LITERATURE REVIEW

Ectopic pregnancy following in vitro fertilization: meta-analysis and single-center experience during 6 years

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Abstract

Background: Ectopic pregnancy (EP) has been reported to occur in 1.4–5.4% of all clinical pregnancies resulting from in vitro fertilization (IVF) and embryo transfer (ET). Data on factors associated with abnormal embryo implantation following assisted conception are limited.

Materials and methods: A systematic review and meta-analysis was performed to determine whether there is an association between the day (cleavage-stage, D3, versus blastocyst, D5) or the type (fresh versus frozen/thawed) of ET and EP rate. Risk factors for EP were evaluated in a retrospective study of 1194 women, who achieved pregnancy at our IVF unit between 2010 and 2016.

Results: Sixteen papers were considered for the meta-analysis. EP rate did not differ between D3 and D5 fresh ET groups (RR = 0.99, 95%CI: 0.76–1.30) and was higher after fresh versus frozen ET (RR = 1.56, 95%CI: 1.25–1.95). At our clinic, 21 (1.76%) pregnancies were documented as ectopic. The risk of EP was associated with tubal pathology (OR = 3.37, 95%CI: 1.39–8.2), previous appendectomy and past chlamydial infection.

Conclusions: Present meta-analysis suggests that EP rate is similar following fresh blastocyst and cleavage ETs, but is significantly reduced after frozen compared with fresh ET. Our own findings demonstrate that tubal pathology has the major impact on EP occurrence following assisted conception.

Introduction

Despite the significant improvement in assisted reproduction techniques (ART) over the last decades, the reported incidence of ectopic pregnancy (EP) following in vitro fertilization (IVF) and embryo transfer (ET) treatment varies significantly between fertility clinics (1.4–5.4% [1–3]) and still exceeds that one (2%) after natural conception [4]. Misdiagnosis or delayed diagnosis of ectopic gestation leads to such complicated conditions, as severe bleeding, hypovolemic shock, uterine of tubal rupture are associated with maternal morbidity and even mortality [5], and determine the importance of studies in this field.

Since first reported by Steptoe and Edwards (1976) [6], risk factors and pathogenetic mechanisms of abnormal embryo implantation after ART treatment have been widely discussed. Pelvic inflammatory disease, tubal pathology, previous pelvic surgery, and uterine cavity abnormalities have been defined as factors mostly contributing to the risk of ectopic pregnancy in women with infertility [7,8]. Among other predisposing agents, smoking, uterine fibroids, endometriosis, obesity, advanced maternal age, and history of a prior ectopic pregnancy have been raised, thus remain contradictory [4,9,10].

The influence of different methods of assisted reproduction on the prevalence of EP is the major topic for discussion in the current literature. Number and quality of transferred embryos, controlled ovarian stimulation (COS) regiments, laboratory, and transfer techniques have been offered as possible contributors to EP occurrence after IVF-ET [11–13]. Numerous trials in the current literature have focused on the analysis of fresh versus frozen/thawed embryo transfer cycles, as well as on defining the appropriate day of embryo replacement (day 3 versus day 5) in regard to minimizing the rate of EP in ART programs. The results of these studies vary significantly within years of publishing and center locations; therefore, accurate management strategy for patients at the risk of ectopic gestation after IVF-ET procedure has not been established.

In order to generate a more precise estimate of the effect of ET strategies on EP rates, a systematic literature review and subsequent meta-analysis was performed. In addition, to analyze the incidence and risk factors for EP following IVF treatment, we...
designed a retrospective cohort study based on our center 6-year experience.

Materials and methods

Systematic review and meta-analysis

Literature search was performed using MEDLINE (from 1974 to March 2016) and EMBASE (from 1977 to March 2016) databases. Medical subject headings (MeSH) included ‘‘ectopic pregnancy’’ (‘‘heterotopic pregnancy’’ and ‘‘extrauterine pregnancy’’), ‘‘IVF’’ (‘‘intracytoplasmic sperm injection’’ and ‘‘ICSI’’), ‘‘in vitro fertilization’’, ‘‘assisted reproduction’’, ‘‘fresh embryo transfer’’, ‘‘frozen embryo transfer’’, and ‘‘embryo transfer’’); ‘‘AND’’ was used to connect the two parts.

First part of the analysis was based on study titles and abstracts: only articles written in English and investigating ectopic pregnancy rates in infertile women after ART treatment, as a prime concern, were included. Meta-analysis, reviews, analysis of cases, and studies presented as abstracts were withdrawn. Articles reporting data from national registers were considered if they met the inclusion criteria.

Further evaluation was done revising full article content. Two authors independently selected articles, extracted data, and discussed disagreement in order to clarify any ambiguities. Data concerning clinical pregnancy (CP), defined by visualization of an intrauterine gestational sac on ultrasound, were assessed. Studies with an obscure description and with no exact numbers of pregnancies were not considered. Ectopic pregnancy was evaluated as verified EP if diagnosed by laparoscopy or by sonography (the presence of an extrauterine gestational sac, including any heterotopic gestation) or as clinical EP if diagnosed by the absence of ultrasound-visualized intrauterine gestation in patients with a persistent abnormally increasing hCG titers. Main outcome measure for present meta-analysis was ectopic per clinical pregnancy rate.

Oocyte donor/recipient cycles were ignored. Trials, mainly published before 2001 and reporting tubal embryo transfer technique (TET), which is possibly contributing to EP rates, were excluded. However, it was considered to retain one study [3] for further assessment, in which TET was performed in majority of IVF cycles. Endometrial preparation regimens (hormone replacement therapy and natural/modified cycle) for cryopreserved ET, preservation techniques (slow freezing and vitrification), COS protocols (antagonist and agonist), and luteal phase support were reviewed. Major clinical characteristics of the included studies are summarized in Table 1.

On the final stage, we defined two broad groups of papers according to the type of embryo replacement. Trials describing EPs resulting from fresh versus frozen/thawed ETs; and from cleavage (day 3, D3) versus blastocyst (day 5, D5) ETs in fresh IVF (ICSI) cycles were selected for separate analysis.

Meta-analysis was performed in Review Manager (Rev-Man v5.3 for Windows, The Nordic Cochrane Center, Copenhagen, Denmark). The heterogeneity of effects was evaluated using a forest plot and statistically with $I^2$. Random effect model was applied if $I^2 > 50\%$. The results were expressed as relative risks (RR) with 95% confidence intervals (CI).

Single-center cohort study

A retrospective cohort analysis of 1194 women, who conceived after IVF-ET procedure, performed at ART Department of FSBI D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology (Saint Petersburg, Russia) from February 2010 to January 2016, was conducted. Approval of the study from institutional Review Board of the Ethics Committee was received. Written informed consent was obtained from all the patients before IVF treatment.

All oocyte recipient, gestational surrogacy programs, as well as cycles with embryo biopsy were excluded. Both fresh and frozen/thawed cycles were considered. Evaluation of all subjects included a detailed medical history, physical examination, and parameters related to the IVF procedure.

For controlled ovarian stimulation, patients underwent standard gonadotropin-releasing hormone (GnRH) antagonist or long agonist protocol. Daily injection of recombinant follicle-stimulating hormone (Gonal-F®, Merck Serono S.A., Darmstadt, Germany, or Puregon®, N.V. Organon, Oss, Netherlands) and/or menopausal gonadotropins (Menopur®, Ferring GmbH, Kiel, Germany) were started at day 2–3 of menstrual cycle, GnRH antagonist (Cetrotide®, Merck Serono S.A., Darmstadt, Germany or Orgalutran®, N.V. Organon, Oss, Netherlands) was administered on day 5–6 of COS depending on follicle size, while GnRH agonist (Decapeptyl®, Ferring, Germany) injections were initiated on menstrual cycle days 19–21. Ovulation was induced by administration of hCG (Pregnyl®, N.V. Organon, Oss,

| Authors | Country | Study period | EP, % | EP definition | OD | HP |
|---------|---------|--------------|-------|---------------|----|----|
| Bu et al. (2016) [17] | China | 2009–2015 | 3.33 | Clinical + verified | NA | Included |
| Cheng et al. (2015) [2] | Taiwan | 1999–2013 | 1.8 | Clinical + verified | Excluded | Included |
| Clayton et al. (2006) [13] | USA | 1999–2001 | 2.1 | Clinical + verified | Excluded | Included |
| Decleer et al. (2013) [1] | Belgium | 2002–2012 | 1.92 | Clinical + verified | Excluded | Included |
| Fang et al. (2014) [12] | China | 2010–2013 | 0.3–2.4 | Clinical + verified | NA | Excluded |
| Huang et al. (2014) [16] | China | 2006–2013 | 2.22–4.62 | Clinical + verified | NA | Included |
| Ishihara et al. (2011) [15] | Japan | Since 2007 | 1.4 | Clinical + verified | Excluded | NA |
| Jun and Milki (2007) [25] | USA | 1998–2005 | 0.9 | Clinical + verified | NA | NA |
| Keegan et al. (2007) [19] | Canada | 1998–2003 | 0.9 | Clinical + verified | NA | NA |
| Li et al. (2013) [11] | China | 2010–2011 | 2.1–3.4 | Clinical + verified | NA | NA |
| Londra et al. (2015) [21] | USA | 2008–2011 | 1.38 | Clinical + verified | Excluded | Included |
| Milki and Jun (2003) [3] | USA | Since 1998 | 3.5–3.9 | Clinical + verified | NA | NA |
| Ng et al. (1998) [26] | Hong Kong | 1992–1996 | 5.4 | Clinical + verified | NA | Excluded |
| Perkins et al. (2015) [18] | USA | 2001–2011 | 1.7 | Clinical + verified | Excluded | Included |
| Rosman et al. (2009) [24] | USA | 1998–2006 | 0.9 | Clinical + verified | Excluded | Included |
| Shapiro et al. (2012) [10] | USA | 2003–2011 | 0.3–2.5 | Clinical + verified | Excluded | Included |
| Wang et al. (2014) [8] | China | 2006–2012 | 3.8 | Clinical + verified | NA | Included |

All listed data were extracted from original articles; NA: data not available; HP: heterotopic pregnancy; OD: oocyte donor/recipient cycles; EP %: overall ectopic pregnancy rate reported by authors.
Netherlands or Ovitrelle®, Merck Serono S.A., Darmstadt, Germany) when at least three follicles reached ≥17 mm in mean diameter by ultrasound.

Transvaginal ultrasound-guided oocyte retrieval was performed 35–37 h after triggering final oocyte maturation. Aspirated oocytes were fertilized 3–6 h after the pick-up by either conventional insemination or ICSI according to the sperm quality. Embryos were cultured in vitro to the day 5 from fertilization. Three to five days after oocyte retrieval only 1 or 2 best quality embryos per patient were transferred to the uterus. The luteal phase was supported with 600–800 mg of vaginal micronized progesterone per day. Vitrification was performed for embryo freezing. Endometrial preparation for patients undergoing cryopreserved ET was performed with hormone replacement therapy (HRT) or in modified natural cycle. Only on day 5, embryos were transferred in cryopreserved cycles.

Four physicians performed all ETs using a similar technique: done with abdominal ultrasound guidance 1–1.5 cm short of the fundus position and using Tefcat catheter (Cook, Ob/Gyn, Spenceer, IN) with the same transfer volume. No TET was performed in the center. Our protocols for COS, endometrial preparation, as well as laboratory procedures have been described elsewhere [14–16].

The main outcomes of the study were clinical pregnancy and verified ectopic pregnancy, defined as characterized above. In order to evaluate risk factor for ectopic gestation after IVF-ET procedure, study population was divided to two groups: cycles, resulting in ectopic pregnancy (n = 21) and those, resulting in intrauterine (clinical) pregnancy (n = 1173). Medical records of the patients were precisely reviewed with respect to risk factors for EP. To determine if EP rate is dependent on the type of ART treatment (fresh versus frozen ET) and the day of ET (cleavage versus blastocyst stage) a subgroup analysis was performed.

Data statistical analysis was done using statistical software (”STATISTICA” version 7, StatSoft Inc., Tulsa, OK). Descriptive statistics for continuous variables were reported as median and range (LQ; UQ). The comparison between two groups was carried out using Mann–Whitney (U) tests for non-parametric statistics and two-sided Fisher’s exact test – for proportions. Risk factor were evaluated using odds ratios (OR) and its 95% CI with univariate logistic regression. The proportions. Risk factor were evaluated using odds ratios (OR) parametric statistics and two-sided Fisher’s exact test – for groups was carried out using Mann–Whitney (U[STATISTICA” version 7, StatSoft Inc., Tulsa, OK).

Subgroup analysis was performed.

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Data statistical analysis was done using statistical software (”STATISTICA” version 7, StatSoft Inc., Tulsa, OK). Descriptive statistics for continuous variables were reported as median and range (LQ; UQ). The comparison between two groups was carried out using Mann–Whitney (U) tests for non-parametric statistics and two-sided Fisher’s exact test – for proportions. Risk factor were evaluated using odds ratios (OR) and its 95% CI with univariate logistic regression. The significance level (p) was set at 0.05 for all statistical tests.

Results

Meta-analysis

Overall, 16 trials were considered for the meta-analysis. Nine of the 16 studies with a total of 7730 EP and 377 196 CP were available to perform D3 versus D5 fresh ET group comparison. The incidence of EP following different ART treatment was 2.11%.

Ectopic gestation rate did not differ between D3 and D5 fresh ET groups (see Figure 1), when assessed by random model: RR = 0.99 (95% CI: 0.76–1.30). Even excluding the study with the most weight and patient population [9] (possibly effecting the results) the RR remained similar: RR = 0.9, 95%CI: 0.60–1.37, random effect model. Furthermore, the elimination of articles reporting data from national registers [15,17,18] did not influence the results: RR = 0.82, 95% CI: 0.49–1.37, random effect model.

A meta-analysis of fresh versus frozen ET cycles revealed a RR of 1.56 (95% CI: 1.25–1.95) for EP occurrence (see Figure 2). The exclusion of the study, reporting small number of TET cycles [3], did not influence the overall RR within the group: RR = 1.52, 95%CI: 1.21–1.90, random effect model. In order to diminish a possible influence of freezing/thawing techniques on the analysis results, we eliminated five studies comprising cryopreserved ET cycles performed before 2001 [1,3,12,19,20], thus, obtained similar risks for ectopic gestation for the group: RR = 1.71, 95%CI: 1.34–2.17, random effect model. Finally, ignoring articles with data from national registers [13,15,18,21], we still received relative results: RR = 1.64, 95% CI: 1.08–2.50, random effect model.

Single-center cohort study

Of the 1194 pregnancies included in our center study population, 21 were documented as ectopic, including one heterotopic pregnancy. The estimated ectopic pregnancy (accounted per CP) rate for all types of ART treatment was 1.76% (21/1173).

The median age of patients was 32 (28;34) years in the EP group and 32 (29;36) years in the CP group (p = 0.39). The duration of infertility was 4.5 (2;6) and 5 (2;8) years, respectively (p = 0.24).

Body mass index (BMI), parity, previous abdominal and pelvic surgeries, history of spontaneous/elective abortion, EP, polycystic

| Study or Subgroup | Day 3 ET Events | Total Day 3 | Day 5 ET Events | Total Day 5 | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------|-------------|-----------------|-------------|--------|--------------------------------|
| Bu Z. et al., 2016| 491 13749       | 47 1852     | 17.5%           | 1.41 [1.05, 1.89] |
| Cheng L-Y. et al., 2015 | 10 564 | 12 627 | 7.1% | 0.93 [0.40, 2.13] |
| Fang C. et al., 2014 | 39 1593 | 6 351 | 6.9% | 1.43 [0.61, 3.36] |
| Ishihara O. et al., 2011 | 104 4966 | 44 3047 | 16.2% | 1.45 [1.02, 2.06] |
| Keegan A.D. et al., 2007 | 8 1673 | 16 1091 | 7.0% | 0.33 [0.14, 0.76] |
| Li R-R. et al., 2013 | 43 1229 | 5 231 | 6.2% | 1.62 [0.65, 4.04] |
| Milki A.A., Jun H.S., 2003 | 22 593 | 13 258 | 9.4% | 0.74 [0.38, 1.44] |
| Perkins K.M. et al., 2015 | 4436 213455 | 2397 127768 | 22.0% | 1.11 [1.05, 1.15] |
| Rosman E.R. et al., 2009 | 8 1983 | 29 2166 | 7.8% | 0.30 [0.14, 0.66] |
| Total (95% CI) | 239805 | 137391 | 100.0% | 0.99 [0.76, 1.30] |
| Total events | 5161 | 2569 |
| Heterogeneity: Tau² = 0.09; Chi² = 26.14, df = 8 (P = 0.0010); I² = 69% |
| Test for overall effect: Z = 0.06 (P = 0.95) |

Figure 1. Forest plot of the comparison of ectopic pregnancy rates following day 3 versus day 5 embryo transfer (random effect model).
Discussion
Findings of the present study demonstrate that ectopic gestation occurs in approximately 2% of all clinical pregnancies in ART cycles. In order to identify risk factors for extrauterine pregnancy after IVF-ET, we performed a systematic literature review and a large data meta-analysis.

It has been previously shown that blastocyst ET reduces the prevalence of EP in ART cycles [2,22,23]. This suggestion is based on the physiology of human implantation, in which embryo enters uterine cavity on blastocyst development stage, and when being transferred to the uterus during IVF cycle, has a larger diameter, shorter time before implantation and a lower likelihood of migration to fallopian tube [4,9,24]. Decreased uterine contractility (cervix-to-fundus) due to progesterone influence in the luteal phase (day 6–7 after oocyte pick up) has also been postulated as a factor minimizing the retrograde travel of the embryo [16,22].

However, comparing pregnancies achieved following days 3 and 5 ET, we did not observe any association between embryo development stage and the incidence of ectopic gestation both in meta-analysis and in our center retrospective study. These findings suggest that the day of embryo replacement might not be a major determinant in affecting ectopic pregnancy rate. Hence, it should be noted that meta-analysis results might be influenced by the disparity between included studies and unavailability to assess other possible contributors to EP occurrence: assisted hatching, aspects of transfer technique, embryo quality, and quantity [1,12,19].

Another purpose of our study was to estimate the influence of the type of ART on ectopic pregnancy rate. Thereby, we compared the incidence of EP, occurring after fresh and frozen/thawed embryo transfer. Results of our meta-analysis demonstrate that fresh ET (regardless of embryo stage) is associated with a higher risk of ectopic gestation, while frozen ET reduces those risks.

Contrary to our findings, a meta-analyzed, published in 2009 [25], showed a slightly higher risk for EP following frozen/thawed compared with fresh ET. The authors suggested that the observed discrepancy might be associated with a marked variability in overall pregnancy rates following frozen ET between various IVF centers. Indeed, differences related to embryo selection and technical aspects of the freezing procedure, which improved significantly in course of time, could possibly affect the outcome. Subsequent to this, five of 14 studies, comprising embryo freezing/thawing ET performed before 2001, were eliminated from present meta-analysis. Even so, the relative risk for ectopic pregnancy following frozen ET was almost 1.7-fold lower than after fresh ET.

Possible explanation for a higher EP rate in fresh non-donor IVF cycles might be the adverse effect of ovarian stimulation. Elevated hormonal levels during COS are believed to alter uterine environment, essential for successful implantation [1,12,15]. Supraphysiologic estrogen and progesterone concentrations may lead to enhanced uterine contractility, affect tubal peristalsis and ciliary beat and possibly contribute to retrograde embryo movement into fallopian tube [4,26].

Several authors reported higher estradiol (E2) concentrations during ART treatment among women with EP compared with those with intrauterine pregnancy [2,16,17]. In addition, recent research of SART registry found that increasing oocyte yield (reflecting E2 level) is correlated with a higher EP rate, yet only in autologous IVF-ET cycles and not in oocyte recipients [17]. It seems plausible that patients undergoing donor–recipient cycles
or cryopreserved ET with any type of endometrial preparation (HRT or in modified natural cycle) are less likely to be exposed to elevated hormonal levels, resulting from ovarian stimulation during IVF procedure, and thus, are at lower risk of ectopic gestation [11,18].

In our series, we did not have information on hormonal levels during COS, either, we failed to identify any difference in EP prevalence between frozen and fresh ET groups. Although our EP-patient population was rather small to allow any definite conclusions to be drawn, present findings are still consistent with those reported previously [1,20,27], suggesting there might be other reasons behind abnormal embryo implantation after ART treatment.

In order to evaluate risk factors for ectopic pregnancy in our program, we analyzed medical history, indications for IVF, and aspects related to IVF procedure. In agreement with other reports [7,8], tubal factor infertility (TFI) was identified as the main risk factor for EP after IVF in this study. Uni- or bilateral tubal pathology, previous appendectomy, chlamydial infection, and tubal factor infertility were associated with ectopic pregnancy occurrence in our series. It is not surprising that the results of the current study are identical to prior reports, as pelvic inflammatory disease and subsequent tubal occlusion have been described as risk factors for EP following both natural and assisted conception [4,5]. During IVF, embryos are transferred directly into the uterine cavity. Nevertheless, unintentional deep fundal or rapid ET in TFI patients may result in direct injection of transfer media into dysfunctional fallopian tube, which may be unable to propel an embryo back to the uterus and, therefore, contribute to abnormal implantation. We also hypothesize that chronic endometritis, described previously to be associated with tubal infertility and past chlamydial infection [28], may account for the impairment of endometrial receptivity, subsequent failure of normal embryo-endometrium interaction and, thereby, embryo migration within upper reproductive tract in search for a better site to implant.

In contrast to other reports [9–10,26], in our center study, there was no statistical evidence of association between ectopic pregnancy and background factors (age, infertility duration, history of ectopic pregnancy), BMI, and parameters of ovarian stimulation. Aspects of the transfer technique (injection pressure, volume, location of the catheter tip), postulated to be contributing factors of EP occurrence, are unified in our practice, thus, could not be evaluated.

It has been speculated that high implantation potential is protective against EP, while poor embryo quality, as well as the use of multiple ET, is a risk factor for extraterine pregnancy [12,23]. Despite this concern, our data show that both the number (single or double ET) and quality of embryos transferred have no effect on ectopic implantation rate following ART treatment, which is in line with other existing reports [13,29].

In summary, it should be noted that the data, presented in our meta-analysis, were highly heterogeneous: quantitate and qualitative aspects of embryo transfer, ectopic pregnancy evaluation, COS, and endometrial preparation regiments varied among the included studies. Farther, some papers did not report preimplantation diagnostic, gestational surrogacy, oocyte donor/recipient program prevalence. Furthermore, there was no availability to assess the influence of significant risk factors for ectopic gestation, such as tubal disease, on the analysis results, as these data were not specified in the majority of the studies. We also recognize our 6-year center study to have some limitations due to retrospective design and its modest size relative to registry researches.

Taken together, our research provide evidence that traditional risk factors, such as tubal infertility and pelvic surgery, still play a major role in EP occurrence in ART cycles. Our findings indicate that the day of embryo replacement has no impact on EP rate, while frozen ET might be beneficial for minimizing EP risk. Also, we need to highlight that individual practices (not national statistics) should evaluate their own data in order to identify potential factors, contributing to EP rate. Finally, further expanded studies are required to estimate risk factors, develop a treatment approach strategy, and reduce the incidence of ectopic pregnancy after IVF-ET.

**Declaration of interest**

The authors report that they have no conflict of interest. No funding was required for this study.

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