

# Incidence of ectopic pregnancy after assisted reproduction treatment

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## ABSTRACT

**Objective:** To assess the ectopic pregnancy risk among women who conceived with assisted reproductive technology (ART) procedures.

**Methods:** We performed a retrospective analysis of pregnancies as a result of ART procedure at McGill University Health Center, Quebec, Canada for the period from 1997 to 2006.

**Results:** The ectopic pregnancy rate was 1.6% and the heterotopic pregnancy rate was 13%. Maternal age, number of embryos transferred, ovarian hyperstimulation syndrome, use of assisted hatching, and Intra Cytoplasmic Sperm Injection (ICSI) were not significant predictors of ectopic pregnancy.

**Conclusion:** Ectopic pregnancy rate in ART pregnancies is comparable to that of spontaneous pregnancies.

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The incidence of ectopic pregnancy (EP) showed a steady increase throughout the twentieth century and plateau at 20 per 1000 pregnancy at late twentieth century.<sup>1</sup> Women with a history of infertility have a higher risk of EP than other women and this made it difficult to separate the effects of fertility treatment, especially ovulation induction, from infertility itself.<sup>2</sup> Some suggested that the ectopic rate associated with assisted reproductive technology (ART) conceptions may be elevated, between 2.2 and 8.6 per 100 pregnancies, compared with the estimated rate of 2.0 per

100 pregnancies.<sup>3-9</sup> This theoretically should be the opposite as embryos are placed within the endometrial cavity bypassing the fallopian tubes and hence less extra-uterine implantation. Heterotopic pregnancy has been considered to be a very rare event, however, at present the actual rate appears to be significantly higher. The 2 main reasons for this increase are the current increased rate of ectopic pregnancies and, above all, the wider use of ovulation induction agents. This latter has been confirmed by different reports indicating a high rate of heterotopic pregnancies after assisted reproduction.<sup>10</sup> This higher rate of incidence has already changed the management of pregnancies resulting from assisted reproduction. Indeed, in these patients, the presence of an intrauterine pregnancy can no longer be considered reassuring and an early transvaginal ultrasonographic assessment is necessary to rule out the possibility of heterotopic pregnancy. In this report, we evaluate the incidence of ectopic and heterotopic pregnancies among women who conceived after ART.

**Methods.** Retrospective analysis of 1569 pregnancies conceived at the period from January 1997 - May 2006, through ART was performed. These pregnancies resulted from 1510 fresh IVF cycles while the other 59 pregnancies were frozen embryos. The numbers of ectopic pregnancies as well as heterotopic pregnancy were estimated separate. Other variables examined and correlated with the occurrence of ectopic pregnancy such as; Intra Cytoplasmic Sperm Injection (ICSI), assisted hatching (AH), number of embryos transferred, ovarian hyperstimulation syndrome (OHSS), and whether the transferred embryos are fresh or frozen. Clinical intrauterine pregnancy was defined as documentation of one or more gestational sacs visible by ultrasound examination; ectopic pregnancy was defined as documentation of one or more gestational sacs

outside of the uterus; and heterotopic pregnancy was defined as a pregnancy that met the criteria for both ectopic and clinical intrauterine pregnancy. Biochemical pregnancies are defined as having an elevated human chorionic gonadotropin [hCG] without a visible gestational sac and no clinical diagnosis of pregnancy.

**Statistical analysis.** The data were not normally distributed as shown by the Shapiro-Wilks test. We used Kruskal-Wallis test to compare continuous variables among the different groups of women. Proportions were compared using Chi-Square test and the results were expressed as mean and standard deviation of the mean. The differences are considered to be statistically significant if  $p < 0.05$ .

**Results.** The mean age of patients who conceived as a result of IVF treatment in this study was  $35.2 \pm 4.2$  years. One thousand and five hundred forty-two (98.3%) of these pregnancies were intrauterine 25 (1.6%) were ectopic pregnancies, and 2 (0.13%) were heterotopic pregnancies. The mean age of those who developed ectopic pregnancies was  $33.7 \pm 4.1$  years compared with  $35.2 \pm 4.2$  years for those who had intrauterine pregnancies. Although the age of patients who had ectopic pregnancies after IVF was younger than those who had intrauterine pregnancies; this difference was not statistically significant with a p-value of 0.2 and 95% CI - 0.7 to 3.3. Among the patients who had assisted reproductive pregnancies; 60% underwent IVF treatment and 40% underwent ICSI. The incidence of ectopic pregnancy among women who underwent ICSI treatment cycles was 1.4% with no cases of heterotopic pregnancy detected, while those who underwent IVF the ectopic pregnancy rate was 1.9% and the heterotopic pregnancy rate was 0.2%. This difference was not significant statistically with a p-value of 0.2 (Table 1). Assisted hatching was carried out in 160

cases. There were 3 cases of ectopic pregnancies among this group and there was no significant difference in the incidence of ectopic pregnancy when this is compared to the group of women who did not undergo assisted hatching before embryo transfer (Table 1). The number of embryos transferred to women who had intrauterine pregnancy was  $2.8 \pm 1.0$  while those who developed ectopic pregnancy had  $2.9 \pm 0.9$  embryos transferred. Ovarian hyperstimulation syndrome was diagnosed in 4.8%. Those women had a higher rate of ectopic pregnancy and this was 4.2% (Table 1). The group of women who did not develop OHSS had an ectopic pregnancy rate of 1.6%. Although there was a difference between the 2 groups of women, this difference was not significant with a p-value of 0.09 (Table 1). None of the women who got pregnant as a result of frozen embryo replacement cycle developed an ectopic pregnancy. We think this result might be a type I error as the number of women in this group was 59.

**Discussion.** Our study shows that the ectopic pregnancy rate among women who conceived after IVF cycle was 1.5%. This is less than the rate of ectopic pregnancy reported in previous studies of assisted reproduction pregnancies.<sup>3-9</sup> Theoretically, differences between conception via ART and natural conception may affect the risk of ectopic pregnancy. As currently performed, the vast majority of ART procedures involve in vitro fertilization and transcervical embryo transfer of multiple embryos. Because neither fertilization nor embryo transfer in IVF-ET involves the fallopian tubes directly, ART might reduce the risk of ectopic pregnancy. Nonetheless, ectopic pregnancies have been documented in IVF cycles, raising questions about the etiology of these ectopic implantations, including whether the transfer of multiple embryos plays a role. The majority of information on ectopic pregnancies among ART conceptions stems from case reports or case series. The few studies with denominator data were small and thus unable to evaluate sufficiently the risk of ectopic pregnancy by important patient subgroups. Limited data from previous studies suggest that tubal factor infertility and prior ectopic pregnancy are associated with an increase in the risk for ectopic pregnancy after ART. The rate of ectopic pregnancy in this study was comparable to that among women who conceive spontaneously. Heterotopic pregnancy rate was 0.13% which is significantly higher than that of the general population (1 in 30000 pregnancies).<sup>11,12</sup> These results were supported by another study which was published recently.<sup>13</sup> Age did not play a role in the risk of ectopic pregnancy. We also examined whether traditional IVF or ICSI has more risk of ectopic pregnancy and the result revealed no significant increase

**Table 1** - The incidence of extra-uterine pregnancy in different assisted reproductive technologies.

Procedure/ complications	Intrauterine pregnancy	Ectopic pregnancy (%)	P value
IVF/ICSI	906/604	17 (1.9) versus 8 (1.4)	NS
Assisted hatching	160	3	NS
No. of ET	$2.8 \pm 1.0$	$2.9 \pm 0.9$	NS
OHSS	70	3	NS
Frozen embryos	59	0	-

NS - not significant,  $p < 0.05$

IVF - In vitro fertilization, ICSI - Intra Cytoplasmic Sperm Injection, OHSS - Ovarian Hyper Stimulation Syndrome, ET - embryo transfer

in the risk of ectopic pregnancy in either one of the procedure. Assisted hatching was shown to increase the risk of ectopic pregnancy in one report,<sup>14</sup> while others contradicted this.<sup>13</sup> We found that assisted hatching was not a risk factor for developing ectopic pregnancy. The mean number of embryos transferred for both groups in this study was similar and did not seem to play a role in the risk of ectopic pregnancy after assisted reproduction. Although, in some studies it was stated that >3 embryos transferred increase the risk of ectopic pregnancy,<sup>13</sup> we did not find that transferring more than 3 embryos increases the ectopic pregnancy rate. Ovarian hyperstimulation syndrome was diagnosed in 4.8% of women undergone assisted reproduction treatment cycle. The ectopic pregnancy rate was higher in these patients but this was not statistically significant. In our study, we found that transferring frozen embryos is somewhat protective against ectopic pregnancy. This might be a type I error as the number of frozen embryo cycles were limited.

In conclusion, we did not find that ART play a role in the incidence of ectopic pregnancy and is comparable to that of the general population. Maternal age, number of embryos transferred, ovarian hyperstimulation syndrome, use of assisted hatching, and ICSI were not significant predictors of ectopic pregnancy.

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