The influence of high responders on the outcome of intracytoplasmic sperm injection

Mohamad El Saed Ghanem (MD), Ehsan Refaie (MD)
Department of Obstetrics & Gynecology, Mansoura Faculty of Medicine

Abstract

Objective: Evaluate the impact of high number of retrieved oocytes on the outcome of ICSI cycles.

Material and methods: A retrospective study performed in Mansoura integrated fertility center. We reviewed 1566 ICSI cycles and compared the patient, cycle features and cycle outcome of ICSI for high responders (> 15 retrieved oocytes corresponding to > 75th percentile) and normal responders (5- 15 oocytes between 25th and 75th percentile). Results: High responders were significantly younger and thinner than the normal responders. The oocyte maturation was significantly lower in high responders. Fertilization rate, Implantation rate and the clinical pregnancy rate revealed significant differences being lower in high responders.

Conclusion: High oocyte yield is detrimental to ICSI outcome. It does not only affect the maturation of oocyte but also affects the fertilization, the implantation and the clinical pregnancy rate.

Key word: High responders, ICSI, implantation, pregnancy rate.

Introduction

The relationship between the number of oocytes retrieved and pregnancy rate following IVF/ICSI cyles has shown conflicting results. Meniru et al 1997 (1), proved that pregnancy rates increased with an increasing number of oocytes. Kably et al 2008 (2), concluded that the best pregnancy rates being obtained with number of oocytes of 10–15. Molina et al 2008 (3) found that 7–16 is the optimal number of oocyte to achieve pregnancy. Hamoda et al 2010 (4) suggested that the numbers of embyos frozen after a fresh IVF cycle are not enhanced by retrieving > 18 eggs.

Bosch and coworkers (2011) (5), concluded that a maximum of 8-9 retrieved mature oocytes is enough to achieve the highest cumulative pregnancy rates and that any protocol of stimulation that results in an increased number of good quality oocytes per cycle will not lead to higher chance for a patient to become pregnant. Sunkara and associates (2011) (6), found that an egg number of around 15 eggs gave the best chance of live birth and there was a decline with 20 or more eggs. Many investigators (7- 9) found that 15 eggs is the optimal number to maximize treatment success while minimizing the risk of OHSS with high number of oocytes > 18. This is a retrospective study to evaluate the impact of high number of retrieved oocytes on the outcome of ICSI cycles; implantation rate and clinical pregnancy rate.

Materials and Methods

A retrospective analysis of patient characteristics, measures of ovarian response, and rates of implantation and pregnancy for first cycles in patients < 35 years of age who underwent ICSI, between October 2006 and October 2011. We compared the outcome of ICSI for high responders (> 15 retrieved oocytes corresponding to > 75th percentile) and normal responders (5- 15 oocytes between 25th and 75th percentile) as defined by Simon et al [10]. All patients underwent ovarian downregulation using leuprolide acetate. Once down regulation was confirmed, leuprolide acetate was decreased and gonadotropin (follicle stimulating hormone or human menopausal gonadotropin) was started at a dose of three to four ampoules per day (75 IU each). The ovarian response was assessed by ultrasound and serum E2 level on the 5th day of gonadotropin administration, and serially thereafter. HCG (10,000 IU) was administered intramuscularly when lead follicles reached 18 mm in diameter. A serum E2 (peak E2) level was obtained on the day of HCG administration. Ultrasound-guided transvaginal oocyte retrieval was performed 34–36 hours later under intravenous sedation. Intracytoplasmic sperm injection was carried out. Cleavage stage embryos were transferred 72 hours or blastocysts after 5 days of follicular aspiration. Pa-

Corresppondence
Ehsan Refaie, MD
Department of Obstetrics & Gynecology,
Mansoura Faculty of Medicine,
Mansoura, Egypt
Tel. 0020502267014
Fax. 0020502267016
Email. refaie_ehsan@yahoo.com

tients undergoing IVF-ET received transvaginal progesterone (400 mg/day) for luteal support starting on the day of oocyte retrieval. Pregnancies were documented by measuring serum hCG 14 days after embryo transfer. At 7 weeks after embryo transfer an ultrasound was performed and the presence of an intrauterine sac confirmed clinical pregnancy.

Statistical analysis

This was performed by using the statistical package for social science program (SPSS) version "16". The qualitative data were presented as frequency and percentages. The quantitative data were examined by using Kalmogrov-Smirnov test to test for normal distribution of the data and when parametric, expressed as mean and standard deviation. Student t test was used, to test for difference in normally distributed quantative data between the two groups. Mann-Whitney-μ test was used for comparison between two groups when data are not normally distributed. Significance was considered when P value less than 0.05.

Results

Table (1) and (2) compare ICSI outcome of normal responder and high responder groups. The high responders were significantly younger (26.45±4.24 vs 28.84±4.49) with significant lower BMI (30.5 ±5.09 vs 32.16±5.66). While causes of infertility, the basal FSH and the total doses of gonadotropins were insignificant in both groups. Inspite of the significant higher number of the retrieved oocytes and the available embryos in the high responders group, they show significant lower mature oocyte yeild (80.69699 ±15.2 vs 84.34809 ±16.5), significant lower fertilization rate (77.70 ±21.8 vs83.21027±20.1) and significant lower implantation rate (10.6 vs13.8). Also the clinical pregnancy rate was significant lower in the high responders when compared to normal responders (31.4 vs. 40.6). Table 3 summarized the ovarian responses, the number of oocytes retrieved and the percentage of blastocyst transfer between pregnant and non-pregnant women. The number of retrieved oocytes were significantly lower when comparing pregnant and non-pregnant groups. Blastocyst transfer was significantly higher in the pregnant group (29.98% vs 9.58%).

Table1: clinical and cycle features of normal compared to high responder

	Normal responder (n=1324)	High responder (n=242)	p
Age	28.84±4.494	26.45±4.248	<0.001
BMI	32.16±5.66	30.5 ±5.09	<0.001
Basal FSH	7.44±4.392	8.01± 4.387	0.063
Indications	N %	N %	p
Male Factor **Unexplained** **Tuba Factorl**	728 54.75% 132 9.96% 464 35.04%	164 67.7% 24 9.91. % 54 22.31%	·0.6641
Total Stim. Dose(Amp)	31.2±5.5	30.9 ±7.2	0.53
HP-FSH Total Dose(Amp)	14.3±4,4	14.2±5.2	0.77
% Maturity (M±Sd)	84.34809 ±16.5	80.69699 ±15.2	0.0007
Source Of Sperm	N %	N %	p
Ejaculate **Testicular biopsy**	1074 81.11 250 18.88	189 78.09 53 21.9	0.69
Fertilization % ((M±SD)	83.21027±20.1	77.70 ±21.8	0.0002
Embryoes Transferred(n) (M±Sd)	3.30 ±0.803	3.39± 0.679	0.065
Grade A T(n)(M±Sd)	2.43±0.97	2.61 ±0.95	0.006
CES Ceavage Embryo (M±Sd)	69.90 ±37.071	79.31 ± 35.301	. 0.001
Blastocyst T(%)	516 38.97%	121 50%	0.36

Table 2: Cycle outcome in normal compared to high responders

	Normal responder			High responder			P
	All cycles	Clev Et	Blst ET	All cases	Clev ET	Blst ET	
Transfers (n)	1324	1202	122	242	220	22	
Pregnancy (n)	538	468	70	76	68	8	
CPR(%)	40.6[a]	38.3[b]	57.3[c]	31.4[a]	30.9 [b]	36.3 [c]	[a] .008 [b] 0.028 [c] 0.01
IR (%)	13.8[d]	12.4[e]	30.07[f]	10.6[d]	9.09[e]	23.8[f]	[d]0.0009 [e]0.010 [f]0.285

Table 3: pregnant vs. non pregnant clinical and laboratory feature

	Pregnant (n=627)	Non pregnant (939)	P,
Age (years) (m±sd)	27.5±5.78	27.40±4.56	0.715
FSH (mIU/ml)(m±sd)	5.9 ±2.3	6.1±3.1	0.143
Retrieved eggs (m±sd)	14.9322034 ±4.09	17.01389 ±5.32	<0.001
MII eggs (m±sd)	13.15 ±3.7	14.86 ±5.36	<0.001
Total cleavage ET(m±sd))	3.4±0.58	3.4±0.59	<0.001
Cumulative embryo score of Cleavage Embro (m±sd)	92.31 ±30.33	90.20±26.9	0.158
Ratio of Blastocyst transfere (%)	188 (29. 98%)	90 (9.58%)	<0.001

Discussion

Since the first IVF-embryo transfer was carried out in 1978, the treatment of infertility has advanced significantly (11). The subsequent introduction of COS for multiple follicular developments significantly increased pregnancy rate (12). Such stimulation protocols have been refined to obtain an optimal number of oocytes and to maximize pregnancy rates (5). However, many controversies are still excisting.

In the present study the main causes of ICSI were male factor, tubal factor and unexplained infertility, while cases with PCOS and endometriosis were not encountered. The high responders were significantly younger with significant lower BMI when compared with normal responders, this in acordance with Hourvitz et al (2009) (13) and Bellver et al (2010) (14).

The retrieved oocytes in this series were significantly lower in pregnant when compared to non pregnant (14 vs 17 oocytes) (table 3). This is confirmatory to Kably et al (2008) (2) and Sunkara et al (2011) (6), who found that the best chance of live birth was associated with the number of eggs around 15 eggs and showed a decline with > 20 eggs.

In the present study the significant lower clinical pregnancy rate in high responders showed the affection of most steps in ICSI including the reduction of oocyte quality, fertilization rate and implantation rate (table 1- 2). These results are contradictory to some investigators who found that the main step to be influenced is the reduction in implantation rate and endometrial receptivity while the oocyte quality improved (9, 15- 22). Papanikolaou et al. (2009) (23), concluded that the theory of impaired oocyte/embryo quality in high responders is unlikely. On the other hand, Van der Gaast, 2006 (24), suggested that milder ovarian stimulation produce fewer but higher quality oocytes without compromising endometrial receptivity and implantation.

The lower implantation rate and clinical pregnancy rate and the deleterious outcome of high responders in ICSI cycles was the debate of many investigators giving the negative effect of high estradiol (10, 15, 22, 29) and progesterone levels on the day of hCG (30, 31, 32) as an explanation.

Valbuena et al 2001 (26) suggested that increasing levels of E2 are deleterious to embryonic implantation because they directly affect the embryo. Others concluded that the high E2 might be related to asynchronous endometrial development (27, 28). Ma et al 2003(29), found that the window of uterine receptivity remains open for an extended period at lower estrogen levels but rapidly closes at higher levels.

Bourgain and Devroey, 2003(33), found that the increase in progesterone has the potential to advance the endometrium, without influencing the embryo and lead to a state of asynchrony between embryo and endometrial dating. Still there is a great argue on the mechanism by which this negative effect occur. Further researches are ongoing to clarify this point.

The pregnancy rate in the present study significantly improved with blastocyst transfer, being transferred in 29.9% in the pregnant cases versus 9.5% in non pregnant cases (table 3). This is in accordance to Chen et al (2007) (34) and Papanikolaou et al (2009) (23), who suggested that blastocyst transfer on day 5 offer the endometrium time to recover from any negative effects of high peak E2 and progesterone levels.

Conclusion

It was concluded that high responders have negative impact on ICSI outcomes with low pregnancy rate. We recommend the use of mild stimulation protocol. Hoping to maximize the pregnancy rate not to maximize the number of oocytes that proved to be negatively associated with pregnancy beyond a certain levels.

References

1. Meniru GI, Craft IL. Utilization of retrieved oocytes as an index of the efficiency of superovulation strategies for in-vitro fertilization treatment. Hum Reprod 1997;12:2129-2132.
2. Kably Ambe A, Estevez Gonzalez S, Carballo Mondragon E, Dura´n Monterrosas L. Comparative analysis of pregnancy rate/captured oocytes in an in vitro fertilization program. Ginecol Obstet Mex 2008; 76:256–260. Spanish
3. Molina Hita Ma. del M, Lobo Martinez S, Gonzalez Varea, Montejo Gadea JM, Garijo Lopez E, Cuadrado Mangas C. Correlation between the number of oocytes and the pregnancy rate in IVF-ICSI cycles.Revista Iberoamericana de Fertilidad y Reproduccion Humana 2008; 25:153–159. Spanish
4. Hamoda H, Sunkara S, Khalaf Y, Braude P, El-Toukhy T. Outcome of fresh IVF/ICSI cycles in relation to the number of oocytes collected: a review of 4,701 treatment cycles. Hum Reprod 2010; 25:147.
5. Bosh E and Ezcurra D.Individualised controlled ovarian stimulation (iCOS): maximising success rates for assisted reproductive technology patients.Reproductive Biology and Endocrinology 2011, 9:82.
6. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles. Hum Reprod 2011; Advance Access, May 10, 2011
7. Lyons CA, Wheeler CA, Frishman GN, Hackett RJ, Seifer DB, Haning RVJr. Early and late presentation of the ovarian hyperstimulation syndrome: two distinct entities with different risk factors. Hum Reprod 1994; 9:792–799.
8. Verwoerd GR, Mathews T, Brinsden PR. Optimal follicle and oocyte numbers for cryopreservation of all embryos in IVF cycles at risk of OHSS. Reprod Biomed Online 2008; 17:312–317.
9. Lee KH, Kim SH, Jee BC, Kim YJ, Suh CS, Kim KC, Lee WD. Comparison of clinical characteristics between early and late patterns in hospitalized patients with ovarian hyperstimulation syndrome. Fertil Steril 2010; 93:2274–2280.
10. Simon C, Cano F, Valbuena D, Remohi J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. Hum Reprod 1995; 10:2432–7.
11. Steptoe PC, Edwards RG: Birth after the reimplantation of a human embryo. Lancet 1978, 12:366.
12. Trounson AO, Leeton JF, Wood C, Webb J, Wood J: Pregnancies in humans by fertilization in vitro and embryo transfer in the controlled ovulatory cycle. Science 1981, 212:681-682.
13. Hourvitz A, Machtinger R, Maman E, Baum M, Dor J, Levron J: Assisted reproduction in women over 40 years of age: how old is too old? Reprod Biomed Online 2009, 19:599-603.
14. Bellver J, Ayllón Y, Ferrando M, Melo M, Goyri E, Pellicer A, Remohí J, Meseguer M: Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertil Steril 2010, 93:447-454.
15. Mitwally MF, Bhakoo HS, Crickard K, Sullivan MW, Batt RE, Yeh J.Estradiol production during controlled ovarian hyperstimulation correlates with treatment outcome in women undergoing in vitro fertilization-embryo transfer. Fertil Steril 2006; 86:588–596.
16. Kyrou D., Popovic-Todorovic B., Fatemi H.M1, Bourgain C, Haentjens P., Van Landuyt L., and. Devroey P Does the estradiol level on the day of human chorionic gonadotrophin administration have an impact on pregnancy rates in patients treated with rec-FSH/GnRH antagonist? Human Reproduction, Vol.24, No.11 pp. 2902–2909, 2009
17. Joo BS, Park SH, An BM, Kim KS, Moon SE, Moon HS. Serum oestradiol levels during controlled ovarian hyperstimulation influence the pregnancy outcome of in vitro fertilization in a concentrationdependent manner. Fertil Steril 2010; 93:442–446.
18. Ng EHY, Yeung WS, Lau EYL, So WWK, Ho PC. High serum estradiol concentrations in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent frozenthawed embryo transfer cycles. Hum Reprod 2000; 15: 250–5.
19. Pena JE, Chang PL, Chang LK, Zeitoun K, Thornton MH II, Sauer MV. Supraphysiological estradiol levels do not affect oocyte and embryo quality in oocyte donation cycles. Hum Reprod 2002; 17:83–7.
20. Ng EHY, Lau EYL, Yeung WSB, Ho PC. Oocyte and embryo quality in patients with excessive ovarian response during in vitro fertilization treatment. J Assist Reprod Genet 2003; 20: 186–91.
21. Saadat P, Boostanfar R, Slater CC, Tourgeman DE, Paulson RJ. Accelerated endometrial maturation in the luteal phase of cycles utilizing controlled ovarian hyperstimulation: impact of gonadotropinreleasing hormone agonists versus antagonists. Fertil Steril 2004; 82:167–71.
22. **Wu Cheng-Hsuan, Kuo Tsung-Cheng, Wu Hsin-Hung, Yeh Guang-Peng and ,Tsa Horng-Der** High Serum Estradiol Levels are not Detrimental to In Vitro Fertilization Outcome Taiwanese Journal of Obstetrics and Gynecology : 46, 54-59 2007
23. Papanikolaou E, Kolibianakis E, Pozzobon C, Tank P, Tournaye H,Bourgain C, Van Steirteghem A, Devroey P. Progesterone rise on the day of human chorionic gonadotropin administration impairs pregnancy outcome in day 3 single-embryo transfer, while has no effect on day 5 single blastocyst transfer. Fertil Steril 2009; 91:949–952.
24. **van der Gaast MH, Eijkemans MJC, van der Net JB, de Boer EJ, Burger CW , van Leeuwen FE, Fauser BCJM , and Macklon NS** Optimum number of oocytes for a successful first IVF treatment **cycle Reproductive BioMedicine Online** : **13,** 476-480 , 2006,
25. Pellicer A, Valbuena D, Cano F, Remohi J, Simon C. Lower implantation rates in high responders: evidence for an altered endocrine milieu during the preimplantation period. Fertil Steril 1996; 65:1190 –5.
26. Valbuena D, Martin J, de Pablo JL, Remohi J, Pellicer A, Simon C. Increasing levels of estradiol are deleterious to embryonic implantation because they directly affect the embryo. Fertil Steril 2001; 76:962–8.
27. Basir GS, O WS, Ng EHY, Ho PC. Morphometric analysis of peri-implantation endometrium in patients having excessively high estradiol concentrations after ovarian stimulation.Hum Reprod 2001; 16:435–40.
28. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Ovulation induction disrupts luteal phase function. Ann N Y Acad Sci 2001; 943:55–63.
29. Ma WG, Song H, Das SK, Paria BC, Dey SK. Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation. PNAS 2003; 100:2963–8.
30. Bosch E, Labarta E. Crespo J, Simo´ C. n, Remohı´ J., Jenkins J.,and A. Pellicer: Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Hum Reprod 2010; 25, No.8 pp. 2092–2100.
31. Van Vaerenbergh I, Van Lommel L, Ghislain V, In't Veld P, Schuit F, Fatemi HM, Devroey P, Bourgain C. In GnRH antagonist/rec-FSH stimulated cycles, advanced endometrial maturation on the day of oocyte retrieval correlates with altered gene expression. Hum Reprod 2009; 24:1085–1091.
32. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 2006; 21:3217-3227.
33. Bourgain C, Devroey P. The endometrium in stimulated cycles for IVF.Hum Reprod Update 2003; 9: 515–522.
34. **Chen QJ, Sun XX, Li L, Gao XH, Wu Y, Gemzell-Danielsson K, Cheng LN** Effects of ovarian high response on implantation and pregnancy outcome during controlled ovarian hyperstimulation (with GnRH agonist and rFSH). Acta Obstet Gynecol Scand. 2007; 86(7):849-54.