Umbilical cord insertion into the lower segment of the uterus at 11 to 13 weeks’ gestation is associated with maternal serum PAPP-A

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Objectives To evaluate whether the location of the placental cord insertion (CI) at 11 to 13 weeks’ gestation affects the maternal serum pregnancy-associated plasma protein-A (PAPP-A).

Methods Cohort study was conducted in patients who underwent the first trimester screening including nuchal translucency and blood test. We additionally documented the CI site. The thickness of the placenta under the CI and the minimum distance on the uterine wall between the internal cervical os and the CI (Dis) were measured. The subjects were divided into two groups. Below the tenth percentile in multiples of median (MoM) of Dis were defined as cases in which CI was located on the lower uterine segment (low CI) and the others were defined as controls.

Results A total of 117 subjects were analyzed. The thickness of the placenta ($r = 0.237$, $p = 0.010$) and Dis ($r = 0.243$, $p = 0.008$) was correlated with the crown-rump length (CRL). The maternal serum PAPP-A MoM in the low CI group was lower than in controls ($0.76 \pm 0.34$ vs $1.16 \pm 0.55$; $p = 0.009$), whereas the other ultrasonographic measurements and maternal demographics were not different between the two groups.

Conclusion CI on the lower segment of the uterus is associated with low maternal serum PAPP-A MoM levels. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: PAPP-A; umbilical cord; placenta; velamentous cord insertion; vasa previa; placenta previa

INTRODUCTION

Placental-form abnormalities such as the development of a bilobar, accessory or succenturiate placenta, velamentous cord insertion (CI) and vasa previa are caused by developmental problems of the placenta. These abnormalities are often observed in cases with a low-lying placenta and CI located on the lower uterine segment both at delivery (Catanzarite et al., 2001; Hasegawa et al., 2006b, 2007) as when studied during the first trimester (Hasegawa et al., 2006a). As the CI site (connecting stalk) is determined at the time of implantation before placental development, we suspected that CI located on the lower uterine segment might be associated with poor placental development and function.

Pregnancy-associated plasma protein-A (PAPP-A) is synthesized primarily by the syncytiotrophoblasts (Bischof et al., 1981; Sinisch et al., 1982) and increases in the maternal serum throughout pregnancy (Sinisch et al., 1985). Previous studies demonstrated that a subset of women with PAPP-A below the fifth centile have an increased risk of intramural growth restriction, extreme preterm delivery, pre-eclampsia and stillbirth (Smith et al., 2002, 2006; Dugoff et al., 2004; Krantz et al., 2004; Spencer et al., 2008; Proctor et al., 2009; Salvig et al., 2010). A low level of PAPP-A is considered a marker of early placental dysfunction. Therefore, we hypothesized that the abnormal development of the placenta in cases with lower CI is associated with a low concentration of maternal serum PAPP-A.

The purpose of this study was to evaluate the potential relationship between the location of the placental CI at 11 to 13 weeks’ gestation and the maternal serum PAPP-A levels.

MATERIALS AND METHODS

This prospective cohort study was conducted to evaluate the association between the locations of the CI at 11 to 13 weeks’ gestation and maternal serum PAPP-A levels. Consecutive subjects under care at the Department of Obstetrics and Gynecology, Bologna University, St Orsola Hospital from January to June 2010, who reported for a nuchal translucency test combined with serum screening (PAPP-A and the free beta-human chorionic gonadotrophin subunit), were included in the study. An ultrasound measurement of fetal nuchal translucency and crown-rump length (CRL) was performed between gestational weeks 11 + 0 and 13 + 6. The ultrasound examination was complemented with the determination of the location of the umbilical cord, the placental thickness and uterine arterial Doppler. Multiple pregnancies were excluded from this study. All women gave their informed consent to participate in the
study, which was approved by the local Hospital Ethics Committee.

The relation of the position between the umbilical CI and the uterine cavity was examined using ultrasonography via the transabdominal approach. The thickness of the placenta under the placental CI site was defined as the minimum distance between the placental umbilical CI and the myometrium. The minimum distance on the uterine wall between the internal cervical os and the CI site (Dis) was measured using the tracing method. In this study, the internal cervical os was ultrasonically defined as the lowest part of the uterine cavity (Figure 1).

To normalize the distribution of ultrasonographic measurements, multiples of median (MoM) of the thickness of the placenta and Dis adjusted by CRL were calculated using weighted log-linear regression. Subjects were divided into two groups. Those below the tenth percentile in the MoM of Dis were defined as cases in which the CI was located on the lower uterine segment (low CI) and the others were defined as controls (normal CI).

Uterine artery blood velocity waveforms were also recorded, visualizing both uterine arteries at the apparent crossover of the uterine and external iliac arteries. The uterine arteries' pulsatility index (PI) and resistance index (RI) were measured at the uterine cervico-corporeal junction. The PI and RI for each uterine artery were obtained by averaging the values of three consecutive waveforms. The mean values were used from the left and right uterine arteries in the analysis.

The ultrasound examination was performed using a Voluson 730 and E8 instrument (GE Healthcare Italia, Milan, Italy) equipped with a transabdominal 4–8 MHz convex probe. Maternal serum PAPP-A was measured using a kit for BRAHMS KRYPTOR automated immunofluorescent assays (Hennigsdorf, Germany; www.kryptor.net/). Samples were measured within 6 h of the blood draw.

The maternal serum levels of PAPP-A were expressed in MoM, which was determined from the CRL measurement at the ultrasound examination for nuchal translucency, maternal weight, smoking status, racial origin, parity and method of conception (Kagan et al., 2008).

The data were entered into a computerized data analysis software program [Statistical Package for Social Science (SPSS), Windows version 17.0; Chicago, IL, USA]. Categorical variables were reported as percentages and were compared using the x² test. Continuous variables were analyzed using the linear regression analysis and the Mann–Whitney U-test. Statistical significances were defined as p-values <0.05.

RESULTS

One hundred seventeen subjects were analyzed. Scatter plots between the thickness of the placenta and the maternal serum PAPP-A and between the Dis and the maternal serum PAPP-A are displayed in Figure 2a and b. Significant correlations between the thickness of the placenta and the maternal serum PAPP-A (r = 0.219, p = 0.017) and between the Dis and the maternal serum PAPP-A (r = 0.293, p = 0.001) were observed.

There were significant correlations between the thickness of the placenta and the CRL (F = 6.78, R = 0.237, p = 0.010) and between the Dis and the CRL (F = 7.22, R = 0.243, p = 0.008). After adjustment for the CRL,
LOW PAPP-A IN LOW CORD INSERTION

Figure 2—(a) Distribution of PAPP-A levels against the thickness of the placenta. (b) Distribution of PAPP-A levels against the distance between the internal os and the cord insertion site (Dis); significant correlations between the thickness of the placenta and the maternal serum PAPP-A (r = 0.219, p = 0.017) and between the Dis and the maternal serum PAPP-A (r = 0.293, p = 0.001) are observed.

Figure 3—Scatter graph between the MoM of distance between the internal os and the cord insertion site (Dis) and the MoM of thickness of the placenta; significant correlation was not demonstrated.

Table 1—Results of ultrasonographic measurements and maternal demographics in patients with low CI and normal CI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low CI (Dis ≤ tenth centile)</th>
<th>Normal CI (Dis &gt; tenth centile)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness of the placenta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In mm</td>
<td>1.25 ± 0.23</td>
<td>1.31 ± 0.36</td>
<td>0.723</td>
</tr>
<tr>
<td>In MoM</td>
<td>0.97 ± 0.15</td>
<td>1.00 ± 0.27</td>
<td>0.837</td>
</tr>
<tr>
<td>Uterine arterial Doppler Resistance index</td>
<td>0.69 ± 0.13</td>
<td>0.70 ± 0.11</td>
<td>0.856</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>1.59 ± 0.67</td>
<td>1.51 ± 0.49</td>
<td>0.979</td>
</tr>
<tr>
<td>Nuchal translucency (mm)</td>
<td>1.52 ± 0.53</td>
<td>1.71 ± 1.02</td>
<td>0.466</td>
</tr>
<tr>
<td>Crown-rump length (mm)</td>
<td>59.6 ± 3.9</td>
<td>61.8 ± 7.9</td>
<td>0.432</td>
</tr>
<tr>
<td>Maternal age</td>
<td>29.8 ± 3.9</td>
<td>30.6 ± 3.8</td>
<td>0.254</td>
</tr>
<tr>
<td>Multiparity (%)</td>
<td>9.1%</td>
<td>14.2%</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI, cord insertion; Dis, distance between the internal os and the cord insertion site.
Values indicate mean ± standard deviation. Statistical analyses were performed using Mann–Whitney test and Fisher’s exact test.

DISCUSSION

We demonstrated correlations between the thickness of the placenta and the maternal serum concentration of PAPP-A and between the Dis and the PAPP-A (Figure 2a and b). This was expected because they are all functions of increasing gestational age. However, a difference in the PAPP-A concentration, between the two subgroups based on the MoM of Dis, still persisted (Figure 4). However, the thickness of the placenta MoM and Dis MoM did not correlate with the PAPP-A MoM.

Cases in which the Dis was below the tenth percentile were associated with low maternal serum PAPP-A levels. As there was no significant relationship between the thickness of the placenta and the Dis (Figure 3), low
PAPP-A levels in low CI subjects did not seem to be dependent on the placental thickness.

The mechanism underlying the development of abnormal placental forms is often explained by the ‘trophotropism’ theory. This is the hypothesis in which the early placenta migrates with advancing gestation to ensure a better blood supply from a more richly vascularized area (Monie, 1965). Therefore, even when the placental CI site is located on or near the internal os at the time of implantation, the placenta is likely to develop on the uterine body apart from the placental insertion site, resulting in velamentous CI or vasa previa.

In contrast to the trophotropism theory, a previous study reported that placenta previa and low-lying placenta were often observed in cases with low placental CI (Hasegawa et al., 2006a). This might indicate that there are some mechanisms by which the umbilical CI site attracts the placental development site to the CI site. However, it is also well-known that placenta previa and low-lying placenta are associated with placental-form abnormalities, largely because of the poor development of the placenta at the part of lower uterine segment (Catanazari et al., 2001; Hasegawa et al., 2006a, 2007).

It is previously reported that low placental CI in the uterus was strongly associated with the development of abnormal forms due to the aforementioned mechanisms. With regard to placental function, we also demonstrated in this study that low placental CI is associated with markers that are indicative of poor placental development from early gestation. Previous reports, even if discordant, have suggested that pregnancies with low PAPP-A during the first trimester are associated with placental damage in the second trimester, small total placental volumes and adverse perinatal outcomes (Smith et al., 2002, 2006; Dougoff et al., 2004; Krantz et al., 2004; Proctor et al., 2009). We speculate that small total placental volumes at the first trimester scan and consequent lower PAPP-A values are more frequent in cases with low CI. The low PAPP-A levels observed in low CI cases might result from low placenta, although the placental location and forms were not evaluated in this study. However, our results suggest that an adverse effect on the placental function in patients whose umbilical CI was located in the lower uterine segment has already occurred during the first trimester.

Some factors that affect the maternal serum PAPP-A levels during the first trimester screening include factors such as IVF treatment, a previous pregnancy, smoking, ethnicity and maternal body weight (Kagan et al., 2008; Amor et al., 2009). In this study, it was revealed that the CI site at 11 to 13 weeks’ gestation also affects maternal serum PAPP-A levels.

In conclusion, we showed that the maternal serum PAPP-A MoM levels are low in cases with a placental CI site located in the lower segment of the uterus. As PAPP-A is an indicator of placental function, it is possible that low CI is associated with poor placental activity beginning in the first trimester.

REFERENCES


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