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Placenta accreta spectrum disorders in pregnancies following *in vitro* fertilization

Abstract

Placenta previa and related pregnancy complications are more common in In vitro fertilization pregnancies compared with spontaneous ones. There is evidence that PAS disorders are more common in pregnancies after IVF. Factors leading to a higher incidence of this pathology in IVF pregnancies have not been fully studied. Possible causes are the advanced age of women undergoing IVF, factors related to infertility itself, causes from the biological part of the In vitro procedure or controlled ovarian stimulation. The study of these factors is crucial for clinical practice as it would improve the outcome of IVF pregnancies.

Keywords: placenta accreta spectrum (pas), *in vitro* fertilization, placenta previa

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Abbreviations: PAS, placenta accreta spectrum; ET, embryo transfer; Fresh ET, ET during ovarian stimulation; FET, embryo transfer of frozen / thawed embryos; IVF, in vitro fertilization

Introduction

The term placenta accreta is widely known in the scientific community and clinical practice and means abnormal penetration of the placenta into the whole or in parts of the myometrium of the underlying uterine wall. The depth of placental penetration into the myometrium is various and thus, modern pathologists have defined this kind of abnormality as a spectrum disorder, with three categories representing the range of pathologic invasiveness of the placenta: placenta accreta (placenta penetrate superficial myometrium), placenta increta (placenta penetrate into the myometrium), and placenta percreta (placenta penetrates through the entire uterine wall even to the surrounding organs).[1] Subsequently, more accurate terminology is introduced - placenta accreta spectrum (PAS) disorders, covering all forms of abnormally invasive placentas.

Placenta accreta is a rare but extremely dangerous complication of pregnancy, which is associated with increased maternal morbidity and mortality. It can be a life-threatening condition because of a risk of massive obstetric hemorrhage and may lead to urgent peripartum hysterectomy.[2] Predicting this pathology is difficult, but the main risk factor is well known - previous cesarean delivery. The more cesarean sections in the same woman, the higher the incidence of PAS disorder.[3] The incidence of cesarean sections has increased dramatically in recent decades, which confronts clinicians with cases of abnormally invasive placenta more often.

Some studies have found a higher incidence of PAS disorders in pregnancies achieved through In vitro fertilization.[4,5] The exact mechanism has not been fully studied. Among the possible are considered advanced age of women undergoing IVF, hormonal stimulation in IVF, factors related to infertility, causes from the biological part of the procedure. As the incidence of IVF pregnancies continues to increase worldwide, the incidence of placenta previa, and in particular accreta, is also increasing, making this issue crucial for clinical practice. The purpose of this review is to present the available data on the relationship between In vitro fertilization methods and placenta accreta and to analyze the possible risk factors for this pathology in couples undergoing infertility treatment.

Placenta accreta spectrum and in vitro fertilization

In recent years, a number of reports have emerged, as well as several studies that have found a higher incidence of placenta accreta among pregnancies achieved by In vitro fertilization. Placenta accreta is often combined with placenta previa, which is more common in pregnancies achieved by In vitro fertilization.[6–8] A large study in Israel[4] found, that the incidence of placenta accreta in pregnant women after IVF was 16/1000 births, while in spontaneous pregnancies it was 1.2/1000 births, without the two groups differing significantly in terms of other major risk factors for placenta accreta. Only the parity of women after IVF was lower and most of the women were nulliparous. Another study found that the incidence of PAS was 0.4% in the general population, reaching 2.2% in pregnant women after IVF and 0.3% in spontaneous pregnancies. Interestingly, pregnant women after IVF in this study had a lower incidence of placenta previa as well as previous cesarean births, which are the major risk factors for placenta accreta.[9] Ultimately, in addition to factors such as age, placenta previa, and previous cesarean section, IVF was found to be an additional independent risk factor for PAS.[10]

The exact mechanism by which IVF may increase the incidence of PAS remains not fully understood, although there are a number of theories. 0It is thought that ovarian stimulation may affect implantation and early embryonic development. During ovarian stimulation, estrogen levels rise to supraphysiological value and this may be a key factor leading to abnormal placentation in patients who become pregnant after an IVF procedure.[5,11] Some authors study the course of pregnancy after IVF with frozen embryos without ovarian stimulation and come to interesting conclusions. There is a higher incidence of placenta accreta in pregnancies after FET compared to pregnancies after fresh ET.[12,13] One study found a higher risk of PAS in pregnancies achieved by frozen-thawed embryo-transfer during a cycle prepared with drugs that stimulate endometrial growth compared to the same procedure, but in a natural cycle without endometrial preparation.[14] Others believe that FET itself may be an independent risk factor for placenta accreta spectrum disorders in IVF pregnancies.[13] Other studies came to the opposite conclusion, finding no difference in the frequency of placenta accreta depending on whether FET or fresh ET was performed in the IVF procedure.[15]

The reasons may lie in the fertilization and cultivation of embryos. Cellular pathways may be altered when fertilization and early embryo

culture occur in vitro. This may change key metabolic pathways in the embryo and trophoblast and be crucial in the first week of pregnancy and during implantation.[16] The increased risk of placenta previa and in particular accreta is not due to lower embryo placement during embryo transfer, as in pregnancies after GIFT (gamete intra-fallopian transfer), where the return of gametes is high in the fallopian tubes, the frequency of placenta previa is also increased. Healy D.L. et al., 2010, investigated the risk factors for obstetric blood loss in singleton pregnancies after IVF in Australia. IVF pregnancies were compared with those in the general population, as well as with spontaneous pregnancies in couples with infertility, as well as with pregnancies after GIFT and FET. There is evidence that IVF is itself a risk factor for more frequent obstetric complications associated with blood loss, regardless of the causes of infertility.[17]

The management strategy for placenta accreta is a challenging problem in obstetrical practice. The usual practice is cesarean hysterectomy because of the increased risk for severe bleeding. The postoperative period in these cases often runs with a number of complications that increases hospital stay and the need for additional treatment.[18–20] In rare cases of placenta accreta, conservative treatment may be applied when there is a desire to preserve the reproductive organs for future pregnancies. Various techniques have been developed for this purpose. Uterine artery embolization technique is most commonly used. Performing uterine artery embolization before expulsion of the placenta reduces the risk of postpartum hemorrhage, perinatal morbidity and mortality, and increases the chances of uterine preservation. After such treatment and preservation of the uterus, questions arise about the possible reduction of the ovarian reserve due to the communication of the ovarian and uterine vessels during embolization.[21] Subsequently, the reduced ovarian reserve may lead to the need of assisted reproduction methods for achieving pregnancy, with reduced number and quality of oocytes and embryos achieved,[22–26] need for different stimulation protocols,[27] individual choice of type of fertilization[28] during In vitro fertilization procedure, and in the end, reduced clinical pregnancy rates.

Conclusion

Studies in recent years have shown that IVF is an independent risk factor for the development of placenta accreta spectrum disorders during pregnancy and related to it increased obstetrical haemorrhage during labor. However, the role of IVF remains relatively small compared to other known risk factors for PAS, most notably placenta previa and previous cesarean section.

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Conflicts of interest

The author declares no conflict of interest.

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