BMC Pregnancy and Childbirth

BioMed Central

Research article

Open Access

Ectopic pregnancy rates with day 3 versus day 5 embryo transfer: a retrospective analysis

Amin A Milki* and Sunny H Jun

Address: Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, U.S.A

Email: Amin A Milki* - milki4@aol.com; Sunny H Jun - shjun@stanford.edu

* Corresponding author

Published: 07 November 2003

BMC Pregnancy and Childbirth 2003, **3**:7

Received: 24 September 2003

Accepted: 07 November 2003

This article is available from: http://www.biomedcentral.com/1471-2393/3/7

Abstract

Background: Blastocyst transfer may theoretically decrease the incidence of ectopic pregnancy following IVF-ET in view of the decreased uterine contractility reported on day 5. The purpose of our study is to specifically compare the tubal pregnancy rates between day 3 and day 5 transfers.

Methods: A retrospective analysis of all clinical pregnancies conceived in our IVF program since 1998 was performed. The ectopic pregnancy rates were compared for day 3 and day 5 transfers.

Results: There were 623 clinical pregnancies resulting from day 3 transfers of which 22 were ectopic (3.5%). In day 5 transfers, there were 13 ectopic pregnancies out of 333 clinical pregnancies (3.9%). The difference between these rates is not statistically significant (P = 0.8).

Conclusions: Our data suggests that the ectopic pregnancy rate is not reduced following blastocyst transfer compared to day 3 transfer. 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.

Background

Ectopic pregnancy has been reported to occur in approximately 2–5% of all clinical pregnancies after IVF-ET [1–4]. Although the direct injection of transfer media with embryos into the fallopian tubes may account for the development of tubal pregnancies after IVF, migration of embryos to the tubes by reflux expulsion from uterine contractions has been proposed as another possible explanation. [3,5]

Uterine junctional zone activity has been shown to decrease with increasing time after oocyte retrieval. [6]. When comparing day 2 to day 3 transfers, Lesny et al. [3] showed a trend for a lower ectopic pregnancy rate in the day 3 transfer group which they attributed to the decreased uterine contractility further along in the luteal phase. Fanchin et al. [7] 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. The larger diameter of the blastocyst was proposed as an additional factor in reducing the rate of tubal pregnancies after day 5 transfer. [8]

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 a 5 year period.

Methods

We reviewed all clinical pregnancies conceived in our IVF program since 1998 when blastocyst transfer was introduced to our center. The incidence of ectopic pregnancy was compared between day 3 and day 5 transfers in the same time period.

The controlled ovarian hyperstimulation protocol consisted of pretreatment with oral contraceptive pills with overlapping GnRH agonist down-regulation followed by FSH/hHMG and hCG, microdose flare or antagonist protocols. Oocytes were inseminated conventionally or by ICSI 3–4 hours after retrieval. Embryos were cultured in groups under mineral oil in 150 μL droplets of P1 medium (Irvine Scientific, Santa Ana, CA, USA) with 10% Serum Substitute Supplement (SSS) at 37 degrees Celsius in a 5% O_2, 5% CO_2 and 90% N_2 environment for 72 hours. For the blastocyst transfer group, the embryos were moved on day 3 into Blastocyst medium (Irvine Scientific) with 10% SSS and cultured for 48 hours before transfer. Additional blastocysts were cryopreserved on day 5 or day 6.

All transfers were performed using a Tefcat catheter (Cook Ob/Gyn, Spencer, IN, USA) 1 to 1.5 cm short of the fundus under transabdominal ultrasound guidance. The transfer volume was 20–30 μL.

Clinical pregnancies were defined by seeing a gestational sac on transvaginal ultrasound or by diagnosing an ectopic pregnancy. Ectopic pregnancies were diagnosed by ultrasound or by laparoscopic visualization of a gestational sac in the fallopian tube or by the absence of an intrauterine gestational sac and rising βhCG levels following the failure of suction D&C to reveal products of conception.

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 623 clinical pregnancies resulting from day 3 transfer of which 22 were ectopic (3.5%). In day 5 transfers, there were 13 ectopic pregnancies out of 333 clinical pregnancies (3.9%). The difference between these rates is not statistically significant (P = 0.8). Of the 22 ectopic pregnancies with day 3 transfer, 9 were in patients with tubal disease compared to 5 out of the 13 ectopic pregnancies with day 5 transfer (P = 0.9). More importantly, the incidence of tubal disease was similar in the day 3 transfer and the day 5 transfer groups, 22 and 24%, respectively (P = 0.4). The mean ages were 37.7(± 4.9) years in the day 3 group and 35.3 (± 4.7) years in the day 5 group (P < 0.01). The mean BMI was similar in both groups. (Table 1)

In our program, we primarily perform cryopreservation at the blastocyst stage. [9] Accordingly, the day 5 transfer group includes the vast majority of the thaw embryo transfers. When these pregnancies are excluded and only fresh transfers are considered, the ectopic pregnancy rate remains similar for day 3 and day 5 at 3.5% (22/615) and 3.3% (9/271), respectively. (P = 0.8)

Discussion

Studies that showed decreased uterine contractility further along in the luteal phase [6,7] 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] Despite these theoretical mechanisms which suggest that day 5 transfer is associated with a lowered ectopic pregnancy risk, our study, which examined close to a thousand pregnancies, failed to show such a trend. It is possible that when a blastocyst is transferred, it does indeed have a lower probability of entering the fallopian tube. 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.

Table 1: Comparison of ectopic pregnancy rates in day 3 versus day 5 embryo transfers

	Day 3-ET	Day 5 Transfer	P-value
EctopicPregnancy/Clinical Pregnancy	22/623 (3.5%)	13/333 (3.9%)	NS
Ectopic Pregnancy/Clinical Pregnancy (Excluding Frozen Embryo transfers)	22/615 (3.5%)	9/271(3.3%)	NS
Mean Age (yrs)	37.7 ± 4.9	35.3 ± 4.7	<0.01
Mean BMI	22.9 ± 3.4	23.2 ± 3.5	NS
%Tubal Disease	22%	24%	NS

A potential source of bias in our study is the fact that blastocyst transfer was offered to patients with more than 3 eight cell embryos on day 3 which is likely to occur in patients with a higher number of oocytes and higher estrogen levels. Specific data on oocyte number is not available for our study, and we do not routinely measure estradiol levels in our program. However, when specifically analyzed in previous studies in the literature [1,2], these parameters were not found to affect the incidence of tubal pregnancy. 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 [11,12] 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. [13] 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. [14] 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%). In the other study, Tarlatzis et al. [15] looked at monozygotic twinning with blastocyst transfer after ICSI and conventional IVF and noted an ectopic pregnancy rate of 2 out of 48 pregnancies (4.2%). Although the purpose of these studies was not related to the issue of ectopic pregnancy and they lacked day 3 controls, the rates of about 4% are in line with what has been reported with day 3 transfers and 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 [16–18] allowing for a good pregnancy rate while avoiding high order multiple gestations [19,20]. In our program, we offer blastocyst transfer to patients of any age [21] if they have more than 3 eight cell embryos. Although some authors have advocated routine blastocyst transfer in all patients [13,22], offering extended culture when there are no eight cell embryos on day 3 has been reported to be detrimental [23]. 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.

Competing Interests

None declared.

Author's Contributions

AAM, faculty attending physician, treated the patients, conceived of the study and co-wrote the manuscript. SHJ, resident, collected the data and co-wrote the manuscript.

References

1. Marcus SF and Brinsden PR: **Analysis of the incidence and risk factors associated with ectopic pregnancy following in-vitro fertilization and embryo transfer.** *Hum Reprod* 1995, **10:**199-203.
2. Strandell A, Thorburn J and Hamberger L: **Risk factors for ectopic pregnancy in assisted reproduction.** *Fertil Steril* 1999, **71:**282-286.
3. Lesny P, Killick SR, Robinson J and Maguiness SD: **Transcervical embryo transfer as a risk factor for ectopic pregnancy.** *Fertil Steril* 1999, **72:**305-309.
4. American Society for Reproductive Medicine and Society for Assisted Reproductive Technology: **Assisted reproductive technology in the United States: 1999 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry.** *Fertil Steril* 2002, **78:**918-931.
5. Russell JB: **The etiology of ectopic pregnancy.** *Clin Obstet Gynecol* 1998, **30:**181-190.
6. Lesny P, Killick SR, Tetlow RL, Robinson J and Maguiness SD: **Uterine junctional zone contractions during assisted reproduction cycles.** *Hum Reprod Update* 1998, **4:**440-445.
7. Fanchin R, Ayoubi JM, Righini C, Olivennes F, Schonauer LM and Frydman R: **Uterine contractility decreases at the time of blastocyst transfers.** *Hum Reprod* 2001, **16:**1115-1119.
8. Schoolcraft WB, Surrey ES and Gardner DK: **Embryo transfer: techniques and variables affecting success.** *Fertil Steril* 2001, **76:**863-870.
9. Behr B, Gebhardt J, Lyon J and Milki AA: **Factors relating to a successful cryopreserved blastocyst transfer program.** *Fertil Steril* 2002, **77:**697-699.
10. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L and Job-Spira N: **Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France.** *Am J Epidemiol* 2003, **157:**185-194.
11. Herman A, Ron-El R, Golan A, Weinraub Z, Bukovsky I and Caspi E: **The role of tubal pathology and other parameters in ectopic pregnancies occurring in in vitro fertilization and embryo transfer.** *Fertil Steril* 1990, **54:**864-868.

12. Verhulst G, Camus M, Bollen N, Van Steiterghem A and Devroey P: **Analysis of risk factors with regard to the occurrence of ectopic pregnancy after medically assisted procreation.** *Hum Reprod* 1993, **8:**1284-1287.
13. Marek D, Langley M, Gardner DK, Confer N, Doody KM and Doody KJ: **Introduction of blastocyst culture and transfer for all patients in an in vitro fertilization program.** *Fertil Steril* 1999, **72:**1035-1040.
14. Pantos K, Athanasiou V, Stefanidis K, Stavrou D, Vaxevanoglou T and Chronopoulou M: **Influence of advanced age on the blastocyst development rate and pregnancy rate in assisted reproductive technology.** *Fertil Steril* 1999, **71:**1144-1146.
15. Tarlatzis BC, Qublan HS, Sanopoulou T, Zepiridis L, Grimbizis G and Bontis J: **Increase in the monozygotic twinning rate after intracytoplasmic sperm injection and blastocyst stage embryo transfer.** *Fertil Steril* 2002, **77:**196-198.
16. Rijnders PM and Jansen CA: **The predictive value of day 3 embryo morphology regarding blastocyst formation, pregnancy and implantation rate after day 5 transfer following in-vitro fertilization or intracytoplasmic sperm injection.** *Hum Reprod* 1998, **13:**2869-2873.
17. Graham J, Han T, Porter R, Levy M, Stillman R and Tucker MJ: **Day 3 morphology is a poor predictor of blastocyst quality in extended culture.** *Fertil Steril* 2000, **74:**495-497.
18. Milki AA, Hinckley MD and Behr B: **Comparison of blastocyst transfer to day 3 transfer with assisted hatching in the older patient.** *Fertil Steril* 2002, **78:**1244-1247.
19. Gardner DK, Schoolcraft WB, Wagley L, Schlenker T, Stevens J and Hesla J: **A prospective randomized trial of blastocyst culture and transfer in in-vitro fertilization.** *Hum Reprod* 1998, **13:**3434-3440.
20. Milki AA, Fisch JD and Behr B: **Two-blastocyst transfer has similar pregnancy rates and a decreased multiple gestation rate compared with three-blastocyst transfer.** *Fertil Steril* 1999, **72:**225-228.
21. Milki AA, Hinckley MD, Gebhardt J, Dasig D, Westphal LM and Behr B: **Accuracy of day 3 criteria for selecting the best embryos.** *Fertil Steril* 2002, **77:**1191-1195.
22. Wilson M, Hartke K, Kiehl M, Rodgers J, Brabec C and Lyles R: **Integration of blastocyst transfer for all patients.** *Fertil Steril* 2002, **77:**693-696.
23. Racowsky C, Jackson KV, Cekleniak NA, Fox JH, Hornstein MD and Ginsburg ES: **The number of eight-cell embryos is a key determinant for selecting day 3 or day 5 transfer.** *Fertil Steril* 2000, **73:**558-564.

Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2393/3/7/prepub