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

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32 **Highlights**
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35 • Vasa previa type I is associated with lower fetal birth weight, placental

36 weight and lower human chorionic gonadotropin (hCG)

37 • Vasa previa type I is associated with slower feto-placental growth supporting

38 the association between hCG synthesis and early placental growth and

39 development due to velamentous insertion.

40 • The location of the cord insertion has an impact on placental function and

41 fetal growth

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**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.

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## 1. Introduction

72      A vasa Previa (VP) is an aberrant chorionic vessel directly connected to the

73 umbilical cord circulation but running between the amniotic and the chorionic layers

74 of the placental free membranes in front of the fetal presenting part [1]. VP are not

75 surrounded by Wharton's jelly and are therefore vulnerable to compression and

76 stretching when the uterine cervix starts to dilated and the fetal presentation

77 engages inside the pelvis. The rupture of the placental membranes may also lead

78 to their rupture and rapid fatal fetal haemorrhage. VP are reported to occur in

79 around 1 in 1200 spontaneous conception [2]. VP are separated into two types

80 based on their anatomical features: type I where the vessel connects the chorionic

81 plate of the placenta to a velamentous cord and type II where it connects a

82 succenturiate or accessory lobe to the main placental mass [3].

83      Velamentous cord insertions are found in 1-1.5% of singleton pregnancies

84 and 6% of twin gestations. Velamentous cords have been associated with obstetric

85 complications including fetal growth restriction, prematurity, congenital anomalies,

86 low Apgar scores, fetal bleeding with acute fetal distress and placental retention

87 [4]. These complications are mainly due to the association between a velamentous

88 cord and VP or associated fetal structural anomalies. However, previous studies

89 have suggested that an abnormal cord insertion can also to be associated with

90 impaired development and function of the placenta [5], and therefore influences

91 fetal growth. A recent study has shown a higher resistance to blood flow in the

92 umbilical arteries of velamentous cords supports this concept [4]. These findings

93 suggest that the insertion of the umbilical cord outside the chorionic placental plate

94 may be lead to abnormal umbilico-placental blood flows and secondary fetal

95 growth restriction

96 Human chorionic gonadotropin (hCG) and its free beta-subunit ($\beta$hCG) are

97 exclusively synthetized by the villous trophoblast [6] and alpha-fetoprotein (AFP) is

98 synthetized by the secondary yolk sac and fetal liver [7]. Both have been used in

99 the 15-20 week triple maternal serum (MS) test for the screening of trisomy 21.

100 Unexplained elevations of MShCG and/or MSAFP have been reported in

101 approximately 1% of the pregnant and associated with an increased risk of adverse

102 pregnancy outcome including miscarriages, low birth weight, preterm labor,

103 abruptio placenta, preeclampsia, intrauterine fetal death and a wide spectrum of

104 fetal and placental malformations [8]. In particular, placental and cord vascular

105 lesions are known to be associated with higher MSAFP [9] and severe utero-

106 placental insufficiency with early onset IUGR and preeclampsia is associated with

107 higher MShCG during the second trimester of pregnancy [10].

108 The aim of this study it to evaluate the possible relationship between mid-

109 gestation triple test serum markers of feto-placental functions and subsequent fetal

110 growth in women diagnosed with VP.

111

## 2. Patients and Methods

113 We conducted a retrospective cohort study of all women with singleton

114 pregnancies diagnosed with a "vasa previa" between 2005 to 2016. We obtained

115    data from our departmental electronic medical records including obstetrical history,

116    modes of conception, sonographic scans, mode of delivery, associated placental

117    pathologies. In addition, we also retrieved data on the results of the 15-20 weeks

118    triple maternal serum test used for the routine screening of trisomy 21 during that

119    period. Multiple pregnancy gestations and singleton pregnancies where the fetus

120    was found to have an abnormal karyotype and/or presented with a structural defect

121    prenatally or at delivery were excluded from the study.

122        All ultrasound examinations in our department are performed using standard

123    ultrasound machines equipped with a transvaginal probe (5- to 9-MHz frequency

124    with a focal range of 6 cm from the transducer tip) and a transabdominal probe

125    (3.5- to 5-MHz frequency). The location of the umbilical cord is recorded at the mid-

126    trimester scan and the presence of a VP is made with transvaginal sonography

127    combined with color/pulsed Doppler as previously described [11]. Gestational age

128    was determined in spontaneous pregnancies by the last menstrual period and in

129    IVF pregnancies according to the date of embryo transfer (ET). Gestational age in

130    all cases was confirmed by measuring the fetal crown-rump length (CRL) up to

131    13+6 weeks and the biparietal diameter (BPD) from 14+0 weeks.

132        In cases of abnormal cord insertion and/or VP diagnosed prenatally or during

133    delivery a full pathological examination of the placenta and membranes is

134    performed as previously described [11]. The study population was then divided into

135    two cohorts: VP type I and VP type II.

136        The study was approved by our institutional Clinical Research Committee.

137

138 ***Triple test serum bioassays***

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140 The assays for triple test analyses have been previously reported [20]. Assays for

141 AFP, HCG and uE3  were performed with the Beckman Coulter Access reagents

142 for AFP, HCG and uE3 with their corresponding calibrators (Beckman Coulter,

143 USA).The measured marker levels were expressed as multiples of the gestation

144 specific normal medians (MoM). Mean values for each serum hormones are

145 calculated for gestational as determined by LMP or date of ET confirmed by

146 ultrasound measurements of CRL or BPD. All values are adjusted for maternal

147 weight. We compared results with reference MoM values calculated from our own

148 local population as established in the Zer Medical Laboratories (ISO 9002 UK,

149 certified and authorized by the Ministry of Health, Israel) as previously described

150 [12]. These included 7482 control cases who had the triple test serum screening

151 between 15.0 and 20.6 weeks of gestation weeks. The following median MOM:

152 AFP 0.997, hCG 0.998, µE3 1.002 were used for the controls.

153 ***Statistical analysis***

154 Standardized kurtosis indicated that the data were normally distributed and

155 thus they are expressed as mean and standard deviation (SD). Proportions were

156 expressed as percentages. Statistical analysis was performed using Student's *t*-

157 test to compare the second-trimester marker between different groups. AFP, hCG

158 and $uE_3$ concentrations presented with a normal Gaussian distribution.

159 Two tailed t-test was used to compare the results among the study subgroup

160 cohorts and control group. The data of the two subgroups of VP were compared

161  using median and geometric mean (ie the antilog of mean log MoM).  A $p$ value <

162  0.05 was considered significant. Calculations were performed in the statistical

163  laboratory at Tel Aviv University using SPSS software (SPSS Inc., version 24

164  Chicago, IL, USA).

165

166  **3. Results**

167      A total 32 cases of VP with complete clinical information and triple test data

168  were included in our study. Twenty-one (65.6%) cases presented with a type I VP

169  and 11 (34.4%) type II VP. The characteristics of the two types of VP are displayed

170  and compared in Table 1. There were no statistical differences in maternal age,

171  prenatal diagnosis and gestational age at diagnosis of VP or delivery by cesarean

172  section between the two study subgroups. There were also no significant

173  differences between the two subgroups for their obstetrical history, mode of

174  conception and gestational age at delivery. In total, 14 women (43.8%) had a

175  pregnancy resulting from IVF. The mean birthweight and placental weight were

176  significantly higher in pregnancies with VP type II than in pregnancies with VP type

177  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

178  gr; $p$<0.0001; respectively). However, the feto-placental weight ratio were

179  significantly lower ($p$=0.02) in pregnancies with VP type II than in pregnancies with

180  VP with VP type I (5.9±0.7 vs 6.8±0.9) (Table 1).

181      Table 2 presents and compares the data of hormonal markers between VP

182  cohort subgroups and the controls from the reference laboratory. The mean hCG

183    level in VP type II was significantly ($p<0.001$) higher than those with type I (2.38

184    MoM vs 1.17 MoM) and compared to controls (2.38 MoM vs 0.99 MoM). AFP

185    MoMs were not significantly ($p = 0.4930$ different between the VP subgroups (1.32

186    vs 1.22 MoM,) but both had significantly higher mean AFP level (type 2; 1.32 vs

187    1.01 MoM; $p= 0.038$ and type 1; 1.22 vs.1.01 MoM; $p=0.012$). No significant

188    difference was found for uE3 MoMs between the VP subgroups and between VP

189    subgroups and controls. There were no significant differences in the levels of mean

190    hCG and AFP MoMs between spontaneously-conceived pregnancies and IVF-

191    conceived pregnancies (1.36 vs. 1.49 MoM; $p=0.63$ and 1.27 vs. 1.19; $p=0.45$).

192

193    **4. Discussion**

194    The results of the present study indicate that a VP type I is associated with lower

195    fetal birth weight, placental weight and lower MShCG. Our findings add to

196    previously published data suggesting that an abnormal cord insertion may be

197    associated with impaired development and function of the placenta, increased

198    resistance to blood flow in the umbilical circulation, and abnormal fetal growth [4,5].

199    The concept of trophotropism was first introduced by Kouyoumdjian et al. [13]

200    in 1980 to explain the preferential implantation and placentation at sites with

201    optimal uterine perfusion. Placental development and remodeling are dependent

202    on factors that determine the relative myometrial perfusion, the insertion of the

203    umbilical cord modifying its initial position according to the placental pole migrating

204    towards the more vascularized uterine area [14]. This could explain why

205    velamentous cords are associated with an increased risk of other placental

206    disorders such as placental abruption, placenta praevia, pre-eclampsia and

207    intrauterine growth restriction and epidemiological data suggests shared genetic

208    and environmental mechanisms associated with altered implantation, migration,

209    invasion and transformation of the spiral arteries [15]. By contrast, marginal cord

210    insertions is associated with decreased placental weight but not fetal weight

211    suggesting a primary developmental disorder with increased utilization of placental

212    reserve [16]. Our data indicate that the association of a VP with a velamentous

213    cord is associated with a decrease in both placental and fetal growth. The

214    abnormal growth and development are more pronounced in the placenta than in

215    the fetus supporting the concept of a primary placental developmental disorder.

216        Assisted reproduction technology (ART) and in IVF in particular is associated

217    with a higher incidence of abnormally shaped placenta, placenta previa and cord

218    insertion outside the placental chorionic plate [17,18]. IVF in particular, increases

219    the risk for VP from 0.06% [18] to approximately 0.4% [17]. Approximately 44% of

220    the pregnancies included in the present study resulted from IVF and 70% of our VP

221    cases presented either with placenta previa or bilobed placenta (Table 1). It has

222    been hypothesized that these placental and cord anomalies could be due to the

223    inadequate orientation of the IVF blastocyst at the time of implantation or to a

224    higher incidence of vanishing twins in IVF than in spontaneous twins [17,19]. It has

225    been hypothesized that deformation of the vasculogenic zone yields a bi-lobate

226    placental shape abnormal cord insertion and a multi-lobate shape result from early

227    influences on the placental growth, such as the shape of the vasculogenic zone, or

228    placental position in the uterus, rather than trophotropism later in pregnancy [20].

229    Our data support also the concept of a primary placental disorder due to

230    placentation away from the normal implantation zone.

231        Elevated levels of MShCG and lower MSAFP have previously been reported

232    in cases of VCI [21]. These studies did not included data on the presence of VP.

233    High MShCG have associated with vascular placental pathology at delivery, such

234    as infarction, ischemic changes, villitis and intervillous thrombosis [22]. It has been

235    suggested that hypoxia increases hCG overproduction in trophoblastic cells

236    cultured in vitro [23] and inadequate trophoblastic migration and remodeling of the

237    uterine vasculature leads to placental hypoxia and secondary hCG overproduction.

238    It has been recently suggested that hCG $\beta$-genes expression is linked to the

239    establishment of the intervillous circulation and thus of the intraplacental oxygen

240    concentration [24] and secretion of hCG in preeclampsia may be linked to

241    premature accelerated differentiation of the villous cytotrophoblasts secondary to

242    chronic intra-placental oxidative stress [25]. We found higher levels of MShCG in

243    VP type II compared to cases with type I and controls (Table 2). These findings

244    also support the concept of a primary placental developmental disorder.

245        Unexplained elevated levels of MSAFP have been associated with thrombotic

246    and inflammatory vascular lesions [22], peri-placental hemorrhage and increased

247    placental thickness [26]. During the second and third trimester of pregnancy AFP is

248    mainly produced by the fetal liver and serum and amniotic levels were used for the

249    antenatal screening of neural tube defects [7]. Higher MS levels are also commonly

250  found in chorioangiomas, intervillous thrombosis and ubilical cord angiomyxomas

251  suggesting a leakage from the fetal circulation [9]. VP are not covered by Wharton

252  Jelly and thus the rise in MSAFP in these cases may also be due to increase

253  diffusion of AFP from the fetal circulation secondary to microtraumatism of the

254  vessels by fetal movements. This could explain why we found higher levels

255  MSAFP in pregnancies with both types of VP compared to controls (Table 2).

256      Yampolsky et al. [27] found that placentas from singleton pregnancies with a

257  displaced cord show a markedly reduced transport efficiency, reflected in a larger

258  value of beta and hence in a smaller birth weight for a given placental weight.

259  Placentas with a non-central cord insertion have also a sparser chorionic vascular

260  distribution, as measured by the relative vascular distance. More recently several

261  authors have recently evaluated the association of different combinations of

262  placental umbilical cord insertions with birth weight discordance in twins. Combiaso

263  et al. [28] found in a large cohort of monochorionic twins a highly significant

264  association between discordant cord insertions and discordant birth weight was

265  observed (p < 0.01). The odds ratios (OR) for birth weight discordance in the

266  discordant cord insertion group compared with the concordant group were 2.3

267  (95% CI: 1.2-4.4) for the normal-marginal and 5.9 (95% CI: 3.8-10.4) for the

268  normal-velamentous cord insertion subgroup. Similarly, Costa-Castro et al. [29]

269  found that monochorionic (MC) twins with and without twin-twin transfusion

270  syndrome (TTTS) VCI is associated with severe birth weight discordance. Chu et

271  al. [30] has previously found that, the vascular numerical terminal villi density of

272  twins with VCI is significantly lower than of those with a more central cord insertion.

273

## Conclusions

275     Our data support the concept of a primary placental developmental disorder

276 in pregnancies presenting with a VP associated with a velamentous insertion of the

277 cord. By contrast, in VP type II where the cord is inserted within the main placental

278 mass, there is no obvious impact on both placental and fetal growth. In VP type I,

279 the primary placental developmental disorder combined with alterations of the

280 umbilical circulation in the velamentous cord could explain the secondary slow fetal

281 growth.

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380

381  **Table 1**

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

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

384

385  Data is presented as number (%) or as mean ± standard deviation.

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387

388

389 **Table 2**

390 Comparison of triple test screening markers between women with diagnosis of

391 vasa previa type I, vasa previa type II and reference laboratory values by two tailed

392 t-test.

393

394

| | hCG[*] | AFP[*] | uE3[*] |
|---|---|---|---|
| Vasa previa type I (n=21) | 1.17[a] | 1.22[d] | 1.02[g] |
| Vasa previa type II (n=11) | 2.38[b] | 1.32[e] | 1.01[h] |
| Reference laboratory (Controls) | 0.99[c] | 1.01[f] | 0.98[i] |

395

396 [*]Comparison of the mean MoM.

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

398 gonadotropin

**$p$ value between a and b < 0.0001**      $p$ value between d and e = 0.493      $p$ value between g and h = 0.897

$p$ value between a and c = 0.149      **$p$ value between d and f = 0.012**      $p$ value between g and i = 0.664

**$p$ value between b and c < 0.0001**      **$p$ value between e and f = 0.038**      $p$ value between h and i = 0.854

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