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MATERNAL-FETAL MEDICINE

Insulin-like growth factor binding protein-1 predicts preterm premature rupture of membranes in twin pregnancies

Giovanni Sisti[1,2] · Sara Paccosi[3] · Astrid Parenti[3] · Viola Seravalli[4] · Mariarosaria Di Tommaso[4] · Steven S. Witkin[2]

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Abstract

Purpose Mechanisms leading to preterm premature rupture of membranes (PPROM) remain incompletely defined. Based on the elevated occurrence of PPROM in twin gestations and recent studies of the involvement of insulin-like growth factor binding protein-1 (IGFBP-1) in the inhibition of collagen production we hypothesized that serum IGFBP-1 levels might be predictive of susceptibility to PPROM in women with twins.

Methods In this prospective study peripheral blood was obtained from 58 women with twin gestations prior to 20 weeks gestation and sera analyzed by ELISA for concentrations of IGFBP-1. Demographic and clinical outcome data were subsequently obtained and associations between IGFBP-1 and PPROM were analyzed by the Mann–Whitney test and receiver operator curve (ROC) analysis.

Results Eight of our subjects developed PPROM. They did not differ from the other women in demographics, medical history or current pregnancy outcome parameters. However, median IGFBP-1 levels were higher in women who subsequently developed PPROM (59.3 ng/ml) than in the other women (46.6 ng/ml) ($p = 0.042$). Using a cutoff value of 53.9 ng/ml the circulating IGFBP-1 level predicted development of PPROM with a sensitivity of 74%, specificity of 75%, a negative predictive value of 97% and a positive predictive value of 20%.

Conclusions Pending validation in larger studies the findings suggest that determination of serum IGFBP-1 levels in women with twin pregnancies may predict the later development of PPROM.

Keywords Insulin-like growth factor binding protein · Preterm premature rupture of membranes · Twins · Sera

Introduction

Preterm premature rupture of the membranes (PPROM), the rupture of fetal membranes before the spontaneous onset of labor and before term, is associated with adverse maternal, fetal, and neonatal outcomes [1]. Premature membrane weakening and subsequent disruption of integrity can arise as a consequence of uterine stretching or contractions or due to the initiation of physiological changes in susceptible women. Multiple factors have been found to increase the likelihood of PPROM including intrauterine infection, sterile inflammation, oxidative stress, nutritional deficiencies, and smoking [2–4]. The occurrence of PPROM is also more common in mothers with twins than in those with singleton pregnancies [5, 6]. Some risk factors for development of PPROM—uterine overdistension, cervical incompetence—have been detected at a higher frequency in twin pregnancies, while other risk factors—clinical chorioamnionitis, placental abruption, infection—occur more frequently in singleton gestations [6]. This suggests that the mechanism leading to PPROM may differ between these two groups.

Insulin-like growth factor binding proteins (IGFBP) are a group of proteins that bind to insulin-like growth factors (IGF) in body fluids and, thereby, regulate their stability and activity [7]. Most research has focused on interactions between IGFBP-1 and IGF-1. The binding of IGF-1 to

✉ Giovanni Sisti
gsisti83@gmail.com

1 Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, 5th floor, 234 East 149th Street, Bronx, NY 10451, USA

2 Department of Obstetrics and Gynecology, Weill Cornell Medicine, New York, NY, USA

3 Department of Health Sciences, University of Florence, Florence, Italy

4 Department of Health Sciences, Obstetrics and Gynecology Branch, University of Florence, Florence, Italy

IGFBP-1 compromises the ability of IGF-1 to bind to the IGF receptor and, thereby, reduces IGF-1-mediated activity [8]. In addition, in the setting of localized inflammation, IGF-1 gene expression decreases while expression of the gene coding for IGFBP-1 increases [8].

IGF-1 is a major inducer of collagen biosynthesis [9]. A second protein intimately involved in collagen production and cytoskeleton reorganization is the β1-integrin receptor [10]. The collagen-inducing activity of both proteins is inhibited by IGFBP-1 [10]. These findings suggest that the concentration of IGFBP-1 may influence the extent of collagen production and fetal membrane maintenance during pregnancy, and that this may be especially relevant to twin gestations where membrane over-distension is more common. Indeed, a previous case–control study found higher IGFBP-1 levels in twins compared to singletons [11].

The aim of the current pilot study was to evaluate the possibility that the circulating maternal IGFBP-1 concentration in mothers with twin gestations may be of clinical value in predicting the subsequent occurrence of PPROM.

Materials and methods

This was a prospective study of women with twin pregnancies who attended the dedicated outpatient twin clinic in our tertiary referral center (Careggi Hospital, University of Florence, Florence, Italy). All subjects were recruited during their routine second trimester prenatal care visit. Inclusion criteria were women who initiated prenatal care at less than 24 weeks and who were able to provide written informed consent. Women with any of the following conditions were excluded from the study: complications of monochorionic twins (i.e., twin-to-twin transfusion syndrome), genetic or structural fetal anomalies, preeclampsia, intrauterine growth retardation (IUGR), usage of vaginal pessary or cervical cerclage during the current pregnancy. The presence of a clinical or biochemical indicator of inflammation or infection was an additional exclusion criterion. The following information was collected by chart review following completion of the laboratory study: demographic characteristics, medical and obstetrical history, information regarding current pregnancy including gestational age at sample collection, number of fetuses, dating information, complications during pregnancy, gestational age at delivery, occurrence of PPROM. The study was approved by the institutional Research Ethics Board at Careggi Hospital (number 10,255). Sample size calculation was not possible, this being the first study to analyze the relation between IGFBP-1 in maternal sera and the occurrence of PPROM.

PPROM was defined as spontaneous rupture of membranes before the onset of active labor and at less than 37 weeks of gestation. The diagnosis of PPROM in our department is based on a history suggestive of PPROM and a sterile speculum examination demonstrating amniotic fluid passing through the cervix and confirmed by ferning test pattern as necessary. All cases of PPROM were managed as per ACOG guidelines [12], with expectant vs. active management according to the clinical scenario and gestational age, with prophylactic antibiotic therapy when appropriate.

Sample collection

Peripheral blood was collected at the first enrollment visit. After clot formation the serum fraction was obtained by centrifugation and stored in aliquots at − 80 °C. All sera were shipped in a single batch on dry ice to the Witkin lab at Cornell for analysis. All samples remained frozen during shipment.

IGFBP-1 assay

Thawed aliquots were assayed in duplicate for concentrations of IGFBP-1 by a commercial ELISA kit (R & D Systems, Minneapolis, MN). Values were converted to ng/ml by reference to a standard curve that was generated in parallel to each assay. The lower limit of sensitivity was 31.2 pg/ml. Laboratory personnel were blinded to all clinical data.

Data analysis

Subjects' demographic characteristics were compared between women with and without PPROM. The Mann–Whitney test was used to compare continuous variables and the Chi-square test was used to compare categorical variables. A receiver operator curve (ROC) was constructed and the best cutoff was calculated using the Youden Index: [$J = \text{sensitivity} + \text{specificity} - 1$]. The statistical analysis was performed using SPSS version 21.0. Differences were considered significant when the p value was less than 0.05.

Results

A total of 58 women were recruited for the study. Of these, 8 subsequently developed PPROM. There were no significant differences between the two groups in terms of age, body mass index, gestational age at sample collection, smoking, race, parity, previous preterm birth, previous PPROM or chorionicity (Table 1). The median gestational age for sample collection was 19 weeks in both groups. The median time of PPROM occurrence was 35 weeks [34–37]. The median time between sample collection and PPROM was 17 weeks [15–20]. In all the cases the median latency time between PPROM and delivery was less than 24 h.

Table 1 Characteristics of the study population

Characteristic	PPROM ($n=8$)	No PPROM ($n=50$)	p value
Monochorionic twins	0	9 (18%)	0.15*
Gestational age blood collection (weeks)	19 (15–20)	19 (14–21)	0.68**
Gestational age at delivery (weeks)	35 (33–36)	36 (34–37)	0.56**
Maternal age (years)	36.0 (34.2–38.7)	35.5 (33.0–40.2)	0.67**
Body mass index (kg/m^2)	21.2 (19.5–22.6)	21.6 (19.9–24.3)	0.89**
Parity > 0	1 (12.5%)	11 (22.0%)	0.37*
Previous preterm birth	1 (12.5%)	0	0.24*
Previous PPROM	0	0	1*
Smoking	0	4 (8.0%)	0.35*
Non-White race	0	2 (4.0%)	0.43*
Serum IGFBP-1 (ng/ml)	59.3 (42.8–66.1)	46.6 (32.2–54.8)	0.042**

*Chi-square test; **Mann–Whitney test

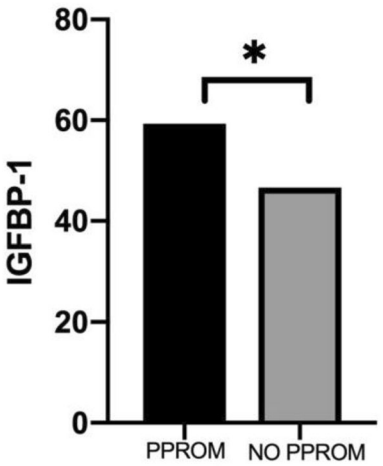

Fig. 1 IGFBP-1 values in PPROM and no PPROM patients. PPROM = 59.3 (42.8–66.1) ng/ml and 46.6 (32.3–54.8) ng/ml) no PPROM ($p=0.042$), *Mann–Whitney test

The relationship between the serum IGFBP-1 level and PPROM is shown in Table 1. The median IGFBP-1 level in women who subsequently developed PPROM exceeded the highest value observed in women with no PPROM. The median (range) IGFBP-1 concentration was 59.3 (42.8–66.1) ng/ml in sera from women with PPROM and 46.6 (32.3–54.8) ng/ml in the women with twin pregnancies and no PPROM ($p=0.042$) (Fig. 1).

An ROC analysis of the ability of the serum IGFBP-1 concentration to predict the subsequent occurrence of PPROM is shown in Fig. 1. The area under the curve is 0.7250. The best IGFBP-1 cutoff value, as determined by the Youden index, was 53.9 ng/ml. This yielded a sensitivity of 74%, with 75% specificity, a positive predictive value of 20% and a negative predictive value of 97% (Fig. 2).

Discussion

To date no studies have investigated the value of IGFBP-1 in maternal sera as a potential biomarker of PPROM susceptibility. Results of the present study demonstrate that an elevated level of IGFBP-1 in the maternal circulation at about 19 weeks gestation in women with twin pregnancies predicts the subsequent occurrence of PPROM. The purported association is biologically plausible. As mentioned above, IGFBP-1 has been shown to inhibit collagen biosynthesis by two independent mechanisms. By its binding to IGF-1 IGFBP-1 prevents IGF-1-mediated collagen production [9, 10]. IGFBP-1 binding to the β1-integrin receptor also interferes with collagen production and reorganization of the cytoskeleton [10]. The retardation of collagen production in fetal membranes during gestation in women expressing elevated levels of IGFBP-1 would be expected to result in a weakened membrane with a higher susceptibility to premature rupture (Fig. 3). In addition, the association of inflammation with elevated transcription of the gene coding for IGFBP-1 and a concomitant decreased transcription of the IGF-1 gene [8] further suggests a potential role of inflammation at the maternal–fetal interface in IGFBP-1-mediated inhibition of collagen production at this site. Maternal plasma IGFBP-1 concentrations have also been associated with additional adverse pregnancy outcomes such as intrauterine growth restriction [13], preeclampsia [14], antiphospholipid antibody syndrome [15] and impaired placental function [16].

The concentration of IGFBP-1 in amniotic fluid is 100–1000 times higher than its concentration in other body fluids [17]. As a consequence, in current clinical practice IGFBP-1 is measured in vaginal secretions as a point of care test to verify the occurrence of PROM and PPROM when medical history and physical examination do not lead to a definitive diagnosis [17–22]. It would be interesting to determine whether there is an association between the amniotic

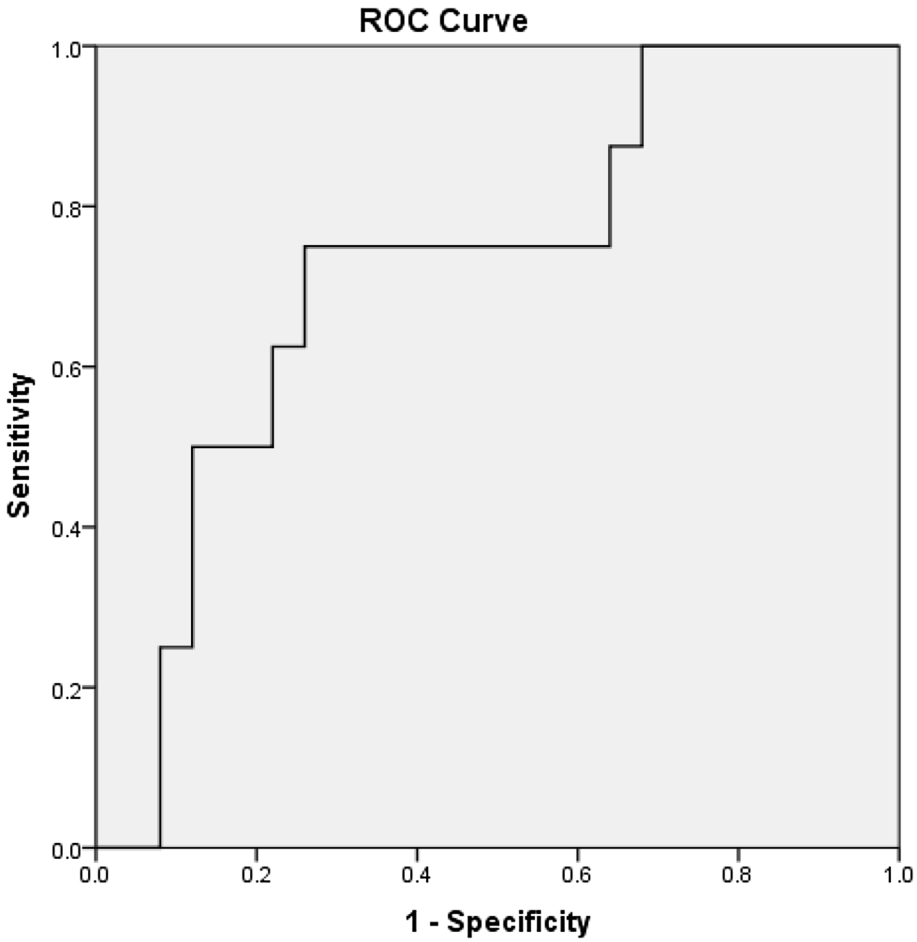

Fig. 2 ROC curve analysis of subsequent PPROM by IGFBP-1 serum concentration in women with twin gestations. The area under the curve is 0.7250, yielding a sensitivity of 74%, specificity of 75%, positive predictive value of 20% and negative predictive value of 97%

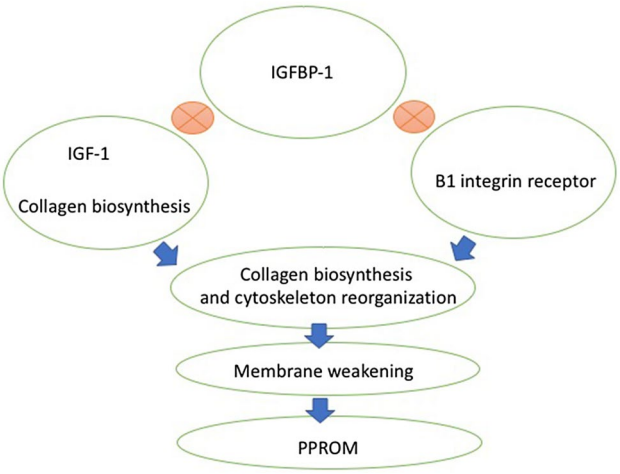

Fig. 3 Suggested mechanisms linking IGFBP-1 to PPROM

fluid IGFBP-1 concentration and susceptibility to develop PPROM in both singleton and multifetal gestations.

The limitations to the present study must be acknowledged. Of the 58 participants in the present prospective study only 8 (13.8%) developed PPROM. Therefore, the present study must be designated as hypothesis testing. Additional investigations of greater numbers of women with twin pregnancies, as well as the analysis of women in different populations, are necessary to validate our hypothesis. The absence of a concomitant investigation of placental pathology or inflammation further limits our ability to define the mechanism of PPROM in each of our subjects. Lastly, potential reasons for elevated IGFBP-1 levels in our PPROM patients—genetic, infectious, immunological—were not evaluated. The identification of mechanisms leading to elevations in IGFBP-1 in pregnancy can lead to investigations to modulate their levels and reduce susceptibility to PPROM.

In conclusion, IGFBP-1 levels in sera at 19 weeks gestation may be of value in predicting susceptibility to the subsequent occurrence of PPROM in twin pregnancies. If validated and the causative mechanism(s) determined, novel studies to lower susceptibility to PPROM can be initiated.

Author contributions GS: project development, data collection, and manuscript writing. SP: samples management, data analysis. AP: data

collection. VS: manuscript writing. MDT: project development, and manuscript writing. SW: data analysis, and manuscript writing.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

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