CEOG Clinical and Experimental Obstetrics & Gynecology

The effect of oocyte reserve on pregnancy rates per oocyte harvest in women aged 36-39

J.H. Check[1,2], A. Whetstone[3], J.K. Choe[1,2], R. Cohen[2,4]

[1] Cooper Medical School of Rowan University, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ; [2] Cooper Institute for Reproductive Hormonal Disorders, P.C. Marlton, NJ
[3] University of Medicine and Dentistry of New Jersey, School Of Osteopathic Medicine, Stratford, NJ
[4] Philadelphia College Of Osteopathic Medicine, Department Of Obstetrics And Gynecology, Philadelphia, PA (USA)

Summary

Purpose: To determine the relative effect of diminished oocyte reserve on clinical viable and live delivered pregnancy rates per transfer and live delivery pregnancy rate per oocyte harvest in women aged 36-39. *Materials and Methods:* A retrospective comparison of pregnancy outcome was performed over a ten-year time period in women with normal oocyte reserve (day 3 serum FSH ≤11 mIU/mL) *vs.* diminished reserve (day 3 serum FSH ≥12 mIU/mL). Pregnancy rate per oocyte harvest equals the odds of conceiving with fresh or frozen embryos from a given retrieval before proceeding to another oocyte retrieval. *Results:* The clinical and viable (at end of first trimester) pregnancy rate per transfer was only 20% lower for the group with diminished oocyte reserve, but was 50% lower for the pregnancy rate per oocyte harvest. *Conclusions:* Mild stimulation for women with diminished oocyte reserve allows a higher percentage of chromosomally normal embryos in women with diminished oocyte reserve, leading to only a 20% lower clinical and viable pregnancy rate per transfer. However, overall, there are less normal total number of normal embryos leading to a pregnancy rate per oocyte harvest only half as good in the group with lower reserve *vs.* normal.

Key words: Mildly advanced age; Oocyte reserve; IVF-ET; Oocyte harvest; Mild ovarian hyperstimulation.

Introduction

There are some studies that suggest that when a woman has diminished oocyte reserve, as evidenced by a high day 3 serum follicle stimulating hormone (FSH) level, there are very poor pregnancy rates despite the transfer of normal appearing embryos [1-4]. There is evidence that the reason for the very poor in vitro fertilization-embryo transfer (IVF-ET) pregnancy rates with diminished oocyte reserve is related to a high rate of meiosis errors leading to aneuploidy [5]. This has led to the conclusion by many clinicians and researchers in the field of infertility that young women with diminished oocyte reserve have the same quality of oocytes as women of advanced reproductive age.

However, there are other studies that find pregnancy rates per embryo transfer in women with diminished oocyte reserve to be only slightly lower than their age peers with normal reserve [6, 7]. The main difference in methodology in those with very poor outcome *vs.* reasonably good outcome was the use of conventional to very high FSH dosage in the former vs. mild to minimal FSH stimulation in the latter [8, 9].

Considering the finding of Nasseri *et al.* of increased rate of aneuploidy in women having IVF-ET with diminished oocyte reserve who had conventional controlled ovarian hyperstimulation, it seems likely that the explanation for poor pregnancy rates demonstrated in some studies is an adverse effect of the high dosage FSH on the process of meiosis leading to non-disjunction of chromosomes [5, 10]. This may be related to the possibility that FSH acting on a specific FSH receptor causes the production of a key enzyme needed for chromosome separation that has been on the verge of being down-regulated by the chronic elevation of FSH. Adding higher levels of serum FSH through exogenous administration causes a critical higher level of serum FSH which now causes down-regulation of this specific FSH receptor, thus leading to a deficiency of this factor which protects against non-disjunction of chromosomes [11].

There are some data suggesting that even with normal oocyte reserve, with the creation of many embryos following conventional controlled ovarian hyperstimulation (COH), there may be just an average of 1.8 chromosomally normal embryos in the cohort that reaches blastocyst stage [12]. The possibility exists that women with normal oocyte reserve actually produce more normal embryos than those with diminished oocyte reserve but the reasons for similar pregnancy rates may be the dilution factor. For example, supposing the average number of normal embryos in women with diminished oocyte reserve is one embryo per retrieval *vs.* two in those with normal reserve. If only two total em-

Revised manuscript accepted for publication September 1, 2014

Table 1. — *Pregnancy rates per embryo transfer in women aged 36-39 according to ovarian oocyte reserve.*

	Clinical pregnancy rate	Viable pregnancy rate	Live delivered
Normal reserve	37.3% (363/971)	32.5% (315/971)	30.7% (298/971)
Diminished reserve	30.5% (150/492)	26.5%	22.2%

bryos are created with mild stimulation in the low reserve group, the one normal embryo will be transferred. However if there are six top embryos in the normal group and only two normal ones, by transferring two there is a four in nine chance that neither of the two normal embryos would be selected.

The riskiest and most costly part of the IVF process is he COH, the oocyte retrieval and embryo development. Embryo transfer is without risk and the least expensive part of IVF. Another way to evaluate the efficacy of IVF-ET is a method termed pregnancy rate per oocyte harvest [13]. This method of evaluation considers the pregnancy rate given the opportunity to transfer back all embryos created (thus fresh and frozen transfers) before the need to do another COH followed by oocyte retrieval [13]. Pregnancy rate per oocyte harvest only evaluates the live delivered pregnancy rate.

The objective of the present study was to determine to what degree does diminished oocyte reserve have a negative impact on the pregnancy rate per oocyte harvest in women aged 36-39.

Materials and Methods

A retrospective review of IVF-ET cycles over a ten-year period in women having the oocyte retrieval between the ages of 36-39 was performed. Two groups were compared – those with normal oocyte reserve with day 3 serum FSH ≤11 mIU/mL and those with diminished oocyte reserve (day 3 serum FSH ≥12 mIU/mL).

Conventional or mild FSH stimulation dosage may have been used for the normal reserve group but only mild stimulation for low reserve group. Only gonadotropin releasing hormone (GnRH) antagonist protocols were compared. Women with a day 3 serum estradiol >50 pg/mL were excluded. Women were eliminated from the study if they proceeded with another IVF-ET cycle before transferring all their cryopreserved embryos unless a live delivered pregnancy occurred.

Results

Table 1 presents the pregnancy rates per transfer according to ovarian oocyte status. The clinical and viable pregnancy rates were approximately 20% lower in the group with diminished oocyte reserve. The live delivered pregnancy rate was 40% lower for the diminished oocyte group.

The live delivered pregnancy rate per oocyte harvest includes the addition of a pregnancy by a subsequent frozen embryo transfer if the fresh only transfer did not result in a pregnancy or ended in a miscarriage as long as all embryos were derived from the given oocyte retrieval. The live delivered pregnancy rate per oocyte harvest was 47.2% (411/971) for normal reserve *vs.* 25.0% (123/492) for diminished reserve. Thus the pregnancy rate per oocyte harvest was almost 50% lower for the decreased oocyte reserve group.

Discussion

The pregnancy rate per oocyte harvest was twice as high for women with normal *vs.* diminished oocyte reserve yet the viable pregnancy rate was only 20% higher per fresh embryo transfer and live delivered only 40% higher. The explanation for the significantly higher pregnancy rate per oocyte harvest relates to higher pregnancy rates per frozen embryo transfer in this group coupled with more frozen embryo transfers in the normal vs. decreased reserve group. It also seems likely that part of the explanation could be related to a dilutional factor in the normal reserve group for fresh embryo transfer, i.e., more abnormal than normal embryos from a chromosome standpoint created and thus a better chance not to transfer one of the normal embryos since there would be a higher percentage of aneuploidy [12]. These data underscore the importance for each IVF center to have a good cryopreservation program if one is not able to be certain which embryos are chromosomally normal.

Despite the pregnancy per harvest being half as good in diminished *vs.* normal reserve, the pregnancy rate per fresh transfer was much more comparable. Thus this study confirms that when the specific principles of mild stimulation modified for diminished oocyte reserve are followed, reasonably good pregnancy rates per embryo transfer can be achieved in those women with diminished oocyte reserve.

Recently there has been a trend toward using mild stimulation even for women with normal reserve. When comparing pregnancy rates based on these data, they should also evaluate the data according to the pregnancy rate per oocyte harvest.

Similar data were presented at the 2012 American Society for Reproductive Medicine (ASRM) meeting in women aged ≤35. The live delivered pregnancy rate per oocyte harvest (age ≤35) were 74.9%) 1226/1719) for women with normal reserve *vs.* 37.8% (144/380) for those with diminished oocyte reserve. However, the live delivered pregnancy rate per transfer was only 15% less for the group with diminished oocyte reserve.

References

[1] Muasher S.J., Eohninger S., Simonetti S., Matta J., Ellis L.M., Liu H.C., *et al.*: "The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome". *Fertil. Steril.*, 1988, *50*, 298.

[2] Fenichel P., Grimaldi M., Olivero J.F., Donzeau M., Gillet J.Y., Harter M.: "Predictive value of hormonal profiles before stimulation for in vitro fertilization". *Fertil. Steril.*, 1989, *51*, 845.

[3] Tanbo T., Dale P.O., Abyholm T., Stokke K.T.: "Follicle-stimulating hormone as a prognostic indicator in clomiphene citrate/human menopausal gonadotropin-stimulated cycles for in vitro fertilization". *Hum. Reprod.*, 1989, *4*, 647.

[4] Roberts J.E., Spandorfer S., Fasouliotis S.J., Kashyap S., Rosenwaks Z.: "Taking a basal follicle-stimulating hormone history is essential before initiating in vitro fertilization". *Fertil. Steril.*, 2005, *83*, 37.

[5] Nasseri A., Mukherjee T., Grifo J.A., Noyes N., Krey L., Copperman A.B.: "Elevated day 3 serum follicle stimulating hormone and/or estradiol may predict fetal aneuploidy". *Fertil. Steril.*, 1999, *71*, 715.

[6] Check J.H., Summers-Chase D., Yuan W., Horwath D., Wilson C.: "Effect of embryo quality on pregnancy outcome following single embryo transfer in women with a diminished egg reserve". *Fertil. Steril.*, 2007, *87*, 749.

[7] Check J.H., Nazari P., Check M.L., Choe J.K., Liss J.R.: "Prognosis following in vitro fertilization-embryo transfer (IVF-ET) in patients with elevated day 2 or 3 serum follicle stimulating hormone (FSH) is better in younger vs older patients". *Clin. Exp. Obstet. Gynecol.*, 2002, *29*, 42.

[8] Check J.H.: "Mild ovarian stimulation". *J. Assist. Reprod. Genet.*, 2007, *24*, 621.

[9] Check J.H.: "Minimal and natural stimulation for IVF". *In:* Bin W. (ed). *Advances in embryo transfer.* Rijeka, Croatia: InTech, 2012, 21.

[10] Check J.H., Slovis B.: "Choosing the right stimulation protocol for in vitro fertilization-embryo transfer in poor, normal, and hyperresponders". *Clin. Exp. Obstet. Gynecol.*, 2011, *38*, 313.

[11] Check J.H.: "Understanding the physiology of folliculogenesis serves as the foundation for perfecting diagnosis and treatment of ovulatory defects". *Clin. Exp. Obstet. Gynecol.*, 2012, *39*, 273.

[12] Baart E.B., Martini E., Elkemans M.J., Van Opstal D., Beckes N., Verhoeff A., *et al.*: "Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human pre-implantation embryos: a controlled trial". *Hum. Reprod.*, 2007, *22*, 980.

[13] Katsoff B., Check J.H., Choe J.K., Wilson C.: "Editorial article: A novel method to evaluate pregnancy rates following in vitro fertilization to enable a better understanding of the true efficacy of the procedure". *Clin. Exp. Obstet. Gynecol.*, 2005, *32*, 213.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com