Reproductive performance in oocyte donors and their recipients: comparative analysis from implantation to birth and lactation

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Objective: To compare reproductive performance among pregnancies initiated with autologous oocytes and donated oocytes.

Design: Retrospective cohort analysis.

Setting: Clínica las Condes Hospital, a tertiary referral center in Chile; Fertility, Centro de Fertilizaçao Assistida, Brazil; and 130 institutions reporting to the Latin American Registry (RLA) of assisted reproductive technologies (ART).

Patient(s): Cohort 1 evaluates 70 women who conceived during an IVF cycle, and simultaneously donated fresh oocytes to other 70 oocyte recipients who also conceived. Cohort 2 evaluates the follow-up of 31,550 pregnancies after IVF and 6,024 pregnancies in oocyte recipients, both reported to the RLA between 1995 and 2005.

Intervention(s): ART with autologous and donor oocytes.

Main Outcome Measure(s): Embryo implantation rate, weight of newborns, gestational age at delivery, perinatal mortality and duration of lactation.

Result(s): Oocyte donors and their recipients share similar embryo implantation rate, weight of newborns, gestational age at delivery, perinatal mortality, and duration of lactation.

Conclusion(s): The establishment of pregnancy is as efficient with autologous as with donated oocytes. Embryos transferred into their progenitors or in different women have similar chances of implantation, weight at birth, and perinatal outcome. Embryo implantation is affected by the age of the recipient, suggesting that uterine senescence plays a role in fecundity. (Fertil Steril® 2010;93:2210–5. ©2010 by American Society for Reproductive Medicine.)

Key Words: Oocyte donors, oocyte recipients, implantation rate, perinatal outcome and lactation

For more than 20 years, oocyte donation has been used to help women overcome infertility associated with a lack of autologous oocytes. This condition can be the result of diseases diminishing the ovarian reserve or part of natural ovarian aging. Couples also use donated oocytes to avoid the transmission of severe genetic diseases. Since the first report of a live birth from oocyte donation in 1984 (1, 2), the request for this form of reproductive treatment has increased worldwide. For example, from 2000 to 2005 the number of procedures in the United States increased from 9,150 to 14,646, representing today almost 12% of all assisted reproductive technology (ART) procedures (3). In the same period in Latin America, the number of oocyte donation transfers increased from 1,471 to 3,516, representing almost 16% of all embryo transfers in the region (4). Initially, oocyte donation was performed with great success in young women who had their ovaries excised or suffered from premature ovarian failure (5). Today, the indications have diversified to include age-related infertility (6), repeated implantation failure, recurrent abortion, or family history of genetic diseases (7, 8, 9).

The high implantation and pregnancy rates achieved in oocyte recipients are comparable and sometimes higher than in young women undergoing autologous IVF/ICSI cycles. This confirms that the single most important determining factor responsible for reproductive success is the age of the women providing oocytes (10).

Today, with the information available on oocyte and embryo donation, we have learned of the capacity of reproductive systems to function without a sense of genetic belonging. A primed uterus accepts any healthy embryo, post partum breasts provide nourishing milk to any suckling baby, and, challenging today's family paradigms, women are gifted with an immense capacity to love babies and build families beyond a genetic identity within family members. Golombok et al. (11), Murray et al. (12), and others have shown in cohort studies that building families in the absence of genetic links between parents and their children (through oocyte donation or semen donation) does not jeopardize the development of a positive family relationship. In fact, in families sharing no genetic link between the mother or father and the child,

Implantation rates according to age in women undergoing regular IVF/ICSI(a) and in oocyte recipients in cohort 2.

Age category	IVF/ICSI		Oocyte recipients	
	No. of transfer cycles	Implantation rate (95% CI)	No. of transfer cycles	Implantation rate (95% CI)
≤ 34 y	52,085	15.7% (15.6–15.9)[a]	2,164	18.1% (17.2–19.0)[b]
35–39 y	35,736	12.0% (11.9–12.2)[c]	3,870	17.5% (16.8–18.2)[d]
≥ 40 y	15,928	7.5% (7.3–7.7)[e]	9,403	16.5% (16.1–16.9)[f]
Total	103,749	13.2% (13.0–13.4)	15,437	16.9% (16.6–17.3)

[a,b] $P=0.001$; [c,d] $P=0.001$; [e,f] $P=0.001$; [b,d] $P=0.001$; [b,f] $P=0.001$ (Chi-square test).

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the paternal and maternal relationships reflect higher levels of warmth and interaction when compared to families with naturally conceived children.

The objective of this study is to provide robust clinical evidence to sustain that "motherhood" can be established as efficiently when embryos originate from autologous or donated oocytes. For the purpose of this study, motherhood is understood as the capacity of a woman to host an embryo during implantation, carry it through pregnancy and safe delivery, and nurture the newborn through successful breastfeeding.

MATERIALS AND METHODS

This is a case-control study of pregnancies and deliveries resulting from IVF and intracytoplasmatic sperm injection (ICSI) cycles and oocyte recipients performed between 1995 and 2005.

Two different cohorts have been analyzed: cohort 1 consists of 140 pregnant women treated in the two collaborating institutions. Seventy women who conceived during an IVF/ICSI cycle simultaneously donated spare oocytes to the other 70 women, who also conceived in that cycle. Therefore, embryos generated from the same cohort of oocytes simultaneously initiated a clinical pregnancy in their progenitor and in a different woman. Cohort 2 consists of 31,550 clinical pregnancies resulting from in vitro fertilization or intracytoplasmatic sperm injection with autologous oocytes ("IVF/ICSI(a)"), and 6,024 clinical pregnancies resulting from IVF/ICSI with donated oocytes, reported to the Latin American Registry of Assisted Reproduction (RLA) between 1995 and 2005.

In both cohorts, comparisons between groups included embryo implantation rate, clinical abortion rate, gestational age at delivery, weight of newborns, perinatal mortality and breastfeeding length.

Implantation rate (IR) was defined as the number of gestational sacs observed by ultrasound at week 5 of amenorrhea, divided by the number of embryos transferred. In contrast to

cohort 1, in which IR was calculated among pregnant women, in cohort 2 the IR was calculated among all women having embryos transferred, regardless of the outcome.

In cohort 1 the weight of newborns was registered as continuous data; in cohort 2 the weight was registered as categorical data. For the purpose of this study, newborns were grouped as weighing less than 2,500 g or greater than 2,500 g at the time of birth.

Perinatal mortality was defined as the sum of stillbirth and early neonatal deaths (i.e., occurring within the first 7 days after birth) (13).

In cohort 1, additional information included the duration in months of exclusive breastfeeding and total breastfeeding. This information was obtained retrospectively, either extracted from pediatric files or through personal interviews held by the research nurse. Although the prolonged interval between breastfeeding and the interview could be a source of error, women seemed to remember their lactation period vividly.

Categorical data were compared with chi square test. A P value of less than 0.05 was considered statistically significant. Continuous data are presented as mean ± SD, and 95% confidence intervals (CIs) were calculated. Because of the nature of this study, no institutional review board was requested.

RESULTS
Age Distribution

In cohort 1, the mean age of oocyte donors was 30.5 years (range, 23–35 years), whereas the mean age of oocyte recipients was 39.8 years (range, 27–50 years). In cohort 2, the age of female partners reported to the RLA are grouped under three age categories: younger than 34 years, 35–39 years, and 40 years or older. Fifty percent of women having IVF/ICSI(a) were ≤ 34 years old and 15.4% were ≥ 40 years old. Conversely, in oocyte recipients, only 14% were ≤ 34 years old, whereas 60.9% were ≥ 40 years old (Table 1).

TABLE 2

Neonatal weight of babies born to women undergoing regular IVF/ICS and oocyte recipients according to gestational order in cohort 1.

Gestational order	Oocyte donors, n (mean ± SD)	Oocyte recipients, n (mean ± SD)	P value[a]
Singleton	25 (3,170 ± 517)	24 (2,980 ± 446)	0.18
Twin	38 (2,057 ± 572)	33 (2,390 ± 577)	0.047
Triplets	27 (1,365 ± 465)	16 (1,658 ± 452)	0.05

[a] Chi-square test.

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Implantation Rate

In cohort 1, the IR was 52.2% (107 gestational sacs per 205 transferred embryos) in oocyte donors and 47.4% (100 gestational sacs per 211 transferred embryos) in oocyte recipients (P=0.82). Table 1 shows the IR in 103,740 transfer cycles of IVF/ICSI(a), and in 15,437 transfer cycles in oocyte recipient (cohort 2). As expected, in IVF/ICSI(a), the IR decreases as the age of the female partner increases. This is also true in oocyte recipients, but the magnitude of the difference—albeit reaching statistical significance—is small (0.6%–1.6%). Furthermore, within every age category, the IR is significantly higher in oocyte recipients than in women undergoing conventional IVF/ICSI(a).

Clinical Abortion Rate

In cohort 1, the clinical abortion rate was 13% (9/70) among oocyte donors, and 19% (13/70) among oocyte recipients (not significant [NS]). In cohort 2, the clinical abortion rate was 18% (5,496/30,536) in women undergoing regular IVF/ICSI(a) cycles, and 19% (996/5,261) in oocyte recipient (NS).

Weight of Newborns and Gestational Age at Delivery

Table 2 shows the neonatal weight at the time of delivery of singletons, twins, and triplets in cohort 1. In this cohort, differences in the mean weight of singletons born to oocyte donors and oocyte recipients do not reach statistical significance (P=0.18). In twins and triplets, the higher birth weight in babies born from oocyte recipients is in the range of significance (P=0.047 and 0.05, respectively).

Alternatively, in cohort 2 the proportion of singletons who weighed more than 2,500 g corresponded to 88.8% (12,980 of 14,621 births) in women undergoing regular IVF/ICSI(a), and to 86.5% (2,048 of 2,368 births) in oocyte recipients. This 2.3% difference in the proportion of newborns weighing ≥ 2500 g has a P value of <0.001. In twins and triplet pregnancies, the magnitude of the difference in the proportion of newborns weighing ≥ 2500 g, was 5.3% and 1% respectively (P < 0.001).

The mean gestational age at birth in cohort 1 was similar when stratified by multiplicity. For singletons born to oocyte donors, the mean gestational age at birth was 38.5 weeks and 37.6 weeks for their corresponding oocyte recipient (NS). In twin pregnancies, the mean gestational age at birth was 34.7 and 36.3 weeks for oocyte donors and oocyte recipient, respectively (NS).

In cohort 2 the proportion of term deliveries for singletons (≥ 37 weeks' gestation) was 86.1% for women undergoing regular IVF/ICSI(a) and 80.1% for oocyte recipients; P < 0.001). In twin pregnancies, the difference between oocyte donors and oocyte recipients was 6.7% (P < 0.001), whereas in triplets the difference (2.3%) was in favor of oocyte recipients (P < 0.001; Table 3).

TABLE 3

Frequency of term delivery in women undergoing regular IVF/ICSI(a) and oocyte recipients according to gestational order in cohort 2.

Gestational order	N	≥ 37 WA	
		%	△ %
Singleton[a]			
IVF/ICSI	13,010	86.1	6
OR	1,941	80.1	
Twin[b]			
IVF/ICSI	2,416	45.2	6.7
OR	391	38.5	
≥ Triplets[c]			
IVF/ICSI	146	10.1	2.3
OR	34	12.4	

Note: Chi-square test comparing IVF/ICSI(a) and oocyte recipients. WA= weeks of amenorrhea; OR = oocyte recipients.
[a] P < 0.001.
[b] P < 0.001.
[c] P < 0.001.

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Perinatal Outcome

In cohort 2, the perinatal mortality rate was similar among the 34,604 babies born after regular IVF/ICSI(a), and among 5,482 babies born to oocyte recipients. As expected (Table 4) it is multiple births that increased perinatal risks, regardless of the source of oocytes (autologous or donated).

Breastfeeding

Information on the length of breastfeeding was obtained in 38 oocyte donors and 37 oocyte recipients of cohort 1. The mean duration of breastfeeding was 6.8 months in both groups, with a maximum length of 18 months in oocyte donors and 28 months in oocyte recipients. Exclusive lactation lasted a mean of 2.5 months in each group.

DISCUSSION

This study is a systematic analysis of pregnancies—from implantation to birth and breastfeeding—among oocyte donors and recipients. Although there is information available in the literature concerning the capacity of women to bear children from donor oocytes, the data presented here add to the already existing knowledge in two aspects. First, this is the first follow-up of cohorts of oocytes that initiated a simultaneous pregnancy in their progenitor and in another woman, both followed-up until birth and lactation. Second, this is the largest set of data, published so far, comparing outcome of pregnancies from implantation to birth in gestations generated after IVF/ICSI with autologous and donor oocytes.

Although this is a retrospective analysis, the information gathered in cohort 1, constitutes one of the best models to try our hypothesis that in the process of becoming mothers, the genetic identity between embryos and their progenitors does not affect intrauterine and neonatal outcome. This study is retrospective because today it is difficult to recruit infertile women treated with ART and willing to donate spare oocytes. Contrary to what happened in the past, today ample access to embryo and oocyte cryopreservation causes women undergoing IVF/ICSI to refrain from becoming oocyte donors. Furthermore, rigorous follow-up of pregnancies and lactation among donors and their recipient is also difficult to accomplish. The main drawback when analyzing cohort 1 is the high proportion of multiple gestations, a continuing problem in Latin America (14), which constitutes a confounding factor when interpreting perinatal outcome.

The second cohort includes data of pregnancies and deliveries in IVF/ICSI(a) patients as well as in oocyte recipient, reported to the RLA between 1995–2005. This cohort has the disadvantage that donors and recipients are not matched; however, it has the advantage of having the largest number of pregnancies in oocyte recipients compared with autologous IVF/ICSI pregnancies, both registered with the same methodology by the RLA.

Embryo Implantation

As seen in cohort 1, despite the age difference between oocyte donors and recipients, no differences were found in the capacity of embryos to implant in their progenitors and in oocyte recipients. In cohort 2, implantation rates among more than 15,437 transfer cycles in oocyte recipients was higher than in 103,749 transfer cycles in IVF/ICSI(a) (16.9% and 13.2%, respectively), demonstrating that a well-prepared endometrium is capable of hosting any normal embryo. Higher implantation rates with donated oocytes can be explained by the fact that most oocyte donors are young and healthy women, whereas women treated with IVF/ICSI(a) comprise a heterogeneous population of women with different degrees of reproductive health. Our data showing a slight but significant decreased implantation rate in oocyte recipients at least 40 years old, compared with oocyte recipients at most 34 years old (Table 1), is consistent with other authors (15), suggesting that there might be a uterine senescence factor that, in addition to poorer oocyte quality, contributes to decreased pregnancy rates in older women with autologous oocytes.

Obstetric Outcome

As described in a well-designed study by Kriegler et al. (16), no specific obstetric morbidity was attributable to the lack of genetic links between fetuses and their mothers, when comparing oocyte recipients with IVF/ICSI(a) pregnancies in women older than 38 years. In the present study, obstetric outcome is restricted to weight of newborns, gestational age at delivery, and perinatal mortality. In matched oocyte donors and recipients, as in cohort 1, no differences were observed in the weight of newborns and gestational age at birth when grouped by order of gestation. It is known that multiple gestations constitute a major risk factor for preterm birth and low-birth weight (17, 18, 19).

In cohort 1, the mean birth weight in singletons from oocyte recipients is slightly lower than their oocyte donors, whereas the difference in twins and triplets favors newborns born to oocyte recipients (Table 2). The same finding occurs with gestational age at birth. Therefore, obstetric outcome does not seem to be affected by the presence or absence of a genetic link between mother and embryo.

In cohort 2, the proportion of single newborns weighing at least 2,500 g was only 2.3% lower in oocyte recipients than in IVF/ICSI(a). Furthermore, Table 3 shows that preterm delivery is only 6% more prevalent among oocyte recipients than women undergoing IVF/ICSI(a). These differences have been attributed to an increased age of recipients, generating more complications during pregnancy (20). To examine this possibility, we studied the weights of 543 singletons born from oocyte recipients and reported to the RLA during 2006; the proportion of term deliveries (neonatal weight > 2,500 g) was not affected by woman's age. Term deliveries represented 84.6% (56/66) of births in women at most 34 years old, 83.2% (124/149) in women 35–39 years old, and

TABLE 4

Perinatal outcome in women undergoing regular IVF/ICSI(a) and oocyte recipients according to gestational order in cohort 2.

	Singleton[a]		Twins[b]		≥ Triplets[c]	
	IVF/ICSI (%)	OR (%)	IVF/ICSI (%)	OR (%)	IVF/ICSI (%)	OR (%)
Stillbirth (%)	121 (0.7)	20 (0.8)	282 (2.2)	40 (1.9)	243 (4.4)	44 (4.9)
Early neonatal death (%)	98 (0.6)	5 (0.2)	201 (1.6)	23 (1.1)	253 (4.6)	35 (3.9)
Live births (%)	17,572 (98.8)	2,600 (99.0)	12,058 (96.1)	2,062 (97.0)	4,974 (90.9)	820 (91.2)
Perinatal mortality	10–13/00		30–38/00		88–90/00	

Note: Chi-square Test comparing IVF/ICSI(a) and OR.
[a] $P = 0.05$.
[b] $P = 0.529$.
[c] $P = 0.106$; OR = oocyte recipient.

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85.4% (280/ 328) in women at least 40 years old (NS). Therefore, we think that, provided there are no general diseases known to affect gestation, the age of the recipient (maximum of 50–55 years old in our study) does not affect the outcome of gestation.

Perinatal Outcome and Breastfeeding

Overall, there were minor differences in perinatal outcome (stillbirth plus early neonatal death) in 35,802 IVF/ICSI(a) pregnancies and 5,482 clinical pregnancies with donated oocytes. When comparing 17,693 singletons born from IVF/ICSI(a) and 2,620 single births in oocyte recipients, perinatal mortality was 13 per thousand for IVF/ICSI(a) and 10 per thousand for oocyte recipients. As expected, the most dramatic effect in perinatal mortality is caused by multiple births rather than the source of oocytes or the genetic similarity between the embryo or fetus and the woman responsible for carrying the fetus through pregnancy and delivery (Table 4).

The duration of lactation (exclusive and total length) was also similar in oocyte donors and recipients, showing that women capable of carrying a successful pregnancy and giving birth to a healthy infant can also nurture the infant with equal competence.

Unfortunately, in this study, obstetric outcome is restricted to the weight of newborns, gestational age at birth, and perinatal mortality. The RLA does not report obstetric morbidity and other complications of pregnancy. Therefore, other confounding factors cannot be ruled out when comparing pregnancy outcome in oocyte donors and recipients.

In conclusion, embryos can implant and cohabit equally well in the uterus of donors and recipients. The similar proportion of term deliveries, healthy newborns, and prolonged lactation in oocyte recipients and their donors is reassuring that, from a clinical perspective, the establishment of motherhood does not require genetic links between the embryo/fetus and the woman.

Furthermore, the abundant psychosocial data showing there is no impediment for strong emotional ties and strength in family links when they are built in the absence of genetic links is also reassuring.

These two sets of evidence contribute to our hypothesis that the capacity of women to deliver children, love them, and build families in the absence of a genetic identity is not the result of an isolated gift from the spirit. In doing so, all biological systems involved in the reproductive process act efficiently and in perfect harmony with the sole purpose of nurturing new life.

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