REVIEW

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In vitro fertilization represents a risk factor for *vasa praevia*

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Abstract

Vasa praevia is a rare but very dangerous obstetrical condition. The purpose of our article is to evaluate data available in literature that indicate *in vitro* fertilization as a risk factor for *vasa praevia*. PubMed Library and Cochrane Database were searched using the keywords *vasa praevia*, *in vitro* fertilization, velamentous cord insertion, *placenta praevia*. The conditions related to *in vitro* fertilization that increase the risk of *vasa praevia* formation were identified and discussed. Also, the diagnosis and management options were reviewed. *In vitro* fertilization represents a risk factor for *vasa praevia* and all such pregnancies should be screened by transvaginal ultrasound for *vasa praevia*.

Keywords: *vasa praevia*, *in vitro* fertilization, velamentous cord insertion, *placenta praevia*.

Introduction

Vasa praevia is an obstetric condition that is associated with significant perinatal mortality and morbidity [1–6]. It occurs when the umbilical cord blood vessels are exposed within the placental membranes between internal os of the cervix and presenting part of the fetus [5, 7–9]. The importance of this pathology is underlined by its most feared complication, fetal death by exsanguinations, which occurs in more than 60% of the prenatally undetected cases [4, 5, 10, 11]. Though the approximate incidence of *vasa praevia* is considered to be one in 2500 pregnancies [12, 13], the true incidence is not known, with a very wide range from one in 10 000 to one in 5200 pregnancies [13, 14] reported in literature. The incidence is considered much higher, one in 365 [15] to one in 700, among patients who conceive through assisted reproductive technologies [16–18]. The most important risk factors for *vasa praevia* are umbilical cord and placental abnormalities, which are more common in pregnancies achieved after *in vitro* fertilization (IVF) [17, 19]. Since the number of IVF pregnancies has been increasing constantly over the last decade, a higher incidence of *vasa praevia* related complications may be encountered in the near future. The main objective of this article is to review data available in literature that indicate IVF as a risk factor for *vasa praevia*. We found no systematic review of the conditions related to IVF pregnancies that are considered risk factors for *vasa praevia* in English literature.

Our review consisted in a search of articles published in English. PubMed Library and Cochrane Database were searched for relevant articles including clinical trials, reviews, guidelines and case reports using the key words *vasa praevia*, *in vitro* fertilization, velamentous cord insertion. The websites of the *International Vasa Praevia Foundation* and the *UK Vasa Praevia Raising Awareness Organization* were also reviewed for links to literature that may not have been indexed in medical databases. Articles assessing the ultrasound diagnosis of *vasa praevia* and the strategy of obstetrical management were included. A number of 204 articles were found. Most of case report articles discuss one up to three cases of *vasa praevia* and focus on the ultrasound criteria for diagnosis and the obstetrical management. Actually, they do not add much to the body of knowledge but they underline the severe potential of the situation. A review of the articles title and abstracts for relevance regarding our topic resulted in a number of 89 articles for review.

Risk factors for *vasa praevia*

Two main types of *vasa praevia* are described: type I with velamentous insertion of the umbilical cord and type II with bilobed or succenturiate placenta [20–22]. In a velamentous insertion, the umbilical cord inserts directly into the membranes through which unprotected vessels then run until they end in the placenta. In type II *vasa praevia*, exposed vessels run through the membranes between lobes of a bilobed placenta [20, 22, 23].

The most important risk factors for *vasa praevia* are velamentous cord insertion [2, 19, 24], second-trimester low-lying placenta or *placenta praevia* [2, 10, 19, 25–27], pregnancies conceived after use of assisted reproductive technologies [2, 10, 19, 27], bilobed and succenturiate lobe placentas situated in the lower uterine segment [2, 10], and multiple pregnancies [2, 10, 14, 17, 19, 27–30]. Considering the risk factors, many authors consider that anomalies of placenta and umbilical cord insertion are prerequisite for *vasa praevia* [2, 8, 10, 19, 24–27, 31, 32].

In vitro fertilization is related to higher incidence of placental abnormalities

Several authors link the abnormal placentation to assisted reproductive procedures, therefore IVF is considered a risk factor for *vasa praevia* [17, 32]. Early in 1984, a multi center study conducted by Jauniaux *et al.* investigated the pathologic features of placentas from singleton pregnancies obtained by IVF and embryo transfer (IVF-ET) [33]. They collected and examined 100 placentas from IVF pregnancies and found that the incidence of bilobate and succenturiate placenta was 22% in the IVF group compared to 6% in the control group. Results were considered statistically significant ($p<0.5$). Their conclusions were confirmed by the study performed by Englert *et al.* that evaluated the macroscopic characteristics of 100 fetal adnexa from pregnancies obtained by IVF-ET and compared with data for normal pregnancies taken from the literature. Material was obtained from 63 singleton, 15 twin, one triplet and one quadruplet pregnancies. They found normal placental morphology but abnormal insertion of the umbilical cord. Marginal (15%) and velamentous (14%) insertions of the umbilical cord were found more frequently than in a general obstetrical population (6% and 1%, respectively). Excluding placentae from multiple pregnancies (which are known to have a higher incidence of abnormal cord insertion), the frequency did not decrease and remained significantly higher than in a normal population ($p<0.01$ and $p<00.001$, for marginal and velamentous insertion respectively [34]. Schachter *et al.* (2002) studied a total of 72 818 deliveries, from 1987 to 2001; 1173 of them resulting from IVF pregnancies, and found 12 cases of *vasa praevia*. The overall incidence of *vasa praevia* was 1:6068 deliveries, similar to reports by other authors and 1:293 among the IVF pregnancies [17]. Romundstad *et al.* (2006) underlined the risk of placental abnormalities in pregnancies following assisted reproductive technology by comparing the incidence of *placenta praevia* following spontaneous and IVF pregnancies in the same mother. The study identified 1349 women who had conceived both naturally and after assisted fertilization in Norway, between 1988 and 2002. They found that the risk of *placenta praevia* was nearly three-fold higher in the pregnancy following assisted fertilization [adjusted odds ratio (OR) 2.9, 95% confidence interval (CI) 1.4–6.1], compared with that in the naturally conceived pregnancy. The study concluded that IVF is associated with an increased risk of *placenta praevia* that may be caused by factors related to the reproductive technology [18].

High levels of estradiol are related to abnormal placentation

The mechanism triggered by the IVF that leads to abnormal placentation is not completely understood [18, 34]. The high levels of estradiol present during the IVF stimulation cycle may interfere with normal placentation due to the stimulating effect on the endometrium. The transfer of a fresh embryo on the same cycle after oocyte retrieval means that implantation will take place in the context of high levels of estrogen due to prior ovarian stimulation. High estradiol concentrations at the time of implantation may theoretically impair the endometrial response to trophoblast invasion, leading to abnormal placentation [35, 36]. Healy *et al.* (2010) have found that obstetric hemorrhage caused by *placenta praevia* and placental abruption are more frequent in IVF pregnancies and have suggested that a possible mechanism is the effect of high estradiol concentrations on the endometrium at the time of implantation [37]. Farhi *et al.* (2010) investigated a possible association between high estradiol concentrations and abnormal placentation by assessing the number and rate of pregnancy complications related to abnormal placentation. They found that the high estradiol concentration group of >10 000 pmol/L had significantly more complications related to abnormal placentation [35].

Abnormal cord insertion in IVF

Velamentous cord insertion represents the insertion of the umbilical cord into the membranes away from the placental margin. This results in the umbilical vessels lacking the protection of Wharton's jelly for the section between the insertion of the umbilical cord and the placental margin. Velamentous insertion of the umbilical cord is associated with *vasa praevia* [8, 38]. There are three possible theories that approach the etiopathogeny of velamentous cord insertion and *vasa praevia*: (1) an initial normal insertion of the umbilical cord can turn into a velamentous one due to the regress of the surrounding chorion frondosum caused by the placental expansion; (2) velamentous insertion of the cord favors the formation of big vessels extending to the margin of the placenta; (3) abnormal morphology of the placenta may be consecutive to distorted uterine anatomy such as myomas, uterine malformations and septa [30, 39–41].

Jauniaux *et al.* (1990) investigated placental shape and umbilical cord insertion among pregnancies obtained by IVF [33, 42]. The distance between cord insertion and placental margin was measured and umbilical cords inserted at less than 2 cm from the placental margin were considered marginal. The incidence of marginal and velamentous cord insertion was 26% and 12% in the IVF group compared to respectively 10% and 2% in the control group. These findings are confirmed by Schachter *et al.* who assessed a total of 72 818 deliveries and found a incidence of velamentous cord insertion of 1:743 in non-IVF pregnancies compared to 1:167 in the IVF group [17]. Ebbing *et al.* (2013) performed a population based study of 634 741 pregnancies between 1999–2009, aiming to determine the prevalence and the risk factors for anomalous insertions of the umbilical cord. They found that the prevalence of velamentous and marginal insertions of the umbilical cord was 7.8% in singletons and 16.9% in twin gestations, with marginal insertion being more common than velamentous [38, 43]. Delbaere *et al.* (2007) conducted the largest study of umbilical cord anomalies after IVF procedures. The study included over 4000 twin pregnancies, between 1995–2004, and concluded that umbilical cord anomalies are more frequent in twins after assisted reproduction and are influenced by the used technique. In twins conceived after IVF, the incidence of velamentous cord insertion was 7.4%, and after intracytoplasmatic sperm injection (ICSI), where a single sperm is injected into an egg, it was 10.4% [44].

A very rare case umbilical cord anomaly after IVF was reported by Canda *et al.* (2013). A patient with unicornuate uterus that achieved pregnancy on the fourth IVF attempt was diagnosed with velamentous and furcate cord insertion with placenta accreta [45]. Another very interesting case was reported by Hasegawa *et al.* (2011). They examined an IVF pregnancy at eight weeks of gestation and found the umbilical cord insertion with a viable fetus located on the septum membrane of dichorionic twin pregnancy, while the other fetus was observed to have vanished. Velamentous cord insertion with long membranous umbilical vessels was notice at delivery [46].

In conclusion, IVF pregnancies are related to higher incidence of multiple gestations [47–56] and abnormal insertion of the umbilical cord [17, 34, 38, 43, 44]. Both conditions are prerequisite for *vasa praevia* [12, 39, 40, 57].

Differences between frozen and fresh embryo transfer

Initially considered a strategy to reduce the rate of ovarian hyperstimulation syndrome, embryo freezing and transfer in another cycle seems to offer even more benefits than the fresh embryo transfer [58].

A preliminary study conducted by Imudia *et al.* (2013) suggests that elective cryopreservation of all embryos in patients with elevated peak serum of estradiol for subsequent cryopreservation and embryo transfer in cycles with a better physiologic hormonal milieu may reduce the odds of small for gestational age newborns and pre-eclampsia in IVF singleton deliveries [59]. Their results are confirmed by Korosec *et al.* (2014), who investigated the outcomes of singleton pregnancy after IVF with fresh or frozen embryo transfer and also the incidence of *placenta praevia*. They found that *placenta praevia* rates are lower in the frozen embryo transfer group, and the newborns had higher gestational weight than in the fresh embryo transfer group [60]. Unfortunately, they did not include the serum estradiol measurements into the analysis. A multicenter, prospective, randomized controlled clinical trial that aims to demonstrate that elective embryo cryopreservation and frozen-thawed embryo transfer will reduce the incidence of pregnancy complications related to placental abnormalities and increase the rate of live births in patients who need IVF to achieve pregnancy was initiated in 2014 by Shi *et al.* Their results are expected to make an impact in embryo transfer strategy [61].

Multiple pregnancy *vs.* IVF *vs. vasa praevia*

Over 20% of all deliveries resulting from IVF/intracytoplasmic sperm injection (ICSI) include more than one fetus [43, 62]. One of the major obstacles in IVF remains the high twin birth rate and the complications related to multiple gestations. These problems can be solved by implementing elective single-embryo transfer (eSET), diminishing the twin birth rate without affecting the overall goal of achieving a healthy infant [47, 56, 63].

Prenatal diagnosis in first or second trimester scan?

Vasa praevia can be diagnosed antenatally using combined abdominal and transvaginal ultrasound and color flow mapping; however, many cases are not diagnosed [64]. The cases not diagnosed antenatally are related to severe complication such as fetal death, low Apgar scores and severe anemia [2, 8, 64–66]. In 1801, the first case of ruptured *vasa praevia* was described in literature [67]. The first report of ultrasonographic diagnosis of *vasa praevia* appeared in the literature in 1987 [68]. Several authors report cases of *vasa praevia* diagnosed using color Doppler [3, 5, 6, 9, 10, 19, 65, 69, 70]. Transvaginal ultrasound is considered extremely important for an accurate diagnostic [2, 4, 16, 39]. Some authors emphasize the importance of tree-dimensional ultrasonography in establishing the diagnosis [20, 71–74]. There are two very important ultrasound exams during the follow-up of a pregnancy: the first trimester morphology scan and the second trimester morphology scan. These should be performed by experienced practitioners and could represent the ideal moment for the diagnosis of *vasa praevia* [28, 75]. Hasegawa *et al.* (2011) assessed the usefulness for predicting *vasa praevia* by detecting a cord insertion site in the lower third of the uterus between 9 and 13 weeks gestation and concluded that ultrasound screening in the first trimester of the cases with low cord insertion is effective for the detection of *vasa praevia* [76].

Sepulveda (2006) undertook a prospective study and screened 533 consecutive pregnancies during the nuchal translucency scan (11–14 weeks) for velamentous cord insertion. They followed all cases until delivery and found that no case of velamentous cord insertion was missed at the first trimester scan. Their study indicated that the diagnosing velamentous cord insertion at the nuchal scan in the first trimester is possible and recommendable [77].

Several authors reported cases of *vasa praevia* diagnosed in the second trimester [13, 28, 39, 75].

Canterino *et al.* (2005) reported a case of *vasa praevia* where 3D sonography with power Doppler angiography was used in order to certify the diagnosis [72].

Cipriano *et al.* analyzed the cost-effectiveness of targeted and universal screening for *vasa praevia* at 18–20 weeks of gestation in singleton and twin pregnancies. They found that screening with transvaginal ultrasound and color Doppler for IVF pregnancies or when the placenta has been found to be associated with one or more risk factors is cost-effective. The same screening in all population is not cost-effective [78].

Management of diagnosed cases

The outcome of a pregnancy with is *vasa praevia* is mainly determined by the early recognition of the pathology. Accurate prenatal diagnosis and Cesarean delivery before rupture of the membranes is associated with a 97% survival rate [11–13, 16, 40]. When the diagnosis is made antenatal, the safest form of delivery is elective Caesarean prior to the onset of labor [39, 79]. Consideration should be given to hospitalization at about 30 to 32 weeks and administration of corticosteroids to

promote fetal lung maturation [39, 80]. The optimal gestational age at delivery is difficult to establish [81]. The largest published series suggests that delivery by elective Caesarean section at 35 to 36 weeks gestation, prior to the formation of lower uterine segment is reasonable, thereby avoiding the risk of membrane rupture and fetal exsanguinations [7, 29, 39, 80, 82]. Several authors reported cases where delivery was delayed after 36 weeks but the risk of spontaneous rupture of membranes [83] and fetal exsanguination must be kept in mind [80].

Fetal therapy *in utero* may represent a solution in the near future [84–86]. The case of patient who underwent successful laser photocoagulation of a type II *vasa praevia* at 32 weeks gestation and subsequently delivered vaginally at term without complications is reported in literature [86].

The prospect of this pathology in the near future

There is an increasing demand for assisted reproductive technology nowadays. Due to present social context regarding the age when women choose to procreate this trend is more likely to continue. Stress is a very common feature among women that undergo IVF procedures and this can also favor the development of placental abnormalities [87]. The increasing number of pregnancies obtained by IVF will make "niche" pathology such as *vasa praevia* more common for the current obstetrician. Although there are many reports in literature that indicate that IVF is a risk factor for *vasa praevia*, the exact mechanism of *vasa praevia* formation is not completely understood. The study of the placentas using immunohistochemistry could offer some answers about the placental vascular changes related to IVF pregnancies [88]. A very interesting idea was to compare the incidence of placental abnormalities in the same mother having both kinds of pregnancy (spontaneous and IVF). This eliminates most of the individual related factors and highlights the risk induced by artificial reproduction technology. Our review identifies the possible etiopathogenic paths described in literature and underlines that IVF generates a complex of factors that favor *vasa praevia* formation. High estrogen levels at the time of implantation and the transfer of more than one embryo may induce anomalies of placentation and umbilical cord implantation and therefore the formation of *vasa praevia*. Our review also suggests that the transfer of a single frozen embryo in another cycle may reduce the rate of abnormal placentation and umbilical cord implantation. The transfer of a single embryo *versus* two embryos remains a disputed subject between IVF centers nowadays, with the balance shifting towards single embryo transfer in most centers [51, 56, 89]. Since the morbidity of this condition is mostly determined by the lack of recognition, a detailed ultrasound screening should be performed in all IVF pregnancies [32]. The transvaginal scan can identify the presence of *vasa praevia* or its high risk factors, such as velamentous cord insertion and abnormal placenta, as early as the first trimester nuchal scan. The diagnosed cases should be monitored closely and cesarean section should be scheduled prior to labor onset.

Conclusions

Awareness of the risk factors, diagnosis and management of *vasa praevia* needs to be raised among obstetricians. Our article highlights that IVF represents a risk factor for *vasa praevia*, and all IVF pregnancies should be screened by transvaginal ultrasound for *vasa praevia*.

Conflict of interests

The authors declare that they have no conflict of interests.

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