Twin and Preterm Labor: Prediction and Treatment

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Abstract Twin pregnancies are increasing. Preterm birth is a major health problem with high incidence all over the world. It is known to have a higher incidence in twin pregnancies as well as being higher in IVF/ICSI pregnancies. Prediction of preterm birth in twins through transvaginal cervical length measurement and vaginal fetal fibronectin measurement are good and well-documented methods. However, this could not be applied to IVF pregnancies. Prevention of preterm birth by administration of vaginal natural progesterone or IM synthetic progesterone injections is not effective in twins. The situation was similar with administration of progesterone to IVF twin pregnancies. Prophylactic cerclage for prevention of preterm birth in twins resulted in an increase of the incidence of preterm birth. Tocolytics also are ineffective, although nifedipine may have a role in treatment of threatened preterm birth in twins.

Keywords Preterm birth · Twins · In vitro fertilization · Transvaginal ultrasound · Cervical length · Vaginal progesterone · Prophylactic cerclage · Twins · High-risk gestation · Preterm labor

Introduction

Twins constitute 2–4 % of all births, and the rate of twinning has increased by 76 % between 1980 and 2009. The rate of

preterm birth <37 weeks among twins is approximately 60 % [1]. Two chief reasons have been attributed to this increase in multiple births: women's choice to postpone their (first) pregnancy, which has resulted in advanced maternal age, and the liberal use of assisted reproductive techniques [2].

Twin pregnancies, compared with singletons, are at increased risk for fetal anomalies, preterm births, aberrant fetal growth, cerebral palsy, and perinatal and infant mortality. Maternal complications associated with twin pregnancies include hypertensive disorders, gestational diabetes, cesarean delivery, postpartum hemorrhage, and maternal mortality [1].

Incidence of Preterm Labor

Fifteen million preterm births occur every year and this number is rising. One million babies die from preterm birth complications annually. Five to eighteen percent is the range of preterm birth rates across 184 countries of the world; >80 % of preterm births occur between 32–37 weeks of gestation, and most of these babies can survive with essential newborn care. (3)

According to the WHO report published 2009, the overall preterm birth rate was 9.6 %. The highest rates of prematurity occurred in Africa, 11.9 %, and North America, 10.6 %. Europe had the lowest rate of 6.2 % [3].

The percentage of singletons born less than 37 weeks of gestation was 11.1 % compared with 61.9 % for multiples. The rate of preterm birth less than 32 weeks of gestation was much more common among multiples than among singletons: 13.3 % versus 1.6 % [4].

Short-term morbidities associated with early preterm delivery include respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, patent ductus arteriosus, and retinopathy of prematurity. Long-term morbidities include cerebral palsy, cognitive defects, and social and

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behavioral problems [5], in addition to the economic burden on the family and the country.

Etiology of Preterm Birth

The causes for preterm birth in twins are classified into three clinical subtypes: preterm birth after (preterm) premature rupture of membranes (PROM), spontaneous onset of labor (these two groups are termed spontaneous preterm birth), and medically indicated preterm birth after iatrogenic obstetrical interventions for maternal-fetal indications [6, 7].

Twin pregnancies are more liable to maternal hypertension, fetal distress, fetal growth restriction, and placental abruption, leading to the need for early termination of the pregnancy [8]. The incidence of preterm birth is reported higher for IVF/ICSI pregnancies [9, 10]. One of the etiological factors that could possibly affect the incidence of preterm birth in IVF twin pregnancies includes obesity. Body mass index (BMI) $>35 \text{ kg/m}^2$ in twins was associated with a threefold increased risk of very early preterm birth (6.1 % vs. 2 %) and a twofold increased risk of very preterm birth (11.5 % vs. 5.9 %) compared with women of normal weight (BMI 18.4–24.9 kg/m^2) [11].

Mechanisms of Preterm Birth

The mechanisms for preterm birth are still unclear. It could be associated either with a premature activation of the physiological contracting process or with a pathological factor responsible for uterine contractions, leading to preterm delivery [12, 13].

In twins, etiological factors for preterm birth include uterine overdistention [14]. Myometrial distention increases myometrial contractility, releases prostaglandins, and upregulates oxytocin receptors, all of which are implicated in the cascade of events that occur in early labor [13]. Factors, such as stretch, placental corticotrophin-releasing hormone, and lung maturity factors, are stronger in multiple pregnancies due to the increased fetal and placental mass [15]. The risk of preterm birth is higher in monochorionic diamniotic twins, which could be explained by the occurrence of twin-to-twin transfusion syndrome (TTTS) in 15 % of this type of twins [16]. Nulliparous women with twin gestations are at significantly higher risk for preterm delivery compared with multiparous women [17]. Fetal sex appears to be a risk factor for preterm delivery in spontaneously conceived dichorionic twin gestations. Twin pregnancies with one or two male fetuses are at higher risk for spontaneous preterm delivery than those with only females [18].

Prediction of Preterm Birth

Cervical length measurement using transvaginal ultrasound is the best method for prediction of preterm birth in twin pregnancies and was demonstrated as sensitive in twins as in singletons [19]. A large number of prospective studies [20–30] have shown the predictive value of midtrimester cervical length measurement in twin pregnancies; these data were collected in two large meta-analyses. The first meta-analysis included 21 studies, 16 in asymptomatic women and only 5 in symptomatic women; the collected data included 3,523 women. The most accurate prediction for preterm birth <32 weeks and <34 weeks was made in asymptomatic women with a cervical length $\leq 20 \text{ mm}$ at 20–24 weeks gestation. Cervical length $\leq 25 \text{ mm}$ at 20–24 weeks gestation had a pooled positive likelihood ratio of 9.6 to predict preterm birth <28 weeks gestation. The predictive accuracy of cervical length for preterm birth was low in symptomatic women [31]. The second meta-analysis using the ROC curve to obtain an optimum cutoff for cervical length indicated a good predictive capacity of short cervical length for preterm birth [32].

Two retrospective studies did not show a predictive value of cervical length measurement but still concluded that the importance of cervical length measurement lies in its strong negative predictive value [33, 34]. Changes of cervical length over time also is a predictor for preterm birth, a cervical length that decreases by 20 % over two measurements is a significant predictor of very preterm birth, even in the setting of a normal cervical length [35]. Serial cervical length measurements in twin pregnancies, is recommended starting <24 weeks [35].

Timing of Cervical Length Measurement

Most published studies agreed on measurement at the midtrimester between 16–24 weeks [36]. A more recent study recommended transvaginal ultrasound for assessment of cervical length between 22–24 weeks for prediction of spontaneous preterm birth in twin pregnancy [37]. However, one study reported cervical measurement from as early as 13 to 34 weeks and concluded that the risk of preterm delivery is increased when shorter cervical length is detected at an earlier gestational age [38]. Similarly, the finding of two cervical length measurements at 20–23 weeks gestation and 3–5 weeks later with a difference of 25 % between each measurement is a good predictor of preterm birth in asymptomatic twins even when cervical length is $>25 \text{ mm}$ [39].

Funneling

Cervical funneling seen at midtrimester had a high sensitivity and specificity for prediction of the preterm birth, which was

higher for gestations born <32 weeks than <35 weeks (86 % and 54 %, and specificity 78 % and 82 %, respectively) [40]. Funneling is seen by transvaginal ultrasound. The patient should be examined in the dorsal lithotomy position with an empty bladder without undue pressure on the cervix, and the examiner should wait for up to 5 minutes to note any changes in cervical length and shape. Funneling is defined as dilatation of the internal os >5 mm in width for a period of at least 3 minutes [40].

The incidence of funneling differs according to position of patient. It was greater in an upright compared with a recumbent maternal position by 12.3 % in singleton and 13.1 % in twin pregnancies before 25 weeks and by 13 % and 21.6 % between 25 and 30 weeks, respectively. Evaluation of the cervix with the woman in the upright position permits earlier detection of funneling. This may enable earlier and more appropriate intervention to avoid spontaneous preterm birth [41].

Situation in IVF Pregnancies

Is there a Role for Midtrimester Cervix Measurement in IVF/ICSI Patients for the Prediction of Preterm Birth?

We performed a prospective, controlled study to compare the midtrimester transvaginal cervical measurement in 222 twins (group A) and 122 singleton ICSI pregnancies (group B) with 51 spontaneous pregnancies (group C). No significant difference in mean cervical length was found between the three groups: group A, 37.6 mm; group B, 37.2 mm, and group C, 39.2 mm, despite a very high incidence of preterm birth (<34 weeks) in the two study groups compared with the spontaneous pregnancy control group: 30.5 % in group A; 17.6 % in group B; and 3.9 % in group C ($P=0.011$). Using the ROC curve to establish the optimum cervical length below which the incidence of preterm birth is expected to be high gave a poor sensitivity and specificity. Our results showed that contrary to the situation in spontaneous pregnancies where cervical length measurement is a good predictor for preterm birth cervical length measurement in singleton, as well as twin ICSI pregnancies, is not a good predictor [42].

These results were confirmed by our recent study [43••] in which we studied the effect of progesterone for prevention of preterm birth in ICSI singleton and twin pregnancies. We measured cervical length as well at midtrimester for all participant pregnant females (unpublished data); similar to our previous results the cervical length was not significantly different between those who delivered preterm <37 weeks (mean cervical length 35.5 mm) and those who delivered >37 weeks of gestation (36.3 mm; $p=0.216$) [43••].

Cervical Fetal Fibronectin and Transvaginal ultrasound cervical measurement in prediction of preterm birth and threatened preterm labor

A retrospective study combining a positive cervical fetal Fibronectin with cervical length measurement <20 mm showed a significantly higher positive predictive value for delivery at all gestational ages than either positive test alone. In twins with normal cervical length, a positive fetal fibronectin test was a strong predictor of spontaneous preterm birth [29].

The negative predictive value of fetal fibronectin testing in predicting delivery within 14 days of testing was 97 % for twin gestations, comparable to 99 % for singletons [44]. A systematic review and meta-analysis showed that cervicovaginal fetal fibronectin provides moderate to minimal prediction of preterm birth in women with multiple pregnancies, but it was most accurate in predicting spontaneous preterm birth within 7 days of testing in women with twin pregnancies and threatened preterm birth [45].

Prevention of preterm birth in Twins

Cerclage in twins

Is there a Role for Prophylactic Cerclage in Twins?

The situation in twins is clearly contrary to that of singletons. A large prospective study compared prophylactic cerclage in twin pregnancies with no cerclage, in reducing preterm birth <32 weeks and found a significant increase in preterm birth rate among those who underwent cerclage and no difference in gestational age at birth [46]. An older meta-analysis reported a similarly significant increase in incidence of preterm birth <35 weeks in twins with a short cervix who underwent cerclage cervix, previous history of preterm birth, in contrast to singletons that had a significant reduction of preterm birth with cerclage [47].

Progesterone

Has a physiological effect on uterine quiescence mediated by a direct effect on intracellular calcium concentration and prostaglandin synthesis [12].

The positive effect of vaginal progesterone on reducing the rate of preterm birth in singleton pregnancies with short cervix, as well as singleton patients with history of previous preterm birth, has been confirmed by a large number of randomized studies [48–54, 55•]. However, in twins the situation was found to be different; two large, randomized, controlled studies—the PREDICT study [56••] and the STOPPIT study [57••]—showed no reduction of the preterm birth rate with natural vaginal progesterone

administration in twin pregnant patients with short cervixes [58]. The effect was similar with 17 hydroxy progesterone weekly IM injections [59–62].

A recently published, randomized, controlled study showed an increase in the rate of preterm birth <32 weeks in symptomatic twins with short cervix who received IM synthetic progesterone injections [63•]. The ineffectiveness of progesterone was similar even when the dose of progesterone was increased to 400 mg per day [64].

One potential explanation of the negative results of prophylactic cerclage and progesterone on twins is that preterm birth in twin pregnancies is more often because of uterine distention and contraction than due to cervical problems [63•].

Role of Progesterone in Prevention of Preterm Birth in IVF Pregnancies

A randomized, placebo-controlled study was performed by our group. The purpose was to study the effect of daily 400 mg of vaginal progesterone suppositories for prevention of preterm birth in singleton and twin ICSI pregnancies. In the total study group, including 306 patients, 161 received progesterone and 145 placebo and no statistical significant difference in preterm birth rate (<37 weeks) was found between both groups ($P=0.6$). Subgroup analysis showed a significant reduction in preterm birth rates in the singleton group that received progesterone. As for the twin pregnancy group, there was no significant difference in preterm birth rate in those who received progesterone versus placebo. The results of our study agreed with the current available literature that progesterone does not prolong twin pregnancies [43••].

Bed Rest

A Cochrane review of randomized trials studying the effect of hospital bed rest in multiple pregnancies found no evidence that this practice should be applied to all multiple pregnancies and should not be recommended for routine clinical practice [65].

Pessaries

One trial under way since 2009 is studying the effect of prophylactic pessary insertion in twin pregnancies with shortened cervix; women will be randomly allocated to receive either a cervical pessary or no intervention. The cervical pessary will be placed in situ at 16 to 20 weeks and kept up to 36 weeks gestation or until delivery. The primary outcome is perinatal death or severe morbidity. Secondary outcome measures are time to delivery, preterm birth rate before 32 and 37 weeks, days of admission in neonatal intensive care unit, maternal morbidity, maternal admission days for preterm birth and costs [66]. Only one small study reported some positive effect of pessary insertion in twins [67].

Management of Threatened Preterm Birth in Twin Pregnancies

Tocolysis and Treatment of Preterm Birth

Mechanism of Action of Tocolysis

Myometrial contractility is a complex process based on myocyte function. It involves the presence of hormonal receptors, ions channels, intercell gap junctions, and regulatory proteins, such as oxytocin, endothelin, tachykinin, and angiotensin [68, 69]. The increase of intracellular calcium concentration is essential for the uterine smooth muscle contraction [69].

β Adrenergic Receptor Agonists

Selective β_2 agonists, such as ritodrine and salbutamol, impair intracellular cyclic AMP concentration and facilitate myometrial relaxation [69, 70]. A Cochrane review including 11 randomized, controlled trials, involving 1,332 women reported that these agents were more efficient than placebo for delaying preterm birth for 2 days [70, 71].

In twins, there is no evidence that selective β_2 agonists prevent preterm birth. A Cochrane review on the use of oral betamimetics for reducing preterm birth in twins showed insufficient evidence to support or refute the use of prophylactic oral betamimetics [72].

Magnesium Sulphate

There is evidence and recommendation to administer magnesium sulphate in expected preterm births, especially very preterm births <30 weeks, for neuroprotection and reduction of incidence of cerebral palsy [73].

As a tocolytic, magnesium sulphate is a calcium antagonist; it decreases calcium intracellular concentration and inhibits contraction process [69]. It has been classed as one of the three most effective drugs for delay of delivery for 48 weeks [74], and its effectiveness was similar in singletons and twins [75].

Prostaglandin-Synthase Inhibitors

Indomethacin, a nonspecific COX inhibitor, is recommended as a tocolytic; however, use should be restricted in duration and limited to pregnancies below 32 weeks because of fetal ductus arteriosus closure risk and decreased urine production responsible for oligohydramnios [13, 71, 76, 77]. The various types of available tocolytics compared with placebo resulted in the highest delay of delivery by 48 hours with prostaglandin inhibitors (odds ratio 5.39) followed by magnesium sulfate (2.76) calcium channel blockers (2.71), beta mimetics (2.41), and the oxytocin receptor blocker atosiban (2.02) [74]. Prostaglandin inhibitors and calcium channel blockers gave the

best results to delay delivery for 48 hours, to reduce respiratory distress syndrome, neonatal mortality, and had the least maternal side effects [74].

Calcium-Channel Blockers

Calcium-channel blockers interfere with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation [13]. A recent systematic review based on 26 trials and 2,179 patients (8 of the studies contained twins) confirmed higher efficiency and lower side-effects incidence in the nifedipine group compared with β adrenergic receptor agonists-treated patients used for acute tocolysis (delay of delivery 48 hours up to 7 days [78]. As for the use of nifedipine for maintenance tocolysis, a recently published, randomized, controlled study comparing the effect of maintenance tocolysis with nifedipine in threatened preterm labor resulted in no significant reduction of perinatal adverse outcome in the study group and the study could not advise the use of nifedipine as maintenance tocolysis [79]. Tocolysis with nifedipine is proven as effective and safe for use in both singleton and twin gestations [80].

In singleton and multiple gestations, the role of tocolysis in the setting of acute preterm labor is to attempt to delay delivery long enough to administer corticosteroids to promote fetal lung maturity [81].

Antibiotics

Infection is one of causal factors of preterm labor with an incidence of 20–40 %, especially before 30 weeks [12]. In the presence of preterm birth with intact membranes, the prophylactic administration of antibiotics is not recommended [82]. But if there is a preterm rupture of the membranes (PROM), studies show a significant decrease of preterm delivery and chorioamnionitis rate in the treated group [83]. In bacterial vaginosis associated with pregnancy, antibiotics were found to eradicate infection, but they showed no effect on the incidence of preterm delivery [84].

Therapeutic Emergency Cervical Cerclage in Twins

Some reports have shown the effectiveness of cerclage in dichorionic twins to save the second twin after delivery of the first twin [85]. The largest study published so far [86] to check the effectiveness of emergency cerclage, which comprised a total of 414 sets of twin gestations and 92 sets of triplet gestations, could not show any significant prolongation of pregnancy duration in the ultrasound indicated cerclage (closed cervical length ≤ 2.5 cm group versus conservative management) [87]. As for triplets, no benefit from cerclage placement was found even when cervical shortening is documented [88].

Conclusions

Preterm birth is a major increasing health problem, especially with twins. Although the prediction of preterm birth is possible in twins by transvaginal ultrasound cervix measurement and possibly measurement of fetal Fibronocten, no effective preventive or treatment measure is available for management of preterm birth in twins. Management should involve decreasing the number of twins resulting from ART procedures, such as single embryo transfer and careful monitoring of ovulation induction. The role of progesterone if started early in pregnancy should be studied.

Compliance with Ethics Guidelines

Conflict of Interest Mona Aboulghar and Yomna Islam declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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