Chapter 9

Preterm Birth in Twins

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Additional information is available at the end of the chapter

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Abstract

Multiple pregnancy differs from singleton pregnancy in several aspects, including increased risk of preeclampsia, fetal malformation, maternal morbidity, and mortality. However, certainly, prematurity is a fundamental concern when twin gestation is approached, due to the frequency of this disease and also to the severity of preterm birth, which unfortunately can also occur near to the fetal viability limit. Labor in twin pregnancy generally occurs before singleton pregnancy. Nevertheless, another factor can contribute to raise even more preterm birth rates in this already high-risk gestation: the short cervix. Although only 1–2% of twin pregnancy present short cervix at transvaginal ultrasound, this association increases the chance of unfavorable outcome for the newborn, frequently causing death of one or both twins. So, many strategies were proposed to minimize this catastrophic situation: follow-up of cervical length to prevent preterm birth, pessary use, progesterone, tocolysis to postpone birth in 48 hours to 7 days in order to use corticosteroids in fetal pulmonary maturation, and magnesium sulfate use to neuroprotection.

Keywords: twin pregnancy, multiple pregnancy, preterm birth, cervical pessary, progesterone, tocolysis, corticosteroids, magnesium sulfate, neuroprotection

1. Introduction

Preterm birth is defined as delivery before 37 weeks of gestation, starting with fetal viability, which is around 23–25 weeks. It is known that prematurity is a great villain among pregnancy diseases due to its extremely high cost. Currently, the technological resources necessary to offer life support to preterm babies in neonatal ICUs cause expenditures of around 2500–5000

American dollars per day of hospitalization. Some preterm babies close to the limit of viability (23–25 weeks) can be hospitalized 100 days, that is, a single preterm baby can cause costs of 250,000–500,000 American dollars to the health system; considering that 10% of deliveries are preterm, we can comprehend that we are dealing with excessively high Figures [1].

Preterm birth may cause a great impact in the life of the affected. Severe complications can be mentioned: death, cerebral palsy, intraventricular hemorrhage (IVH), sepsis, retinopathy of prematurity, behavioral deficits (attention deficit hyperactivity disorder—ADHD) or learning deficits, respiratory distress syndrome (RDS), increase need for mechanical ventilation/CPAP, pulmonary dysplasia, and necrotizing enterocolitis [2].

Twin pregnancy is responsible for 2% of all pregnancies, but 15% of extreme preterm birth (≤32 weeks) occurs in twins. Therefore, measures for preterm delivery prevention are of vital importance in health systems management worldwide [3].

Twin pregnancy for itself is a condition associated with prematurity due to uterine over distension, and usually twins are born before the 37th week of pregnancy. The average time of twin pregnancy in a group not selected by the cervix was 35.83 ± 8.7 weeks, and in 50% of the newborns, delivery was prior to 37 weeks [4].

However, twin pregnancy does not occur frequently in the population in general; it accounts for approximately 1–2% of the deliveries. With the couples decision to postpone pregnancy, which has happened in the last 20 years, giving priority to women's presence in the labor market, the necessity of recurring to assisted reproduction techniques has increased, and the twin pregnancy rates, in their turn, have been increasing [5].

It is important to notice that the association of risk factors may be of extreme importance in multiple pregnancy: smoking, infections, vaginal discharge and association with Mullerian malformations, cervix amputation surgeries, the presence of the previous preterm delivery, or identification of short cervix may be catastrophic if associated with twin pregnancy [6]. Hence, in twin pregnancy anamnesis and physical examination have a more important role in detecting risk patients, and more rigorous observation of the uterine cervix may be considered in cases of duplicated risk factors.

In essence, if during prenatal examinations in the period between the 18th and 24th weeks the presence of short cervix is identified, the patient will receive the indication of the use of vaginal progesterone [7], and cervical pessary will be indicated that besides presenting a low index of collateral effects, promotes an important benefit in extending twin pregnancy and, mainly, significantly improving the condition of delivery of the newborn to the cares of the neonatal ICU in situations of preterm birth. The group of preterm birth treated only with progesterone is generally more severe than preterm birth in association with pessary and progesterone; in our present series of cases, we obtained a mean gain of 34 days in singleton pregnancy, and in twins probably similar gain is obtained, as our data will show below.

We can attempt to modify its incidence prior to the occurrence of any modification to the maternal organism. This prevention is called primary prevention. It is known that smoking is an important cause of preterm birth. So, tobacco should be avoided even before pregnancy, although stopping smoking in due time is also a recommended practice [8].

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Another example of primary prevention is the preeclampsia, which causes placental insufficiency and frequently culminates in preterm delivery (spontaneous or iatrogenic). Today, we know that the acetylsalicylic acid (ASA) can modify placentation if started in the 12th week of pregnancy and dramatically reduces the incidence of premature preeclampsia, thus reducing prematurity caused by this process [9].

It is known that the previous spontaneous preterm birth (SPB) is one of the main risk factors for a second spontaneous preterm delivery, and any interventions which are developed or studied with the intention of interfering in this event, modifying its natural course and increasing the final gestation time, will be characterized as primary prevention.

Furthermore, we can prevent prematurity after the beginning of the first signs of maternal modification; however, still prior to preterm birth labor being installed, it is called secondary prevention.

In twin gestation, one of the first signs of maternal modification, which may culminate in preterm delivery, is premature cervical shortening. Therefore, interference in the process of cervix modification can be considered secondary prevention of prematurity. Currently, some aspects in cervix evaluation may increase its risk in case of being detected in concomitance with short cervix (≤25 mm) [10], as the presence of funneling and the presence of intra-amniotic sludge [11].

Thus, interventions which interfere in these aspects of cervix modification, are characterized as secondary prevention. It may be stated that the example of progesterone, which modifies the endocervical glandular echo (EGE) and the speed of cervix diminishing; the cervical pessary, which modifies the uterocervical angle (UCA), may reduce funneling and sustain the uterus upon the perineal striated muscles; cervical cerclage in cases of isthmus-cervical incompetence to maintain uterine cervix closed; or, furthermore, the use of antibiotics in the treatment of intra-amniotic "sludge," which may interfere in cervix inflammation and modify its shortening.

The tertiary prevention of preterm birth consists of interventions when labor has already started and tocolysis, i.e. inhibition of premature labor by drugs, is a good example of it, and normally is preconized between 23-24 and 34 weeks of gestation.

So far, there is no evidence that tocolysis is able to indefinitely extend gestation; however, the therapy is efficient to delay delivery between 48 hours and 7 days, time enough for carrying out and for the effectiveness of corticosteroid application. These drugs, in their term, have the function of effectively acting in fetal pulmonary maturation, reducing the perinatal respiratory complications and also intestinal ones (necrotizing enterocolitis), and of the central nervous system, as, for instance, intraventricular hemorrhage.

Some recent studies reveal that the use of corticoid in gestations with high risk of preterm delivery is of great importance; however, its repetition in multiple doses is not advisable. Its usage is to be restricted to no more than two courses, and the second one is to be carried out only if the fetus effectively and irrevocably is going to be born prematurely.

Repetitive corticoid cycles are banned as evidence in tests with animals and studies in human beings have revealed that neuronal migration and neuronal apoptosis are modified in fetuses

exposed to high doses of this drug. Recent studies have revealed that even perinatal mortality increases (RR 1.12) in pregnant women using this medication, single cycle, for protection against complications caused by prematurity [12].

Also is considered another form of tertiary prevention of preterm birth the use of magnesium sulfate for fetal neuroprotection during labor or previous to delivery, in gestations below 32th week, administered between 12 and 24 hours prior to delivery.

2. Prevention of preterm birth

According to the WHO, preterm birth is today the main cause of death in the first 5 years of life in the world. Thus, prevention of prematurity is of extreme importance to minimize the morbidity/mortality perinatal and the high costs involved with this disease.

Primary prevention begins with a good detection index of the problem. The previous preterm birth is undoubtedly a significant predictor of prematurity, and this is also valid for twin pregnancies [6]. The more premature the previous delivery was, the higher the risk of recurrence. In addition, other factors can contribute to increase preterm birth rates in multiple pregnancies, as race, schooling, smoking, and short cervix.

Some studies showed higher prematurity rates in black, younger, and low-schooling level pregnant women [13]. Smoking and primiparity seem to be related to shorter gestational age at birth too in twin pregnancy [8].

In secondary prevention of preterm birth, cervix evaluation is an important strategy, once uterine overdistension in multiple pregnancy can perhaps contribute to higher rates of short cervix and, therefore, higher rates of prematurity. So, many efforts were made to improve the prediction and prevention of preterm birth in twin pregnancy, in order to enhance the newborn prognosis, and cervix evaluation is one of them [14].

Transvaginal ultrasound for uterine cervix evaluation is currently the main tracking method for this severe disease [15], and second trimester ultrasound, between 18 and 24 weeks, is considered the best period to make the cervical transvaginal ultrasound.

A retrospective cohort study in twin pregnancy concludes that cervical shortening between 18 and 25 weeks of gestation was a good predictor of SPB [16].

In twins, the association of preterm birth frequently caused by uterine overdistension is largely aggravated by the presence of short cervix, and this association is more evidenced because of high indexes of preterm birth incompatible with extrauterine life.

It is true that a small performance improvement in this association of problems may completely change the prognostics of the newborn. Therefore, the recommendation of carrying out transvaginal ultrasound of the uterine cervix is of vital importance for diminishing preterm delivery in twin gestation.

In twin pregnancy, with the previous spontaneous preterm birth or late miscarriage but with atypical history of cervical insufficiency, strict follow-up of the uterine cervix is necessary

from the 16th week of gestation, with transvaginal sonographic evaluation weekly, until the 24th week. If short cervical length (≤25 mm) is detected, a mechanical treatment (cerclage or cervical pessary) should be performed until 48 hours after diagnosis [7].

In the uterine cervix analysis, the evaluation of the cervical length ≤25 mm is considered the main predictor of preterm birth risk [10]. Also, other factors can be considered as preterm birth predictors, for instance, the presence of funneling signal [17], the presence of intra-amniotic sludge [11], the absence of endocervical glandular echo (EGE) [18], and the presence of uterocervical angle >105° [19], as well as progressive diminishing of the cervix of more than 2 mm/week [15], must be considered also in twin pregnancy (Video https://mts.intechopen.com/download/index/process/279/authkey/236271ca370424655923c0bb7a7179a0).

2.1. Fetal fibronectin (fFN)

The fFN test consists of detection of this cervicovaginal glycoprotein, collected between 24 and 34 weeks and 6 days. In normal conditions, fFN should not be present at high concentrations (cutoff is 50 ng/mL) after 20 weeks, and the objective of this test is to predict spontaneous preterm birth within 7:10 days [20]. False-positive results can occur in the sample contaminated with blood and within 24 hours after intercourse or cervical examination (as transvaginal ultrasound or vaginal examination), and it should not be performed in cases of premature rupture of membranes and cervical dilatation ≤3 cm

The American College of Obstetricians and Gynecologists (ACOG) [7] does not recommend its use in asymptomatic women with multiple pregnancy as routine, and some reviews have failed finding enough evidence to support fFN screening [21], once perinatal outcome was not affected by this intervention, although lower incidence of preterm birth before 37 weeks was reached.

However, in symptomatic women, this test can be useful to decide the best moment to administer antenatal corticosteroids in order to promote fetal pulmonary maturation. Published studies in multiple gestation that evaluated fFN test and cervical changes presented high sensitivity and high negative predictive value in predicting preterm birth [22, 23]. Probably, the association of these factors can enhance the approach of twin pregnancies and should be seriously considered in prevention of prematurity.

2.2. Progesterone

The use of progesterone is the main prophylaxis for preterm birth in singleton pregnancies; however, in twin pregnancies its performance does not seem to be that good. Currently, the most recent study with the highest series of cases—a meta-analysis of individual data—concludes that the utilization of progesterone for twin pregnancies presents favorable evidence when used in twins with short cervix (≤25 mm) as it presents a high number of cases by case studies and different clinical tests participated in this meta-analysis. However, a more detailed case-by-case study shows that 70% of the sample was taken from one clinical study only [24] favorable to utilization and another five studies with lower casuistry (30% of the sample) evidence that the medication does not present benefits in twin pregnancy [25].

A randomized clinical trial published in 2015 [4] with casuistry of about 200 twin pregnancies, not selected by cervix, compared the use of progesterone and expectant management in twin pregnancies and did not find differences between the groups. In another multicenter trial (STOPPIT), 500 twin pregnancies, not selected by cervix also, were randomized, and their perinatal outcomes were statistically not different for none of the evaluated perinatal outcomes [26].

Therefore, according to this author's opinion, we can affirm up to the present moment that isolated progesterone is not efficient in the prevention of preterm birth in not selected twin pregnancies; however, in association with short cervix, it can be considered.

2.3. Cerclage

Prophylactic cervical cerclage in multiple pregnancies is controversial, since the systematic review of randomized trials was not convincing in proving its efficacy in reducing perinatal death and neonatal morbidity. Even ultrasound-indicated cerclage (i.e., in short cervix) does not seem to show benefit in twin gestations. However, care must be taken in this analysis, once there are few trials and the number of patients included was not so impressive [27]. On the other hand, one author suggested improvement in perinatal outcome when cervical cerclage is indicated in asymptomatic twin pregnant women that present cervical dilatation (physical examination-indicated cerclage) at 16–24 weeks [28].

ACOG does not recommend cerclage in the incidental short cervix [7], but there is some evidence of benefit of this procedure when short cervix occurs in suspicious but not typical history of cervical insufficiency. The diagnosis can be performed by weekly transvaginal ultrasound since the 16th week. So, cerclage could be performed after shortening of the cervix in these cases, except in exposed membranes, chorioamnionitis, sepsis, and when there is no cervical length measurable [16].

2.4. Cervical pessary

Therefore, the Federal University of São Paulo (UNIFESP) has opted for treating the selected cases of preterm birth risk by short cervix, associated to the above-stated risk factors or previous preterm delivery. The standard treatment would be naturally micronized progesterone in the dosage of 200 mg/day, vaginally, or the combination of this therapy associated to cervical pessary AM-Ingamed. As of 2014, all the cases have been treated with pessary plus progesterone in the Department of Screening of Preterm Delivery of the UNIFESP.

This conduct was based on the studies of ProTwin and PECEP-Twins, which identified that twins with short cervix could benefit from the usage of the cervical pessary [29, 30].

Since January 2014 we have obtained 30 cases of dichorionic twin gestations with short cervix (≤25 mm). The gestational age of diagnosis varied between 18 and 27 weeks and 6 days (mean age of 24 weeks and 3 days ± 2.8 weeks). The mean cervical length of these gestations at the time of the pessary placement was 14.9 ± 6.8 mm, which reveals an extremely high risk.

In our series of cases, the mean gestational age of delivery was 34.59 ± 2.72 weeks, and in a group of 32 cases of dichorionic twin gestation, not selected by cervix, the mean delivery time

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was 35.83 ± 8.7 weeks. It shall be pointed out that between the time of delivery of the group with cervical pessary and the group not selected by cervix there was a small difference of 1.24 weeks—despite a big difference among the groups regarding the risk due to the cervix—with statistically no significant difference between the groups (P = 0.11). The mean interval of permanence with cervical pessary was 10.18 ± 3.6 weeks.

The result was 79% of the preterm deliveries below 37 weeks, 42% of premature newborns below 34 weeks, 17% below 32 weeks, and 4% below 28 weeks; in comparison, the study published by Fox et al. (2016) with similar case studies (cervix 11.9 ± 4.5 mm with 25.9 ± 2.1 weeks) obtained 44.4% of prematurity below 34 weeks and 28.6% below 32 weeks in patients treated with vaginal progesterone, only [31]. In the group of twins not selected by cervix, preterm birth below 37 weeks is obtained in 50% of the cases, preterm birth below 34 weeks in 19%, below 32 weeks in 9%, and no preterm delivery was registered below 28 weeks, as shown in **Table 1**.

It is important to notice that before 32 weeks (very high risk for adverse neonatal outcome) the group treated by pessary plus progesterone had a better performance if compared to the group treated only by progesterone, regarding cervical length in this group which was 3.0 mm lower.

A recent randomized clinical trial from Egypt (El-refaie's study), compared to the use of progesterone *versus* expectant management in twin pregnancies with short cervix. The number of SPB was considerably lower in progesterone group below 34 and 32 weeks, respectively, 53% (expectant) *versus* 35% (progesterone) and 30% (expectant) *versus* 12% (progesterone group); the mean cervical length was very similar between groups, close to 22 mm [32].

These data from El-refaie's trial are similar to data of twin pregnancy from UNIFESP. In this study pessary plus progesterone group (mean cervical length 14.3 ± 7.1 mm) presents a better performance when compared to El-refaie controls (with short cervix) and also to progesterone group (with short cervix) below 37, 34, 32, and 28 weeks. It is importantly emphasized that UNIFESP controls are not selected by cervix and its performance is better because this group presents lower risk when compared with all other groups. Another important issue is

Author	Treatment	Cervical length (mm)	Mean gestational age of delivery (weeks)	37weeks	34weeks Birth	32weeks Before	28weeks
UNIFESP short cervix	Pessary plus Progesterone	14.9± 6.8	34.59±2.72	79%	42%	17%	4%
Fox, N short cervix	Progesterone	11.9± 4.5	33.3 ± 3.9	Data not available	44.4%	28.6%	Data not available
UNIFESP not select by cervix	No treatment	Data not available	35.83± 8.7	50%	19%	9%	0

Table 1. Comparison of cervical length, mean gestational age of delivery, and percentage of deliveries according to the gestational age between different groups of treatment: pessary plus progesterone in short cervix twin pregnancy, only progesterone in short cervix twin pregnancy, no selected by cervix, and no treated twin pregnancy.

regarding the mean of cervical length which is lower in UNIFESP pessary plus progesterone group than El-refaie's groups, which cause higher risk to SPB to pessary group; so but the performance is better for pessary, despite high risk mentioned (**Figure 1**).

Considering the birthweight of twins not selected by cervix (n = 32), the mean weight of the biggest twin was 2.492 ± 643 g, and of the smallest twin, it was 2.195 ± 665 g; in comparison, in the twin group with short cervix treated by pessary plus progesterone (n = 24), the weight of the biggest one was 2.148 ± 434 g (p = 0.028), and of the smallest twin, it was 2.037 ± 425 g (p = 0.327), presenting a statistically significant difference between the groups for the biggest newborn, but no statistic difference for the smallest one. This result allows the conclusion that for the most vulnerable newborn (smallest one), the use of the cervical pessary was sufficient to modify the statistic difference expected, by cervical length difference, and in accordance with the difference registered between taller twins.

Furthermore, the use of the cervical pessary did not influence the weight difference between the fetuses. For the group not selected by cervix, the mean difference was 12 ± 6%; for the group of twins with short cervix, the difference was 11 ± 2% (p = 0.375).

This small difference demonstrates clear similarity between treated high-risk cases and cases of habitual twin pregnancy without involvement or diagnosis of complication factors in the prenatal routine (**Table 2**).

This study is according to a prospective, multicenter, randomized clinical trial conducted in Spain (PECEP-Twin). The primary outcome was SPB before 34 weeks of gestation. Neonatal morbidity and mortality were also evaluated. Cervical length was measured in 2287 women.

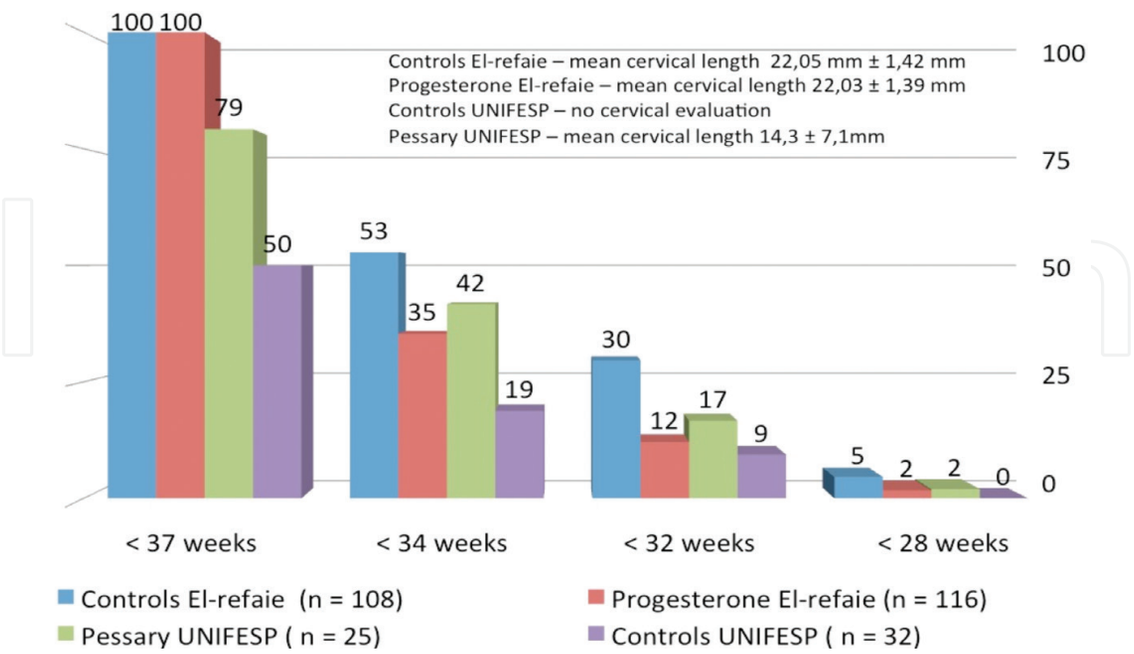

Figure 1. Comparison of percentage of SPB per gestational age between twin pregnancy from El-refaie's trial with short cervix (expectant and progesterone group) and UNIFESP twin pregnancy treated by pessary plus progesterone for short cervix and UNIFESP controls without selection by cervix.

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	Not selected by cervix	Short cervix	P
Biggest twin	2.492 ± 643g	2.195 ± 665g	0.028 *
Smallest twin	**2.148 ± 434g**	**2.037 ± 425g**	**NS**
Discordance of weight between twins	12 ± 6%	11 ± 2%	NS

Table 2. Comparison of birthweight and discordance of weight between groups with short cervix/treated by pessary plus progesterone twin pregnancy ***versus*** not selected/not treated twin pregnancy.

Figure 2. Comparison between the Arabin cervical pessary (blue) and the AM-Ingamed cervical pessary (yellow): They are similar regarding design, size, and texture. The dimensions (largest lower diameter × smallest upper diameter x height) of the most frequently used Arabin pessary are 70 × 32 × 25 mm, and of the Ingamed cervical pessary the dimensions are 70 × 30 × 25 mm.

Pregnant women (n = 137) with a sonographic cervical length (≤25 mm) were randomly selected to receive an Arabin cervical pessary (**Figure 2**) or expectant management (1:1 ratio). SPB < 34 weeks of pregnancy was significantly less frequent in the pessary group than in the expectant group (16.2% *vs*. 39.4%); relative risk, 0.41. No significant differences were observed in composite neonatal morbidity outcome (5.9% *vs.* 9.1%); relative risk, 0.64. No serious adverse effects associated with the use of a cervical pessary were observed or neonatal mortality (none) between the groups.

So, the insertion of a cervical pessary was associated with a significant reduction in the SPB rate. They propose the use of a cervical pessary for preventing preterm birth in twin pregnancies with short cervix [30], corroborating our data.

3. Tocolysis in multiple gestation

When an acute preterm labor is detected, it is possible to use tocolytic drugs to reduce uterine activity, and this is considered part of tertiary prevention. However, the diagnosis of preterm labor is not always simple, being generally defined as painful and regular contractions leading to cervical changes after the 20th week and before the 37th week of pregnancy.

The main goal of tocolysis is not to prevent preterm delivery, once the effectiveness for it is not proven [33]. However, tocolytic drugs can postpone delivery in 48 hours to 7 days, which is essential to manage antenatal corticosteroids to accelerate fetal pulmonary maturation and to transfer the patients to a tertiary care center when necessary [34, 35].

Tocolytic drugs should be administered when there is a clear benefit to the newborn, once the majority of these drugs has side effects to the mother and, sometimes, also to the fetus. So, it can be used from viability (23–24 weeks of pregnancy) until the 34th week, as most guideline recommendations propose. In special cases, they can also be used before viability, for example, in patients after an intra-abdominal surgery, when the cause of preterm labor is self-limited [34, 36, 37].

Contraindications for tocolytics include lethal fetal anomaly, preterm premature rupture of membranes, chorioamnionitis, severe preeclampsia and eclampsia, maternal hemorrhage with hemodynamic instability, suspected placental abruption, intrauterine fetal demise, and compromised fetal status [34].

Nowadays, the main drugs used in tocolysis are beta-agonists (as terbutaline), calcium channel blockers (as nifedipine), cyclooxygenase inhibitors (as indomethacin), and oxytocin receptor antagonist (as atosiban), as exposed in **Table 3**.

The ACOG recommends as first-line treatment in acute preterm labor in multiple pregnancy calcium channel blockers and cyclooxygenase inhibitors due to fewer side effects of these drugs [7]. In UNIFESP, the preference is for calcium channel blockers and oxytocin receptor antagonists.

3.1. Calcium channel blockers

The main drug of this class used in preterm birth inhibition is nifedipine, and many dosing regimens were proposed. Among tocolytics, nifedipine was the only drug that seems to statistically reduce neonatal morbidity and to increase gestational age at birth [38, 39].

In addition to being inexpensive, nifedipine is also administered orally and has less adverse maternal effects when compared to beta-agonists. When present, hypotension, flush, and headaches usually are not severe [37, 39].

The recommendation in UNIFESP is an initial dose of 10 mg orally every 20 minutes (maximum of 30 mg in 1 hour) until inhibition is reached, followed by 20 mg orally every 8 hours for up to 48 hours [40].

3.2. Oxytocin receptor antagonists

Atosiban is an oxytocin receptor antagonist and presents minimum side effects to both mother and fetus in inhibition of preterm labor. This is a positive aspect, since it leads to a better acceptance and compliance to treatment [39].

Meanwhile, this medication has a high cost and is administered intravenously. In the United States, atosiban is not available, because the US Food and Drug Administration (FDA) refused

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Drug Class	Recommended Regimen Dose	Characteristics and observations
Calcium Channels Blockers (Nifedipine)	Starting dose: 10mg orally every 20 minutes (maximum 30mg in one hour) until inhibition Maintenance dose: 20mg orally every 8 hours for up to 48h	Few maternal side effects (hypotension, flush, headaches)
Oxytocin receptor antagonists (Atosiban)	bolus of 6.75mg followed by a 300mcg/min infusion for 3 hours, and then 100mcg/min for up to 45 hours	Any contraindication, few side effects. Safety and efficacy questioned before 28 weeks of pregnancy (not available in the USA)
Beta-Agonists (Terbutaline)	Starting dose: 2.5-5.0mcg/min intravenously every 20-30min until inhibition (maximum: 25mcg/min) – maintain this dose for 12 hours After, decrease 2.5-5mcg/min every 20-30min and the minimum dose is maintained for more 12 hours	Many maternal side effects (tachycardia, tremor, palpitations, dyspnea, hyperglycemia, pulmonary edema). We suggest avoid its use in multiple pregnancy when possible
Cyclooxygenase inhibitors (Indomethacin)	Starting dose: 100mg per rectum Maintenance dose: 25mg orally every 6 hours for up to 48h	Should be used before 32 weeks of gestation and for no more than 48 hours, once it is related to premature constriction of the ductus arteriosus of the fetus and can be a cause of oligohydramnios

Table 3. Principal drugs used nowadays in tocolysis, with recommended regimen dose and important characteristics of them.

to approve it as a tocolytic due to the results of one trial, which questioned safety of this drug in pregnancies before 28 weeks. Perhaps, these findings can be explained by the concentration of oxytocin receptors that increases as more advanced the pregnancy is [41].

In UNIFESP, as in Europe, this tocolytic class is considered an interesting choice, and its administration begins with a bolus of 6.75 mg followed by a 300 mcg/min infusion for 3 hours and then 100 mcg/min for up to 45 hours [40].

3.3. Beta-agonists

The beta2-agonists cause relaxation of the myometrium, and the most studied drugs of this tocolytic class were terbutaline and ritodrine, which is no more commercialized in the United States.

Although efficient in postpone preterm labor, terbutaline is also known by many side effects to the mother (as tachycardia, tremor, palpitations, dyspnea, hyperglycemia and pulmonary edema) and to the fetus (tachycardia and neonatal hypoglycemia) [41, 42]. So, if possible, in multiple pregnancy, beta-agonists should be avoided to inhibit preterm labor.

In UNIFESP, when necessary, for example, in the absence of calcium channel blockers and atosiban, terbutaline is used by continuous intravenous infusion. The starting dose is 2.5–5 mcg/min, increasing 2.5–5 mcg/min every 20–30 minutes until inhibition has been reached (maximum dose is 25 mcg/min), and maintain this dose for 12 hours. Then, the infusion can be decreased 2.5–5 mcg/min every 20–30 minutes, and the minimum dose of terbutaline is maintained for more 12 hours [40].

3.4. Cyclooxygenase inhibitors

Indomethacin is considered a first-line drug for acute preterm labor in multiple pregnancy by the ACOG [7], once it is known its efficacy in postpone delivery by at least 48 hours after initiated the treatment.

However, it is important to be aware of adverse effects related to indomethacin. During treatment period, the mother is at higher risk of gastritis, esophageal reflux, and platelet dysfunction. And, the major risk is the premature constriction of the ductus arteriosus of the fetus and oligohydramnios due to reduction of fetal renal blood flow [43, 44].

If necessary, indomethacin can be administered for a maximum period of 48 hours and should be avoided after 32 weeks of gestation; when these complications are more common, it is important to notice that before 32 weeks the risk decreases, but is not zero [37, 41].

Loading dose recommended is 100 mg per rectum and then 25 mg orally every 6 hours up to 48 hours [40].

3.5. Prophylactic tocolysis

There is no evidence of benefit in using prophylactic and long-term tocolytic drugs to avoid preterm birth in multifetal pregnancy. Besides, the prolonged use of these medications leads to increase maternal side effects, including death [7].

4. Corticosteroids

Antenatal glucocorticoid treatment with corticosteroids is routinely used in women at risk of preterm delivery under 34 weeks of gestation [45]. Corticosteroids promote fetal lung

development between the 24th and 34th week of gestation [46] and reduce mortality of the preterm infant after delivery [47]. An important consequence of lung immaturity in preterm birth is the respiratory distress syndrome (RDS), and it is the great responsibility for the early neonatal mortality and the high cost of neonatal intensive care [47]. Preterm babies present higher risk of neurological impairment [48], which is the reason why the strategies for reduction of the risk of neonatal RDS and IVH in preterm delivery have received considerable attention [49].

A single course of corticosteroids reduces the risk of RDS from 40 to 21% in babies born before 32 weeks of gestation [46]. In recent publication (2017) of Cochrane Reviews, it was observed that treatment with antenatal corticosteroids was associated with an overall average reduction in IVH of 45%, average reduction in RDS of 34%, moderate to severe RDS was reduced to 41% compared with no exposure to antenatal corticosteroids, with less need for neonatal respiratory support, with a reduction in the need for mechanical ventilation/CPAP, fewer infants receiving corticosteroids needed surfactant, and was associated with a reduction in the incidence of necrotizing enterocolitis, as shown in **Table 4** [2].

However, an experimental study in Wistar rats in UNIFESP [50] evidenced that the groups presented different numbers of apoptotic neurons in the hippocampus, more precisely on the region named cornu ammonis 1 (CA1) and dentate gyrus (DG) after a single course of corticosteroids. The number of apoptotic neurons in the DG region was increased after corticosteroid use (by directly receptor activation), which caused, probably, the decrease in cell death in the CA1, as a compensatory reaction.

The increased apoptosis in DG and reduced cell death in the CA1 region can indicate the existence of an indirect compensatory pattern (statistically significant difference). A new balance was obtained in different areas of the hippocampus. There is no evidence in literature that the decrease in the number of apoptotic cells in CA1 is due to direct action of betamethasone, but the results suggest that this minor mortality is a compensation of a previous lesion in DG [50]. It is possible that inconclusive data referred to neurodevelopmental latency after corticosteroids (RR 0.64) described in Cochrane Review (**Table 4**), can be justified by abnormal neuronal apoptosis in the hippocampus.

Another important finding was described in a multicenter, cluster-randomized trial, within six countries (Argentina, Zambia, India, Kenya, Pakistan, and Guatemala) to standard care or an multifaceted intervention with teaching pregnant women how and when to use corticosteroids, including facilitation of the antenatal corticosteroid use with distribution of a kit with drug, material, and knowledge for application. The primary outcome was 28-day neonatal mortality among infants less than the 5th percentile for birthweight.

Fifty control clusters with 50,743 livebirths (2258 less than 5th percentile for birthweight [4%]) and 51 intervention clusters with 47,394 livebirths (2520 less than 5th percentile [5%]) completed follow-up. About 45% (1052/2327) of women in intervention clusters who delivered less-than-5th-percentile infants received antenatal corticosteroids compared with 10% (215/2062) in control clusters ($p < 0{\cdot}0001$).

Correlation with corticosteroids	Absolut value	RR	95% CI	N participants	Number of studies
Reduction perinatal death	28%	0,72	0.58 - 0.89	6729	15
Reduction neonatal death	31%	0.69	0.59 - 0.81	7188	22
Reduction IVH	45%	0.55	0.40 - 0.76	6093	16
Reduction in RDS	34%	0.66	0.56 - 0.77	7764	28
Reduction severe/mod RDS	41%	0.59	0.38 - 0.91	1686	6
Reduction mechanical ventilation / CPAP	32%	0.68	0.56 - 0.84	1368	9
Reduction necessity of surfactant	32%	0.68	0.51- 0.90	3556	5
Reduction of necrotizing enterocolitis	50%	0.50	0.32 - 0.78	4702	10
Death in childhood after exposure to corticoids	32%	0.68	0.36 - 1.27	1010	4
Neurodevelopmental delay	46%	0.64	0.14 - 2.98	82	1
Increasing tolerance of glucose in group of corticosteroids		2.71	1.14 - 6.46	123	1
Systemic infection in the first 48 hours after birth	40%	0.60	0.41 - 0.88	1753	8
AG had an lower than 7 Apgar score of 5 min.	19%	0.81	0.67 - 0.98	2419	10
Reduction developmental delay in childhood	51%	0.49	0.24 - 1.00	518	2
Increase of cerebral palsy	40%	0.60	0.34 - 1.03	904	5

Table 4. Correlation between complications of SPB and use of corticosteroids (Cochrane Review, 2017 [2]).

Among the less-than-5th-percentile infants, 28-day neonatal mortality was 225 per 1000 live-births for the intervention group and 232 per 1000 livebirths for the control group (relative risk [RR] 0·96, 95% CI 0·87–1·06, p = 0·65), and suspected maternal infection was reported in 236/2361 (10%) women in the intervention group and 133/2094 (6%) in the control group (odds ratio [OR] 1·67, 1·33–2·09, p < 0·0001).

Among the whole population, 28-day neonatal mortality was 27·4 per 1000 livebirths for the intervention group and 23·9 per 1000 livebirths for the control group (RR 1·12, 1·02–1·22, p = 0·0127), and suspected maternal infection was reported in 1207/48219 (3%) women in the intervention group and 867/51523 (2%) in the control group (OR 1·45, 1·33–1·58, p < 0·0001).

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Despite the increased use of antenatal corticosteroids in low-birthweight infants in the intervention groups, neonatal mortality did not decrease in this group and increased in the population overall. For every 1000 women exposed to this strategy, an excess of 3·5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased [12].

4.1. When and how to use corticosteroids for lung maturation

The treatment consists in betamethasone administration intramuscularly two 12 mg doses 24 hours apart or dexamethasone intramuscularly four 6 mg doses every 12 hours.

A single course of corticosteroids must be considered in twin pregnancy between 24th and 33rd week that have high risk of preterm delivery within 7 days, including for those with ruptured membranes and if the first course was administered previously more than 14 days. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation. A rescue course of corticosteroids can be considered before 7 days from the first dose if there is some clinical indication for that [51].

A new recommendation from the ACOG suggests that in pregnancy during the 34–37th week, the use of corticosteroids could be beneficial, even during this late period of pregnancy, regardless of the number of fetuses [7, 52].

Administration of corticosteroids can be considered in twin pregnancy between the 34th and 37th week which are in risk of preterm birth within 7 days and which have not received the previous course of betamethasone [52].

Unfortunately, according to the WHO, in Brazil only 30% of preterm birth received antenatal corticosteroids to lung maturation between 2010 and 2011 [53], whereas several pregnancies received unnecessary corticosteroids, without real indication for that [54].

5. Neuroprotection: the use of magnesium sulfate

In 1995, it was suggested that magnesium sulfate was a neuroprotector, decreasing the prevalence of cerebral palsy in very-low-birthweight newborns [55]. Since then, several studies have been conducted to elucidate this aspect.

Despite clinical trials have failed proving reduction of infant death, the use of antenatal magnesium sulfate for neuroprotection statistically diminished the risk of cerebral palsy in the survivors [56, 57]. Therefore, its use is recommended in cases of high risk of imminent preterm birth, in single and multiple pregnancies, in gestations <32nd week, and after viability [7, 34].

Many mechanisms were proposed to explain the neuroprotective effect of magnesium sulfate, but the exact one is actually unknown. Other questions about magnesium sulfate that are not yet clarified are best dose regimen, treatment duration, and risks or benefits of retreatment. An interesting point that were recently approached is that the exposure to magnesium

proximal to delivery (<12 hours) seems to be related to more significant reduction of cerebral palsy when compared to the last infusion of this drug more than 12 hours before delivery [58].

In UNIFESP, this drug is administered intravenously, with a loading dose of 4 g in 20 minutes, followed by 1 g/h for up to 24 hours or until delivery [40]. Monitoring these pregnant women (by continuous evaluation of patellar reflex, respiratory frequency, urine output) is essential to prevent magnesium toxicity. Myasthenia gravis and myocardial compromise are contraindications for the use of magnesium sulfate, and adjusted dose should be used in patients with renal insufficiency [59].

6. Conclusion

The evaluation of the clinical history of the previous preterm birth and the presence of short cervix (≤25 mm) are the best predictors of preterm delivery in twin pregnancy. Transvaginal ultrasonography for evaluation of the uterine cervix between the 18th and 24th week should be indicated for its cost-effectiveness.

The use of isolated vaginal progesterone in multiple pregnancies with short cervix presents evidence that justifies its use; however, this evidence is to be confirmed by other clinical tests due to the potential bias of the most recent meta-analysis.

Most guidelines do not recommend the use of prophylactic cerclage in patients with short cervix; however, in selected cases of extreme severity, it can be considered.

The use of a cervical pessary does not present solid evidence; however, some studies point out, although with a low level of evidence, that it may be beneficial.

As the low index of complications and the absence of highly efficient intervention in twins justify the utilization of the association of progesterone and cervical pessary, for this author it seems to be better than observing the evolution of the clinical condition.

The use of corticosteroids, between 24th–25th and 34th week, must be indicated in pregnancy in the imminence of delivery or with a high risk of preterm birth and must be avoided in pregnancy with intermediate or low risk, as there are studies which point out undesired effects of this treatment in the short and medium term.

Tocolytics is to be used under the 34th week in order to gain time for carrying out corticosteroids. The first-option drugs in twin pregnancy are the calcium channel blockers.

The use of magnesium sulfate in deliveries under the 32nd week is recommended by the main scientific societies, for the purpose of neuroprotection in twin pregnancy.

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