Prognostic factors in oocyte donation: an analysis through egg-sharing recipient pairs showing a discordant outcome

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Objective: To analyze prognostic factors that are associated with a discordant outcome in egg recipients sharing oocytes from the same donor.
Design: Matched case-control single-center study.
Setting: Private infertility clinic.
Patient(s): Four hundred forty-four recipients (222 pairs) sharing oocytes from the same donor and showing a discordant outcome.
Intervention(s): Controlled ovarian hyperstimulation of egg donors, oocyte donation, intracytoplasmic sperm injection, and ET in egg recipients.
Main Outcome Measure(s): Recipient age, obstetric (gravidity, parity) and gynecologic variables (previous uterine surgery, uterine fibroids, uterine malformations, endometriosis, history of tubal infertility), previous oocyte donation cycles, duration of E_2 replacement, received cumulus-oocyte complexes, mature (MII) oocytes, fertilized oocytes, transferred embryos, mean embryo score, transfer difficulty, and semen parameters.
Result(s): No significant differences were found in the above-mentioned prognostic factors between the study and control groups.
Conclusion(s): Recipient- and cycle-related prognostic factors investigated in our study were not associated with a discordant outcome in recipient pairs sharing oocytes from the same donor. Other possible prognostic factors involving oocyte donor heterogeneity, embryo aneuploidy rates, male factor infertility, and endometrial receptivity should be further investigated. (Fertil Steril® 2007;88:1548–53. ©2007 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, shared oocytes, discordant outcome

For more than two decades, oocyte donation has been used successfully as a treatment option for a variety of indications, including premature ovarian failure, natural menopause, reduced ovarian reserve, and previous failed IVF attempts, or for the prevention of genetic anomalies. After oocyte donation had become widespread and experience with larger series had become available, several studies investigated different prognostic factors that could influence the outcome. To date the majority of published studies are of a retrospective nature analyzing a more or less large consecutive series of recipients. The most studied prognostic factors include donor and recipient age, oocyte donation indication, endometrial thickness, and duration of estrogen replacement (1–14).

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Few studies are of matched case-control design analyzing recipient outcome with sibling oocytes from the same donor (15–18). To our knowledge there are only three published studies (19–21) analyzing several recipient factors (demographic and cycle data, male factor, and ET difficulty) at the same time in oocyte recipients with a discordant outcome, but these studies reach divergent conclusions. We wanted to verify in our large series of oocyte donation recipients the existence of prognostic factors that could predict discordant outcome.

MATERIALS AND METHODS

All oocyte donation cycles performed in a private fertility center between January 2002 and June 2006 were analyzed retrospectively. A study group and a control group were created by using paired recipient cycles in which an egg donor's oocytes from the same cycle were distributed to two different recipients. Only recipients having a fresh ET were taken into account. A discordant outcome was

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observed in a proportion of these recipient cycles; one recipient had a clinical pregnancy, the other had a negative pregnancy test 14 days after the ET procedure. Recipients participated only once in either the study or the control group. Recipients who participated in both the study and the control groups were excluded.

Before treatment, careful clinical assessment was carried out in the oocyte recipient candidates including a general physical and gynecologic examination, blood tests (hematology, biochemistry, and serology), a cervical smear, and a pelvic ultrasound scan. The uterine cavity was assessed by either hysterosalpingography or hysteroscopy. Correctional interventions were performed when necessary. Oral E_2 valerate (Progynova; Schering Spain, Madrid, Spain) was used in a constant-dose regimen for the endometrial preparation. Patients on standby received up to 6 mg a day, and the duration of the treatment varied in accordance with the availability of the oocytes. Endometrial thickness was not routinely measured during the whole study period; transabdominal measurements made at the time of the ET were registered from 2005 on. From the day of the oocyte retrieval, 800 mg of micronized vaginal P (Utrogestan; Laboratorio Seid, Barcelona, Spain) was added.

Oocyte donation was performed according to the Spanish Act on Reproduction. Donation was anonymous and altruistic, and donors were required to be between 18 and 35 years of age. A conventional clinical and psychological workup was performed, including karyotype. The ovarian stimulation protocols and laboratory procedures used were described previously (22). The intracytoplasmic sperm injection (ICSI) procedure was performed routinely to avoid immature oocytes being given to the recipients and to enhance fertilization rate. Mature oocytes generally were split evenly between the two recipients (201 stimulation cycles), although in some cases (21 cycles) two or three extra oocytes were allocated to recipients with severe male factor infertility or previous low fertilization rate. In the majority of the cycles frozen-thawed sperm, obtained during the first appointment, was used for convenience purposes for the patients living abroad, thus eliminating the need to be present on the day of oocyte retrieval.

Developing embryos were classified according to their morphologic appearance with the use of a modification of the combined embryo score described by Coroleu et al. (23), taking into account the number of blastomeres, their form, and the percentage of cytoplasmic fragmentation, with an optimal quality embryo scoring a maximum of 10. Embryos were transferred into the uterine cavity 2 or 3 days after the ICSI procedure. The ET procedure was performed with use of abdominal ultrasound guidance. The biologist who performed the embryo loading and assisted during the transfer evaluated the level of transfer difficulty as follows: without any difficulty (smooth introduction of the catheter and prompt injection of the embryos), with moderate difficulty (longer or more difficult introduction of the catheter), or with high difficulty (the use of tenaculum).

In case of pregnancy, hormonal replacement therapy was continued during 100 days after the embryo replacement. Each pregnancy with at least one intrauterine sac revealed by ultrasonography approximately 5 weeks after transfer was considered to be a clinical pregnancy.

Statistical Analysis

Values are expressed as mean ± SD. Metric variables were analyzed by the paired *t*-test and nominal variables by the χ^2 test. A P value of $< .05$ was considered to be statistically significant.

RESULTS

All egg donor stimulation cycles performed in our center that led to a fresh ET between January 2002 and June 2006 were analyzed retrospectively. In 637 donor cycles, the oocytes of the same egg donor were shared between two different recipients. In 263 donor cycles (41.4 %), a discordant outcome was observed. Two hundred twenty-two donor cycles were further analyzed after application of the exclusion criteria. Forty-one donor cycles were excluded from analysis. In those recipients who participated more than once in the study group or the control group only the first cycle was taken into account, and if the recipient cycle appeared at the same time in the study and the control groups it was excluded altogether.

Recipient age and different indications for oocyte donation are summarized in Table 1. Ninety and 94 recipients had a previous pregnancy (miscarriage, induced abortion, or extrauterine pregnancy) in the pregnant and the nonpregnant group, respectively (NS). At least one live birth was recorded in 47 and 51 patients in the two groups, respectively (NS). Fifty-five and 64 recipients had a previous oocyte donation attempt (NS).

Previous uterine surgery was recorded in 15 and 17 patients; out of these 14 and 16 were myomectomies, respectively (NS). A deformed uterine cavity was noted in 2 patients in both groups. Submucosal fibroids were resected systematically before the oocyte donation attempt. The presence of intramural uterine fibroids was seen on transvaginal ultrasound scans in 31 and 27 patients, respectively (NS). Uterine malformations were discovered in 2 patients (unicorn uterus and bicornuate uterus) in the pregnant group and also in 2 patients (unicorn uterus and small uterine septum) in the nonpregnant group.

Thirty and 29 patients had a history of tubal factor infertility (previous extrauterine pregnancy, tubal obstruction, and hydrosalpinges), respectively (NS). Surgical interventions for pelvic endometriosis were performed in 24 patients in both groups (NS).

Cycle-related variables (duration of estrogen replacement, received cumulus-oocyte complexes, mature oocytes, fertilized oocytes, number of available day 2 embryos, transferred embryos, proportion of day 2 versus day 3 transfers, and mean embryo score), and transfer difficulty are shown in

TABLE 1

Recipient characteristics.

	Pregnant group	Nonpregnant group	*P*
No. of recipients	222	222	—
Age (y)[a]	40.1 ± 5	39.6 ± 5.5	.38
Indication for oocyte donation[b]			.09
Reduced ovarian reserve (n)	127	119	—
Early/natural menopause (n)	59	50	—
Previous IVF failures (n)	35	47	—
Genetic anomaly (n)	1	6	—

Note: Values are mean ± SD.
[a] Paired *t*-test.
[b] χ^2 Test.

Bodri. Discordant outcome in egg-sharing oocyte recipients. Fertil Steril 2007.

Table 2. Data concerning sperm parameters used for the fertilization by ICSI are shown in Table 3.

DISCUSSION

This matched case-control study did not show any significant difference in a number of variables that are often regarded as important prognostic factors and that could influence the outcome of oocyte donation cycles. We have evaluated recipient-related (age, obstetric/gynecologic variables, and previous oocyte donation attempts) as well as cycle-related variables (duration of E_2 replacement, number of received mature oocytes, number of transferred embryos, embryo quality, transfer difficulty, and semen parameters).

Several studies have investigated prognostic factors of oocyte donation including the effect of recipient age on the outcome (3–7, 9, 10, 12). The majority of these single-center studies comprised consecutive series of recipient cycles ranging from 141 to 1,001. Only three authors found a negative effect of recipient age on clinical pregnancy and/or implantation rates (4, 6, 7). A more recent, large single-center study (8) with 3,089 cycles found a significant decrease in

TABLE 2

Cycle-related and ET data.

	Pregnant group	Nonpregnant group	*P*
No. of recipients	222	222	—
Duration of E_2 replacement (d)[a]	30 ± 13.4	31 ± 16.1	.24
Duration of E_2 replacement ≥50 days (n)[b]	20	32	.08
Received cumulus-oocyte complexes[a]	7.3 ± 2	7.4 ± 2.2	.3
Mature (MII) oocytes[a]	5.5 ± 1.2	5.6 ± 1.3	.58
Fertilized oocytes (2PN)[a]	4.0 ± 1.4	3.9 ± 1.5	.3
Day 2 embryos[a]	3.6 ± 1.4	3.4 ± 1.4	.15
Total No. of transferred embryos	465	464	—
Transferred embryos[a]	2.1 ± 0.5	2.1 ± 0.6	.9
Day 2 ET, n (%)[b]	125 (56)	122 (55)	.77
Day 3 ET, n (%)	97 (44)	100 (45)	—
Mean embryo score/replacement[a]	8.52 ± 1.04	8.37 ± 1.13	.07
Transfer difficulty[b]			.10
Without difficulty, n (%)	182 (82)	164 (74)	—
Medium difficulty, n (%)	31 (14)	42 (19)	—
High difficulty, n (%)	9 (4)	16 (7)	—

Note: Values are mean ± SD.
[a] Paired *t*-test.
[b] χ^2 Test.

Bodri. Discordant outcome in egg-sharing oocyte recipients. Fertil Steril 2007.

TABLE 3

Parameters of sperm used for fertilization with ICSI.

	Pregnant group	Nonpregnant group	*P*
No. of recipients' partners	222	222	—
Fresh sperm sample (n)[a]	53	55	.82
Frozen sperm sample (n)	169	167	—
Patients with normozoospermia (n)[a]	88	83	.23
Patients with abnormal sperm parameters[b] (n)	111	125	—
Patients with testicular biopsy (n)	1	2	—
Donor sperm (n)	22	12	—

[a] χ^2 Test.
[b] Oligospermia, asthenospermia, teratospermia, or combination of these anomalies, according to WHO 1999 Guidelines (33).

Bodri. Discordant outcome in egg-sharing oocyte recipients. Fertil Steril 2007.

pregnancy and implantation rates for recipients 45 years of age and older. Nevertheless the difference was only about 5%, and older recipients still had a highly acceptable pregnancy rate. This evidence suggests that the possible age-related decline in uterine receptiveness is small. Studies based on a similar principle to that used in our study, where donor oocyte quality was controlled by using sibling oocytes from the same donor, reached divergent conclusions (15–17). A prospective study by Navot et al. (15) with 51 oocyte donation cycles in each treatment arm demonstrated a similar clinical pregnancy, delivery, and miscarriage rate between the two groups. A retrospective analysis by Borini et al. (16) with a similar number of cases (57 cycles) showed significantly lower clinical pregnancy and implantation rates in the older group of recipients who were between 40 and 49 years of age. Conversely, Abdalla et al. (17) found a similar reproductive outcome in a series of 51 cycles sharing oocytes from the same donor. No significant difference in recipient age was found between the study and control groups described here.

In our study no differences were observed in the obstetric (previous pregnancies and previous live births) or the gynecologic variables (uterine fibroids, uterine malformations, previous uterine surgery, history of tubal disease or endometriosis) of the two patient groups. According to previous studies (7, 18) the history of endometriosis in the recipient had no negative influence on oocyte donation; this finding is also supported here. A similar number of patients had previous oocyte donation cycles in the two groups. Previous studies investigating cumulative pregnancy rates after oocyte donation found no decline in per cycle success up to four cycles (9, 10). Furthermore, Spandorfer et al. (24), who studied the effect of a previous oocyte donation cycle, found no difference between different attempts up to three. However, in a subgroup analysis it was found that patients who had a successful delivery after their first attempt were twice as likely to have an ongoing pregnancy after their second attempt. This finding was not corroborated by Moomjy et al. (7), who did not find any statistical difference in pregnancy or implantation rates in recipients with a previous pregnancy or delivery.

The relationship between uterine fibroids and infertility is still being debated (25). Several studies have evaluated the effect of fibroids on pregnancy and implantation rates in patients undergoing IVF. These studies have generally found an overall negative impact, especially when the cavity was distorted. Gianaroli et al. (26) in a retrospective age-matched case-control study found a lower implantation rate and higher miscarriage rate in patients with inner myometrium fibroids who underwent IVF. There are more studies available on the effect of myomectomy in infertile patients; nevertheless, postintervention pregnancy rates vary widely, between 10% and 80%. In this study no significant difference in the occurrence of intramural fibroids or the rate of previous myomectomies was found between the two patient groups. It must be noted, however, that neither implantation nor miscarriage rates could be investigated in the study because of its design. In line with several other studies no influence of oocyte donation indication was noted (7, 9, 10).

The measurement of endometrial thickness is often used as a noninvasive tool to assess uterine receptiveness during the preparation for oocyte donation; nevertheless, there is debate about its real predictive value (11, 12). A large retrospective study by Remohí et al. (11) showed no significant difference in the outcome according to endometrial thickness or serum E_2 levels. There is probably no endometrial thickness limit below which implantation is impossible. Because routine endometrial thickness measurements were performed only in the second half of the study period, this variable was not analyzed in the present study.

The synchronization of donor and recipient cycles during oocyte donation is of paramount importance. Remohí et al. (13) demonstrated that pregnancy is achievable even with long E_2 replacement of more than 65 days. The ideal duration of estrogen replacement was investigated in several studies. Too short substitution periods (<10 days) are not advisable

because of a higher risk of subsequent miscarriage (14). Soares et al. (8) found that in a large series of oocyte recipients the success rate drops significantly from 7 weeks onward. In the present study no statistically significant difference was observed in the mean duration of E_2 replacement or in the proportion of patients with a long substitution period of more than 50 days.

No significant difference was found in the sperm parameters used for fertilization by ICSI in the two study groups. This is in accordance with the findings of Oehninger et al. (27), who found no difference in pregnancy and implantation rates between patients with oligoasthenoteratospermia treated by ICSI and patients with normozoospermia treated by conventional IVF in an oocyte donation program. Nevertheless a more sophisticated analysis of sperm parameters on a chromosomal/genetic level could unravel other factors that might influence embryo development and overall outcome. This is especially true in the setting of oocyte donation where good oocyte quality is generally considered constant and unidentified male factor infertility could have a significant impact on cycle outcome.

The study by Nasseri et al. (19) investigated, for the first time, factors that could determine a discordant outcome in 81 recipient pairs. They did not find any difference in recipients' age or cycle characteristics but found a negative impact of abnormal semen parameters and transfer difficulty on the outcome.

The study of García-Velasco et al. (20) evaluated several prognostic factors such as recipient age, serum E_2 levels, endometrial thickness, indications for oocyte donation, abnormal semen parameters, embryologic data, and transfer catheters used. They did not find any significant differences in the variables studied and concluded that cycle outcome could be influenced by chance or by some as yet untested factor. Our findings are in line with those of the above-mentioned study; nevertheless it is worth mentioning that García-Velasco et al. used a rather complicated matching procedure allowing recipient cycles to be taken into account more than once. Furthermore, obstetric and gynecologic recipient factors were not evaluated at all in their study. In the study described here strict exclusion criteria were used to assure that every recipient was included only once in the study.

The study of Zenke and Chetkowski (21) reached opposite conclusions to the present study, stating that uterine pathology, thin endometrium, and difficult ET are the most important recipient-related determinants of success in oocyte donation. Besides the small sample size (41 recipient pairs), it should be noted that their patient population was somewhat older than ours (39–40 vs. 43 years) and had a high overall rate of uterine pathology (up to 31.7% in the nonpregnant group) including severe cases of uterine pathology such as Asherman's syndrome, diethylstilbestrol exposure, or the presence of dystrophic uterine calcifications.

Although donor oocyte quality was controlled in the present study by design, there is some evidence that suggests that donor heterogeneity could be the most important prognostic factor in oocyte donation. Harris et al. (28) performed a retrospective analysis of 243 donor cycles studying donor heterogeneity by robust statistical methods. They concluded that a large proportion (85%–90%) of the variation among donors cannot be explained by donation- or recipient-related characteristics alone and that this unexplained donor heterogeneity was a major factor affecting oocyte donation outcome. Furthermore, Reis Soares et al. (29) investigated aneuploidy rates in a small series of oocyte recipients and found a high rate of chromosomally abnormal embryos (56.6%) compared with controls. They concluded that aggressive ovarian stimulation protocols yield large oocyte cohorts that are prone to form embryos with a higher rate of chromosome abnormalities. A more recent study by Munné et al. (30) found similar aneuploidy rates of 57% in 124 egg donor cycles. Another interesting finding was the great variability between different egg donors that showed a normal distribution, with almost one third of the donors having fewer than 30% of normal embryos.

Successful implantation depends on both the quality of the embryo and adequate endometrial receptivity. Pantos et al. (31) investigated the clinical value of endometrial pinopode detection in a mock preparation cycle, as a tool to improve oocyte donation cycle outcome in recipients with previous implantation failure. In the majority of the study patients a new modified transfer cycle was suggested, which significantly improved clinical pregnancy and live birth rates in subsequent attempts. Recently even more sophisticated methods have been developed to investigate possible markers of endometrial receptivity. Henriquez et al. (32) in a small series of patients found a significant decrease in the endometrial expression of monoamine oxidase A in recipients with previous oocyte donation failures compared with control groups of successful recipients and fertile women.

In conclusion, in the present retrospective study of egg recipients sharing oocytes from the same donor and showing a discordant outcome, no specific recipient- or cycle-related variable was found to be associated with success or failure. Further studies are needed to investigate prognostic factors such as oocyte donor heterogeneity, embryo aneuploidy rates, male factor infertility, and endometrial receptivity that could have a relevant influence on cycle outcome.

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