds of cervical assessment and defined outcome parameters such as gestational age at delivery, morbidity, mortality, and long-term follow-up separate for mono- and dichorionic twins.

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Conflict of interest

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