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Oocyte quality in patients with severe ovarian hyperstimulation syndrome

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Objective: To study the oocyte quality in patients with ovarian hyperstimulation syndrome (OHSS).

Design: Retrospective study.

Setting: The Egyptian IVF-ET Center.

Patient(s): Forty-two patients who developed severe OHSS (group A) were studied for the mean number of oocytes retrieved, percentage of high-quality oocytes, embryo quality, and fertilization, implantation, and pregnancy rates; these patients were compared with an age-matched control group who did not develop OHSS (group B; $n = 183$) after superstimulation for IVF or intracytoplasmic sperm injection.

Intervention(s): In vitro fertilization and ICSI.

Main Outcome Measure(s): Fertilization and pregnancy rates.

Result(s): In group A, the mean number of oocytes retrieved was significantly higher, whereas the percentage of high-quality oocytes and the fertilization rate were significantly lower than that in group B. There were no statistically significant differences in the quality of embryos transferred or the implantation or pregnancy rate between the groups. The percentage of high-quality oocytes and the fertilization rate were significantly lower in patients with polycystic ovaries (PCO) in both groups.

Conclusion(s): The inferior quality and maturity of oocytes in OHSS reduced the fertilization rate but did not affect the quality or the number of embryos transferred or the pregnancy rate. The effect on oocyte quality could be due to the prevalence of PCO in this group of patients. (Fertil Steril® 1997;68:1017–21. © 1997 by American Society for Reproductive Medicine.)

Key Words: Oocyte maturity, oocyte quality, OHSS, pregnancy rate, PCO

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication of ovulation induction by gonadotropins (1). It was reported previously that OHSS is usually associated with high levels of estradiol on the day of hCG administration (2) and a large number of follicles visualized by ultrasound (3). The implications of these factors on the quality and maturity of oocytes, on the fertilization rate, and on the pregnancy rate (PR) are not clearly known. The objective of the present report was to study the oocyte quality, fertilization rate, and PR in patients with severe OHSS. To the best of our knowledge, this is the first study in the literature to look at these indices in patients with OHSS.

MATERIALS AND METHODS

We retrospectively studied 42 patients (group A) who developed severe OHSS during ovulation induction for IVF or intracytoplasmic sperm injection (ICSI) during a period of 6 years. The controls were an age-matched group of 183 patients who were stimulated for 183 consecutive cycles of IVF or ICSI and reached the ET stage during the same period but did not develop OHSS (group B).

All patients received our standard long protocol of

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Table 1 Patient Characteristics in Both Groups

Characteristic	OHSS (n = 42)	Control (n = 183)	P value
Mean age (y)	29.8 ± 6.3	32.1 ± 7.8	NS
Mean duration of infertility (y)	6.2 ± 3.1	6.7 ± 2.2	NS
No. with PCO pattern	31 (73.8)	26 (14.2)	<0.001
No. with menstrual disorders*	25 (59.5)	21 (11.5)	<0.001
Mean estradiol level (pg/mL) †	6,700 ± 2,350	2,640 ± 1,710	<0.001

Note: Data are means ± SD or n (%). NS = not significant.
* Amenorrhea or oligomenorrhea.
† Determined on day of hCG administration.

GnRH agonist analogue (GnRH-a) and hMG, which was described before (4). An ultrasound pattern of polycystic ovaries (PCO) and a history of menstrual irregularities were recorded in both groups. Patient characteristics and data on stimulation are shown in Table 1.

The diagnosis of severe OHSS was made using the classification of Golan et al. (5). All patients in group A had ovarian enlargement of >10 cm in diameter, ascites, dyspnea, and abdominal pain. Four patients had hydrothorax. All patients received our routine treatment of severe OHSS, including transvaginal ascitic fluid aspiration and intensive intravenous fluid therapy (6).

Oocyte maturity was diagnosed by extrusion of the first polar body in cases of ICSI and by the appearance of the cumulus-corona cell complex in IVF. Expanded, fluffy cumulus cells and expanded corona cells denoted maturity (7). Oocytes were considered to be of high quality if they showed signs of maturity and were round and even in shape, with an extended corona radiata and cumulus mass and no granular cytoplasm (8). They also were characterized by the absence of aggregations of organelles and vacuoles (9).

Group A was divided into two subgroups. In group A1 (n = 31), PCO was diagnosed by ultrasound. The ovaries showed sonographic features of small, peripherally placed follicles with an echo-dense stroma known as the necklace sign (10). Twenty-five patients in this subgroup had menstrual irregularities in the form of amenorrhea or oligomenorrhea. In group A2 (n = 11), there were no ultrasound manifestations of PCO or menstrual disturbances. Group B (n = 183) patients also were divided according to the same criteria into two subgroups. In group B1 (n = 26), PCO was diagnosed by ultrasound; this group included 21 patients with oligomenorrhea or amenorrhea. In group B2 (n = 157), there were no ultrasound manifestations of PCO.

The quality of the embryos was assessed on the basis of morphologic appearance (11). Clinical pregnancy was diagnosed by the rise of β-hCG and the appearance of an intrauterine sac by ultrasound.

Comparisons between group means were done using the Student's t-test, analysis of variance was used to compare more than two groups, and comparison between proportions was done using the χ^2 test. $P < 0.05$ was considered statistically significant.

This study was conducted with institutional review board approval.

RESULTS

Table 2 shows the total number of oocytes retrieved, the percentage of high-quality oocytes, the fertilization rate per retrieved oocyte, the mean number of embryos transferred, the implantation rate, and the PR in groups A and B. Significantly more oocytes were retrieved in group A than in group B, but there was a lower percentage of high-quality oocytes and a lower fertilization rate in group A.

Cryopreservation was done at the pronuclear stage. In group A, 174 embryos cleaved (83%), as compared with 1,748 (88%) in group B.

There were no statistically significant differences in the number of cleaved embryos per transfer, the implantation rate, or the PR between groups A and B. There was no statistically significant difference in grade-one embryos per transfer between group A and group B.

Table 3 shows the total number of oocytes, oocyte quality, implantation rate, and PR in subgroups A1, A2, B1, and B2. There was a highly significant lower percentage of high-quality oocytes and fertilization rates in subgroups A1 and B1 as compared with A2 and B2. There was no statistically significant difference in the oocyte quality or fertilization rate between subgroups A1 and B1. There were no statistically significant differences in the mean number of

Table 2 Results of Treatment for Patients With OHSS and Controls

Variable	OHSS (Group A) (n = 42)	Control (Group B) (n = 183)	P value
No. of oocytes retrieved	1,068	2,365	
Mean no. of oocytes per puncture	25 ± 8.5	12.9 ± 6.4	<0.001
No. of high-quality oocytes	682 (63.9)	1,791 (85.7)	<0.001
No. of fertilized oocytes	444 (41.6)	1,373 (58.1)	<0.001
No. of cryopreserved embryos	234	522	
Mean no. of embryos per transfer	3.9 ± 1.1	3.9 ± 1.3	NS
No. of clinical pregnancies	13 (31)	60 (32.8)	NS
Implantation rate (%)	11	11.4	NS
No. of miscarriages	4 (30.8)	12 (20)	NS

Note: Data are means ± SD or n (%), except as noted. NS = not significant.

Table 3 Results of Treatment in Subgroups A1, A2, B1, and B2

Variable	A1 (n = 31)	A2 (n = 11)	B1 (n = 26)	B2 (n = 157)	P value
Total no. of oocytes	837	231	478	1,887	
Mean no. of oocytes per puncture	27 ± 8.1*	21 ± 6.6	18.4 ± 7.8	12 ± 4.4*	<0.001
No. of high-quality oocytes	502 (60)	180 (78)*	296 (62)	1,495 (79.2)*	<0.001
No. of fertilized oocytes	301	143	205	1,168	
Percent with fertilization per puncture	36	62*	43	61.9*	<0.001
No. of cryopreserved embryos	146	88	69	453	
Mean no. of embryos per transfer	3.9 ± 1.2	3.9 ± 1.1	3.9 ± 1.2	3.9 ± 1.3	NS
Mean no. of grade-one embryos per transfer	1.9 ± 0.9	2 ± 1	1.9 ± 1.1	1.8 ± 0.9	NS
Percentage of women who got pregnant	9 (29)	4 (36)	8 (30.7)	52 (33.1)	NS
Implantation rate (%)	10.7	11.6	11.9	11.2	NS

Note: Data are means ± SD or n (%), except as noted. NS = not significant.
* Significantly different.

embryos per transfer, the implantation rate, or the PR among the four subgroups. The mean number of grade-one embryos per transfer did not differ significantly among the four subgroups.

DISCUSSION

There is a general consensus in the literature that embryo quality correlates with implantation rate and PR (12). The quality of embryos in IVF is dependent upon the quality of oocytes, fertilization, and the laboratory conditions for in vitro culture (13). In the present study, the same stimulation protocol and the same culture conditions were used for all patients in both groups. Because there was no statistically significant difference in the mean age between the groups, it is assumed that the fertilization rate, quality of embryos, and implantation rate will depend upon the quality of oocytes.

In the present study, the total numbers of high-quality oocytes and fertilized oocytes were higher in OHSS cycles, whereas the percentage of mature oocytes and the fertilization rate per retrieved oocyte were significantly lower in the OHSS group. This may represent recruitment of more divergent cohorts of follicles and does not suggest an overall decrease in oocyte quality. It seems that the lower fertilization rate in this study is related to the lower percentage of mature and good-quality oocytes.

Van Blerkom (9) described an approach to oocyte evaluation that associated oocyte morphology with developmental outcome. Oocytes with vacuoles may fertilize but rarely develop beyond the early cleavage stages. Gregory et al. (14) showed a direct correlation between the activity of the cumulus-corona complex and fertilization and implantation rates. It also was reported that the primary explanation for the declining implantation ability of embryos with advancing age is low oocyte quality (15).

Patients with severe OHSS usually have a larger number of oocytes and a higher estradiol level (6). In the present study, both the mean number of oocytes and the mean estradiol levels were significantly higher in the OHSS group than in the control group. It is not clear whether the extremely high levels of estradiol had any effect on the quality of the oocytes or the lower fertilization rate in this group. Our data showed no statistically significant difference in the mean number or quality of embryos transferred between the groups. This suggests that the lower fertilization rate was compensated for by the larger number of oocytes. It is possible that high-quality embryos result only from fertilization of good-quality oocytes, and because the percentage of good-quality oocytes was lower in the OHSS group, the final number of good-quality embryos was not different between the groups.

The implantation rates and PRs were not significantly different between the groups. This may support the finding that the quality of the transferred embryos was not different between the groups. It also seems that the very high levels of estradiol in the OHSS group did not affect the implantation rate or endometrial receptivity. This is supported by previous work that reported high PRs in patients with severe OHSS (6). However, these data are contradictory to previous reports that suggested that superphysiologic levels of estradiol may decrease endometrial receptivity (16, 17). It also was reported that a very high oocyte retrieval rate was associated with lower fertilization and implantation rates in women treated with GnRH and hMG (18).

In the present study, 31 patients (74%) in group A were diagnosed as having PCO, compared with only 26 patients (14.2%) in group B. This significant prevalence of PCO in group A is probably the most important predisposing factor for the development of OHSS and the negative effect on the oocyte maturity and fertilization rate in this group. This was confirmed further by comparing the data of groups

A1 and B1, which showed that the effect on oocyte quality and fertilization rate was due to PCO rather than OHSS. It was reported previously that patients with PCO (1) and ovulatory causes of infertility (18) were vulnerable to the development of OHSS after stimulation by hMG. Smitz et al. (2) reported that 8 of 10 patients with severe OHSS were hyperandrogenic. Aboulghar et al. (19) reported that PCO was present in all 18 patients who developed severe OHSS.

We believed that group A could be classified into high responders (A2), in whom there was a high estradiol level and a large number of big follicles; the mean number of oocytes retrieved was significantly lower than in PCO, and the percentage of mature and good-quality oocytes was significantly higher than in the PCO group (A1). The fertilization rate was higher in this subgroup; however, there was no difference in the quality of embryos to be transferred. In this subgroup, the incidence of severe OHSS tends to be less than in the PCO subgroup, and if the syndrome develops, it usually runs a milder course.

Blankstein et al. (3) reported that patients with PCO had more follicles of all sizes when compared with the control group, most prominently with respect to the medium-size and small follicles. This may explain the lower percentage of mature oocytes and the higher percentage of poor-quality oocytes in PCO. It is generally recognized that oocytes from relatively immature follicles have a lower fertilization rate than those from preovulatory follicles (20).

Several studies have compared the results of IVF in patients with PCO and in a control group that consisted of age-matched patients who underwent IVF-ET during the same study period by an identical ovarian stimulation protocol (21, 22). The higher incidence of failure of fertilization suggested that the oocytes obtained in patients with PCO were of reduced quality, with resultant poor fertilizing potential (23). Some characteristic endocrine disorders in patients with PCO, such as increased androgen production in ovaries and elevated tonic LH secretion during the follicular phase, may reduce the success rate of IVF. Elevated serum LH stimulates the theca cells to increase the synthesis and release of androgens, which might exert an atretic effect on the growing follicles (24).

It also was reported (22) that there was a lower PR per follicle aspiration in patients with PCO and that the incidence of failure of fertilization was significantly higher in a PCO subgroup, thus reflecting the reduced quality of the oocytes. Cano et al. (25) described a group of patients with PCO who had lower fertilization rates and embryos that did not implant. These findings may provide an explanation why patients with PCO have lower pregnancy potential during in vivo stimulation protocols.

In conclusion, the present work has shown that in patients with severe OHSS, the quality and maturity of the oocytes and the fertilization rates are significantly lower than in the control group, yet this did not affect the quality and the number of the transferred embryos or the PR. The inferior oocyte quality in patients with OHSS is probably due to the high prevalence of PCO in these patients.

REFERENCES

1. Rizk B, Aboulghar MA. Modern management of ovarian hyperstimulation syndrome. Hum Reprod 1991;6:1082–7.
2. Smitz J, Camus M, Devroey P, Erad P, Wisanto A, Van Steirteghem AC. Incidence of severe ovarian hyperstimulation syndrome after GnRH agonist/HMG superovulation for in vitro fertilization. Hum Reprod 1990;5:933–7.
3. Blankstein J, Shalev J, Saadon T. Ovarian hyperstimulation syndrome: prediction by number and size of preovulatory ovarian follicles. Fertil Steril 1987;47:597–602.
4. Aboulghar MA, Mansour RT, Serour GI, Amin YM. The prognostic value of successful in vitro fertilization in subsequent trials. Hum Reprod 1994;9:1932–4.
5. Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv 1989;44:430–9.
6. Aboulghar MA, Mansour RT, Serour GI, Sattar MA, Amin YM, Elattar I. Management of severe ovarian hyperstimulation syndrome by ascitic fluid aspiration and intensive intravenous fluid therapy. Obstet Gynecol 1993;81:108–11.
7. Wolf DP. Oocyte quality and fertilization. In: Wolf DP, editor. In vitro fertilization and embryo transfer: a manual of basic techniques. New York: Plenum Press, 1988:129.
8. Veeck LL. Extracorporeal maturation: Norfolk, 1984. Ann NY Acad Sci 1985;442:357–67.
9. Van Blerkom J. Human oocyte maturation and fertilization I and II. In: Course XI: contemporary methods of sperm, oocyte, and embryo morphology assessments. Montreal: American Fertility Society, 1993:121–33.
10. Navot D, Bergh PA, Laufer N. Ovarian hyperstimulation syndrome in novel reproductive technologies: prevention and treatment. Fertil Steril 1992;58:249–61.
11. Erenus M, Zouves C, Rajamahendran P, Leung S, Fluker M, Gomel V. The effect of embryo quality on subsequent pregnancy rates after in vitro fertilization. Fertil Steril 1991; 56:707–10.
12. Roseboom TJ, Vermeiden JPW. Evaluation of embryo scoring systems and their value in predicting in vitro fertilization outcome. Assist Reprod Rev 1995;5:53–9.
13. Mesrogli M, Nitsche UDH, Degenhardt F, Dieterle S, Scholosser HW. Rate of early abortion after in vitro fertilization and embryo transfer. Geburtshilfe Frauenheilkd 1991;51:688–93.
14. Gregory L, Booth AD, Wells C, Walker SM. A study of the cumulus corona cell complex in in vitro fertilization and embryo transfer; a prognostic indicator of the failure of implantation. Hum Reprod 1994;9:1308–17.
15. Hull MGR, Fleming CF, Hughes AO, McDermott A. The age-related decline in female fecundity: a quantitative controlled study of implanting capacity and survival of individual embryos after in vitro fertilization. Fertil Steril 1996;65:783–90.
16. Paulson RJ, Sauer MV, Lobo RA. Factors affecting embryo

implantation after human in vitro fertilization: a hypothesis. Am J Obstet Gynecol 1990;163:2020–3.
17. Forman RG, Eychenne B, Nessmann C, Frydman R, Robel P. Assessing the early luteal phase in in vitro fertilization cycles: relationships between plasma steroids, endometrial receptors, and endometrial histology. Fertil Steril 1989; 51:310–6.
18. Pellicer A, Ruiz A, Castellvi RM, Calatayud C, Ruiz M, Tarin JJ, et al. Is the retrieval of high number of oocytes desirable in patients treated with gonadotrophin-releasing hormone analogues (GnRHa) and gonadotrophins? Hum Reprod 1989;4:536–40.
19. Aboulghar MA, Mansour RT, Serour GI, Elattar I, Amin Y. Follicular aspiration does not protect against the development of ovarian hyperstimulation syndrome. J Assist Reprod Genet 1992;9:238–92.
20. MacDougall MJ, Tan SL, Balen A, Jacobs HS. A controlled study comparing patients with and without polycystic ovaries undergoing in vitro fertilization. Hum Reprod 1993;8:233–7.
21. Urman B, Fluker MR, Ho Yuen B, Fleige-Zahrdka BG, Zouves CG, Moon YS. The outcome of in vitro fertilization and embryo transfer in women with polycystic ovary syndrome failing to conceive after ovulation induction with exogenous gonadotropins. Fertil Steril 1992;57:1269–73.
22. Homburg R, Feldberg D, Berkowitz D, Ashkenazi J, Levy T, Ban Rafael Z. In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. Fertil Steril 1993;60:858–63.
23. Kodama H, Fukuda J, Karube H, Matsui T, Shimizu Y, Tanaka T. High incidence of embryo transfer cancellations in patients with polycystic ovarian syndrome. Hum Reprod 1995;10:1962–7.
24. Billig H, Furuta I, Hsueh AJW. Estrogen inhibits and androgen enhances ovarian granulosa cell apoptosis. Endocrinology 1993;133:2204–12.
25. Cano F, Garcia-Velasco JA, Millet A, Remohi J, Simon C, Pellicer A. Oocyte quality in polycystic ovaries revisited: identification of a particular subgroup of women. J Assist Reprod Genet 1997;13:254–61.