

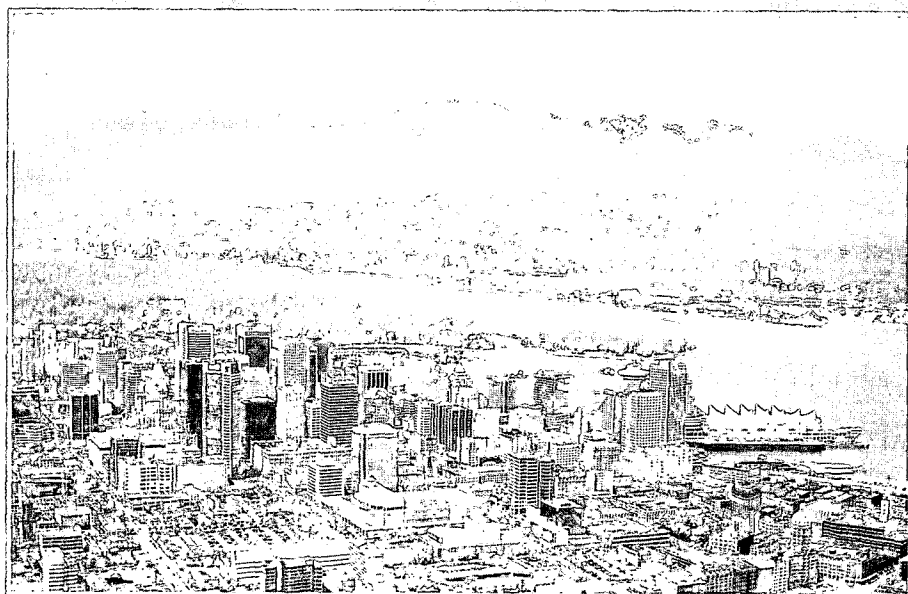
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Assisted embryo hatching improves pregnancy rates (PRs) in women aged 40-43 years

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SUMMARY

The purpose of the current study was to assess the pregnancy prognosis following in vitro fertilization-embryo transfer (IVF-ET) in women age 40 to 43 when assisted hatching (AH) was available and 3 day embryo transfer (ET) and close monitoring of endometrial development were utilized. 275 stimulation cycles were retrospectively reviewed. The overall pregnancy rate (PR) per transfer was 12.9%. Patients with 3 or more embryos transferred had a PR of 11.8% without AH and 26.9% with use of AH while those with 1 or 2 embryos transferred had PRs of 0.0% and 6.2%, respectively. Thus, the results indicate that using AH, women age 40-43 who are able to generate at least 3 embryos can attain a reasonable PR without the need for donor oocytes.

INTRODUCTION

Pregnancy rates (PRs) following in vitro fertilization-embryo transfer (IVF-ET) decrease considerably in patients ≥ 40 , with poor oocyte quality, the most important etiologic factor (Navot et al, 1991; Munne et al, 1995). In contrast to animals, human endometrial receptivity does not significantly reduce PRs (Sauer et al, 1991) as long as adjustments are made for endometrial thickness (Check et al, 1994) and the need for extra progesterone (P) (Meldrum, 1993).

Various authors have reported lower PRs and increased spontaneous abortion rates following IVF in women ≥ 40 compared to younger patients (4-12% vs 19-30%) (Padilla et al, 1989). One of the most recent extensive reviews of PRs in women age 40-43 following IVF-ET was published by Bopp et al (1995). Bopp et al, reported a clinical PR/stimulation, retrieval and transfer of 7.3%, 9.3%, and 14.3% and a delivery rate of 5.1%, 6.5%, and 10.0%.

The study presented herein evaluated the Cooper Center for IVF's experience with women 40-43 undergoing IVF-ET. Furthermore, the objective of this study was to determine whether assisted embryo hatching and 3 day transfers improve pregnancy outcome in women 40-43 years old.

MATERIALS AND METHODS

Two hundred seventy-five consecutive IVF stimulation cycles from 11/91 to 4/95 in women 40-43 years old were evaluated. Ovarian hyperstimulation regimens included luteal phase leuprolide acetate followed by human menopausal gonadotropin (Meldrum et al, 1989), short flare protocol (Garcia et al, 1990) or clomiphene citrate (100mg x 5 days) followed by gonadotropins (Shanis et al, 1995).

Cycles were cancelled if there was a poor response to stimulation. However, if at least 3 mature follicles developed, oocyte retrievals were performed. Embryo transfers were deferred and all embryos cryopreserved if there was evidence of inadequate endometrial development, i.e., either the endometrial thickness was < 10 mm or the homogeneous hyperechogenic echo pattern was observed (Check et al, 1991; Check et al, 1993).

Cycles were stratified by their use of assisted hatching (AH). Prior to November of 1993, AH was not available. After 1993, patients had the option of using AH. Patients in the AH group were prescribed methylprednisolone and doxycycline. The corticosteroids were given to prevent the woman's immune system from attacking the embryo through the breach in the zona (Cohen et al, 1990b) and the antibiotic was given to retard infection.

Assisted hatching using the zona drilling technique was performed as previously described (Cohen et al, 1990a; Check et al, 1995). Even cryopreserved embryos had AH as previously described (Check et al, 1996).

Outcome measures included: PRs per stimulated cycle, retrieval and transfer. If the fresh transfer was deferred, the results of the first frozen ET were reported in adjusted PRs. Clinical pregnancy was defined as evidence of a gestational sac. Ongoing pregnancy was defined as pregnancy that successfully demonstrated a viable fetus on ultrasound after completion of the first trimester.

RESULTS AND CONCLUSIONS

The cancellation rates before oocyte retrieval was 26.5% (73 cycles). After oocyte retrieval, ET was cancelled in 31.8% (63 cycles). The clinical PR/stimulated cycle, retrieval and transfer were 6.5%, 8.9%, and 12.9%, respectively. The ongoing PRs/stimulated cycle, retrieval and transfer were 5.4%, 7.4%, and 10.8%, respectively.

A comparison of the PR by number of embryos transferred and use of AH, showed that the PRs were the highest (26.9%) when at least 3 embryos were transferred following AH as compared to 11.8% if no AH.

The women who achieved a pregnancy had an average of 11.5 ± 6.5 oocytes retrieved as compared to only 6.4 ± 5.3 oocytes retrieved in those that did not conceive. In 53 cycles where only 1 or 2 embryos were transferred, only 3 clinical pregnancies (5.7%/transfer) and 1 ongoing (1.9%/transfer) pregnancy were achieved. Assisted hatching did not improve the PR when only 1 or 2 embryos were available for transfer (6.2% with AH and 6.9% without AH).

The adjusted PRs that included the first frozen ET for these patients were 7.6%/stimulation, 10.4%/retrieval and 13.3%/transfer in women age 40-43.

These results support the hypothesis that there is a hatching defect in the embryos of older women that precludes them from implanting. The ZP which is formed during the time of oocyte maturation may have chemical or physical characteristics that are different from the ZP of an oocyte from a younger patient that cause it to harden. The ZP may be more resistant to lysins produced by the embryo which might be necessary for zona thinning preliminary to hatching and subsequent implantation (Cohen et al, 1992). It might also be that oocytes produced by these older patients have inadequate mitochondria which are unable to meet the energy requirements of freeing the embryo from the ZP (Schoolcraft et al, 1994). Performing AH aids the embryo in overcoming the hatching deficiency allowing it to shed its zona and implant earlier during the window of implantation (Cohen et al, 1992).

The production of a sufficient number of quality eggs decreases with age. However, some women 40-43 years old are still capable of producing at least 3 embryos and we demonstrated that these women have a good prognosis for achieving a pregnancy following IVF-ET. These conclusions were also reported by Widra et al (Widra et al, 1996). Hull et al, however, did not find increased PRs in women ≥ 40 years old who had more than 3 embryos available for transfer (Hull et al, 1996). This discrepancy in findings may be due to the small number of older women in Hull's study, or the fact that Hull et al, did not use AH.

In conclusion, there is a good prognosis for that subgroup of older women 40-43 years old that are still capable of responding well to ovarian hyperstimulation as long as AH is performed with 3 day transfers.

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