Oocyte Quality in Polycystic Ovaries Revisited: Identification of a Particular Subgroup of Women

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Purpose: *Our purpose was to assess the endocrine status of women with polycystic ovaries (PCO) undergoing IVF, and to compare oocyte quality with endocrine markers of the syndrome, in an attempt to define a subpopulation with poor quality oocytes.*

Methods: *This was a retrospective study. Patients were first endocrinologically analyzed: serum levels of androgens (T, androstenedione, DHEAS), FSH, and LH as well as glucose and insulin after an oral glucose tolerance test (OGTT) were recorded and are expressed as absolute values and area under the curve (AUC). Subsequently, they were followed over a 2-year period in which patients underwent several attempts of IVF as well as serving as oocyte donors. Patients were divided into three groups: group I (n = 4) was women who displayed embryos unable to implant in 15 IVF cycles and 10 ovum donation cycles in which they served as donors; group II (n = 16) was PCO patients in whom IVF (n = 38) and/or oocyte donation cycles (n = 42) resulted in pregnancies; and group III (n = 13) was IVF patients with normal appearance of the ovaries by ultrasound. The endocrine status was compared with the IVF results.*

Results: *There was no difference among groups in the endocrinological parameters tested, except for the OGTT which identified women in group I as having higher serum glucose and insulin levels than patients in groups II and III. Similarly, the OGTT showed higher serum glucose values in group II compared to group III. Women in group I were also obese. Patients in group III were older than PCO patients and needed more gonadotropins to reach an ovarian response which resulted in a reduced number of oocytes retrieved. Fertilization was also impaired in group I, in which no pregnancy was recorded.*

Conclusions: *This study shows that there is a particular subgroup of PCO patients with lower fertilization rates and embryos unable to implant. These patients are obese and nonhyperandrogenic and show derangements of insulin secretion.*

KEY WORDS: polycystic ovary; oocyte quality; insulin resistance; in vitro fertilization; insulin; glucose.

INTRODUCTION

Several reports have addressed the outcome of IVF in women with classical polycystic ovary syndrome (PCOS) (1,2) as well as patients with polycystic-appearing ovaries (PCO) by ultrasound (3). Unfortunately, any discussion on PCOS is hampered by the fact that there is no consensus definition of this, albeit frequent, clinical finding. While some leading groups require the presence of hyperandrogenism (clinical or biochemical) and chronic anovulation together with PCO (4), other authorized groups claim that the polycystic appearance of the ovaries can provide a unifying diagnostic criterion, which is certainly lacking (3,5). In addition, it has been shown that the incidence of PCO in normal subjects is as high as 23% (6). Menstrual disorders will be associated in 75% of the women, but the remaining 25% will have regular menses with a PCO pattern by ultrasound as the isolated finding (6). Regardless of the definition employed, it is quite obvious that women with such characteristics are usually treated in IVF programs, their actual performance being of concern.

Both types of patients are characterized by having a high response to gonadotrophins (1–3,7) resulting in a higher number of oocytes obtained. In patients with PCOS, reduced fertilization rates have been observed compared with normal subjects (1–3), a finding similar

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to that observed in high responders (8,9). When the ultrasound appearance alone has been employed to analyze the outcome, controversial findings have been reported regarding oocyte quality (3,7). Extending the experience to oocyte donation, however, has shown that oocytes displayed by women with PCOS (10,11) and PCO (7) and high responders (12) have chances of fertilization and implantation similar to those derived from endocrinologically normal ovaries. Moreover, it has been shown in vitro that the morphological appearance and metabolic activity of embryos from PCOS patients are similar to, if not better than, those observed in embryos of women with tubal disease (13).

Taking together all the above information, it has to be agreed that, as a general rule, oocyte quality is not affected in PCOS or PCO. However, those involved in the management of these patients know that some will systematically provide oocytes which will fertilize at lower rates and result in embryos unable to implant, either in their own uterus or in recipients. We have been interested in identifying this particular subgroup of patients. To this end, we analyzed the endocrine status of women with PCO. These patients have subsequently been followed for a 2-year period in which they have undergone several attempts of IVF as well as serving as oocyte donors. From this group of patients, a subgroup was identified as producing embryos unable to implant, but when becoming recipients of donated oocytes because of repeated IVF failure, all became pregnant in the first attempt at ovum donation, providing the rationale for the definition of these women as having oocytes of poor quality.

MATERIALS AND METHODS

Subjects and Ovarian Stimulation Protocols

Twenty infertile women were included in the present study defined as having PCO because of the morphological appearance of the ovaries by transvaginal ultrasound (14), regardless whether they had additional symptoms (oligomenhorrea, hirsutism, etc.) that could induce the case to be a PCOS. The ovary was defined as being polycystic if there were multiple (>5), small (2-to-8 mm) cysts arranged peripherically around a dense core of stroma and the appearance of these cysts had not changed in two ultrasound examinations separated by, at least, 15 days. They were retrospectively classified into two groups according to whether their oocytes yielded embryos which systematically failed to implant (group I; $n = 4$) or embryos able to implant in their own and/or recipient uteri (Group II; $n = 16$). Indications for IVF in group I were male infertility ($n = 1$), tubal infertility ($n = 1$), and failed induction of ovulation ($n = 2$). For group II, indications were male infertility ($n = 5$), tubal infertility ($n = 5$), endometriosis ($n = 1$) and failed induction of ovulation ($n = 5$). Male infertility was defined according to WHO criteria (15). The study was approved by the Ethical Committee of our Institution and written consent was obtained from all participants. Patients in group I underwent a total of 15 (mean, 3.8 ± 0.5) IVF cycles and served as donors in 10 cycles (mean, 2.8 ± 0.6). Women in group II underwent 38 (mean, 2.4 ± 0.4) IVF attempts and 42 (mean, 2.9 ± 0.7) ovum donation cycles.

The protocol for ovarian stimulation started by pituitary desensitization with daily subcutaneous administration of 1 mg leuprolide acetate (LA; Procrin; Abbott S.A., Madrid, Spain) and began, in the luteal phase of the menstrual cycle or coincidental with pill number 15 of an artificial cycle, oral contraceptives (Neogynona; Schering Spain, Madrid). Serum E_2 levels <60 pg/ml and negative vaginal ultrasonographic scans were used to define ovarian quiescence. On days 1 and 2 of ovarian stimulation, 2 ampoules/day hMG (Pergonal; Serono Laboratories, Madrid, Spain) was administered together with 2 ampoules of high-purity FSH (Neo-Fertinorm, Serono). On days 3, 4, and 5 of ovarian stimulation, 1 ampoule/day of each gonadotrophin preparation was administered to each patient. Beginning on day 6, hMG and FSH were administered on an individual basis according to serum E_2 and transvaginal ovarian ultrasound scans. The criteria for hCG administration (10,000 IU; Profasi; Serono) were the presence of two or more follicles >1.9 cm in greatest diameter, and serum E_2 levels >800 pg/ml. Leuprolide acetate and FSH/hMG injections were discontinued on the day of hCG administration. Oocyte retrieval was scheduled 36–38 hr after hCG injection. The luteal phase was supported with vaginal micronized P (400 mg/day; Utrogestan, Lab. Besins-Iscovesco, Paris, France). Implantation was defined as the presence of a gestational sac by transvaginal ultrasound. Four types of embryos were established, ranging from type 1 to 4 (8). Type 1 embryos were the best and were defined as round and well-shaped blastomeres without fragments.

Control Group

A group of 16 women (group III) with regular cycles and normal ultrasonographic appearance of the ovaries was recruited as controls from the IVF program. They

voluntarily accepted to have their basal gonadotropin and androgen levels tested as well as to undergo an oral glucose tolerance test (OGTT). The ovarian stimulation protocol has been described above. Only one patient agreed to donate oocytes. Thus, data concerning performance in ovum donation cycles were not available for comparison in the controls.

Protocol of Steroid Supplementation for Recipients

A total of 52 women entered the ovum donation program and received oocytes from the 20 PCO patients acting as donors. Indications for oocyte donation in the recipients of group I (n = 10) were menopause (n = 4), failed IVF (n = 3), and low response (n = 3). Recipients from group II (n = 42) entered the program because of premature menopause (n = 16), low response to gonadotropins (n = 19), and failed IVF (n = 7).The protocol of steroid replacement for patients with ovarian function began with daily subcutaneous administration of 1 mg LA in the secretory phase of the previous cycle. Hormonal replacement started on day 1 of the cycle with the administration of E_2 valerate (Progynova; Schering Spain, Madrid), 2 mg/day, on days 1 to 8; 4 mg/day from day 9 to day 11; and 6 mg/day from day 12 on. After 13 days of E_2 valerate administration, patients were ready to receive oocytes and they waited until such became available. In the case of spotting during E_2 valerate administration, 10 mg medroxyprogesterone acetate (MEP; Progevera; Schering Spain) was administered for 5 days, and a new cycle begun.

On the day of recovery of donated oocytes, 100 mg/day natural progesterone in oil was administered i.m. Embryo transfer was performed 48 hr following oocyte recovery using the vaginal route. The regimen of 6 mg/day EV and 100 mg/day P was maintained for 15 days, after which a urinary β-hCG analysis was performed. In the case of positive results, E_2 valerate was increased to 8 mg/day and P was maintained at the same dosage until day 100 of pregnancy.

Endocrine Evaluation of Patients

In eumenorrheic women, all basal blood sampling (FSH, LH, and androgens) was done during the first 4 days of the menstrual cycle. In women with menstrual disorders, blood was collected after MEP-induced menstrual bleeding. The OGTT was performed in the same phase of the cycle after overnight fasting and administration of an oral hypertonic glucose solution (75 g). Serum glucose and insulin were measured at 0, 30, 60, 90, and 120 min. Body mass index (BMI) was calculated according to the formula weight/height^2.

Serum E_2, FSH, LH, T, and androstenedione were measured employing commercially available RIA kits (bioMérieux, Charbonniéres les Bains, France). Insulin (CIC bio international, Gif-sur-Yvette, France) and DHEAS (Diagnostic Products Corporation, Los Angeles, CA) were also measured by RIA. Serum glucose was measured in an automatic analyzer employing an enzymatic-colorimetric assay (Gernon, Lindau, Germany). The inter- and intraassay coefficients of variation (CVs) for E_2 at a concentration of <40 pg/ml were 2.8 and 4.3%, respectively. For FSH at a concentation of 8 mIU/ml, CVs were 3.3 and 2.8%; for LH, at a concentration of 6.4 mIU/ml, 5.2 and 3.9%, respectively; for T, at a concentration of 0.2 ng/ml, CVs were 5.4 and 3.6%; for androstenedione at a concentration of 0.4 ng/mL, 12 and 3.1%, respectively; for DHEAS at a concentration of 210 mM, CVs were 4.8 and 4.1%; and for insulin at a concentration of 12 μIU/ml, CVs were 8 and 13.7%.

The conversion factors for SI units were as follows: E_2, 1 pg/ml = 3.671 pmol/l; T, 1 ng/mL = 3.467 nMol/L; androstenedione, 1 ng/ml = 3.496 mmol/L; DHEAS, 1 μg/mL = 0.0027 μmol/L; insulin, 1 μU/ml = 7.175 pmol/L; and glucose, 1 mg/dl = 0.05551 mmol/L.

Statistical Analysis

Data are expressed as mean ± standard error of the mean (SEm). Student's t test and chi-square test were used to discriminate between groups. Analysis of variance (ANOVA) was employed to differentiate among more than two groups. Tukey's and Scheffe's tests were used when ANOVA showed significant differences. Significance was defined as $P < 0.05$. The statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL).

RESULTS

Endocrine evaluation of the patients included in the study was carried out in baseline conditions. Table I shows serum FSH, LH, androstenedione, T, and DHEAS levels in each of the established groups. There was no significant difference among groups, suggesting that patients initially classified as PCO by ultrasound were biochemically similar to controls. Clinically, however, 13 (65%) of our patients had oli-

Table I. Basal Serum Gonadotropin and Androgen Levels in the Three Groups of Patients Established

	Group I (n = 4)	Group II (n = 16)	Group III (n = 16)
FSH (mIU/ml)[a]	3.9 ± 0.8	4.5 ± 0.4	3.5 ± 0.6
LH (mIU/ml)[a]	2.7 ± 1.2	5.7 ± 0.8	4.4 ± 0.7
LH/FSH[a]	0.7 ± 0.4	1.4 ± 0.2	1.2 ± 0.2
Androstenedione (ng/ml)[a]	1.8 ± 0.1	2.0 ± 0.2	2.2 ± 0.1
Testosterone (ng/ml)[a]	0.2 ± 0.1	0.3 ± 0.1	0.4 ± 0.1
DHEAS (μg/ml)[a]	1.5 ± 0.2	1.8 ± 0.2	1.7 ± 0.1

[a] Nonsignificant by ANOVA.

gomenorrhea, 5 (25%) were hirsute, 4 (20%) were obese, and 3 (15%) had an LH/FSH >2. Concerning women in group I, 3 had oligomenorrhea and 3 had a BMI >25. Peripheral hyperandrogenism was not detected in these patients.

Blood glucose and insulin responses during the OGTT are expressed as absolute values as well as the area under the curve (AUC) in Fig. 1. Blood serum levels were similar among groups at baseline levels. After glucose ingestion, serum glucose differed significantly ($P < 0.005$) in each group at 30, 60, 90, and 120 min, except for groups I and II at 60 min, which showed no difference. Similarly, glucose AUC values in each group were significantly ($P < 0.005$) different from the others.

Serum insulin levels are also shown in Fig. 1. Baseline values were similar among groups. The absolute levels reached in group I after the OGTT were significantly ($P < 0.005$) higher than those found for groups II and III. Serum levels of insulin in group II after 30 min were significantly ($P < 0.05$) higher than in group III. Insulin AUC values showed significant ($P < 0.05$) differences in group I compared to groups II and III. The glucose-to-insulin AUC molar ratio during the OGTT was significantly ($P < 0.05$) lower in patients included in group I (13.6 ± 2.4 mmol/L per min) compared to groups II (27.2 ± 2.3 mmol/L per min) and III (20.7 ± 1.3 mmol/L per min). Similarly, the ratio was also significantly ($P < 0.05$) different when groups II and III were compared.

Table II shows the age and BMI in each group. Women included in group III were significantly ($P < 0.05$) older than patients in groups I and II. Concerning weight, women in group I had a significantly ($P < 0.05$) higher BMI than patients in groups II and III. Some of the ovarian stimulation parameters are also

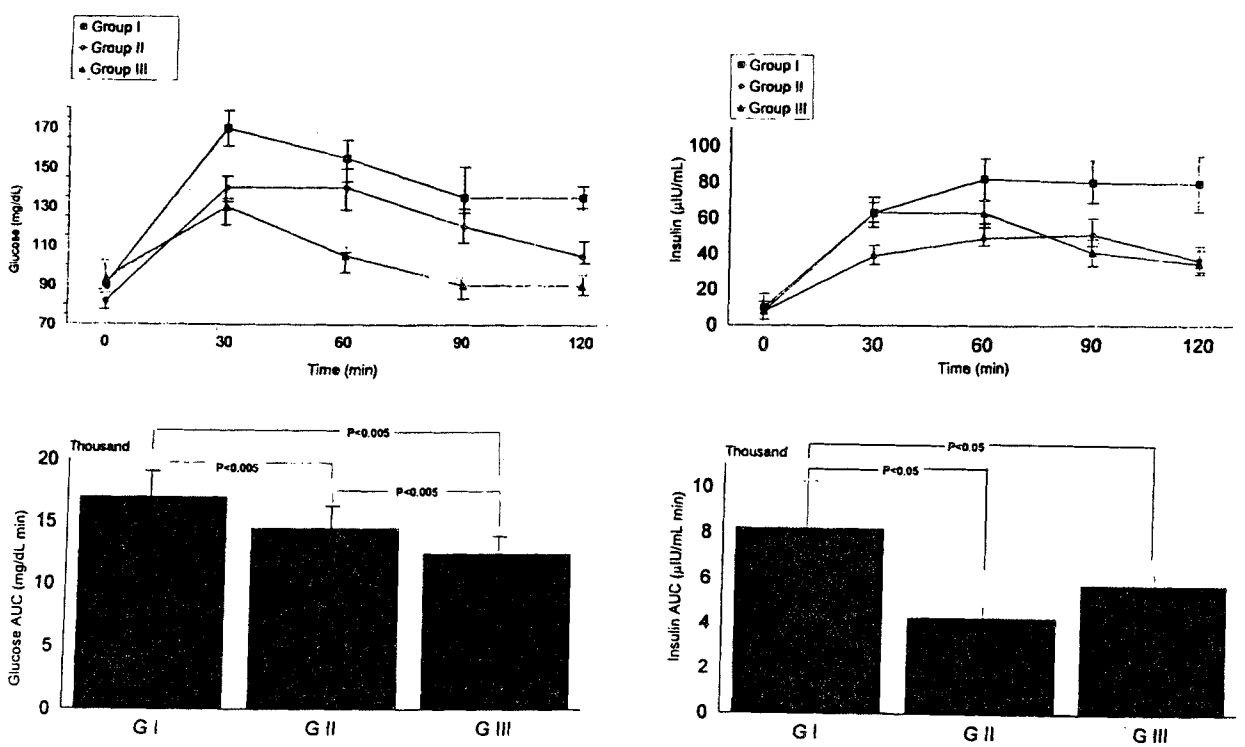

Fig. 1. Serum glucose and insulin levels after an OGTT expressed as absolute values (top figures) and the area under the curve (AUC) (bottom figures) in the three groups established.

Table II. Epidemiologic and IVF Characteristics of Each Group

	Group I	Group II	Group III
Age (yr)	31.8 ± 0.4	31.8 ± 0.4	33.9 ± 0.8*
BMI (kg/m^2)	25.1 ± 0.5*	22.9 ± 0.3	22.2 ± 0.5
Days of stimulation	9.6 ± 0.9	9.4 ± 0.3	9.9 ± 0.3
No. ampoules	24.0 ± 2.1	23.7 ± 1.1	31.2 ± 2.4*
E_2 on day of hCG (pg/ml)	3103 ± 333	2577 ± 181	1791 ± 350*
No. oocytes retrieved	23.8 ± 3.0	23.7 ± 1.9	9.9 ± 1.0*

* $P < 0.05$ by Scheffe test.

listed in Table II. For a similar number of days of stimulation, women included in group III needed significantly ($P < 0.05$) more ampoules of FSH/hMG, reached significantly ($P < 0.05$) lower E_2 levels, and produced significantly ($P < 0.05$) fewer oocytes than patients in groups I and II.

The outcome of IVF and ovum donation is shown in Table III. Fertilization rates employing sperm from donors' partners were significantly ($P < 0.05$) lower in group I compared to groups II and III. Fertilization in donated oocytes did not differ between group I and group II. Total fertilization, considering own and donated oocytes, again displayed a significant ($P < 0.05$) difference in favor of group II oocytes.

The quality and number of embryos transferred in each group are also shown in Table III. While there was no difference among groups considering embryo quality after 48 hr in culture, a significantly ($P < 0.05$) lower number of embryos was replaced in group I compared to groups II and III. Women included in group III had significantly ($P < 0.01$) higher pregnancy and implantation rates than patients in groups II and I (null). Similarly, when pregnancy and implantation were compared in groups I and II regarding own and recipient transfers, group II embryos showed higher ($P < 0.01$) successful rates.

DISCUSSION

The aim of our study was to evaluate the actual IVF performance of oocytes derived from PCO women. The data show that, although 80% of patients displayed oocytes and embryos able to implant in their own or recipient uteri, the remaining 20% of women produced embryos unable to implant. Since all four patients characterized by such a poor IVF outcome with their own embryos became pregnant, and carried a pregnancy to term, as they received donated oocytes, we employed this rationale to establish a particular subgroup of PCO patients with poor quality oocytes. The endocrine and IVF data obtained from this group have been compared to the data provided by PCO women whose oocytes resulted in implanting embryos at least

Table III. IVF Outcome in Groups I and II Considering Their Own Transfers ("Own") as Well as the Outcome in Recipients ("Donated") from the Ovum Donation Program

	Group I	Group II	Group III
Fertilization (%)			
Own	25.7 ± 5.7*	56.3 ± 4.7	55.1 ± 5.3
Donated	58.0 ± 9.6	70.8 ± 4.6	
Total	33.7 ± 5.3**	64.0 ± 3.4	
Embryo quality			
Own	1.9 ± 0.8	1.6 ± 0.6	1.6 ± 0.7
Donated	1.8 ± 0.9	1.7 ± 0.5	
Total	1.8 ± 0.8	1.7 ± 0.6	
Embryos transferred			
Own	2.6 ± 0.6*	3.8 ± 0.3	4.1 ± 0.3
Donated	4.0 ± 0.5	4.5 ± 0.1	
Total	3.7 ± 0.4	4.1 ± 0.1	
Pregnancies/transfer			
Own	0/15 (0)	6/38 (15.8)	7/16 (43.8)***
Donated	0/10 (0)***	22/42 (52.4)	
Total	0/23 (0)***	28/80 (35.0)	
Implantation			
Own	0/38 (0)	9/151 (6.0)	12/65 (18.5)***
Donated	0/40***	36/189 (19.4)	
Total	0/78 (0)***	45/340 (13.2)	

* $P < 0.05$ by Scheffe test.
** $P < 0.05$ by Student's t test.
*** $P < 0.01$ by chi-square test.

in one attempt and a control group of normal-appearing ovaries undergoing IVF during the study period.

The data presented herein show that our population of PCO patients was formed mainly of endocrinologically normal subjects, since no differences among groups were found (see Table I). The incidence of such a population of women is as high as 23% (6); it therefore seems logical to find these patients included in IVF programs for various reasons, including failed induction of ovulation with gonadotrophins. Furthermore, 65% of them had menstrual disturbances, 25% were hyperandrogenic, 20% were obese, and 15% had an altered LH/FSH ratio. Two particular observations were seen in women included in group I: elevated BMI, indicating obesity, and derangements of insulin secretion. The latter were characterized by elevated serum glucose and insulin levels after the OGTT and a reduced glucose-to-insulin molar ratio, thus confirming insulin resistance. The association between obesity and insulin resistance has long been recognized, although the intrinsic mechanisms for this relationship remain unclear (15).

Insulin resistance in women in group I was a constant finding. The association of peripheral insulin resistance and PCOS is well established. Insulin stimulates estrogen and progesterone in human granulosa cells from normal and PCOS ovaries, despite the apparent paradox of insulin resistance at classic target tissues (16). Although it has been suggested that insulin may act via the type I insulin-like growth factor (IGF) receptor to explain the controversial findings, it has recently been shown that the action of insulin in PCOS is mediated by its own receptor (17). Insulin may increase the local production of P (17), which in turn may be detrimental to the oocyte. In amphibians, P alters the frog oocyte membrane to induce the resumption of meiosis (18). If this is the case in humans, high local P concentrations may induce oocyte postmaturity affecting implantation (19). Alternatively, the action of insulin on steroidogenesis may increase the local production of androgens (17). Andersen (20) has shown that there is a negative correlation between the pregnancy potential of individual oocytes and the follicular fluid levels of T and androstenedione. The fact that our patients showed neither biochemical nor biological peripheric hyperandrogenism does not exclude the possibility that insulin may induce local production of androgens, which results in oocytes of lower quality. A final explanation that cannot be completely ruled out is the possibility that insulin may be acting in part through the IGF type I receptor. We (21) have shown that the addition of IGF-I to immature human oocytes obtained from unstimulated ovaries and cultured in vitro results in resumption of meiosis. Thus, insulin could be inducing oocyte postmaturity through this mechanism as well.

It is also of interest to note that women included in group II had elevated insulin levels after the OGTT. This observation has been reported previously by Filicori *et al.* (22), who found no differences in the molar glucose-to-insulin ratio between PCOS and PCO, suggesting that insulin resistance is not a feature of patients that they described as having multifollicular ovaries. Our patients included in group II, however, showed significant differences compared to controls, although women in group I had a more profound reduction in their molar glucose-to-insulin ratio than patients included in the remaining groups. It is our view that what we are observing here is women with PCO and different degrees of hyperinsulinemia and insulin resistance. It seems that women with PCO may have a wide range of clinical manifestations. At one extreme of this range are women phenotypically normal, eumenorrheic, with no signs of hyperandrogenism, but with ultrasonographically-appearing PCO. At the other end are women who have full-blown expression of the syndrome (23). In the middle, one can find different clinical entities with the common ultrasonographic findings. It is tempting to speculate that as long as PCO is characterized by a ultrasonographic picture with no endocrinologic disturbances, the microenvironment of the ovary may be appropriate and the quality of the oocytes may not be affected. However, as endocrine disturbances such as insulin resistance and elevated LH levels appear, the quality of the oocytes is affected. This has been shown previously concerning high tonic LH levels in PCOS women (24) and is further reinforced by the present study, in which a relationship between insulin resistance and poor oocyte quality is demonstrated.

The second concept addressed here is whether PCO women have the same IVF outcome as normal patients. For analysis, one has to focus on group II compared to group III. Fertilization rates were similar. Implantation rates, however, were clearly diminished in PCO cycles compared to controls. This picture was not observed in recipients from group II. Although we do not have ovum donation cycles in group III for comparison, a 19.4% implantation is what we can expect from this reproductive technique (10,12). Therefore, the data suggest that oocyte quality was not altered in group II, i.e., 80% of PCO women display oocytes and embryos of normal quality. This is in agreement with

previous observations employing the ovum donation model (7,10,11).

Reduced implantation was observed in group II, which may be attributed to an altered endocrine milieu. In fact, PCO women behave as high responders when they undergo ovarian stimulation for IVF. We have consistently found lower implantation rates in high responders (8,12,25), which are the consequence of, at least in part, high estrogen levels (25). Our patients in group II had significantly higher serum E_2 levels than control subjects, suggesting that implantation failure was due to an endocrine cause.

This concept does not hold true for women included in group I, in whom two parameters suggested poor oocyte quality: (a) lower fertilization rates, despite a similar distribution of male infertility in the established groups; and (b) null implantation in own and recipient uteri. Moreover, the fact that all patients became pregnant in the first attempt at ovum donation when they were recipients strongly suggests that impaired oocyte and embryo quality was the cause of poor IVF outcome. We believe that the fact that fewer embryos were replaced in this group does not justify null implantation and, therefore, cannot be used as an explanation for the results of the study. Identification of this particular subgroup of women may also explain why we and others have found reduced fertilization in high responders (8,9): these patients may be mixed in the population of high responders analyzed in previous reports, resulting in lower fertilization rates. Whether intracytoplasmic sperm injection (ICSI) may improve fertilization rates in these patients is a question that remains open. However, this is not the main point because the resulting embryos are also unable to implant.

Higher fertilization was observed in recipients of donated oocytes than in the donors. This is not surprising because this study was undertaken before ICSI was systematically applied for male infertility. There was a tendency to employ donor semen in recipient cycles in which sperm quality in the male partner was reduced, explaining the picture observed in Table III.

In summary, this study has identified a particular subgroup of PCO women who produce oocytes and embryos of lower quality. These patients have been defined as being obese and having insulin resistance. The mechanism of this association is yet to be determined.

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