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ORIGINAL ARTICLE *Infertility*

A novel transnational fresh oocyte donation (TOD) program based on transport of frozen sperm and embryos

A. La Marca[1,*], M. Dal Canto[2,3], M. Buccheri[2], M. Valerio[2], M. Mignini Renzini[2,3], A. Rodriguez[4], and R. Vassena[4]

[1]Clinica EUGIN, University of Modena and Reggio Emilia, 41123 Modena, Italy [2]Clinica EUGIN, 41123 Modena, Italy [3]Biogenesi, Reproductive Medicine Centre, Monza, Italy [4]Clínica EUGIN, Barcelona 08029, Spain

*Correspondence address. Clinica EUGIN and University of Modena and Reggio Emilia, 41123 Modena, Italy. E-mail: alamarca@eugin.it; antonio.lamarca@unimore.it

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STUDY QUESTION: What is the clinical efficacy of an oocyte donation program based on the transportation of frozen semen and embryos between two countries?

SUMMARY ANSWER: The transnational oocyte donation program is efficient and reliable and it could provide a first-line strategy to overcome the lack of donors in some countries.

WHAT IS KNOWN ALREADY: While there is increasing need for donated oocytes, in many countries the availability of donors is still insufficient to cover the therapeutic demands, and patients are referred abroad for treatment. Since embryo cryopreservation is reliable and efficient, we propose a strategy based on frozen embryos instead of frozen oocytes to satisfy the increasing demand for cross border oocyte donation.

STUDY DESIGN, SIZE, DURATION: This is a retrospective cohort study including 630 patients treated from December 2015 to July 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Infertile women were treated with elective vitrified-thawed embryo shipping and embryo transfer (ET) between two IVF clinics, one in Spain and one in Italy.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 2617 embryos were created for the 630 patients and the survival rate after warming was 98.5%. After the first ET the live birth rate (LBR) was 30.6%. In 476 patients (75.5%), embryos were transferred at the cleavage stage (Day 2 or 3) and the LBR was 29.2%. Vitrified blastocysts were available for 154 patients (24.5%) and the LBR was 35%. Among patients who did not achieve a pregnancy after the first frozen ET (FET), 92.5% had at least one frozen embryo for successive procedures. 213 patients underwent a second FET. The LBR at the second FET was 30%. The cumulative LBR at the end of the observation period was 39.3%.

LIMITATIONS, REASONS FOR CAUTION: The study design was retrospective. A direct comparison with vitrified oocyte donors cycle and subsequent fresh ET would have permitted to compare this strategy versus the current standard based on vitrified gametes.

WIDER IMPLICATIONS OF THE FINDINGS: The LBR found in our study is more than acceptable and seems to be higher than what reported with vitrified oocytes. The transnational fresh oocyte donation program may have several advantages over the shipment of vitrified oocytes: similarly to the fresh oocyte donation program it allows for personalized care in oocyte recipient, which is provided by assigning a flexible number of oocytes, and at the same time it maintains the benefit of a frozen ART program permitting scheduling flexibility. The TOD program is efficient and may be proposed as a first-line strategy for distance and inter-countries oocyte donation programs.

STUDY FUNDING, COMPETING INTEREST(S): None.

TRIAL REGISTRATION NUMBER: NA.

Key words: oocyte donation / transnational transport / embryo vitrification / infertility / cumulative live birth

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Introduction

IVF with donor oocytes has increasingly become a treatment strategy for women who cannot rely on their own oocytes. The American Society for Assisted Reproductive Technology (SART) reported that more than 9000 donor oocyte cycles were initiated in 2014–2015 (www.sartcorsonline.com). The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) also reported 133 679 oocyte donor cycles between 2008 and 2010 in 40 countries, with an overall increase in cycles of 35.8% between 2008 and 2010 (Dyer *et al.*, 2016).

These figures highlight the need for donated oocytes. Nevertheless, in many countries, the availability of donors is still insufficient to cover the therapeutic demands, and patients are referred abroad to be treated.

Recent improvements in oocyte cryopreservation have radically changed oocyte donation programs, uncoupling the donation from the reception both in space and time. Oocyte vitrification provides high survival rates after warming, and pregnancy and live birth rates (LBR) similar to cycles with fresh oocytes (Rienzi *et al.*, 2017). This has led to the development of cryobanks of donated oocytes, with several recipient programs currently 100% based on the use of vitrified donor oocytes. Donor egg banking provides relative benefits in terms of scheduling flexibility and may permit better phenotypical matching, especially with uncommon phenotypes. Most importantly, donor oocyte banking has also made it possible to transfer oocytes across borders. This is a second revolution on the oocyte donation program as it increases access to treatment, as women living in countries with low availability of donors can use donated oocytes donated abroad, locally.

However, while single-center studies (Cobo *et al.*, 2015) report comparable success rate when using vitrified and fresh oocytes, this does not seem to be confirmed in larger cohorts. In an analysis of cycles performed in more than 460 US clinics, vitrified oocyte cycles were reported to give lower LBR per started cycle (43.0 versus 49.4%; a relative risk (RR) 0.87, 95% CI: 0.80–0.95), after adjusting for significant confounding factors (Crawford *et al.*, 2017). More recently, a retrospective analysis of 2013 through 2015 aggregate US national data including 30 160 IVF cycles with either fresh or cryopreserved donor oocytes indicated that fresh donor oocytes produced significantly higher LBR per recipient cycle start than cryopreserved donor oocytes (51.1 versus 39.7%) and concluded that fresh oocyte donation must, therefore, still be considered the 'gold standard' in oocyte donation (Kushnir *et al.*, 2018)

Compared to oocytes, the performance of embryo cryopreservation has proven to be more reliable and efficient (Shi *et al.*, 2018; Zhang *et al.*, 2018). Because of the very high survival rate after thawing and the high implantation rate of vitrified embryos, the proportion of frozen embryo transfer (FET) cycles is estimated to contribute 24.7% of the total number of transfer performed in Europe in 2014 (De Geyter *et al.*, 2018). The LBR from elective FET has been reported to be comparable to fresh ET (50.2 and 48.7%, respectively) (Shi *et al.*, 2018).

Accordingly, we propose a strategy based on frozen embryos instead of frozen oocytes to satisfy the increasing request of cross border oocyte donation. This is based on the shipment of frozen sperm from the country of the recipient to the country of the oocyte donor. Here the thawed sperm is used to inseminate fresh donor oocytes and the resulting embryos are then frozen and transported back to the referring IVF center. This model allows for a new program for transnational oocyte donation (TOD) (Fig. 1).

The objective of this study is to describe in detail a novel fresh oocyte donation program based on transportation of frozen semen and embryos between two countries, and to report on the clinical outcomes of such a program.

Materials and Methods

Design and ethical approval

This is a retrospective cohort study of anonymized donor oocyte IVF cycles with elective vitrified-thawed embryo shipping and ET from December 2015 to July 2017 between two IVF clinics, one in Spain and one in Italy. This study has been approved by the local Ethical Committee.

Patient characteristics

The indications for oocyte donation were as follows: advanced female age, history of failed IVF cycles with own oocytes, low ovarian reserve, poor oocyte quality, genetic or chromosomal abnormalities transmissible to offspring, and spontaneous or iatrogenic menopause. All recipients underwent endometrial preparation with oral contraceptives for 21 days (0,150 mg levonrogestrel + 0,030 mg ethynilestradiol, Egogyn, Bayer, Italy) if they had irregular periods, with an injection of GnRH agonist (GnRHa; Decapeptyl, Ipsen Pharma, Italy) depot on the 17th day of the oral contraceptive. Recipients with regular periods were administered a GnRHa depot in the midluteal phase of the previous menstrual cycle. Estrogen preparation started from the first day of either menses after the administration of the GnRHa, with patches (150 mg/3 days) or pills (6 mg/day) for all recipients. Vaginal progesterone (400 mg/12 h) was then started to prepare the endometrium for the ET. The progesterone support was started 2–3 or 5 days before the transfer of 2–3 or 5 days embryos, respectively.

Donor characteristics

All oocyte donors (age 20–35 years) had normal ovaries at transvaginal ultrasound, adequate ovarian reserve as evidenced by an antral follicular count above 10, and displayed a correct response to ovarian stimulation, i.e. a progressive and gradual increase in follicular sizes, concordant with FSH administration. All donors were stimulated with exogenous gonadotrophins (recombinant FSH), while the pituitary suppression was based on the GnRH antagonist fixed from the sixth day of ovarian stimulation. Ovulation was triggered when three or more follicles ≥18 mm diameter were present on both ovaries. The ovulation trigger used was 0.3 mg of the GnRH agonist Triptorelin (Decapeptyl Ipsen, Pharma Biotech, France).

After donor oocyte retrieval, the decision of how many oocytes should be assigned to each recipient was personalized and based on several factors such as the couple infertility history, previous pregnancies and live births for either partners, the presence of male factor, the state of the uterine cavity, co-morbidities which may affect implantation and pregnancy, and the need for advanced embryo testing such as PGD. The decision was supported by an internal algorithm which has been developed through almost 20.000 clinical cases, with the goal of guaranteeing high LBR which remain stable across a wide variety of clinical situations, in keeping with the dual objective of providing the highest standard of care while managing a limited resource. In this retrospective study the mean (±SD) number of oocytes retrieved from donors and assigned to individual recipients was 11 ± 2.1 and 6.8 ± 1.0, respectively

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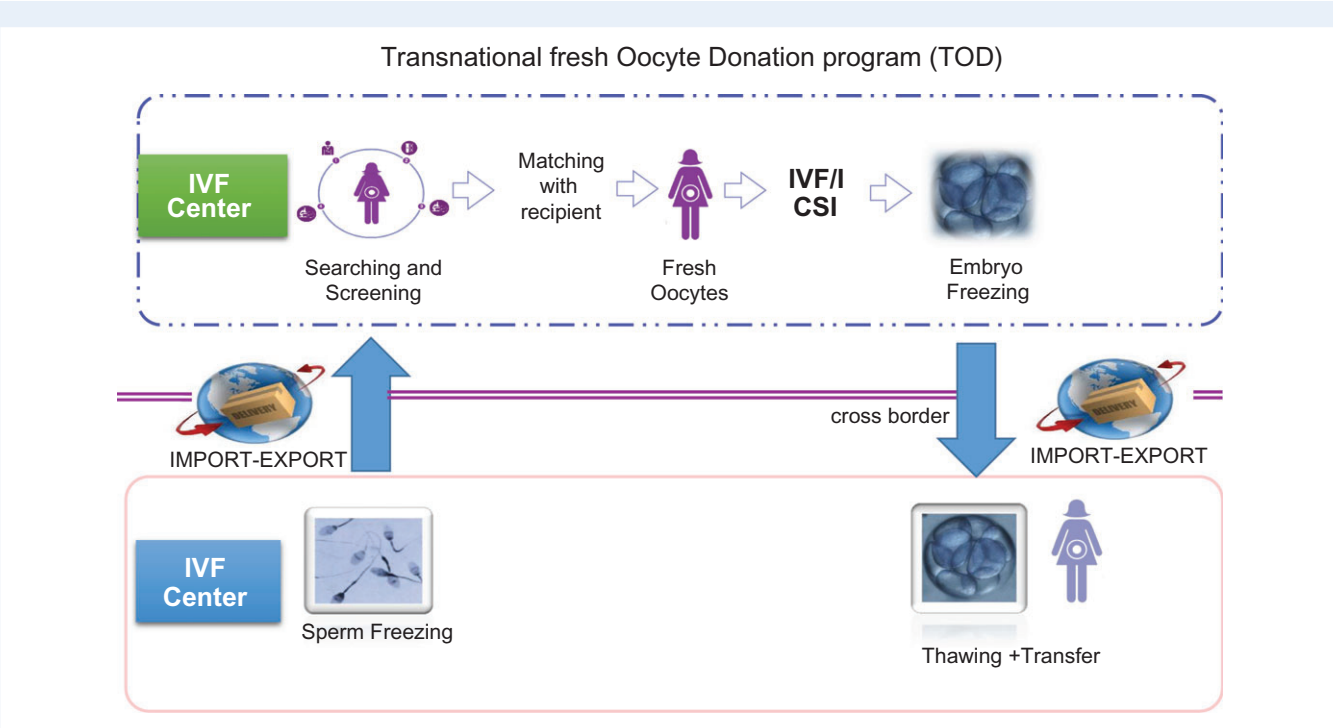

Figure 1 A schematic representation of the transnational oocyte donation program.

Freezing, thawing and shipping procedures

All the couples enrolled for IVF with donor eggs at Clinica Eugin Modena, Italy had the husband's sperm frozen. All sperm samples were selected by gradients (Sil-Select stock solution, Fertipro, Belgium). Samples with ≥1 million sperm and ≥10% total motility (progressive + non-progressive) after preparation were cryopreserved. Sperm samples were diluted 1:1 with cryoprotectant (Cryosperm, Origio, Denmark), loaded into straws (CBS High Security sperm 0.5 ml straw, Cryo Bio System, France) and cryopreserved in liquid nitrogen vapor.

The shipment of frozen samples (sperms or embryos/blastocysts) from Italy to Spain and vice versa was done in collaboration with Labcourrier SL (Valencia, Spain) by car using a Dryshipper that maintained the material in liquid nitrogen vapor.

After oocyte collection from donors, the frozen sperm sample was warmed and sperm were prepared by removing the cryoprotectant with PureSperm Wash (Nidacon, Molndal, Sweden), followed by centrifugation for 5 min at 250 g. Fertilization was evaluated 16–18 h after ICSI and the oocytes presenting two pronuclei and two polar bodies were maintained for subsequent culture steps. Fertilized oocytes were cultured in G-TL medium (Vitrolife, Sweden) until D + 3 or D + 5. In this oocyte donor program, the decision on when to cryopreserve embryos was mainly based on the number of two pronucleate (PN) embryos obtained. If this number was at least 5, the embryos were left in culture and vitrified at the blastocyst stage, while if the 2PN were <5, they were vitrified at D2–3. Only viable embryos and blastocysts were vitrified according to the Kitazato Vitrification protocol (Kitazato BioPharma Shizouka, Japan) using the cryotop directly into liquid nitrogen. Day 2–3 embryos were considered viable for cryopreservation if they had at least two cells with no more than 30% of cellular fragmentation, and more than six cells with no more than 30% of cellular fragmentation, respectively. Blastocysts were considered viable for cryopreservation if they had cavitated.

On the day of FET, the embryos/blastocysts were warmed according to Kitazato Thawing protocol (Kitazato BioPharma Shizouka, Japan). The cryotop was quickly removed from liquid nitrogen and immersed for 1 min in thawing solution pre-warmed to 37°C. After this step, embryos were moved into the dilution solution for 3 min, then into the washing solution 1 for 5 min and to the washing solution 2 for 1 min. Finally, the embryos/blastocysts were transferred to a culture dish containing the appropriate culture medium (Cleav for Day 2 embryos and Blast for 3-day embryos and blastocysts, Origio, Denmark) and incubated at 37°C, under 6% CO_2 and 5% O_2 (balance N_2) until ET.

The single- or double-ET procedure was performed with either K-SOFT 5000 catheters (Cook, Australia) or Wallace PEB623 SURE PRO ULTRA (Smiths Medical International Ltd., UK) with the assistance of transabdominal ultrasound.

Statistical analysis

In this study we aimed to report the LBR; clinical pregnancy rate has also been reported. The cumulative LBR (CLBR) was evaluated by adding the live births achieved by successive FETs to the first one. In order to calculate the CLBR, women that did not achieve a live birth with the first ET, and did not came back for a second FET before July 2017, were censored (conservative statistical approach). Descriptive statistics was applied to the data. Categorical variables have been analyzed using the Chi-square test. Statistical analysis has been performed with the software Stata Soft version 12. The statistical significance was set at $P < 0.05$.

Results

Between October 2015 and July 2017, 630 patients have been treated in the TOD program. The characteristics of patients and the main reasons for the treatment are reported in Table I.

The oocytes were obtained in the Spanish center from 630 healthy donors aged 26.2 ± 4.4 years. The average number of mature oocytes inseminated per recipient was 6.8 ± 1 (range 6–11). The mean number

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Table I Demographic characteristics of patients

n	630
Female age (mean ± SD)	42.3 ± 4.2
Patients ≥45 years (%)	28
BMI, kg/m^2 (mean ± SD)	22 ± 4.7
Male age (mean ± SD)	44.2 ± 6.5
Main reason for the oocyte donation(%)	
Female age	40
Menopause or reduced ovarian reserve	25
Failure of homologous IVF	21
Other	14
Origin of sperm (%)	
Male partner	89
Sperm donor	11

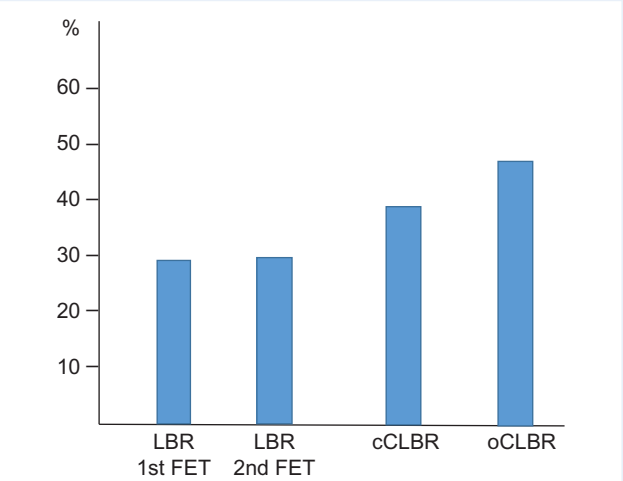

Figure 2 The live birth rate after the first and second frozen embryo transfer and the conservative (cLBR) and optimistic (oLBR) calculation of the cumulative live birth rate.

of 2PN and frozen embryos per couple was 4.9 ± 1.5 and 4.1 ± 1.5, respectively. The embryos were vitrified and shipped to Italy to be transferred. A total of 2617 embryos were created for the 630 patients; 1066 embryos were warmed for the first ET;1051 survived and were transferred (98.5% survival rate). Clinical pregnancy (CP) and live birth (LB) rates (R) were 43% and 30.6% respectively after the first FET (Fig. 2). In 476 patients (75.5%), embryos were transferred at the cleavage stage (D2 or D3) and the LBR was 29.2% Single and twin pregnancy rates were 73 and 27%, respectively. Vitrified blastocysts were available for 154 patients (24.5%) and the CPR and LBR were 44 and 35%, respectively. Single and twin pregnancy rates were 98.3 and 1.7%, respectively. The median number of days in between donor oocyte pick up in Spain and recipient FET in Italy was 63.

Among patients who did not achieve the live birth after the first FET, 85.3% had at least one frozen embryo for successive procedures (18% of patients had one embryo, 82% had at least two frozen embryos) while only 14.7% of them had none (Fig. 3).

Up to July 2017, 213 patients underwent a second FET. The LBR at the second FET was 30% (n = 64 live births), a result comparable to the first FET ($P > 0.05$). Conservative CLBR at the end of the observation period was 39.3% (Fig. 2). Nevertheless, 273 of the remaining 373 women (73.1%) who did not achieve a live birth after the second FET still had at least one embryo available for a third FET (mean 0.9 ± 1.1 embryos per patient).

Discussion

This study reports the clinical outcomes of an oocyte donation program based on the shipment of frozen sperm and embryos between countries. This system eliminates the need to align the timing of donor oocyte retrieval with the ET to recipients, but unlike the use of frozen oocytes provided by most cryobanks, it allows the fertilization of fresh donor oocytes.

Oocyte donation remains one of the most important unmet treatment needs in countries like Italy, France and Germany (Audibert and Glass, 2015). In Italy, gamete donation has been forbidden from 2004 (Law 40/2004), to 2014 when the Italian Constitutional Court declared the constitutionality of heterologous treatment in ART. Nevertheless, Italian patients and clinicians face the problem of very limited availability of oocyte donors locally. Hence, local treatment with donated oocytes has only been possible by using vitrified donor oocytes from foreign cryobanks.

Usually, donor oocyte cryobanks provide sets of four to six mature vitrified oocytes per patient, claiming results similar to those obtained with the use of fresh oocytes. In the last report of Italian IVF registry, data relative to the pregnancy rate with the use of vitrified donor oocytes have been reported. In 2015, 1137 such cycles were performed with a biochemical pregnancy rate of 30.8% (www.iss.it/pma). Unfortunately, the clinical, ongoing and LBR have not been reported. However, even considering an optimistic loss of 10% of pregnancies, the delivery rate should be well below 29.5%, the datum reported by the European IVF register where mainly cycles with fresh donor oocytes are included (De Geyter et al., 2018).

The strategy that we propose, on the other hand, has proven to be reliable and efficient (the CPR and LBR were 43 and 30.6%, respectively).We found a high number of embryos available for the couples after the insemination of fresh donor oocytes and a very high embryo survival rate after thawing. The LBR was high after the first FET and several couples had frozen embryos for future use. During the observation period, several non-pregnant patients come the clinic for a second FET. The LBR after the second FET was 30% hence the cumulative LBR (CLBR) has been calculated as 39.3%. Of course, this can be considered a conservative calculation of the CLBR since a high percentage of non-pregnant women still have vitrified embryos available. According to an optimistic approach, it may be assumed that women who did not return for a second FET had the same chance of a live birth as those who did return for treatment. In this case the CLBR would have been 48.7%. Probably, a realistic expectation for CLBR after two FETs in our program should be somewhere in between the rates found with the conservative and optimistic statistical approach (39.3 and 48.7%, respectively).

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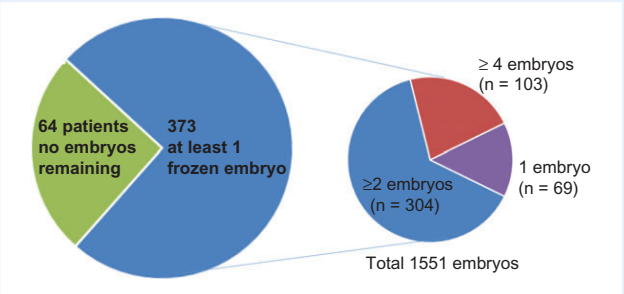

Figure 3 Of the 437 patient that did not achieve a live birth after the first FET, 373 had at least one remaining frozen embryo, with the vast majority having at least two for successive embryo transfer.

We have found a trend for a better clinical performance with the freezing and transferring of blastocysts instead of embryos at the cleavage stage. The LBR was 35 and 29.2% with the blastocyst or cleavage stage ET respectively, and since a SET was performed in only 15% of cases when cleavage embryos were available versus 95% of cases for blastocyst stage transfer, the rate of twins was 27 versus 1.7%, respectively. For this reason, very early after the initiation of this program we have increased the number of cases where embryos are cultured up to Day 5, and in the last semester of the study period the number of procedures involving ET at the blastocyst stage reached 50%.

An efficient program for cross border oocyte donation is extremely important from both clinician's and patient's perspectives. Every year thousands of couples travel outside of their country of residence to seek treatments with heterologous gametes (Shenfield *et al.* 2010). Infertility and ARTs have a known impact on the psychosocial well-being of patients (Cousineau and Domar, 2007; Pasch *et al.*, 2016) and the need to go abroad to undergo reproductive care abroad adds further emotional and practical complexity to treatment (Culley *et al.*, 2011; Hudson *et al.*, 2011; Madero *et al.*, 2017). Moreover, traveling abroad imposes additional financial strain associated with traveling expenses. An easily accessible treatment in patients own cultural and medical context, and the reduction of expenses for traveling abroad constitute very positive aspects of this new strategy.

For all these reasons, vitrified oocytes are widely used in countries with low availability of donors. However, when compared to this strategy, the TOD program seems to provide several advantages. The use of frozen embryos from fresh oocytes is associated with a higher LBR per started cycle when compared to vitrified oocytes; this may be due to true loss of developmental ability in vitrified oocytes, imperfect warming technique in the receiving centers and the impossibility of tailoring the number of assigned oocytes to the patient's needs. The use of fresh oocytes may permit a personalized care for the oocyte recipient, which is provided by a flexible number of oocyte assigned. This personalization is impossible to carry out with pre-prepared packs of oocytes and this is probably the basis for why cryopreserved oocyte donation cycles (involving shipping as opposed to having more cryopreserved oocytes on site) do more poorly than the 'gold standard' of fresh donor oocytes.

When using frozen oocytes, a standard number of four to six oocytes is usually assigned to a couple. In our program a mean number of 6.8 was used. Clinicians, for instance, have the possibility to personalize the number of oocytes if a male factor or low fertilization risk is recognized. In the end this might lead to an overall higher availability of transferrable embryos for the patients and to standardized results across a wide variety of clinical situations. Moreover, the assignment of a certain number of oocytes in a fresh program guarantees that they will all be available for fertilization, while even very competent vitrified program will lose 5–10% of assigned oocytes after warming.

An international transport program for gametes and embryos requires an excellent organization and collaboration between the centers. For example, the transport of embryos for thousands of kilometers of course can expose the couple to a risk, even if very low, of loss of embryos. For this reason the collaborating centers must be optimally synchronized and must rely on specialized transport companies. Regarding medico-legal aspects, the TOD program would work perfectly if the two collaborating countries have similar requirements for donor eligibility, including the policy related to donor anonymity and donor identity disclosure. The logistics of transnational gamete donation may become challenging if federal regulations differ and recipient's country requires specific tests that are not in place in the donor's country.

In conclusion, in this large retrospective study, we have shown that the TOD program is efficient and reliable. The widespread use of this strategy as a first-line program to overcome the lack of donors in some specific countries may be anticipated.

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Authors' roles

A.L.M.: design of the study, statistical analysis, preparation of draft and final text. M.D.C.: design of the study, data acquisition, preparation of draft and final text. M.B.: data acquisition. M.V.: data acquisition. M.M.R.: comments on the draft and approval of final text. A.R.: comments on the draft and approval of final text. R.V.: design of the study, data acquisition, preparation of draft and final text.

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Conflict of interest

None.

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