Evaluation of the Impact of Vasa Previa on Feto-Placental Hormonal Synthesis and Fetal Growth

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Highlights

• Vasa previa type I is associated with lower fetal birth weight, placental weight and lower human chorionic gonadotropin (hCG)

• Vasa previa type I is associated with slower feto-placental growth supporting the association between hCG synthesis and early placental growth and development due to velamentous insertion.

• The location of the cord insertion has an impact on placental function and fetal growth
Abstract

Introduction: A vasa previa (VP) refers to aberrant chorionic vessels which can either connect the chorionic plate to a velamentous cord (type I) or a succenturiate or accessory lobe to the main placental mass (type II). It is unclear if VP has an impact on placental and fetal growth.

Methods: Retrospective cohort study of 32 singleton pregnancies diagnosed with VP. The levels of maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated estriol (uE3) were measured at 15-18 weeks as part of the triple test screening for Trisomy 21. The data were subdivided according to the type of VP and compared with those of a control group with central cord insertion and no succenturiate or accessory placental lobe.

Results: Twenty one (65.6%) parturient women presented with VP type I and 11 (34.4%) with VP type II. The mean birthweight and placental weight was significantly higher in pregnancies with VP type II than in pregnancies with VP with VP type I (3037.3±400.9 gr vs 2493.5±491.6 gr; p=0.004 and 511.0±47.2 gr vs 367.1±64.3 gr; p<0.0001; respectively). The mean hCG level in VP type II was significantly (p<0.001) higher than those with type I (2.38 MoM vs 1.17 MoM) and compared to controls (2.38 MoM vs 0.99 MoM).

Conclusions: We found that in VP type II, there is no obvious impact on both placental and fetal growth. Contrary to VP type I, being associated with slower feto-placental growth probably due to smaller placental mass.
KEYWORDS: Vasa previa, triple test, serum markers, prenatal, ultrasound, birthweight
1. Introduction

A vasa Previa (VP) is an aberrant chorionic vessel directly connected to the umbilical cord circulation but running between the amniotic and the chorionic layers of the placental free membranes in front of the fetal presenting part [1]. VP are not surrounded by Wharton’s jelly and are therefore vulnerable to compression and stretching when the uterine cervix starts to dilated and the fetal presentation engages inside the pelvis. The rupture of the placental membranes may also lead to their rupture and rapid fatal fetal haemorrhage. VP are reported to occur in around 1 in 1200 spontaneous conception [2]. VP are separated into two types based on their anatomical features: type I where the vessel connects the chorionic plate of the placenta to a velamentous cord and type II where it connects a succenturiate or accessory lobe to the main placental mass [3].

Velamentous cord insertions are found in 1-1.5% of singleton pregnancies and 6% of twin gestations. Velamentous cords have been associated with obstetric complications including fetal growth restriction, prematurity, congenital anomalies, low Apgar scores, fetal bleeding with acute fetal distress and placental retention [4]. These complications are mainly due to the association between a velamentous cord and VP or associated fetal structural anomalies. However, previous studies have suggested that an abnormal cord insertion can also to be associated with impaired development and function of the placenta [5], and therefore influences fetal growth. A recent study has shown a higher resistance to blood flow in the umbilical arteries of velamentous cords supports this concept [4]. These findings
suggest that the insertion of the umbilical cord outside the chorionic placental plate may be lead to abnormal umbilico-placental blood flows and secondary fetal growth restriction.

Human chorionic gonadotropin (hCG) and its free beta-subunit (βhCG) are exclusively synthetized by the villous trophoblast [6] and alpha-fetoprotein (AFP) is synthetized by the secondary yolk sac and fetal liver [7]. Both have been used in the 15-20 week triple maternal serum (MS) test for the screening of trisomy 21. Unexplained elevations of MShCG and/or MSAFP have been reported in approximately 1% of the pregnant and associated with an increased risk of adverse pregnancy outcome including miscarriages, low birth weight, preterm labor, abruptio plenta, preeclampsia, intrauterine fetal death and a wide spectrum of fetal and placental malformations [8]. In particular, placental and cord vascular lesions are known to be associated with higher MSAFP [9] and severe utero-placental insufficiency with early onset IUGR and preeclampsia is associated with higher MShCG during the second trimester of pregnancy [10].

The aim of this study it to evaluate the possible relationship between mid-gestation triple test serum markers of feto-placental functions and subsequent fetal growth in women diagnosed with VP.

2. Patients and Methods

We conducted a retrospective cohort study of all women with singleton pregnancies diagnosed with a "vasa previa" between 2005 to 2016. We obtained
data from our departmental electronic medical records including obstetrical history, modes of conception, sonographic scans, mode of delivery, associated placental pathologies. In addition, we also retrieved data on the results of the 15-20 weeks triple maternal serum test used for the routine screening of trisomy 21 during that period. Multiple pregnancy gestations and singleton pregnancies where the fetus was found to have an abnormal karyotype and/or presented with a structural defect prenatally or at delivery were excluded from the study.

All ultrasound examinations in our department are performed using standard ultrasound machines equipped with a transvaginal probe (5- to 9-MHz frequency with a focal range of 6 cm from the transducer tip) and a transabdominal probe (3.5- to 5-MHz frequency). The location of the umbilical cord is recorded at the mid-trimester scan and the presence of a VP is made with transvaginal sonography combined with color/pulsed Doppler as previously described [11]. Gestational age was determined in spontaneous pregnancies by the last menstrual period and in IVF pregnancies according to the date of embryo transfer (ET). Gestational age in all cases was confirmed by measuring the fetal crown-rump length (CRL) up to 13+6 weeks and the biparietal diameter (BPD) from 14+0 weeks.

In cases of abnormal cord insertion and/or VP diagnosed prenatally or during delivery a full pathological examination of the placenta and membranes is performed as previously described [11]. The study population was then divided into two cohorts: VP type I and VP type II.

The study was approved by our institutional Clinical Research Committee.
Triple test serum bioassays

The assays for triple test analyses have been previously reported [20]. Assays for AFP, HCG and uE3 were performed with the Beckman Coulter Access reagents for AFP, HCG and uE3 with their corresponding calibrators (Beckman Coulter, USA). The measured marker levels were expressed as multiples of the gestation specific normal medians (MoM). Mean values for each serum hormones are calculated for gestational as determined by LMP or date of ET confirmed by ultrasound measurements of CRL or BPD. All values are adjusted for maternal weight. We compared results with reference MoM values calculated from our own local population as established in the Zer Medical Laboratories (ISO 9002 UK, certified and authorized by the Ministry of Health, Israel) as previously described [12]. These included 7482 control cases who had the triple test serum screening between 15.0 and 20.6 weeks of gestation weeks. The following median MOM: AFP 0.997, hCG 0.998, µE3 1.002 were used for the controls.

Statistical analysis

Standardized kurtosis indicated that the data were normally distributed and thus they are expressed as mean and standard deviation (SD). Proportions were expressed as percentages. Statistical analysis was performed using Student’s t-test to compare the second-trimester marker between different groups. AFP, hCG and uE3 concentrations presented with a normal Gaussian distribution.

Two tailed t-test was used to compare the results among the study subgroup cohorts and control group. The data of the two subgroups of VP were compared
using median and geometric mean (ie the antilog of mean log MoM). A $p$ value $< 0.05$ was considered significant. Calculations were performed in the statistical laboratory at Tel Aviv University using SPSS software (SPSS Inc., version 24 Chicago, IL, USA).

3. Results

A total 32 cases of VP with complete clinical information and triple test data were included in our study. Twenty-one (65.6%) cases presented with a type I VP and 11 (34.4%) type II VP. The characteristics of the two types of VP are displayed and compared in Table 1. There were no statistical differences in maternal age, prenatal diagnosis and gestational age at diagnosis of VP or delivery by cesarean section between the two study subgroups. There were also no significant differences between the two subgroups for their obstetrical history, mode of conception and gestational age at delivery. In total, 14 women (43.8%) had a pregnancy resulting from IVF. The mean birthweight and placental weight were significantly higher in pregnancies with VP type II than in pregnancies with VP type I ($3037.3\pm400.9$ gr vs $2493.5\pm491.6$ gr; $p=0.004$ and $511.0\pm47.2$ gr vs $367.1\pm64.3$ gr; $p<0.0001$; respectively). However, the feto-placental weight ratio were significantly lower ($p=0.02$) in pregnancies with VP type II than in pregnancies with VP with VP type I ($5.9\pm0.7$ vs $6.8\pm0.9$) (Table 1).

Table 2 presents and compares the data of hormonal markers between VP cohort subgroups and the controls from the reference laboratory. The mean hCG
level in VP type II was significantly ($p<0.001$) higher than those with type I (2.38 MoM vs 1.17 MoM) and compared to controls (2.38 MoM vs 0.99 MoM). AFP MoMs were not significantly ($p = 0.4930$) different between the VP subgroups (1.32 vs 1.22 MoM,) but both had significantly higher mean AFP level (type 2; 1.32 vs 1.01 MoM; $p= 0.038$ and type 1; 1.22 vs.1.01 MoM; $p=0.012$). No significant difference was found for uE3 MoMs between the VP subgroups and between VP subgroups and controls. There were no significant differences in the levels of mean hCG and AFP MoMs between spontaneously-conceived pregnancies and IVF-conceived pregnancies (1.36 vs. 1.49 MoM; $p=0.63$ and 1.27 vs. 1.19; $p=0.45$).

4. Discussion

The results of the present study indicate that a VP type I is associated with lower fetal birth weight, placental weight and lower MShCG. Our findings add to previously published data suggesting that an abnormal cord insertion may be associated with impaired development and function of the placenta, increased resistance to blood flow in the umbilical circulation, and abnormal fetal growth [4,5].

The concept of trophotropism was first introduced by Kouyoumdjian et al. [13] in 1980 to explain the preferential implantation and placentation at sites with optimal uterine perfusion. Placental development and remodeling are dependent on factors that determine the relative myometrial perfusion, the insertion of the umbilical cord modifying its initial position according to the placental pole migrating towards the more vascularized uterine area [14]. This could explain why
velamentous cords are associated with an increased risk of other placental disorders such as placental abruption, placenta praevia, pre-eclampsia and intrauterine growth restriction and epidemiological data suggests shared genetic and environmental mechanisms associated with altered implantation, migration, invasion and transformation of the spiral arteries [15]. By contrast, marginal cord insertions is associated with decreased placental weight but not fetal weight suggesting a primary developmental disorder with increased utilization of placental reserve [16]. Our data indicate that the association of a VP with a velamentous cord is associated with a decrease in both placental and fetal growth. The abnormal growth and development are more pronounced in the placenta than in the fetus supporting the concept of a primary placental developmental disorder.

Assisted reproduction technology (ART) and in IVF in particular is associated with a higher incidence of abnormally shaped placenta, placenta previa and cord insertion outside the placental chorionic plate [17,18]. IVF in particular, increases the risk for VP from 0.06% [18] to approximately 0.4% [17]. Approximately 44% of the pregnancies included in the present study resulted from IVF and 70% of our VP cases presented either with placenta previa or bilobed placenta (Table 1). It has been hypothesized that these placental and cord anomalies could be due to the inadequate orientation of the IVF blastocyst at the time of implantation or to a higher incidence of vanishing twins in IVF than in spontaneous twins [17,19]. It has been hypothesized that deformation of the vasculogenic zone yields a bi-lobate placental shape abnormal cord insertion and a multi-lobate shape result from early influences on the placental growth, such as the shape of the vasculogenic zone, or
placental position in the uterus, rather than trophotropism later in pregnancy [20].

Our data support also the concept of a primary placental disorder due to placentation away from the normal implantation zone.

Elevated levels of MShCG and lower MSAFP have previously been reported in cases of VCI [21]. These studies did not include data on the presence of VP. High MShCG have associated with vascular placental pathology at delivery, such as infarction, ischemic changes, villitis and intervillous thrombosis [22]. It has been suggested that hypoxia increases hCG overproduction in trophoblastic cells cultured in vitro [23] and inadequate trophoblastic migration and remodeling of the uterine vasculature leads to placental hypoxia and secondary hCG overproduction.

It has been recently suggested that hCG β-genes expression is linked to the establishment of the intervillous circulation and thus of the intraplacental oxygen concentration [24] and secretion of hCG in preeclampsia may be linked to premature accelerated differentiation of the villous cytotrophoblasts secondary to chronic intra-placental oxidative stress [25]. We found higher levels of MShCG in VP type II compared to cases with type I and controls (Table 2). These findings also support the concept of a primary placental developmental disorder.

Unexplained elevated levels of MSAFP have been associated with thrombotic and inflammatory vascular lesions [22], peri-placental hemorrhage and increased placental thickness [26]. During the second and third trimester of pregnancy AFP is mainly produced by the fetal liver and serum and amniotic levels were used for the antenatal screening of neural tube defects [7]. Higher MS levels are also commonly
found in chorioangiomas, intervillous thrombosis and umbilical cord angiomyxomas suggesting a leakage from the fetal circulation [9]. VP are not covered by Wharton Jelly and thus the rise in MSAFP in these cases may also be due to increase diffusion of AFP from the fetal circulation secondary to microtraumatism of the vessels by fetal movements. This could explain why we found higher levels MSAFP in pregnancies with both types of VP compared to controls (Table 2).

Yampolsky et al. [27] found that placentas from singleton pregnancies with a displaced cord show a markedly reduced transport efficiency, reflected in a larger value of beta and hence in a smaller birth weight for a given placental weight. Placentas with a non-central cord insertion have also a sparser chorionic vascular distribution, as measured by the relative vascular distance. More recently several authors have recently evaluated the association of different combinations of placental umbilical cord insertions with birth weight discordance in twins. Combiaso et al. [28] found in a large cohort of monochorionic twins a highly significant association between discordant cord insertions and discordant birth weight was observed (p < 0.01). The odds ratios (OR) for birth weight discordance in the discordant cord insertion group compared with the concordant group were 2.3 (95% CI: 1.2-4.4) for the normal-marginal and 5.9 (95% CI: 3.8-10.4) for the normal-velamentous cord insertion subgroup. Similarly, Costa-Castro et al. [29] found that monochorionic (MC) twins with and without twin-twin transfusion syndrome (TTTS) VCI is associated with severe birth weight discordance. Chu et al. [30] has previously found that, the vascular numerical terminal villi density of twins with VCI is significantly lower than of those with a more central cord insertion.
Conclusions

Our data support the concept of a primary placental developmental disorder in pregnancies presenting with a VP associated with a velamentous insertion of the cord. By contrast, in VP type II where the cord is inserted within the main placental mass, there is no obvious impact on both placental and fetal growth. In VP type I, the primary placental developmental disorder combined with alterations of the umbilical circulation in the velamentous cord could explain the secondary slow fetal growth.

Acknowledgment

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References


17


Table 1

A comparison of characteristics between parturient women with vasa previa type I to those diagnosed with vasa previa type II.

<table>
<thead>
<tr>
<th></th>
<th>Vasa previa type I (n=21)</th>
<th>Vasa previa type II (n=11)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years; mean ± SD)</td>
<td>32.1±5.2</td>
<td>33.7±3.8</td>
<td>0.366</td>
</tr>
<tr>
<td>Gestational age at diagnosis (weeks; mean ± SD)</td>
<td>25.9±5.9</td>
<td>27.9±4.8</td>
<td>0.438</td>
</tr>
<tr>
<td>Prenatal diagnosis (%)</td>
<td>17 (81.0)</td>
<td>9 (81.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Delivery by cesarean section (%)</td>
<td>20 (95.2)</td>
<td>10 (90.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Elective cesarean section (%)</td>
<td>6.3 (30.0)</td>
<td>6.6 (60.0)</td>
<td>0.139</td>
</tr>
<tr>
<td><strong>Mode of conception (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>13 (61.9)</td>
<td>5 (45.5)</td>
<td>0.465</td>
</tr>
<tr>
<td>IVF</td>
<td>8 (38.1)</td>
<td>6 (54.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Obstetric history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravidity (mean ± SD)</td>
<td>2.2±0.9</td>
<td>2.1±0.8</td>
<td>0.653</td>
</tr>
<tr>
<td>Parity (mean ± SD)</td>
<td>0.6±0.7</td>
<td>0.6±0.7</td>
<td>0.945</td>
</tr>
<tr>
<td><strong>Neonatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth week (mean ± SD)</td>
<td>36.4±1.4</td>
<td>37.4±1.5</td>
<td>0.438</td>
</tr>
<tr>
<td>Birth weight (gr; mean ± SD)</td>
<td>2493.5±491.6</td>
<td>3037.3±400.9</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Placental weight (gr; mean ± SD)</td>
<td>367.1±64.3</td>
<td>511.0±47.2</td>
<td>&lt;<strong>0.0001</strong></td>
</tr>
<tr>
<td>Feto-placental weight ratio (mean ± SD)</td>
<td>6.8±0.9</td>
<td>5.9±0.7</td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>

Data is presented as number (%) or as mean ± standard deviation.
Table 2
Comparison of triple test screening markers between women with diagnosis of vasa previa type I, vasa previa type II and reference laboratory values by two tailed t-test.

<table>
<thead>
<tr>
<th></th>
<th>hCG*</th>
<th>AFP*</th>
<th>uE3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasa previa type I</td>
<td>1.17a</td>
<td>1.22d</td>
<td>1.02g</td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasa previa type II</td>
<td>2.38b</td>
<td>1.32e</td>
<td>1.01h</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference laboratory</td>
<td>0.99c</td>
<td>1.01f</td>
<td>0.98i</td>
</tr>
<tr>
<td>(Controls)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Comparison of the mean MoM.

AFP = alpha-fetoprotein, uE3 = unconjugated estriol, hCG = human chorionic gonadotropin

\[ p \text{ value between a and b} < 0.0001 \quad \text{p value between d and e} = 0.493 \quad \text{p value between g and h} = 0.897 \]
\[ p \text{ value between a and c} = 0.149 \quad \text{p value between d and f} = 0.012 \quad \text{p value between g and i} = 0.664 \]
\[ p \text{ value between b and c} < 0.0001 \quad \text{p value between e and f} = 0.038 \quad \text{p value between h and i} = 0.854 \]