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ORIGINAL ARTICLE

ECTOPIC PREGNANCY RATES WITH CLEAVAGE STAGE EMBRYO TRANSFER AT DAY 3 VERSUS BLASTOCYST STAGE TRANSFER AT DAY 5: A PROSPECTIVE ANALYSIS

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ABSTRACT: OBJECTIVE: The purpose of our study was to compare the tubal pregnancy rates between day 3 and day 5 transfers. As theoretically blastocyst transfer is said to decrease the incidence of ectopic pregnancy following IVF-ET due to the decreased uterine contractility reported on day 5. **METHODS:** A prospective analysis of all clinical pregnancies conceived in our IVF program between May 2010 to April 2011 was performed. The ectopic pregnancy rates were compared for day 3 and day 5 transfers. **RESULTS:** There were 44 pregnancies resulting from day 3 transfers of which one was ectopic (2.27%). In day 5 transfers, there was also one ectopic pregnancies out of 66 clinical pregnancies (1.52%), difference between these rates was not statistically significant (P>0.05) **CONCLUSION:** This suggests that the ectopic pregnancy rate is not reduced following blastocyst transfer on day 5 compared to cleavage stage embryo on day 3. While there may be several benefits to extended culture in IVF, the decision to offer blastocyst transfer should be made independently from the issue of ectopic pregnancy risk.

KEYWORDS: Blastocyst transfer, Cleavage stage Embryo Transfer, Ectopic Pregnancy.

INTRODUCTION: Ectopic pregnancy has been reported to occur in approximately 2–5% of all clinical pregnancies after IVF-ET.[1] The direct injection of transfer media with embryos into the fallopian tubes and migration of embryos to the tubes by reflux expulsion from uterine contractions may account for the development of tubal pregnancies after IVF.[2] Uterine junctional zone activity has been shown to decrease with increasing time after oocyte retrieval.[3] These findings suggest that blastocyst transfer should be associated with a lower incidence of ectopic pregnancy compared to cleavage stage transfer.[4]

The larger diameter of the blastocyst was proposed as an additional factor in reducing the rate of tubal pregnancies after day 5 transfer.[5] Fanchin et al reported a significant reduction in retrograde uterine contractility, from the cervix to the fundus, 7 days after hCG administration compared to both 4 days after and the day of hCG injection. These findings suggest that blastocyst transfer should be associated with a lower incidence of ectopic pregnancy compared to cleavage stage transfer. [6] The larger diameter of the blastocyst was proposed as an additional factor in reducing the rate of tubal pregnancies after day 5 transfer.[7]

Despite these theoretical considerations, large series that specifically compare the incidence of ectopic pregnancy with blastocyst versus cleavage stage transfers are lacking in the literature. The purpose of our study is to shed light on this issue by examining the ectopic pregnancy rates after day 3 transfer compared to day 5 transfer in our program over one year.

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METHODS: A prospective analysis of all clinical pregnancies conceived in our IVF program between May 2010 to April 2011 was performed. The ectopic pregnancy rates were compared for day 3 and day 5 transfers.

Three hundred patients aged 25-40 years undergoing in-vitro fertilization (IVF)/intra-cytoplasmic sperm injection (ICSI) cycle between May 2010 and April 2011 who met the inclusion criteria set namely, 2-20 years of infertility, having minimum five oocytes at oocyte pick up and endometrial thickness of 7 mm and more indicating good ovarian response, having normal uterine cavity and basal Follicle stimulating hormone level (FSH <10mIU/ml), were included in our study.

Complete work-up, baseline investigations and post-menstrual diagnostic hysteroscopy was done, and then patient was given Long Protocol, Gonadotropin releasing hormone (GnRH) agonists started on cycle day 21 daily doses given subcutaneously till cycle day 3. Hormonal evaluation–Serum FSH, Luteinizing hormone (LH), Estradiol (E_2) and trans-vaginal sonography were done on day 3 to confirm down regulation.

Induction with recombinant FSH (rFSH) was started once pituitary down regulation was confirmed, for five days (day 3 to 7). Follicular monitoring was initiated done from day eight. Patients were scheduled for oocyte retrieval once at least 3 follicles reached 18 mm size and then Injection human chorionic gonadotropin (hCG) 10,000 IU was given. Transvaginal sonography guided oocyte retrieval was done 36 hours after giving hCG.

The retrieved oocytes were then incubated for 3-4 hours in IVF-30 media and then depending on maturity of oocytes and previous IVF performance, IVF/ ICSI was performed. Eighteen hours post-insemination, fertilization was confirmed. The fertilized oocytes were then transferred into a cleavage medium and incubated. Embryos were observed on day 2 and transfer was scheduled byrandom allocation into two groups based on availability of three good quality embryos:

Group-1 included patients undergoing embryo transfer on day 3, and Group-2 in which extended culture was done and blastocyst were transferred on day 5. Random allocation of patients was done equally so that study population was comparable. Not more than three embryos/ blastocysts were transferred. All transfers were performed using Edward-Wallace catheter. Luteal support was given for eighteen days post retrieval. Serum beta-hCG was performed on day fifteen following embryo transfer and if positive then transvaginal sonography was performed fifteen days later to confirm intra-uterine pregnancy.

Clinical pregnancies were defined by seeing a gestational sac on transvaginal ultrasound. Ectopic pregnancies were diagnosed by transvaginal ultra sound by visualization of a gestational sac in the fallopian tube. The rate of ectopic pregnancies for day 3 and day 5 transfers was compared. Chi-square testing was used for statistical analysis. Significance was set at $P < 0.05$. Institutional review board approval was obtained for chart review.

RESULTS: There were 44 clinical pregnancies resulting from day 3 transfer of which 1 were ectopic (2.27%). In day 5 transfers, there was 1 ectopic pregnancy out of 66 clinical pregnancies (1.51%). The difference between these rates is statistically not significant ($P > 0.05$).Ectopic pregnancy with day 3 transfers and day 5 transfers was observed in patients with tubal disease. The incidence of tubal disease was similar in the day 3 transfer and the day 5 transfer groups, 35.33 and 28%, respectively and the difference was statistically not significant ($P > 0.05$). The mean ages were 32.46 (± 4.3) years in the day 3 group and 32.04 (± 4.4) years in the day 5 group ($P > 0.05$).

DISCUSSION: Studies that showed decreased uterine contractility further along in the luteal phase would imply that the ectopic pregnancy rates should be reduced after a day 5 transfer compared to a cleavage stage transfer. It has also been postulated that the larger size of the blastocyst may decrease the chances of the day 5 embryo from migrating to the fallopian tube.[8] It is possible that when a blastocyst is transferred, it does indeed have a lower probability of entering the fallopian tube.[9]

However, the blastocyst that does reach the tube may have a higher tendency to implant there while the day 3 embryo has 2 additional days, compared to the day 5 embryo, to migrate back into the uterine cavity. Although the patients in the blastocyst transfer group were on the average 2 years younger than those in the day 3 group, it is unlikely that this small difference could have had an impact on increasing the ectopic pregnancy rate in the day 5 group.

If anything, the rate of ectopic pregnancy has been reported to increase with age [10]. Another confounding factor could be the prevalence of tubal disease in the two patient populations studied, as tubal pathology has been shown to be a major risk factor for the development of an ectopic pregnancy with IVF. The incidence of tubal disease is unlikely to be a source of bias in our study since it was similar in our day 3 and day 5 transfer groups.

Although a comparison of the incidence of ectopic pregnancy between cleavage stage transfer and blastocyst transfer has not been the specific subject of any prior study in the literature, information on this issue can be found in a report by Marek et al.[11] In their study, the authors compared the pregnancy rates in their program when they switched from day 3 to day 5 transfer for all patients. The ectopic pregnancy rates can be extrapolated from their tabulated data as being 1% (2/199) with day 3 and 1.3% (2/159) with day 5 transfers. The findings of this smaller series confirm the absence of a decrease in ectopic rates after blastocyst transfer.

The literature contains 2 additional studies that incidentally report data allowing the computation of the ectopic pregnancy rate with blastocyst transfer without any information on day 3 transfers. In one study, Pantos et al[12] examined the influence of age on the pregnancy rate after blastocyst transfer and mentioned 4 ectopic pregnancies out of a total of 99 pregnancies (4%).

Although the purpose of these studies was not related to the issue of ectopic pregnancy and they suggest that blastocyst transfer does not reduce the likelihood of tubal pregnancy.

CONCLUSION: We believe that blastocyst transfer is a valuable tool that has enabled IVF programs to more accurately select the embryos with the highest potential for implantation [13] allowing for a good pregnancy rate while avoiding high order multiple gestations.[14] In our program, we offer blastocyst transfer to patients of any age[15] if they have more than 3 eight cell embryos. We suggest that programs establish the criteria that work for them for offering blastocyst culture and transfer.

However, based on the results of this study, the presence of risk factors favoring ectopic pregnancy should not be taken into account in the decision making for choosing to transfer on day 3 or day 5.

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Variable	Day 3 ET	Day 5 Transfer	P- value
Ectopic Pregnancy/ Clinical Pregnancy (%)	1/44 (2.27%)	1/66(1.51%)	NS (P < 0.05)
Mean AGE (years)	32.46+- 4.3	32.04+- 4.4	NS (P < 0.01)
Mean BMI	22.9 +-3.4	23.2 +- 3.5	NS
Tubal disease (%)	53 (35.33%)	42 (28%)	NS

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