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Prevention of spontaneous preterm birth in twins – are there any effective interventions?

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2021

Prevention of spontaneous preterm birth in twins – are there any effective interventions?

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Abril 2021

Porto, 15 de abril de 2021

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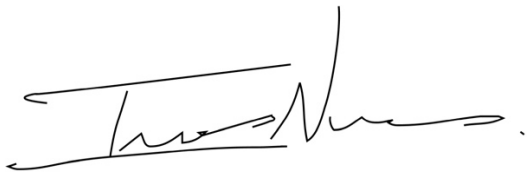

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Agradecimentos

À Prof. Doutora Inês Nunes, por toda a ajuda, compreensão e disponibilidade ao longo do processo. Agradeço a amabilidade, interesse e rigor que sempre fizeram parte da sua orientação.

À Dr.ª Joana Dias, pela colaboração e sugestões enriquecedoras. Muito obrigada por toda a disponibilidade e simpatia.

Aos meus avós, pela semente. Aos meus pais, por serem porto seguro. Aos meus irmãos, pelo apoio, em especial à Inês, por ser luz e exemplo. Aos meus amigos, por me acompanharem neste percurso.

Resumo

Introdução: O parto pré-termo ocorre, por definição, antes das 37 semanas de gestação e constitui uma das principais complicações obstétricas. Está associado a um aumento da morbi-mortalidade perinatal. O parto pré-termo ocorre em aproximadamente 50% das gestações múltiplas. Assim, a gestação múltipla constitui um importante fator de risco independente para o parto pré-termo espontâneo.

Objetivos: Avaliar a melhor evidência sobre a eficácia das intervenções disponíveis para a redução do risco de parto pré-termo espontâneo na gravidez múltipla.

Desenvolvimento: A identificação das gestações múltiplas com risco acrescido de parto pré-termo espontâneo é essencial para prevenir eficazmente a sua ocorrência. O colo curto (≤25mm), em grávidas assintomáticas no segundo trimestre, e os níveis elevados de fibronectina fetal (>50 ng/mL), em grávidas com pródromos de parto pré-termo e também em grávidas assintomáticas, são os melhores preditores de risco de parto pré-termo nas gestações múltiplas. A progesterona vaginal constitui uma intervenção eficaz na prevenção de parto pré-termo, particularmente antes das 32 semanas de gestação, em mulheres com um colo curto, estando potencialmente associada a um aumento do risco de parto pré-termo em gestações com colos de maior comprimento. A ciclorrafia, quando realizada por indicação clínica, parece ser benéfica como medida preventiva quando há dilatação cervical de 1-5 cm, estando associada a uma importante diminuição da mortalidade neonatal. Não existe evidência científica de que o uso de pessário cervical, tocólise e alectuamento sejam medidas eficazes na prevenção do parto pré-termo nas gestações múltiplas.

Conclusão: Nas gestações múltiplas, a vigilância deverá incluir métodos eficazes de rastreio de risco acrescido de parto pré-termo, nomeadamente a medição ecográfica do comprimento do colo. De acordo com a evidência atual, as intervenções eficazes para a prevenção do parto pré-termo em gémeos são a progesterona vaginal, em mulheres com colo curto, e a ciclorrafia, na presença de dilatação cervical. No entanto, esta é uma área de investigação contínua que carece de melhor evidência com vista a uma orientação mais uniforme e consensual destas grávidas.

Abstract

Introduction: Preterm birth is defined as a delivery that occurs before 37 weeks of gestation and is a major adverse obstetric outcome. It is associated with an increase in perinatal morbidity and mortality. Preterm birth occurs in approximately 50% of twins and thus multiple gestation is an important independent risk factor for spontaneous preterm birth.

Aim: To determine which are the most effective interventions in the reduction of the risk of spontaneous preterm labour in multiple gestations.

Discussion: Identifying multiple gestations with an increased risk of spontaneous preterm birth is essential in order to apply targeted preventive interventions. The best predictors of preterm birth in multiple gestations are a short cervix (≤25mm), in asymptomatic women in midtrimester ultrasound, and elevated levels of fetal fibronectine (>50 ng/mL), in women with preterm birth symptoms and in asymptomatic women. Vaginal progesterone is an effective intervention in preventing preterm birth, particularly before 32 weeks of gestation, in women with a short cervix; however, it may be associated with an increased risk of preterm birth in longer cervical lengths. Physical examination-indicated cervical cerclage is also an effective intervention when there is a 1-5 cm cervical dilation, and it is associated with an important decrease in neonatal mortality. Cervical pessary, tocolysis and bed rest have no benefit in preventing preterm birth in multiple gestations.

Conclusion: In multiple gestations, surveillance should include effective methods of screening for increased risk of preterm birth, including midtrimester cervical length measurement. Current evidence suggests that vaginal progesterone in women with a short cervix and cervical cerclage when there is cervical dilation are effective interventions in preventing preterm birth. Further research is still necessary to establish a standardized approach to these patients.

Keywords: *preterm birth; multiple pregnancy; twins; cervical cerclage; progesterone; Arabin pessary*

Abbreviations

17-OHPC	17-α-hydroxyprogesterone caproate
AFP	alpha fetoprotein
aOR	adjusted odds ratio
CI	confidence interval
CL	cervical length
CRH	corticotrophin-releasing hormone
fFN	fetal fibronectine
HR	hazard ratio
IGFBP-1	insulin-like growth factor binding protein-1
IL-8	interleukin-8
IM	intramuscular
MMP-8	matrix metallo protein-8
mshCG	chorionic gonadotrophin
NICU	neonatal intensive care unit
OR	odds ratio
PAF	platelet activating factor
PAPP-A	plasma protein A
PTB	preterm birth
RR	relative risk
SP-A	surfactant protein-A
SPTB	spontaneous preterm birth
w	weeks of gestation
WHO	world health organization

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1. Introduction

The World Health Organization (WHO) defines preterm labour as a delivery that occurs at less than 37 weeks or 259 days of gestation. Preterm labour has a high prevalence worldwide and is a major perinatal health problem, particularly when it happens before 34 weeks and more relevantly before 32 weeks of gestation. Globally, the incidence of preterm labour is approximately 11%, varying between 5% in Northern Europe and 15% in some Asian and African countries.[1] According to the Portuguese Society of Paediatrics, the incidence of preterm labour in Portugal is 8% and 1,2% of births occur before 32 weeks of gestation.[2] Regarding twin gestations, they represent 18% of all preterm births and the incidence of preterm labour is twelve times higher when compared with that of singleton gestations. In twins, preterm labour before 37 weeks of gestation occurs in approximately 50% of the gestations and 10% are associated with preterm labour before 32 weeks of gestation.[3,4]

Preterm labour is the main cause of morbidity and mortality in the perinatal period. In fact, in 2015, complications associated with preterm labour represented the main cause of death in children younger than 5 years old.[5] Complications derived from preterm labour include short and long-term manifestations. The risk of long-term sequelae increases with short-term complications such as acute respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis, sepsis or retinopathy. There is an increase in the severity of complications associated with preterm labour with decreasing gestational age. For all these reasons, prevention of preterm labour is of extreme importance.[6]

Twin gestations have been reported to be increasing in frequency worldwide, representing 3 to 4% of all gestations. The increase in multiple gestations is usually explained by the increase of maternal age and by the increasing use of medically assisted reproductive techniques.[7] However, in the United States of America, according to the National Center for Health Statistics, after a steady increase in the twin birth rate since the 1980s, there was a 4% decline between 2014 and 2018. The analysis of the results by maternal age found that this decline only happened in the 30 and over age group (10% reduction) and with more relevance in the 40-54 age group (23% reduction).[8] It is believed that this decrease could be associated with the advancement of medically assisted reproductive techniques, mainly regarding the number of embryos needed to be transferred per cycle to have a successful implantation, which has been decreasing.

Multiple gestations are associated with a higher perinatal morbidity - the main contributor of which is preterm labour and, consequently, prematurity. Although multiple gestations represent a small fraction of all pregnancies, they represent an important proportion of all gestations that result in preterm labour. In fact, multiple gestation alone is a risk factor for preterm labour. Approximately

two-thirds of multiple gestations are dichorionic[9] and chorionicity is a major factor at play in the incidence of preterm labour. Monochorionic gestations are associated with a higher risk of preterm labour and prenatal complications and the main reason seems to be the twin-to-twin transfusion syndrome. Other complications associated with monochorionic gestations that influence the incidence of prematurity are intrauterine growth restriction and twin anemia-polycythemia sequence.[3] Before 34 weeks of gestation, preterm labour is approximately ten times more frequent in dichorionic twins and sixteen times more frequent in monochorionic twins when compared with singleton gestations.[10]

The aetiology of preterm labour can be divided into spontaneous and iatrogenic. Before 36 weeks of gestation, 60% of all preterm births are spontaneous.[11] Twin pregnancies are associated with a higher risk of maternal and perinatal complications and a higher rate of obstetric interventions. Therefore, approximately one-third of premature births in this context are iatrogenic. The most common iatrogenic indications to terminate pregnancy before term are related to hypertensive disorders of pregnancy, more specifically pre-eclampsia. Spontaneous preterm birth in multiple gestations can have several different causes that can differ from spontaneous preterm birth in singleton pregnancies, given the fact that multiple gestations have certain and specific physiologic characteristics derived from the bigger dimensions of the placenta tissue and the fetuses. This includes a bigger uterine distention and a higher quantity of production of corticotrophin-releasing hormone (CRH) by the placenta and surfactant protein-A (SP-A) by the fetal lungs, factors that increase the contractility of the myometrium and may contribute to the process associated with preterm labour.[12]

2. Objectives

The objective of this literature review is to determine which interventions are effective in the reduction of the risk of spontaneous preterm labour in multiple gestations.

3. Methodology

An integrative literature review was conducted. A bibliographic search in MEDLINE was carried out using relevant keywords and with particular focus on systematic reviews and meta-analysis, randomized-controlled trials and prospective studies, published in the last 30 years, written in English and with full-text available. The search was performed using the following queries with MeSH keywords: multiple gestation AND vaginal progesterone; multiple gestation AND cervical pessary; multiple gestation AND cervical cerclage; multiple gestation AND tocolysis; multiple

gestation AND bed rest. The results were screened by analysing the titles and abstracts in order to identify relevant articles. The articles were collected and organized using Mendeley Desktop 1.19.4 and Mendeley Web Importer.

The quality of the body of evidence of each intervention to reduce spontaneous preterm birth in twins was assessed using the GRADE approach.[13]The GRADE approach results in an assessment of the quality of evidence in four grades: (i) high: we are very confident that the true effect lies close to that of the estimate of the effect; (ii) moderate: we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (iii) low: our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect; and (iv) very low: we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

4. Risk factors for spontaneous preterm birth in multiple gestations

Regarding preterm birth in general, some associated risk factors that are important to note include: history of abortion with uterine surgery evacuation, cervical surgery, uterine malformations (congenital or acquired), ethnicity (non-hispanic black women seem to have a higher incidence of preterm birth), extremes of maternal age and body mass index, maternal chronic health problems such as hypertension, type 1 diabetes mellitus, renal insufficiency and depression, infection/inflammation (chorioamnionitis and genital tract infections), short interpregnancy interval, smoking, maternal alcohol and substance abuse and stress. Some fetal factors like male sex, certain congenital anomalies and intra-uterine growth restriction are also associated with a higher risk of preterm birth.[14]

Preterm birth in twins is most likely multifactorial, and multifetal gestations by themselves are associated with an increased risk of preterm birth and prematurity. Certain physiologic characteristics related to the larger fetal size, placental mass and amniotic fluid volume may trigger delivery, resulting in a higher incidence in preterm birth. The possible contributors for preterm labour in this population include increasing uterine stretch, higher production of corticotrophin-releasing hormone (CRH) by the placenta and augmented secretion of surfactant proteins and lipids by the fetal lung into the amniotic fluid.[15]

Mechanical uterine stretch has been proven, in animal and *in vitro* experiments, to increase the expression of gap junctions, oxytocin receptors and inflammatory signaling proteins in the myometrium.[15]

Multiple gestations, due to their bigger placenta, produce higher quantities of CRH when compared with singleton gestations. CRH plays an important role in labour onset when its levels increase exponentially and it has been hypothesized that it leads to myometrial contraction by changing the progesterone and estrogen balance, favouring an estrogenic environment.[15]

Fetal lung production of surfactant protein-A (SP-A) and platelet activating factor (PAF) might stimulate myometrial contractility and lung maturity. Lung maturation occurs earlier in twins (32 weeks) than in singletons (36 weeks).[15]

Additionally, it is important to consider other risk factors that may be useful in accessing the overall risk of preterm birth. Previous history of preterm singleton birth is associated with an approximately 3 times higher risk of preterm birth in multiple gestations, especially when the previous birth is spontaneous.[16,17] Urinary tract infections seem to be associated with preterm birth before 35 weeks and conception by in-vitro fertilization is associated with a higher rate of preterm birth before 37 weeks of gestation. Some nutritional factors such as iron-deficiency anemia, high third trimester serum ferritin levels, fasting and ketonuria are associated with an increased risk of preterm birth. Calcium supplementation in women with low calcium intake and a higher intake of omega-3 fatty acids are associated with a lower incidence of preterm birth.[18]

5. Prediction of spontaneous preterm birth in multiple gestations

In order to apply targeted interventions to women with increased risk of preterm labour, it is important to be able to identify this group of women. The identification of strong, cost-effective predictors of preterm birth is therefore essential for its prevention.

5.1 Cervical length

Many strategies used nowadays to reduce the incidence of spontaneous preterm birth are applied specifically to women with a short cervix. A short cervix is traditionally defined by transvaginal ultrasound in the second trimester as a measured length inferior or equal to 25 mm. A short cervical length has been established as a good predictor of spontaneous preterm birth in asymptomatic women with both singleton or multiple gestations.[19]

In asymptomatic women with twin pregnancies, a cervical length inferior or equal to 20 mm, between 20 and 24 weeks, is associated with a higher risk of preterm birth before 32 (sensitivity: 39%; specificity: 96%; positive likelihood ratio: 10.1; negative likelihood ratio: 0.64) and 34 weeks (sensitivity: 29%; specificity: 97%; positive likelihood ratio: 9.0; negative likelihood ratio: 0.74). A cervical length inferior or equal to 25 mm detected at the same gestational age is associated with preterm birth before 28 weeks, with a positive likelihood ratio of 9.6. However, a normal cervical length is not accurate in predicting the absence of risk of preterm birth. A short cervical length is a

less accurate predictor when detected after 24 weeks of gestation, providing minimal changes on the pre-test probability of preterm birth.[20]

Repeated measurements of cervical length over time have not proven to be useful since the predictive accuracy for preterm birth, between 28 and 34 weeks, in multiple pregnancies is low to moderate, with a sensitivity of 47-73%, a specificity of 84-89%, a positive likelihood ratio of 3.8-5.3 and a negative likelihood ratio of 0.3-0.6. The predictive accuracy of cervical length for preterm birth is not statistically significant when measured over time comparing with a single initial or final measurement.[21]

In multiple gestations, the use of transvaginal sonography to determine cervical length and the subsequent risk of spontaneous preterm birth seems to be most advantageous in asymptomatic women, between 18 to 24 weeks of gestation and one single time. [20,21]

5.2 Fetal fibronectine

Fetal fibronectine is a glycoprotein that is produced in fetal tissues and can be found in the amniotic fluid and placental tissue. It plays a role in the implantation and attachment of the placenta to the endometrium throughout gestation. It can be measured in cervicovaginal secretions in early gestation and at term. But it is often not detected between 20 and 37 weeks in normal gestations that are delivered at term. It is hypothesised that fetal fibronectine can be found in the cervix and vagina when there is damage to the fetal membranes and therefore it could be used as a predictive test for preterm labour. Its use as a predictive test has been given more relevance for its high negative predictive value, mainly in symptomatic women, suggesting that it could be used as a tool in women with symptoms of preterm labour to exclude the probability of preterm labour onset.[22]

A 2010 systematic review[22] was conducted in order to determine if the measurement of cervicovaginal fetal fibronectine was useful in the prediction of spontaneous preterm birth in multiple gestations (11 studies with 1009 asymptomatic women and 4 studies with 212 symptomatic women were included). It was shown that fetal fibronectine has limited accuracy in spontaneous preterm birth prediction in both symptomatic and asymptomatic women with multiple gestations. In asymptomatic women, the pooled sensitivity was 33-45%, specificity 80-94%, positive likelihood ratio 2-5.5 and negative likelihood ratio 0.68-0.76. The measurement of fetal fibronectine was most accurate in predicting spontaneous preterm birth before 32 weeks of gestation in asymptomatic women and within 7 days of measurement in women with threatened preterm labour (pooled sensitivity 85%, specificity 78%, positive likelihood ratio 3.9, negative likelihood ratio 0.2). It also showed a relevant negative predictive value: only 1.6% of women with a negative test for cervicovaginal fetal fibronectine and threatened preterm birth delivered within the next 7 days.

In a more recently published systematic review[23] that included 16 studies with 2347 women, symptomatic women had a rate of delivery within 14 days of testing significantly higher when fetal fibronectine test was positive (odds ratio 13.95, 95 % CI 4.33-44.98), there was also a significant association with preterm birth before 32 (odds ratio 28.47, 95% CI 1.32-612.60) and 34 weeks of gestation (odds ratio 3.07, 95% CI 1.44-6.57). Regarding asymptomatic women, a positive fetal fibronectine test was associated with a significant increase in preterm birth before 32 (odds ratio 10.54, 95% CI 5.66-19.64), 34 (odds ratio 8.07, 95% CI 5.28-12-33) and 37 weeks of gestation (odds ratio 6.21, 95% CI 4.34-8.87).

A retrospective cohort study[24] was conducted in order to determine if the combined use of fetal fibronectine test and cervical length measurement between 22 and 32 weeks of gestation was useful in predicting spontaneous preterm birth in asymptomatic multiple gestations. Cervical length was considered short if lower than 20 mm and fetal fibronectine was considered positive when higher or equal to 50 ng/mL. A positive fetal fibronectine test and short cervical length were associated with a higher rate of spontaneous preterm birth before 28 to 37 weeks of gestation (adjusted hazard ratio 4.75, 95% CI 1.98-11.35). The combination of both was a better predictor for preterm birth at all gestational ages than either test alone and was most useful from 28 to 32 weeks of gestation. Sub-analysis showed that a positive fetal fibronectine test was a better predictor of spontaneous preterm birth than a short cervical length (fFN adjusted hazard ratio 5.86, 95% CI 3.11-11.05 versus short CL adjusted hazard ratio 1.53, 95% CI 0.90-2.61). In the short cervical length group, the time from testing to delivery was significantly shorter in women who also had a positive fetal fibronectine test. It is important to note that in women with both positive tests, the group who had a previous history of preterm birth had a significantly higher rate of preterm birth before 35 weeks of gestation. In summary, it is suggested that the quantification of fetal fibronectine and cervical length measurement, between 22 and 32 weeks of gestation, could be useful as a screening method for preterm birth in asymptomatic multiple gestations. The frequency of testing is still unknown, but every 2 to 3 weeks seems to be reasonable.

Regarding women with multiple gestation and symptoms of imminent preterm birth, a more recent retrospective study[25] showed no statistically significant prediction of preterm birth when cervical length was inferior or equal to 20 mm. However, a positive fetal fibronectin test was a strong predictor of preterm birth within 7 (odds ratio 6.8, 95% CI 1.3-34.9) and 14 days of testing (odds ratio 9.8, 95% CI 2.1-45.1).

Therefore, the evidence strongly suggests that the fetal fibronectine test in twins is an accurate predictive test to assess the imminent risk of preterm birth, both in symptomatic and asymptomatic women with a short cervix. This test can be useful to reduce unnecessary interventions in women with short cervix.

5.3 Other biochemical predictors

Other biochemical predictors have been studied in this field and the findings of a recently published systematic review[23] show a positive association with preterm birth for the following biomarkers: elevated maternal serum human Chorionic Gonadotrophin (mshCG), elevated maternal serum Alpha Fetoprotein (AFP), low 25-Hydroxy Vitamin D values, positive phosphorylated Insulin-like Growth Factor Binding Protein-1 (phIGFBP-1) test and high interleukin-8 (IL-8) levels. A positive Matrix Metallo Protein-8 (MMP-8) test was associated with delivery within 7 days of testing. On the other hand, low Pregnancy Associated Plasma Protein A (PAPP-A) levels, elevated relaxin serum levels, a positive granulocyte elastase test, the presence of maternal intrauterine infection (including chorioamnionitis and positive amniotic fluid culture) and bacterial vaginosis showed no increase in preterm birth.

Despite the presented data showing a positive association of some biomarkers in the prediction of preterm birth in multiple gestations, further investigation is still necessary to evaluate their clinical role.

5.4 Cervical Funneling

Cervical funneling represents an opening of the internal os of the cervix superior or equal to 3 mm evaluated by transvaginal ultrasound. It was shown to be a predictor of preterm birth before 32 weeks of gestation in twins, when accessed at 22 weeks of gestation, having a similar predictive value as cervical length measurement. Spontaneous funneling between 18 and 26 weeks of gestation is associated with a higher risk of preterm birth before 32, 35 and 37 weeks of gestation (sensitivity 24-53%, specificity 87-94%, positive likelihood ratio 2.2-6.1, negative likelihood ratio 0-0.8). The fact that it represents a measurement that is difficult to quantify objectively makes it less useful clinically as a predictor of spontaneous preterm birth than cervical length measurement.[3,26,27]

5.5 Amniotic fluid sludge

Amniotic fluid sludge is identified by ultrasound and characterized by dense aggregates close to the internal cervical os, with imaging similar to gallbladder sludge. A retrospective cohort study[28] including twin pregnancies with a short cervical length between 16 and 26 weeks of gestation showed that amniotic fluid sludge was associated with earlier delivery (27.2 ± 5.6 weeks versus 31.0 ± 4.05 weeks, $P< 0.01$) and higher incidence of preterm birth before 26 (odds ratio 7.63; 95% CI, 1.745-38.19), 28 (odds ratio 6.75; 95% CI, 1.72-27.63) and 30 weeks of gestation (odds ratio 5.41; 95% CI, 1.45-21.3). Additionally, the presence of amniotic fluid sludge was also associated with a higher rate of histological chorioamnionitis, lower birthweight, longer stay in NICU and neonatal death (odds ratio 12.25; 95% CI, 2.16-122.50). In women with a short cervical length, the presence of

amniotic fluid sludge is an additional risk factor for extreme preterm birth and neonatal mortality and morbidity.[28]

6. Prevention of spontaneous preterm birth in singleton pregnancies

Currently, there are many interventions studied and applied to reduce the risk of spontaneous preterm birth in singleton pregnancies. In order to discuss the relevant methods applicable to multiple gestations, it is important to firstly understand the available methods used in singleton pregnancies.

Bed rest, at home or in hospital, has proven to be ineffective in preterm birth prevention (risk ratio 0.92, 95% CI 0.62-1.37) and because of its associated maternal adverse effects, both mental and physical (such as the increased risk of venous thrombosis and musculoskeletal symptoms), and a potential increase of financial healthcare costs it is not recommended in singleton gestations.[29]

The recently published PROLONG Study proved, contrarily to the previous findings, that the administration of a weekly intramuscular injection of 250 mg of 17-OHPC has no benefit in reducing the incidence of recurrent preterm birth before 35 weeks of gestation (relative risk 0.95, 95% CI 0.71-1.26).[30]

Additionally, cervical pessary has also been proven not beneficial in preventing preterm birth before 34 weeks of gestation in asymptomatic singleton pregnancies with a short cervical length (relative risk 0.80, 95% CI 0.43-1.49).[31]

However, the use of vaginal progesterone has been proven effective in reducing the rate of preterm birth in asymptomatic women with a short cervix in the second trimester, with a significant reduction of risk of preterm birth before 33 weeks of gestation (relative risk 0.62, 95% CI 0.47-0.81). The incidence of preterm birth before 28 to 36 weeks is overall significantly lower when vaginal progesterone is administered. These benefits are not associated with any harmful maternal, neonatal and early childhood (until 2 years of age) effects. In fact, vaginal progesterone is linked with a decrease in the incidences of respiratory distress syndrome, neonatal morbidity and mortality, low birthweight and admission to NICU. The evidence thus supports the clinical application of the second trimester ultrasound screening of the short cervix, in the general population, and the subsequent administration of vaginal progesterone if short, in order to reduce preterm birth and its associated perinatal morbidities and mortality.[32]

The findings of the recently published EPPPIC meta-analysis[33] suggest that in asymptomatic women at risk of preterm birth because of previous history of preterm birth or short cervix, vaginal progesterone reduces the risk of preterm birth before 34 weeks of gestation (relative risk 0.78, 95% CI 0.68-0.90) and the reduction is more significant in women with a short cervix. Despite 17-OHPC not showing a statistically significant reduction in preterm birth, there was no clear evidence of difference in progesterone treatment effect based on the indication (short cervix or

previous history) or route of administration. Therefore, vaginal progesterone may be useful in preventing preterm birth in women with a previous history of preterm birth regardless of cervical length, but further research in this subgroup is still necessary.

Cervical cerclage has also been shown to be beneficial in the prevention of preterm birth before 35 weeks of gestation in women with a short cervix before 24 weeks of gestation if they also have a prior history of previous spontaneous preterm birth (relative risk 0.7, 95% CI 0.55– 0.89). The incidence of preterm birth between 24 and 37 weeks of gestation is also overall lower and there is a significantly lower perinatal morbidity and mortality (relative risk 0.64, 95% CI 0.45– 0.91) when cervical cerclage is used.[34,35]

In summary, the available methods that show a benefit in preventing spontaneous preterm birth in singleton pregnancies are the administration of vaginal progesterone in women with a short cervix in the second trimester transvaginal ultrasound or a previous history of preterm birth; as well as cervical cerclage in women with a short cervix and a previous history of preterm birth.

7. Prevention of spontaneous preterm birth in multiple gestations

7.1 Cervical Cerclage

Cervical cerclage is a surgical procedure first introduced in the 1950s that provides mechanical support to maintain the structural integrity of the cervical canal in order to narrow the cervix and prevent its opening and shortening, thus preventing preterm birth. The McDonald technique is the most commonly used. In general, according to the American College of Obstetricians and Gynecologists, cervical cerclage can be history-indicated (based on obstetric history), ultrasound-indicated (when a short cervical length is detected) or physical examination-indicated (when there is advanced cervical dilation).[36]

7.1.1 History-indicated

A Cochrane review published in 2014[37] including 128 women with multiple gestations evaluated the use of history-indicated and ultrasound-indicated cervical cerclage (cervical length inferior to 25 mm). It did not include any trial comparing the different cerclage protocols. Cervical cerclage, for all indications pooled together, showed no difference in neonatal mortality or morbidity and preterm birth before 34 weeks or 35 weeks of gestation.

In a systematic review and meta-analysis published in 2019[38] that included 2 randomized controlled trials and 4 cohort studies regarding history-indicated cerclage performed at 12-16 weeks of gestation, the data was limited and cervical cerclage did not seem to be beneficial in reducing

preterm birth before 28 to 37 weeks of gestation or in improving perinatal outcomes, regardless of previous preterm birth history.

7.1.2 Ultrasound-indicated

Regarding ultrasound-indicated cerclage, in the 2014 Cochrane review mentioned above, there was no difference in preterm birth, but there was an increase in low birthweight, very low birthweight and respiratory distress syndrome. However, due to the small sample size and heterogeneity in the subgroups, it was not possible to clearly conclude its harmfulness. There was no available data on long-term neurodevelopment outcomes in early childhood.

A systematic review and meta-analysis, published in the following year,[39] included 49 asymptomatic twin pregnancies with a short cervical length (inferior to 25 mm) detected by transvaginal ultrasound prior to 24 weeks of gestation. There was no significant statistical difference in the preterm birth before 34 weeks of gestation and in most secondary outcomes, except in very low birth weight (<1500 g) (adjusted odds ratio 2.22, 95% CI 1.07–5.73) and respiratory distress syndrome (adjusted odds ratio 3.88, 95% CI 1.09–21.03) which were more frequent in the cerclage group. It is important to note that the analyzed trials were designed to include singleton and multiple gestations, with a small number of twin gestations being randomized.

A retrospective cohort study also published in 2015[40] analyzed the use of cervical cerclage in asymptomatic twin pregnancies with a transvaginal cervical length inferior or equal to 25 mm at 16 to 24 weeks of gestation. The McDonald technique was predominantly used and there was no difference in gestational age at delivery when compared with the Shirodkar technique. There was no statistically significant change in the incidence of spontaneous preterm birth before 28, 32 and 34 weeks of gestation; however, when analyzing the cervical length inferior or equal to 15 mm subgroup, cervical cerclage was associated with a delay in labour onset by almost 4 weeks (12.5±4.5 versus 8.8±4.6 weeks, P<0.001), decreasing significantly the incidence of spontaneous preterm birth before 34 weeks by 49% (adjusted odds ratio 0.51, 95% CI 0.31-0.83) and of NICU admissions by 58% (adjusted odds ratio 0.42, 95% CI 0.24-0.81). Additionally, cervical cerclage was not associated with an increase in adverse perinatal outcomes. There was no difference in the incidence of preterm birth in women with or without a history of preterm birth. The retrospective quality of the study and its small number of participants (small sample in the inferior or equal to 15 mm subgroup), precluded the recommendation to implement cervical cerclage.

In 2019, a systematic review[38] was published in the American Journal of Obstetrics and Gynecology in which 16 studies with a total of 1211 women were included. Its findings suggested that cervical cerclage in women with a cervical length inferior to 15 mm was beneficial in the delay of labour by approximately 4 weeks and in reducing the risk of preterm birth before 32 (relative risk, 0.61, 95% CI 0.41-0.90), 34 (relative risk 0.57, 95% CI 0.43-0.75) and 37 weeks of gestation (relative risk 0.86, 95% CI 0.74-0.99). Recent data suggests that in multiple gestations a smaller target of

cervical length, inferior to 15 mm or even shorter, could support the benefit of cervical cerclage. Following this publication, different letters to the editors advised caution in drawing conclusions based on this systematic review as it was based on retrospective cohort studies and that data from randomized trials suggesting an increase in preterm birth and perinatal complications was not taken into account. Therefore, until further evidence is available, mainly from randomized control trials, cervical cerclage is currently not recommended in multiple gestations with a short cervix.[41–43]

In summary, there is currently no strong evidence supporting the use of cervical cerclage in the prevention of preterm birth in multiple gestations with a short cervix.

7.1.3 Physical examination-indicated

In the 2019 systematic review mentioned,[38] physical examination-indicated cerclage was also evaluated. In women with a cervix dilation superior to 10 mm, cervical cerclage prolonged the duration of pregnancy by approximately 7 weeks and reduced the incidence of preterm birth before 24 (relative risk 0.35, 95% CI 0.18-0.67), 28 (relative risk 0.41, 95% CI 0.20-0.85), 32 (relative risk 0.50, 95% CI 0.38-0.65) and 34 weeks of gestation (relative risk 0.56, 95% CI 0.45-0.69), improving perinatal outcomes.

In a recent randomized controlled trial (TWIN-PEIC)[44] the selected participants were asymptomatic women with diamniotic gestations between 16 weeks 0/7 days and 23 weeks 6/7 days of gestation and with cervical dilation of 1 to 5 cm. The objective was to determine if physical examination-indicated cerclage was effective in decreasing the incidence of preterm birth in multiple pregnancy. All the participants in the cerclage group, similarly to previous studies, received indomethacin and antibiotics. There was a decreased rate of preterm birth in all gestational ages (less than 34 (relative risk 0.71, 95% CI 0.52-0.96), 32 (relative risk 0.65, 95% CI 0.46-0.92), 28 (relative risk 0.49, 95% CI 0.26-0.89) and 24 weeks (relative risk 0.35, 95% CI 0.16-0.75)). Cervical cerclage increased the latency between diagnosis and delivery by approximately 5.6 weeks (mean difference 5.6, 95% CI 2.0-9.3) and also decreased perinatal mortality by 78% (relative risk 0.22, 95% CI 0.1-0.5). The Data and Safety Monitoring Board stopped the study due to the significant difference in perinatal mortality between the arms. There was a low number of subjects with a previous history of preterm birth and approximately 83% of all women had a cervical length inferior to 25 mm before cervical dilation. Data is not available on how many gestations with a short cervix progressed to cervical dilation.

A summary of the relevant results regarding cervical cerclage in the aforementioned studies can be found in the annexed table I.

7.2 Cervical pessary

Cervical pessary is a non-invasive intervention that includes, most commonly, the insertion of an Arabin pessary: a flexible silicone device in the shape of a ring with varying diameters. The larger diameter is designed to support the pelvic floor and the smaller diameter to surround the cervix. Its mechanism of action is not entirely known, but it is theorized that it directs the cervical canal more posteriorly, shifting the weight of the fetus anteriorly, and/or protects the immunological barrier between the amnios and the vaginal flora.[45]

A systematic review published in 2020[31] included twelve studies with both singleton and multiple pregnancies at high-risk of preterm birth in asymptomatic women (N=4687). This was defined as a short cervix on a midtrimester ultrasound, previous preterm birth, multiple gestation and uterine anomalies or previous excisional cervical procedures. The trials evaluating multiple gestations included unselected multiple gestations, multiple gestations with cervical length inferior to 38 mm and multiple gestations with cervical length inferior or equal to 25 mm. The majority of the studies used the Arabin pessary. It is of utmost importance to refer that in most of the included trials there was a concomitant use of vaginal progesterone that might have altered the results. Additionally, singleton gestations were also included, hindering the analysis of twin gestations' subgroup. In the following sub-sections, the main findings of this systematic review will be presented.

7.2.1 Unselected multiple gestations

Regarding unselected multiple gestations, 2 studies with a total of 1985 women were included and the rate of spontaneous preterm birth before 28, 32, 34 and 37 weeks of gestation was not significantly different in the pessary group when compared with the no pessary group, with low to high quality of evidence. There was also no comparable difference regarding perinatal complications. There was an increase in the incidence of vaginal discharge (relative risk 2.96, 95% CI 2.46-3.57; number needed to treat for harm 4, 95% CI 4-5), and cesarean section delivery (relative risk 1.13, 95% CI 1.06-1.21; number needed to treat for harm 13, 95% CI 8-29) in the pessary group. Indications for cesarean delivery were not disclosed.

7.2.2 Multiple gestations with a short cervical length

Comparing the use of pessary in multiple gestations with a cervical length inferior to 38 mm (4 studies) there was no significant difference in spontaneous preterm birth before 28, 32, 34 and 37 weeks of gestation, with low to moderate quality of evidence. In the pessary group, the use of tocolytic agents was less frequent (relative risk 0.69, 95% CI 0.49-0.98; number needed to treat for benefit 8, 95% CI 4-59) and there was an increase in the occurrence of vaginal discharge (relative

risk 1.93, 95% CI 1.66-2.23; number needed to treat for harm 4, 95% CI 3-5). There was no significant difference regarding perinatal complications.

In multiple gestations with cervical length inferior or equal to 25 mm, the use of pessary did not prevent spontaneous preterm birth in all gestational ages (before 28, 32, 34 and 37 weeks of gestation) and there was no difference in the incidence of adverse perinatal outcomes. There was a significant increase in vaginal infection (relative risk 1.96, 95% CI 1.01-3.79; number needed to treat for harm 8, 95% CI 4-147) and discharge (relative risk 1.86, 95% CI 1.51-2.28; number needed to treat for harm 3, 95% CI 2-5) in the pessary group.

In summary, there is no current evidence supporting the efficacy of the use of cervical pessary in order to reduce the incidence of spontaneous preterm birth in asymptomatic women with multiple gestations and a midtrimester cervical length inferior or equal to 25 mm, inferior to 38 mm or in unselected multiple gestations.

7.3 Vaginal Progesterone

Progesterone plays an important physiological role in pregnancy support by inhibiting myometrial contraction.[12] Benefits of vaginal progesterone in the prevention of preterm birth in asymptomatic singleton pregnancies with a short cervix have been well established.

7.3.1 Unselected multiple gestations

A 2019 Cochrane review including 16 trials and 4548 women, evaluated the effects of progesterone, vaginal or intramuscular, in reducing preterm birth in multiple pregnancies. Much like in singleton gestations, 17-OHPC has no beneficial effect in preventing adverse perinatal outcomes or preterm birth before 28 or 37 weeks of gestation, with an increase in preterm birth before 34 weeks (relative risk 1.54, 95% CI 1.06- 2.26). Vaginal progesterone, with doses ranging from 90-400 mg per day, was also not associated with a difference in the incidence of preterm birth before 28, 34 and 37 weeks of gestation. Additionally, there were fewer caesarean section deliveries in women who received vaginal progesterone and most neonatal outcomes were also similar in the two groups, except for mechanical ventilation, which was less frequently used when vaginal progesterone was administered.[46],[47]

In summary, the use of progesterone, vaginal or intramuscular, in unselected twin gestations is not associated with a decrease in preterm birth incidence or an improvement in neonatal adverse outcomes.

A more recent double-blind randomized trial (EVENTS trial) was published and provided new insight on the topic.[48] In this particular trial, vaginal progesterone was administered earlier in the gestation course and in a higher dose when compared with previous trials, more specifically 600 mg daily (300 mg twice) starting at 11 to 14 and until 34 weeks of gestation. It was shown that the use of vaginal progesterone in unselected multiple gestations has no benefit in the reduction of spontaneous preterm birth, and may actually increase its incidence when compared with the placebo group. Preterm birth between 24+0 and 33+6 weeks of gestation occurred in 10,4% of individuals in the progesterone group and in 8.2% in the placebo group (odds ratio 1.35, 95% CI 0.88-2.05, P=0.17; hazard ratio 1.29, 95% CI 0.87-1.91, P=0.237). The rate of spontaneous preterm birth between 24+0 and 33+6 weeks of gestation was higher in monochorionic rather than in dichorionic gestations and in women with history of preterm birth when compared with nulliparous women. There was weak evidence (P=0.08) that suggested an increase in preterm birth in women with a cervical length superior or equal to 30 mm (odds ratio 1.61, 95% CI 1.01-2.59) and a potential reduction in women with a cervical length inferior to 30 mm (odds ratio 0.56, 95% CI 0.20-1.60). Vaginal progesterone use was not associated with maternal complications such as pre-eclampsia, gestational diabetes and intrahepatic cholestasis. There was also no evidence of deleterious neonatal effects such as stillbirth or neonatal death and poor fetal growth.

In contrast with previous findings, the use of vaginal progesterone was shown to be harmful at times, increasing the risk of spontaneous preterm birth. This may be related to the use of progesterone at a higher dose and started earlier, conferring a long duration of high-dose therapy. Further research is necessary to evaluate this correlation.

7.3.2 Multiple gestations with a short cervical length

A recent meta-analysis of individual patient data[19] studied the incidence of preterm birth, before 33 weeks of gestation, in asymptomatic multiple gestations with a short cervix (inferior or equal to 25 mm), comparing vaginal progesterone (100-400 mg/day) versus placebo or no intervention. Treatment was initiated at different times, starting between 20 to 24 weeks of gestation in all of the trials included but one, in which it was administered between 18 and 21 weeks of gestation. The use of vaginal progesterone significantly reduced the incidence of preterm birth before 30 (relative risk 0.47, 95% CI 0.25–0.86), 32 (relative risk 0.51, 95% CI 0.34–0.77), 33 (relative risk 0.69, 95% CI 0.51-0.93), 34 (relative risk 0.71, 95% CI) and 35 weeks of gestation (relative risk 0.83, 95% CI). Regarding spontaneous preterm birth, there was a reduction in its incidence before 33 (relative risk 0.67, 95% CI) and 34 weeks of gestation (relative risk 0.71, 95% CI 0.56–0.91). It also significantly reduced the rate of neonatal death, composite neonatal morbidity and mortality, respiratory distress syndrome, very low birth weight and several other neonatal complications. When evaluated 4-5 years after birth, children didn’t show any significant difference in neurodevelopment.

In the two trials conducting this follow-up, vaginal progesterone did not affect the incidence of preterm birth and, although this topic still requires further investigation, progesterone might have a neuro-protective effect. There were also no adverse maternal effects associated with the use of vaginal progesterone - at 400mg, there was no difference in the incidence of vaginal pruritus or discharge, gastrointestinal symptoms, skin rash or intrahepatic cholestasis of pregnancy. This is in contrast with the findings of a previous randomized controlled trial, that was also included in the meta-analysis, in which there seemed to be a dose-dependent increase of intrahepatic cholestasis of pregnancy.

It is important to note that one study, that included women with a cervical length between 20 and 25 mm, represented 74% of the final sample used in the meta-analysis and it had a moderate risk of bias. This single study provided an important proportion of the data included and its results favoured the use of progesterone, thus weighing significantly in the final results of the meta-analysis.

In the EVENTS trial[48], only in a post-hoc analysis and with a weak level of evidence, the use of vaginal progesterone (600mg/day from 11-14 weeks to 34 weeks) reduced the cumulative incidence of spontaneous preterm birth before 32 weeks of gestation in women with a cervical length inferior to 30 mm (hazard ratio 0.23, 95% CI 0.08-0.69), increasing the risk when the cervical length is superior or equal to 30 mm. After 32 weeks of gestation, there was also an increase in the incidence of preterm birth for women with a short cervical length (hazard ratio 1.42, 95% CI 0.31-6.43). This data shows that, for women with a short cervix and multiple gestation, the use of vaginal progesterone is beneficial in delaying preterm birth before 32 weeks of gestation. Because the incidence of preterm birth was only registered after 24 weeks of gestation, vaginal progesterone may have a positive effect in allowing late miscarriages to be early preterm births. In fact, the incidence of birth between the date of randomization and 24 weeks of gestation was higher in the placebo group (2.6% of pregnancies in the progesterone group and 4.4% in the placebo group), but the incidence of preterm birth between randomization and 34 weeks of gestation was slightly higher in the progesterone group (16.7% in the progesterone group and 15.8% in the placebo group). This again favours vaginal progesterone - it may be beneficial in delaying preterm birth before 32 weeks of gestation.

A summary of the relevant results regarding vaginal progesterone in the previously mentioned studies can be found in the annexed table II.

7.4 Prophylactic Oral Tocolysis

Tocolysis consists on the use of certain medications to delay the birth of a fetus in women with preterm contractions, allowing the best management to improve perinatal outcomes. For example, it may allow timely transfer of the pregnant patient to a tertiary care hospital or allow the

stimulation of fetal lung maturity with corticosteroids. Beta-adrenergic agonists, calcium channel blockers, magnesium sulphate, prostaglandin inhibitors and oxytocin receptor antagonists are examples of tocolytic drugs.[49]

Beta-adrenergic agonists (including beta-1 and beta-2 agonists) decrease the activity of myosin light-chain kinase, therefore causing myometrial relaxation and decreasing the frequency of contractions. When given to women in preterm labour, they can delay birth by 2 to 7 days. Potential maternal side effects include cardiac arrythmias, pulmonary oedema, postpartum haemorrhage and even death.

Regarding multiple gestations, there is still insufficient evidence supporting the use of prophylactic oral betamimetics in order to prevent preterm birth. A Cochrane review including five trials (classified as low-quality evidence) found no reduction in preterm birth before 37 (relative risk 0.85, 95% CI 0.65-1.10) or 34 weeks of gestation (relative risk 0.47, 95% CI 0.15-1.50) when compared with a placebo group. There was no significant difference in the incidence of low birthweight, small-for-gestational age or neonatal mortality between groups.[50]

7.5 Bed Rest

The indication of bed rest is based on the theory that excessive work and physical activity could be associated with preterm birth, and bed rest could decrease uterine activity.[29]

A 2010 Cochrane review[51] including seven trials concluded that in hospital bed rest does not reduce the incidence of preterm birth or perinatal mortality, although it suggested that it improves fetal growth since the incidence of low birth weight (below 2500g) was inferior in this group (relative risk 0.92, 95% CI 0.85-1.00). However, it is important to note that hospitalization has social and financial effects, bringing a disruptive stress factor to pregnant women and their family, contributing also to healthcare services overload.

According to the available evidence, bed rest is not routinely recommended as an intervention to prevent preterm birth in uncomplicated multiple gestations.

8. Summary and Final Remarks

Preterm birth is associated with important deleterious effects on neonatal health and potential long-term complications, being a source of increased healthcare costs. Multiple gestations are at an increased risk of spontaneous and iatrogenic preterm birth, resulting in adverse perinatal and maternal outcomes. Therefore, it is of extreme importance to be able to identify those at a higher risk of preterm birth in order to implement an adequate monitoring strategy and also to apply interventions that may delay the time of birth. The stronger predictors of preterm birth in multiple

gestations are short cervical length and elevated fetal fibronectine levels, the latter being especially useful in evaluating the risk of imminent preterm birth.

The main issue resides in the few effective available interventions to reduce the risk of spontaneous preterm birth in multiple gestations with an increased risk for this outcome. And according to the presented evidence this may be primarily due to an absence of evidence/ agreement on the best method to predict increased risk of preterm birth in this population – what is the best cut-off to consider a cervix short in twins? Is the evidence behind fibronectine as a predictive test enough to implement it in clinical practice in asymptomatic patients? These are just a few questions that one may rise and that still need further investigation.

This review provides a summary of the most recent and relevant evidence regarding the topic, using the GRADE methodology; however, the integrative nature of the conducted synthesis limits the quantification of the efficacy of each intervention, combining the findings of all the presented studies. Current evidence suggests that bed rest, tocolysis and cervical pessary have no effect in preventing preterm birth with moderate, low and moderate levels of quality of evidence, respectively. Vaginal progesterone in women with a short cervical length decreases the incidence of preterm birth, particularly before 32 weeks of gestation (low to moderate quality of evidence). Physical examination-indicated cervical cerclage, when there is a 1-5 cm cervical dilation, is successful in preventing preterm birth in multiple gestations and is associated with an important reduction in neonatal death (moderate quality of evidence). A summary of the available interventions to reduce preterm birth in twins with its associated GRADE classification can be found in the annexed Table III. We believe that this work may help clinicians to easily understand the available evidence in which to support the best clinical management of the risk of preterm birth in twin pregnancies. Nevertheless, further research is still necessary to establish a standardized approach to these patients.

Directions for future research:

- Evaluate the efficacy of cervical cerclage for a shorter cervical length (<15 mm) with prospective studies.
- Confirm the efficacy of vaginal progesterone, in women with a short cervical length, in turning late miscarriages into early preterm births by registering the incidence of preterm birth earlier in the gestation.
- Determine which dose of progesterone is more cost-effective in the reduction of preterm birth risk in twins, and evaluate its perinatal effects.
- Determine which cervical length is more discriminative of preterm birth risk in twins.
- Evaluate the efficacy of different interventions when preterm birth risk stratification is assessed using fetal fibronectine levels, alone or in combination with cervical length measurement.
- As mechanisms of spontaneous preterm birth in twins is different than in singletons, other biochemical predictors may be studied in this population; and may be included in predictive combined models with cervical length measurement.

Table I. Cervical Cerclage in Twin Pregnancies – summary of the most relevant studies

Study design	**Systematic review**	**Systematic review and meta-analysis**	**Retrospective cohort study**	**Systematic review and meta-analysis**	**Randomized controlled trial**
Author, Year	Rafael TJ, 2014	Saccone G, 2015	Roman A, 2015	Li C, 2019	Roman A, 2020
Sample Size	128	49	140	1211	30
Results	History-indicated and ultrasound-indicated: No reduction in PTB<34w (RR 1,16) and <35w (RR 1,11). Ultrasound-indicated: Increased risk of low birth weight (RR 1.39), very low birth weight (RR 3.31) and respiratory distress syndrome (RR 5.07).	Ultrasound-indicated: No reduction in PTB<24-37w (PTB<34w aOR 1.17). Increase in very low birth weight (aOR 2.22) and respiratory distress syndrome (aOR 3.88).	Ultrasound-indicated: No reduction in SPTB<28-34w (SPTB<34w aOR 0.37). CL ≤15 mm was associated with a prolongation of gestation by 4 w, reduction of SPTB<34w by 49% (aOR 0.51) and admission to NICU by 58% (aOR 0.42).	History-indicated: No reduction in PTB<28-37 w. Ultrasound-indicated (CL<15 mm): Prolongation of pregnancy by 3.89 w. Reduction of PTB<37w (RR 0.86), <34w (RR 0.57) and <32w (RR 0.61). Physical examination-indicated (cervical dilation >10 mm): Prolongation of pregnancy by 7 weeks. Reduction of PTB<24w (RR 0.35), <28w (RR 0.41), <32w (RR 0.50) and <34w (RR 0.56), with an improvement in perinatal outcomes.	Physical examination-indicated (cervical dilation 1-5 cm): Reduction in PTB<34w (RR 0.71), <32w (RR 0.65), <28w (RR 0.49) and <24w (RR 0.35). Prolongation of gestation by 5.6 weeks and decrease in perinatal mortality by 78% (RR 0.22).
Conclusion	No benefit in PTB prevention, with an increase in neonatal complications.	No benefit in PTB prevention, with an increase in neonatal complications.	Effective in preventing PTB, prolonging the duration of pregnancy and improving neonatal outcomes in women with a short cervix.	Effective in preventing PTB and prolonging the duration of pregnancy in women with a short cervix and in women with cervical dilation.	Effective in preventing PTB, prolonging the duration of pregnancy and decreasing perinatal mortality in women with cervical dilation.
Comments			Small sample in the subgroup with CL≤15 mm (32 in the cerclage and 39 in the control group).	Caution in interpreting results (only included retrospective cohort studies and excluded data from randomized trials that suggests that there is an increase in PTB and perinatal complications).	

PTB – preterm birth; w – weeks of gestation; RR – relative risk; aOR – adjusted odds ratio; SPTB – spontaneous preterm birth; CL – cervical length; NICU – neonatal intensive care unit.

Table II. Vaginal progesterone in Twin Pregnancies – summary of the most relevant studies

Study design	**Meta-analysis of individual patient data**	**Systematic review**	**Double-blind randomized trial**
Author, Year	Romero R 2017	Dodd JM 2019	Rehal A 2020
Sample Size	303	4548	1169
Results	Dose: 100-400 mg/day. CL≤25 mm: Reduction in PTB<30w (RR 0.47), <32w (RR 0.51), <33w (RR 0.69), <34w (RR 0.71) and <35w (RR 0.83). Reduction in SPTB<33w (RR 0.67) and <34w (RR 0.71). Reduction of neonatal death (RR 0.53), composite neonatal morbidity and mortality (RR 0.61), respiratory distress syndrome (RR 0.70), very low birth weight (RR 0.53) and use of mechanical ventilation (RR 0.54).	Unselected, vaginal progesterone: Dose: 90-400 mg/day. No reduction in PTB<28w (RR 1.53,), <34w (RR 0.90) and <37 w (RR 0.97). Reduction in caesarean section deliveries (RR 0.92) and mechanical ventilation (RR 0.70). Unselected, IM progesterone: Dose: 250 mg/week; 500 mg/twice weekly. No reduction PTB<28w (RR 1.08) and <37w (RR 1.05). Increase in PTB<34w (RR 1.54).	Dose: 600 mg/day. Unselected: Increase in 24w<SPTB<33+6w (OR 1.35, P=0.17; HR 1.29). 24w<SPTB<33+6w higher in monochorionic gestations (OR 1.91, P=0.006) and in women with history of preterm birth (OR 2.631, P=0.010). Weak evidence (P=0.08) of harm to women with CL≥30 mm (OR 1.61) and potential benefit to women with CL<30 mm (OR 0.56). Higher incidence of PTB<24w in the placebo group (4.4% versus 2.6%; OR 0.57). Higher incidence of PTB<34w in the progesterone group (16.7% versus 15.8%; OR 1.10). CL<30 mm: Reduction of SPTB<32w (HR 0.23). Increase of 32w<SPTB<33+6w (HR 1.42).
Conclusion	Effective in preventing PTB and improving neonatal outcomes in women with a short cervix.	No benefit in preventing PTB in unselected pregnancies.	No benefit in preventing PTB in unselected pregnancies. Possibly effective in preventing PTB<32w in women with a short cervix, increasing the risk in women with longer cervical lengths.
Comments			The findings that favored the use of vaginal progesterone are exploratory, resulting from a post hoc analysis.

PTB – preterm birth; w – weeks of gestation; RR – relative risk; OR –odds ratio; SPTB – spontaneous preterm birth; CL – cervical length; HR – hazard ratio; IM – intramuscular.

Table III. Summary of Interventions to Reduce Spontaneous Preterm Birth in Twins (GRADE)

Intervention	Recommendation	GRADE
Cervical Cerclage	Physical examination-indicated: cervical dilation 1-5 cm	⊕⊕⊕⊖ Moderate
Cervical Pessary	No benefit	⊕⊕⊕⊖ Moderate
Vaginal Progesterone (100-600 mg/day)	Short cervix (CL≤25/<30 mm)	⊕⊕⊖⊖ - ⊕⊕⊕⊖ Low to moderate
Tocolysis	No benefit	⊕⊕⊖⊖ Low
Bed rest	No benefit	⊕⊕⊕⊖ Moderate

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