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ASSISTED REPRODUCTION TECHNOLOGIES

Similar reproductive outcomes between lesbian-shared IVF (ROPA) and IVF with autologous oocytes

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Abstract

Purpose To compare reproductive outcomes of the ROPA method (reception of oocytes from partner) to IVF with autologous oocytes. To study the impact of the absence of a genetic link between the embryo and its recipient in reproductive outcomes.

Methods Retrospective multicentric cohort study performed from January 2011 to December 2020 in 18 fertility clinics in Spain. A total of 99 ROPA (73 couples) and 2929 non-ROPA cycles (2334 couples or single patients) of women younger than 38 years old with no known female fertility disorder were included. Clinical outcomes were compared between both groups and included positive pregnancy test, clinical pregnancy, miscarriage, ectopic pregnancy, pre-term birth, live birth, weeks of gestation at birth, and newborn weight at birth.

Results No differences were found between groups in clinical outcomes. The total clinical pregnancy rates per embryo transfer were 57% and 50.2% ($p=0.15$) and the live-birth rates were 46.1% and 40.9% ($p=0.14$) for the ROPA and non-ROPA groups, respectively. When adjusted to age and BMI of donors and recipients, there were also no differences in live-birth rates between both groups. The cumulative live-birth rate per ROPA cycle was 73.7% and the cumulative live-birth rate per couple was 78.3%.

Conclusion Clinical outcomes following the ROPA method and IVF with autologous oocytes were found to be similar. These findings suggest no impact of the absence of genetic ties between the embryo and the uterus on reproductive treatments' outcomes. Data regarding the outcomes of the ROPA method are reassuring.

Keywords Assisted reproductive techniques · Co-IVF · Fertilization in vitro · LGBT · Lesbian · Oocyte donation · Shared IVF

Introduction

Female couples seeking to build a family with their own gametes must use some form of assisted reproduction (ART). While most female couples accessing care in fertility clinics undergo intrauterine insemination (IUI) with donated semen due to its more cost-effective and less invasive nature, in vitro fertilization (IVF) provides additional benefits [1]. IVF not only has higher success rates when compared to IUI but may result in more than one embryo, which can be used in case of failure or for further children [2–5].

The ROPA method (from Spanish: *recepción de ovocitos de pareja*; in English: reception of oocytes from partner), also called lesbian-shared IVF or co-IVF, consists of an assisted reproductive technique for female couples in which a member of the couple provides the oocytes (donor or genetic mother), and the other receives the resulting

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embryo and gestates (recipient or gestational mother) [6, 7]. With the ROPA method, both women actively participate in the generation of their child, which means they are able to share biological motherhood [8, 9]. Women may choose the ROPA method due to medical reasons. Examples of medical conditions which may prompt the use of the ROPA method include one member of a lesbian couple having impaired ovarian function or one member of a lesbian couple having a condition limiting or contraindicating pregnancy. The ROPA method provides flexibility so that women may choose the role they wish to play in the process. Additionally, women may swap roles in different occasions (reverse ROPA), undergo both roles at the same time (reciprocal ROPA), and may turn a ROPA treatment into a "one-way" IVF at any time [10–14].

Little information has been published about the ROPA method despite its extensive use for the last decade in many countries [15].

The ROPA method is equivalent to IVF with donated oocytes from the clinical and laboratory perspective, with the only difference being that donation takes place within the couple and does not involve a third party. In addition, the oocyte provider in ROPA is not usually subject to the thorough selection process undergone by third party donors. Therefore, the oocyte provider in ROPA may not be a young, healthy woman with good ovarian reserve, no fertility issues, and no history of unfavorable reproductive or obstetric outcomes [16]. It is questionable whether the good prognostic features of oocyte donation procedures may eventually mask a negative impact of the absence of a genetic link between the embryo and the uterus [17]. This potential bias is not expected in the ROPA method, since there is no previous selection of a young third party oocyte donor.

It is well known that oocyte donation pregnancies are associated with a higher incidence of obstetric complications, such as preeclampsia, low birth weight, pre-term birth, and caesarean section [18, 19]. Inadequate immunological recognition caused by a genetically unrelated embryo can lead to deficient placentation, which would ultimately explain the higher incidence of these phenomena [20–22]. It is not clear if pregnancies with donated semen are also associated with an increased risk of preeclampsia, due to lack of prior maternal semen exposure and recognition [23, 24].

When considering that immunological maladaptation may be caused by a person carrying a genetically unrelated embryo, we hypothesized that immunological maladaptation may also lead to poorer reproductive outcomes, including lower pregnancy rates and higher risk of miscarriage. We theorized that comparing the clinical outcomes of ROPA and IVF treatments with autologous oocytes and donor semen may allow us to evaluate the true impact of the absence of a genetic link between the uterus and the embryo on reproductive outcomes.

Objective

The aim of the study is to assess whether the absence of genetic links between the uterus and the embryo has any impact on the outcomes of ART, by comparing the reproductive outcomes of ROPA to IVF with autologous oocytes and donated sperm.

Methods

This was a multicenter retrospective cohort study comparing IVF cycles between ROPA couples using partner eggs and donor sperm to patients using autologous eggs and donor sperm. The study protocol was approved by the local Institutional Ethical Review Board.

Inclusion criteria were female couples who underwent the ROPA method and patients who underwent an IVF with autologous oocytes and donated sperm. Female patients older than 37 years, antimullerian hormone (AMH) levels below 1.2 ng/mL, antral follicle count (AFC) below 5, ovulatory disorders, endometriosis, uterine fibroids, adenomyosis, history of recurrent implantation failure, or recurrent miscarriage were excluded. Data from an individual's first egg retrieval and only cycles with single oocyte retrieval were included. All inclusion and exclusion criteria were applied to both ROPA (recipients and donors) and non-ROPA patients. Cycles performed from January 2011 (the year ROPA method was introduced in our clinical practice) to December 2020, in 18 different fertility clinics of the same group in Spain, were included.

Data were anonymously retrieved from electronic medical records. These included the following variables: age, body mass index (BMI), AFC, stimulation protocol, oocyte retrieval details, embryo transfer details, oocyte data, and embryo data.

The primary endpoint was the live-birth rate (LBR), defined as the number of deliveries resulting in at least one live-born. Secondary outcomes included positive pregnancy test rate (defined as serum levels of beta human chorionic gonadotropin (b-hCG) > 10 IU/ml after embryo transfer), clinical pregnancy rate (defined as the presence of at least one intrauterine gestational sac on ultrasound), miscarriage rate (defined as any pregnancy loss before week 12, including biochemical miscarriage with a positive b-hCG test without evidence of a gestational sac and clinical miscarriage after confirmation of an intrauterine gestational sac), ectopic pregnancy rate (defined as a gestational sac located outside the uterine cavity), gestational age (GA) at birth, pre-term birth rate (defined as live birth after 24 weeks and before 37 weeks of gestation), and newborn weight.

After assessing normality of the continuous variables, parametric (*T*-test) and non-parametric (Mann–Whitney) tests were used to compare normally and non-normally distributed variables respectively. The chi-square test was used to compare categorical variables. Multivariate analysis was performed using logistic regression, excluding potential confounders (including age, which was significantly different between groups). We used a significance level of 0.05. Cases with missing data were excluded, on a *per analysis* basis.

Results

Characteristics of the sample

Patients and protocols' features

A total of 99 ROPA cycles (73 couples) and 2929 IVF cycles with autologous oocytes (2334 patients) were included. Both ROPA and non-ROPA cycles were performed during all the years included in the study, despite a progressively larger number of cycles in more recent years for both groups (Table 1).

Regarding couples who underwent ROPA, there were no significant differences between donors and recipients regarding age, BMI, or AFC (Table 2). The difference of ages within each couple showed no pattern ($p = 0.70$).

Comparing the ROPA and the non-ROPA samples, the mean age of both donors and recipients was 2.4 and 2.5 years higher in the non-ROPA group respectively. No differences were found regarding BMI. In addition, there were no differences between groups regarding ovarian stimulation protocol, endometrial preparation for frozen embryo transfer (FET), and estradiol levels on the day of triggering or transfer programming (Table 3).

Table 1 Distribution (number and percentage) of cycles per year

Year	ROPA	Non-ROPA
2011	2 (2.0%)	155 (5.3%)
2012	4 (4.0%)	226 (7.7%)
2013	7 (7.1%)	255 (8.7%)
2014	9 (9.1%)	319 (10.9%)
2015	10 (10.1%)	296 (10.1%)
2016	11 (11.1%)	303 (10.3%)
2017	12 (12.1%)	282 (9.6%)
2018	14 (14.1%)	326 (11.2%)
2019	17 (17.2%)	414 (14.1%)
2020	13 (13.1%)	353 (12.1%)

Table 2 Comparison of patients' main basal features within the ROPA group (recipients versus donor)

	ROPA recipient mean (SD)	ROPA donor mean (SD)	*p*
Age	32.6 (3.4)	32.7 (3.1)	> 0.99
Body mass index	24.0 (3.9)	24.4 (5.5)	0.72
Antral follicle count	13.7 (7)	15.5 (12.2)	0.67

Oocytes and embryos

The ROPA group obtained more mature oocytes than the non-ROPA group (10.1 vs. 7.7; $p < 0.01$). In addition, a higher number of good quality embryos, according to the Spanish ASEBIR classification (embryos grade A: 0.59 vs. 0.44; $p = 0.03$; embryos grade B: 1.47 vs. 0.81; $p < 0.01$), and a higher number of viable embryos (2.84 vs. 1.76; $p = 0.02$) were obtained in this group (Table 4).

Outcomes

Fresh embryo transfer

There were no differences in clinical outcomes after fresh embryo transfer between ROPA and IVF with autologous oocytes, including positive pregnancy test (56.9% vs. 58.8%; $p = 0.80$), clinical pregnancy (47.7% vs. 50.2%; $p = 0.71$), miscarriage (16.9% vs. 16.9%, $p > 0.99$), and live-birth (40.0% vs. 41.3%; $p = 0.34$) rates. Furthermore, the ectopic pregnancy rates (0% and 0.6%; $p > 0.99$) did not show significant differences between groups. In the same way, mean gestational age at delivery (38.1 weeks vs. 38.9 weeks; $p = 0.56$), pre-term birth rate (17.6% vs. 11.4%; $p = 0.44$), and newborn weight (2568 g vs. 2980 g; $p = 0.10$) were not significantly different (Table 5).

Table 3 Comparison of patients' basal characteristics and cycle details between the ROPA and the non-ROPA groups

	ROPA	Non-ROPA	*p*
Age (recipient)	32.6 (3.4)	35.14 (2.8)	**< 0.01**
Age (donor)	32.7 (3.1)		**< 0.01**
BMI (recipient)	24.0 (3.9)	23.8 (4.2)	0.22
BMI (donor)	24.4 (5.5)		0.47
Stimulation and PGT-a			
FSH total dosage	1675 (778)	1709 (677)	0.74
Estradiol levels on day of triggering	2177 (1760)	1750 (1375)	0.11
PGT-a	6.4%	6.9%	> 0.99

Table 4 Comparison of features related to oocytes and embryos between the ROPA and the non-ROPA groups

	ROPA	Non-ROPA	*p*
Oocytes and Embryos			
Number of oocytes retrieved	12.4 (7.9)	10.3 (7.0)	**< 0.01**
Number of mature oocytes obtained	10.1 (6.4)	7.7 (5.6)	**< 0.01**
Number of embryos classified as A	0.59 (1.2)	0.44 (1.1)	**0.03**
Number of embryos classified as B	1.47 (2.3)	0.81 (1.5)	**< 0.01**
Number of viable embryos	2.84 (3.8)	1.76 (2.6)	**0.02**
Frozen embryo transfers			
Type of cycle			
Natural	19.7%	17.3%	0.17
Hormonal replacement	80.3%	79.5%	0.36
Ovarian stimulation	0%	3.2%	0.10
Endometrial thickness (last measurement in follicular phase)	9.1 (1.6)	9.1 (3.1)	> 0.99
Estradiol levels (last measurement in follicular phase)	1180 (1918)	963 (1405)	0.56

Table 5 Comparison of the main reproductive outcomes between ROPA and non-ROPA IVF in fresh and frozen embryo transfers (rates are per transfer)

	ROPA	Non-ROPA	*p*
Fresh embryo transfer			
Positive pregnancy test rate	56.9%	58.8%	0.80
Clinical pregnancy rate	47.7%	50.2%	0.71
Miscarriage rate	16.9%	16.9%	> 0.99
Ectopic pregnancy rate	0%	0.6%	> 0.99
Live-birth rate	40.0%	41.3%	0.47
Gestational age at delivery	38.1 weeks (3.4)	38.9 weeks (2.2)	0.56
Preterm birth rate	17.6%	11.4%	0.44
Weight of the newborn	2568 (585)	2980 (596)	0.10
Frozen embryo transfer			
Positive pregnancy test rate	69.8%	59.5%	0.12
Clinical pregnancy rate	66.7%	51.4%	**0.02**
Miscarriage rate	17.4%	18.3%	> 0.99
Ectopic pregnancy rate	0%	0.3%	> 0.99
Live-birth rate	52.4%	41.3%	0.05
Gestational age at delivery	39.2 weeks (1.5)	39.1 weeks (2.4)	0.39
Preterm birth rate	0%	12.3%	0.15
Weight of the newborn	3098 (464)	3169 (649)	0.81

Frozen embryo transfer

Concerning clinical outcomes following frozen embryo transfer, only the clinical pregnancy rate was significantly higher in the ROPA group (66.7% vs. 51.4%; $p = 0.02$). All the other clinical rates were similar or in favor of the ROPA group as well. Differences were not statistically significant, including positive pregnancy test rate (69.8% vs. 59.5%; $p = 0.12$), miscarriage rate (17.4% vs. 18.3%; $p > 0.99$), ectopic pregnancy rate (0% vs. 0.3%; $p > 0.99$), and live-birth rate (52.4% vs. 41.3%, $p = 0.09$). In addition, no differences were found regarding gestational age at delivery (39.2 weeks vs. 39.1 weeks; $p = 0.39$), pre-term birth rate (0% vs. 12.3%, $p = 0.15$), and newborn weight (3098 g vs. 3169 g; $p = 0.81$) (Table 5).

First embryo transfer

Regarding only the first embryo transfer of each cycle, 86.1% of the ROPA cycles had a fresh embryo transfer (in a "synchronous cycle") vs. 75.4% in the non-ROPA group ($p = 0.04$). No differences were found in clinical outcome rates, including positive pregnancy test (53.8% vs. 60.5%; $p = 0.39$), clinical pregnancy (46.2% vs. 52.3%; $p = 0.40$), miscarriage (11.6% vs. 9.2%, $p = 0.85$), ectopic pregnancy (0% and 0.6%; $p > 0.99$), and live birth (34.6% vs. 43.1%; $p = 0.26$). There were also no differences regarding mean gestational age at delivery (37.6 weeks vs. 38.9 weeks; $p = 0.08$), pre-term birth rate (18.2% vs. 13.2%; $p = 0.63$), and newborn weight (2701 g vs. 3054 g; $p = 0.20$) (Table 6).

Overall outcomes

Considering fresh and frozen embryo transfers altogether, no significant differences were found in any of the clinical outcomes, including the rates of positive pregnancy test (63.3% vs. 58.3%; $p = 0.27$), clinical pregnancy (57% vs. 50.2%; $p = 0.15$), miscarriage (17.2% vs. 16.9%; $p > 0.99$), ectopic pregnancy (0% vs. 0.5%; $p > 0.99$), and live birth (46.1% vs. 40.9%; $p = 0.14$). Gestational age at delivery (39.1 weeks vs. 38.7 weeks; $p = 0.17$), pre-term birth rate (7.9% vs. 12.1%; $p = 0.61$), and newborn weight (2809 g vs. 3072 g; $p = 0.17$) also had no significant differences (Table 6).

Table 6 Comparison of the main reproductive outcomes between ROPA and non-ROPA in first transfer and cumulative rates (rates are per transfer)

	ROPA	Non-ROPA	*p*
First embryo transfer			
Fresh embryo transfer rate	86.1%	75.4%	0.04
Positive pregnancy test rate	53.8%	60.5%	0.39
Clinical pregnancy rate	46.2%	52.3%	0.40
Miscarriage rate	11.6%	9.2%	0.85
Ectopic pregnancy rate	0%	0.6%	> 0.99
Live-birth rate	34.6%	43.1%	0.26
Gestational age at delivery	37.6 weeks (3.4)	38.9 weeks (2.4)	0.08
Preterm birth rate	18.2%	13.2%	0.63
Weight of the newborn	2701 g (210)	3054 g (609)	0.20
Cumulative rates (including all fresh and frozen embryo transfers)			
Positive pregnancy test rate	63.3%	58.3%	0.27
Clinical pregnancy rate	57.0%	50.2%	0.15
Miscarriage rate	17.2%	16.9%	> 0.99
Ectopic pregnancy rate	0%	0.5%	> 0.99
Live-birth rate	46.1%	40.9%	0.14
Gestational age at delivery	39.1 weeks (2.4)	38.7 weeks (2.6)	0.26
Preterm birth rate	7.9%	12.1%	0.61
Weight of the newborn	2809 (578)	3072 (620)	0.17

Table 7 Odds ratio of main clinical outcomes between ROPA and IVF with autologous oocytes, resulting from multivariate analysis excluding age and BMI of both donors and recipients

	Odds ratio (ROPA vs. IVF with autologous oocytes)	*p*
Positive pregnancy test rate	1.24	0.47
Clinical pregnancy rate	1.18	0.55
Miscarriage rate	1.78	0.46
Live-birth rate	1.19	0.55

The differences in the odds ratios for the main clinical outcomes after multivariate analysis controlling for potential confounders (age and BMI) were not statistically significant. The odds ratio for a live birth between ROPA and non-ROPA IVF was 1.19 ($p = 0.55$) (Table 7).

ROPA method

The total live-birth rate per embryo transfer in the context of a ROPA method was 46.1%. Cumulative live-birth rate per cycle was 73.7%. Globally, 78.3% of the couples achieved at least one live birth in the course of ART treatments.

Discussion

Despite its wide use in the last decade, there is a lack of information in medical literature regarding ROPA [25]. In this study, we compare the outcome of this technique to IVF with autologous oocytes and donated sperm in patients of good prognosis. This is a way not only to assess the applicability of the ROPA method in clinical practice, but also to evaluate the clinical impact of the absence of any genetic link between the embryo and the recipient [18].

When comparing donors and recipients of the ROPA method, no differences were found regarding age, BMI, or AFC. It was found that both donors and recipients were younger in the ROPA group compared to the non-ROPA group. No differences were found in ovarian stimulation or endometrial preparation protocols. However, the number of retrieved oocytes was significantly higher in the ROPA group (an average of 2.4 more mature oocytes).

There were no statistically significant differences in clinical outcomes following fresh embryo transfer between groups. However, such comparison is hampered by the fact that all fresh embryo transfers in the non-ROPA group were carried out in an ovarian stimulation cycle, while all fresh transfers performed in the ROPA group took place in artificial endometrial preparation cycles [6].

Theoretically, the most reliable way to assess the clinical impact of the absence of genetic ties between the embryo and the recipients would be through the analysis of frozen embryo transfers alone, since there were no differences in endometrial preparation protocols between groups in such cases. Clinical pregnancy rate of FET was significantly higher in the ROPA group, but this did not reflect on live-birth rate. In addition, no differences were found in miscarriage or ectopic pregnancy rates, gestational age at birth, pre-term birth rate, and weight of the newborn. However, it is important to notice that such an approach is also susceptible to bias, since the ROPA group had a higher number of good quality embryos, and the best embryos were the first to be used in the fresh transfer cycles. Therefore, the ROPA group had a higher number of good quality spare embryos to freeze.

When focusing on the first embryo transfer, there was a higher proportion of fresh embryo transfers in the ROPA group, in the so-called "synchronous cycle." This may be explained by the absence of risk of late ovarian hyperstimulation syndrome in these patients, since the woman submitted to embryo transfer did not undergo ovarian stimulation [6, 26]. Regardless of whether it is a fresh or vitrified transfer, we found no differences regarding the various clinical outcomes between both groups.

Globally, ROPA treatments had a cumulative live-birth rate per cycle of 73.7%, and a cumulative live-birth rate

per couple (i.e., percentage of couples ending up with at least one live birth in any cycle) of 78.3%.

These results point to similar reproductive outcomes between the ROPA method and IVF with autologous oocytes. These findings also suggest that the absence of genetic ties between the embryo and the recipient has no impact on fertility treatments' outcome. In view of live-birth rates, the findings of this study are reassuring to ROPA patients.

This study has some limitations. This is a retrospective cohort study, which implies some data could not be retrieved. The sample of ROPA treatments was reduced because of stringent exclusion criteria, that eliminated advanced age and fertility disorders to avoid potential confounders, even though, in the end, the sample size was similar to the series published to date [25]. Another important limitation is that there were differences in age between both groups. Patients in the ROPA group were younger, which may be explained by the fact that same-sex couples do not have a lag period, when trying natural conception. These patients know in advance they will need assisted reproduction to procreate so they are expected to search for the help of ART earlier in life [27, 28]. Such difference in age is probably the cause of a higher number of mature oocytes and viable embryos being obtained in the ROPA group.

Patients were excluded in the presence of any disorder that might have an impact on fertility. However, some patients may have undergone previous less complex fertility treatments, such as insemination. Even though there are many couples choosing IVF in a first stance due to its higher success rates, based on previous studies, one may assume the ROPA group is less likely to have previous inseminations, since many female couples go directly to a double-parented method, excluding ad initium the possibility of insemination [1, 29]. Likewise, patients in the non-ROPA group include heterosexual couples with infertility of unknown origin, while virtually, none of the female couples has a background of infertility [28]. Therefore, we can suspect the control group could have a worse prognosis due to occult factors.

Previous studies report an increase in pregnancy complications following oocyte donation, such as hypertensive disorders [30]. In this study, we focused merely on the outcomes of fertility treatments. The ROPA method may be an interesting way to study the true impact of oocyte donation on further obstetric complications in the future.

Conclusion

The ROPA method and IVF with autologous oocytes were found to have similar reproductive outcomes, including positive pregnancy test, clinical pregnancy, miscarriage, ectopic pregnancy, pre-term birth, live birth, weeks of gestation at birth, and newborn weight at birth. Similar outcomes were found both after fresh and frozen embryo transfers. These findings suggest no impact of the absence of genetic ties between the embryo and the uterus on live-birth rates following IVF.

Based on the results of this study, data regarding the reproductive outcomes of the ROPA method seem reassuring.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Pedro Brandão and Nathan Ceschin. The first draft of the manuscript was written by Pedro Brandão and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent, data, materials, and/or code availability Giving the retrospective nature of the work, the anonymized processing of data and the fact that no individual data were used, patients' consent was not required.

Anonymized data was used in this research project, i.e., there was a technical and functional separation between the researcher and the people who performed the anonymization and kept the information that made re-identification possible.

The personal data was treated according to Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016, concerning the protection of natural persons with regard to the processing of personal data and the free circulation of such data.

Declarations

Ethics approval The study protocol, named 2011-VLC-093-PB, was approved by the Institutional Ethical Review Board of IVIRMA Valencia.

Competing interests The authors declare no competing interests.

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