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Review Article

Ivf and the Risk of Ectopic Pregnancy. How To Avoid It

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Abstract

The aim of this review is to investigate the correlation between assisted reproduction technologies (ART) and the risk of ectopic pregnancy. Ectopic pregnancy is the most important cause of maternal mortality at early months of pregnancy and precocious diagnosis would be desirable to avoid complications. Of all the naturally (spontaneous) conceived pregnancies, about 1-2% is an ectopic pregnancy (EP) while incidence of EP, in patients undergoing to *in vitro* fertilization is 2, 1-9, 4 % and 11% in those with tubal infertility. The significant risk factor for ectopic pregnancy was tubal factor infertility, zygote intrafallopian transfer (ZIFT), more than 2 transferred embryos, frozen embryo transfer, the day of embryo transfer (ET) and deep fundal transfer. Moreover, a different hormonal milieu *in vitro* fertilization (IVF) cycles, may cause a defective embryo implantation. High progesterone levels may decrease the uterine contractility compared to a spontaneous pregnancy, hindering the embryo implantation during fresh ET. Several hypotheses have been proposed to explain why ART may be a risk factor for aberrant implantation of embryo during IVF cycle and to date, it is not clear the impact of ART on ectopic pregnancy. Further research into the relationship between EP and potential embryo implantation would be desirable.

Keywords: *In vitro fertilization; Assisted reproduction technologies; Ectopic pregnancy; Embryo transfert*

Abbreviations: ART: Assisted reproduction technologies; EP: Ectopic pregnancy; ZIFT: zygote intrafallopian transfer; IVF: *In vitro* fertilization.

Introduction

Ectopic pregnancy (EP) is any pregnancy that develops in a different location from the uterine body while heterotopic pregnancy is defined as an ectopic pregnancy coexisting with a synchronous intrauterine pregnancy [1]. Main ectopic site is the fallopian tubes (most of 96%) [2]. More rarely (less than 10% of all EP) ectopic pregnancies can affect cervix, ovary, abdomen, interstitial portion of fallopian tube and caesarean section scar. EP represents the 15% of all pregnancy-related maternal deaths in the first trimester of pregnancy [3]. Of all naturally conceived pregnancies about 1-2% is an ectopic pregnancy [4], while the incidence of EP, in patients undergoing *in vitro* fertilization (IVF), is 2, 1-9, 4 % [5], and 11% in those with tubal infertility [6]. Theoretically, the assisted reproduction techniques do not involve the tube, then they should not increase the risk of EP, but it seems to be not true. In 1976 the first IVF was performed, hesitating in a tubal pregnancy. The ectopic pregnancy is more frequent in patients undergoing *in vitro* fertilization treatment than in the general population, but the reason is largely unknown. Although several scientific studies are based on statistical bias or insufficient samplate to perform a correct estimation of the risk of EP, assisted reproduction technologies (ART) represent a risk factor for EP and a lot of possible theories have been proposed [2]. The main known risk factors for EP include: a prior ectopic pregnancy, tubal damage (for pelvic inflammatory disease and/or previous adnexal surgery), a previous cesarean section and IVF [3]. As contributing factors those are smoking and patient's age. The aim of this review is to investigate the correlation between assisted reproduction technologies (ART) and risk of ectopic

pregnancy. ART is considered a risk factor for EP for two main reasons: first of all, infertile women who undergone IVF, have different clinical characteristics than general population (e.g. tubal damage); the second reason is probably due to a different hormonal milieu at the time of embryo transfer. Furthermore, technical aspects of IVF procedures must be taken into account. The differences between IVF and natural conception (such as ovarian stimulation, high progesterone levels, tubal pathology) would explain the increased incidence of EP in this group [7].

Tubal factor and ART (assisted reproduction technologies)

Tubal factor infertility has been considered one of the most important causes of EP, both in natural pregnancy and in IVF (*in vitro* fertilization) pregnancy. PID (pelvic inflammatory disease), favored by sexual promiscuity, previous ectopic pregnancy and tubal surgery have been considered a consistent risk factors. Not surprisingly, being the tubal damage a major cause of infertility, ectopic pregnancy is more present in women undergoing assisted reproduction. The literature reports that the tubal damage is the major risk factor for ectopic pregnancy in IVF cycles. Clayton *et al*. [8] have conducted an observational study to assess the ectopic pregnancy risk among women who conceived with ART. Authors conclude that the risk for EP was higher in patients with tubal factor infertility (odds ratio [OR] 2.0, 95% confidence interval [CI] 1.7–2.4; referent group ART for male factor), endometriosis (OR 1.3, 95% CI 1.0 –1.6) and in women affected by unexplained infertility (OR 1.4, 95% CI 1.2–1.6). It is reasonable to believe that the increased risk of EP in cases of unexplained infertility and endometriosis is due to unrecognized tubal defect [8]. In a Cochrane review published in 2010, the authors wanted to assess the value of surgical treatments for tubal disease prior to IVF. They concluded that surgery should be considered in infertile women with hydrosalpinges prior to IVF treatment. In particular, it would be desirable to perform unilateral salpingectomy in case of unilateral hydrosalpinges and bilateral salpingectomy in case of bilateral hydrosalpinges. A new surgical technique, laparoscopic tubal occlusion, has recently been proposed as an alternative to laparoscopic salpingectomy to improve IVF pregnancy rate in women affected by hydrosalpinges [9]. Tubal anatomy is important to consider prior to IVF technique in women suffering from tubal infertility specially in those with previous adnexal surgery, PID, endometriosis and ectopic pregnancy history.

Hormonal factors and ART (assisted reproduction technologies)

Many authors support the hypothesis of the different hormonal milieu in IVF cycle, leading to defective embryo implantation. The ovarian stimulation before *in vitro* fertilization (IVF) causes a hormonal change that leads to a different condition in the uterus and may also impair tubal peristalsis, worsening the tubal cilia and muscle function. In an IVF-ET cycle, for example, the excess of progesterone, caused by a greater number of corpora lutea and implemented by luteal support, could increase relaxation of the uterine musculature compared to a spontaneous pregnancy [6].

In particular, Zhu *et al*. in a retrospective study described an increase of the peristaltic cervix-fundus waves and a reduction of the fundus-cervix waves during controlled ovarian hyperstimulation (COH) cycles, after progesterone administration [10]. Moreover, progesterone causes regression of cilial movements within the tube by antagonizing the effect of estrogen that promotes the differentiation of ciliated cells and ciliogenesis.

Instead, other studies didn't show a direct correlation with regard to the level of estrogens. In the past, it was also hypothesized an association between ectopic pregnancy and high levels of estrogens, leading to an abnormal tubal embryo carriage [11]. Recently, Wang *et al*. have shown an increased risk of EP due to high levels of progesterone and estradiol on the day of human chorionic gonadotropin (HCG) administration [12]

Perhaps, the choice of ovulation inducing drugs, may play a role in determining the risk of EP. Sahin *et al*. [13] compared the rate of ectopic pregnancy in women who underwent IVF treatment using recombinant hCG (rhCG) or GnRH agonists. The EP rates were higher (5.3 %) in the GnRH agonist triggered group than in the hCG triggered group (1.4 %) maybe due to an insufficient luteal support (decreased receptivity of the endometrium) and higher implantation potential of embryos in correlation with a higher number of good quality embryos obtained in these cycles.

In a 2008 article, the authors suggest various mechanisms of embryo implantation to explain the different incidence of EP in spontaneous pregnancy and *in vitro* fertilization. IVF Biological factors, rather than mechanical factors, are involved in the occurrence of EP after IVF. During IVF, the embryo develops in different macromolecules and nutrients from natural environment that negatively may influence the preimplantation embryo quality. In this context they demonstrated a high expression of E-cadherin (adhesion molecule) in post-IVF tubal pregnancies, compared with negative or weak staining in spontaneous ectopic tubal pregnancies. So, the embryo quality could influence the final site of implantation: in IVF cycle, embryo has lower implantation capability because of E-cadherin overexpression on trophoblastic cells that would explain the increased risk of EP in patients undergoing IVF, also in women without tubal pathology. Moreover, during IVF cycle, the embryo may be "non sticky" at the time of embryo transfer because of delayed expression of endometrial adhesion molecules resulting in aberrant implantation. The concept of delay in implantation following embryo transfer results in particular trend of beta HCG value in the ectopic pregnancies: the value of the serum beta HCG is different compared with a spontaneous pregnancy being 1.5 days later. The risk of ectopic pregnancy in IVF is higher when the embryo quality is poor and it is always related to the molecular patterns expressed by the trophoblast [2]. In relation to the preimplantation embryo quality, it is also important to consider maternal age and therefore oocytes aging. When women undergo IVF with egg donation, they have a lower risk of EP. This phenomenon is related to embryonic best potential linked to younger oocytes (donors, in fact, are selected among young women without infertility) [8]. Reveal *et al*. [2] suggested a model to explain the aberrant implantation of the embryo in IVF cycle: the transferred embryo, rolls on uterine cavity to achieve a good implantation area. Normally, both endometrium and embryo produce adhesion molecules that improve the capability of implantation of embryo in right temporal and spatial conditions. When this process does not occur correctly, ectopic pregnancy could happen.

IVF (*In Vitro* Fertilization) techniques

The IVF-ET is a laboratory technique by which an egg is fertilized by partner's sperm *in vitro*. The oocytes for IVF-ET retain the "cumulus oophorus-corona radiata" a special complex of cells, indispensable during the fertilization of oocytes by sperm. The ICSI is a micromanipulation technique that involves the injection of a single sperm cells into the oocyte in order to obtain fertilization. Unlike IVF, oocytes are denuded by "cumulus oophorus" and the best ones are selected to be injected. The semen is properly treated to select sperm with higher fertilizing capacity. The risk of ectopic pregnancy in assisted reproductive technology (ART) varies depending on the type of technique. The embryo, in the early stages of development, is surrounded by an outer coating called the "pellucid zone". During the implantation that zone opens, allowing the expansion of the embryo and its root. This process is called "hatching". During the cycle of *in vitro* fertilization it is possible to practice a thinning of the "pellucid zone" that promotes embryo implantation, and then pregnancy. It would seem that this procedure does not increase the risk of ectopic pregnancy.

A correct volume of embryo transfer has been associated with ectopic pregnancy risk. The average volume of transfer is equal to 15-20 µl. In fact, laboratory tests have shown that a greater volume of embryo transfer would increase the risk of migration of the embryo into the fallopian tube, with a greater chance of ectopic pregnancy. No information is available about the type of fluid injected [6]. Another aspect to consider is the depth of the fundal transfer. Nazari *et al*. showed an increased risk of ectopic pregnancy when a deep fundal transfer was performed [14]. Huang *et al*. [7], in a recent retrospective study including more than 30.000 *in vitro* fertilization embryo transfer (IVF-ET), compared the risk of EP in fresh cycles vs frozen-thawed cycles. FET (FET: frozen-thawed embryo transfer) cycles appear to be associated with a statistically lower incidence of EP in comparison to fresh embryo transfer (EP per clinical pregnancy was 4.62% for the fresh transfer group compared with 2.22% for the frozen-thawed cycle group), probably due to the negative effect of ovarian stimulation on endometrial receptivity and uterine contractility. Ovarian stimulation would be likely linked with an increased risk of ectopic pregnancy [7]. In addition, the authors concluded that the fresh ET cycles had the highest risk of EP, followed by day-3 embryo FET cycles and blastocyst FET cycles [7]. Furthermore, Shapiro *et al*. [15], in a retrospective study included 2150 blastocyst transfers (1.460 fresh autologous blastocyst and 690 autologous blastocysts FET), concluded that thawed ET was associated with significantly reduced incidence of EP [15]. These data supports the hypothesis that ovarian stimulation leads to an increased risk of ectopic pregnancy [15].

In a current prospective randomised clinical trial, including one hundred and forty non-donor fresh embryo transfers, Saharkhiz *et al*. proposed an ultrasound uterine length measurement as a method to improve the pregnancy rate during embryo transfer (ET). In particular, in the group of women whom ET were performed at a depth of 1-1.5 cm from the uterine fundus, there have been better clinical and ongoing pregnancy and implantation rates and less abortion rate. No ectopic pregnancy was reported [16]. About the number of embryos used during ET, the risk of EP is increases when 3 o more embryos are transferred. However, when two embryos are transferred, the incidence of EP varies according to the technique (fresh embryo transfer, FET cycles). So ectopic risk may be complicated by the use of multiple transfers [7].

About zygote intrafallopian transfer (ZIFT) e gamete intrafallopian transfer (GIFT), Clayton *et al*. have showed an increase of ectopic pregnancy after ZIFT (3.6%) compared with IVF-ET cycles (2.2%) (OR 1.65, 95% CI 1.13–2.40) maybe due to direct transfer of embryos into the fallopian tubes. However, this hazard was not observed in GIFT procedures. Anyway, the observation whether ZIFT or GIFT has a detrimental effect on the site of pregnancy is limited by small sample sizes. The power of the studyt may not be sufficient to detect any small statistical differences [8].

With regard to intra-cytoplasmic sperm injection (ICSI), in which fertilization of the oocytes took place by injection of sperm cells according to the sperm quality, it can be said that this technique does not increase the risk of ectopic pregnancy. This is because women who undergo ICSI usually are not infertile, and the male factor is paramount [8].

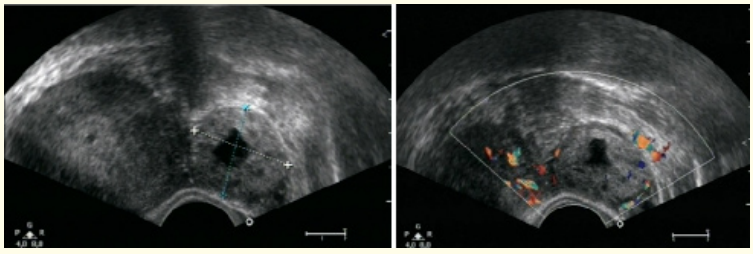

Figure 1: *Suspect images posterior to the ovary measuring 37x29x26 mm with anhaechoic center and hyperhechoic ring (left Falloppian Tube)*

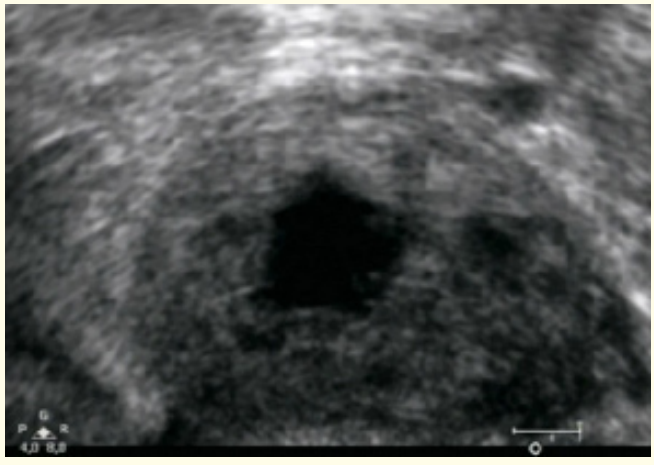

Figure 2: *Enlarging the previous picture, it is possible to see the yalk sac.*

Discussion

Ectopic pregnancy is the most important cause of maternal mortality in the early months of pregnancy [17] and early diagnosis would be desirable to avoid complications. Gynecologists have to recognize the risk factors for EP in women undergoing *in vitro* fertilization (IVF) cycles. In the present review, we analyzed a lot of studies, to clarify the correlation between assisted reproduction technologies (ART) and the risk of ectopic pregnancy. It's well known that embryo transfer does not involve the Fallopian tube, so it would be reasonable to assume that *in vitro* fertilization technique (IVF) might decrease the risk of ectopic pregnancy. Nevertheless, the risk of ectopic pregnancy in women undergoing IVF is higher that in general population and the reason is still unknown. The main known risk factors for EP include: a prior ectopic pregnancy, tubal damage (for pelvic inflammatory disease and/or previous adnexal surgery), a previous cesarean section and IVF [2]. As contributing there are factors like smoking and patient's age. ART could be considered a risk factor for EP for two main reasons. First of all, infertile women undergoing IVF, have different clinical characteristics than general population (ex: tubal damage). Being the tubal damage a major cause of infertility, ectopic pregnancy is more present in women undergoing assisted reproduction as shown by Clayton *et al*. [8]. Sometimes, according to recent data published in a Cochrane review (2010), it might be desirable to perform unilateral salpingectomy in case of unilateral hydrosalpinges and bilateral salpingectomy in case of bilateral hydrosalpinges. Besides, a new surgical technique, laparoscopic tubal occlusion, has recently been proposed as an alternative to laparoscopic salpingectomy to improve IVF pregnancy rate in women affected by hydrosalpinges. [9]. According to the recent findings, the choice of ovulation inducing drugs, may play a role in developing ectopic pregnancy. Sahin *et al* observed that the administration of GnRH agonists correlate with an increase of EP rates (5.3 %) comparing to the hCG triggered group (1.4 %). The authors suggested that the major risk of EP during administration of GnRH agonists may be linked to an insufficient luteal support (decreased receptivity of the endometrium) and higher implantation potential of embryos in correlation with a higher number of good quality embryos obtained in these cycles [13].

Furthermore, technical aspects of IVF procedures must be taken into account. Clayton *et al*. have showed an increase of ectopic pregnancy rates after zygote intrafallopian transfer (ZIFT) (3.6%) compared with IVF-ET cycles (2.2%) maybe due to direct transfer of embryos into the fallopian tubes. Moreover recent studies have shown that FET (frozen-thawed embryo transfer) cycles appear to be associated with a statistically lower incidence of EP in comparison to fresh embryo transfer (EP per clinical pregnancy was 4.62% for the fresh transfer group compared with 2.22% for the frozen-thawed cycle group), probably due to the negative effect of ovarian stimulation on endometrial receptivity and uterine contractility [7] and the rate of ectopic pregnancy likely depends on the day of embryo transfer. In fact the use of blastocyst seems to correlate with lower percentage of ectopic pregnancy [7] as well as the transfer of 2 or fewer embryos is protective against ectopic pregnancy [8]. At last, an ultrasound uterine length measurement has also been advanced by Saharkhiz *et al*. which encourage an embryo transfer at a depth of 1-1.5 cm from the uterine fundus, in order to reduce the aberrant embryos implantation [16].

In conclusion, several hypotheses have been proposed to explain why ART may be a risk factor for aberrant implantation of embryo during IVF cycle and to date it is not clear the impact of ART on ectopic pregnancy. Further research into the relationship between EP and potential embryo implantation would be desirable. The physician should give special focus on women planning pregnancy with a history of tubal infertility during IVF cycle in order to prevent the occurrence of ectopic pregnancy.

Conflict of interest

The authors declare that no potential conflict of interest exists.

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