International Multicenter Egg Donation Program (IMEDO): preliminary outcomes

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Introduction

Italy has been the last European country to regulate medically assisted reproduction. The regulation was introduced in 2004 by Law 40. Law 40 was a very restrictive law and cancelled in Italy the possibility for couples to undergo heterologous assisted reproduction. Law 40 resisted to a referendum to cancel it in 2005. From that moment all Italian couples who wanted to undergo heterologous reproduction had to perform the techniques outside of Italy. In 2014, finally the Constitutional Court declared as unconstitutional the ban on using donor sperm and eggs in infertility treatments, thus opening the way to heterologous assisted reproduction. But unfortunately in Italy ten years of prohibition have cancelled the altruism of the Italian girls, and in Italy now there are only very few egg donors (1).

Two other events were observed simultaneously: a) age on rise of patients in Italy approaching the assisted reproduction and b) improvements in oocytes cryopreservation techniques.

Age of patients

The report of the Italian Ministry of Health in 2016 on 2014 data said that the average age of the patients was 36.7 years. The average age increased from 35.25 years in 2005 to 36.7 in 2014. This means that many of these patients were over the age of 40.

Therefore, the egg donation request is high and certainly on the rise, and could not be fulfilled in Italy. Despite the heterologous fertilization in Italy was allowed, the Italian couples continued to go out of Italy for egg donation techniques.

Improvement of cryopreservation techniques

Cryopreservation and sperm transport is a technique for a longtime established. Publications of Sherman, 1954 (2) illustrate cryopreservation of sperm in detail.

From the first pregnancy achieved with a frozen oocyte (Chen, 1986) (3), the oocyte cryopreser-
vitation techniques have grown more slowly. Two cryopreservation methods are routinely used: slow-freezing or vitrification. In our work the method chosen was vitrification that has now become the method of choice for oocyte cryopreservation (4, 5).

The high request of heterologous fertilization (especially egg donation) and the improvements in cryopreservation techniques, stimulated centers of assisted reproduction in creating strategies for the collection, cryopreservation, transport abroad and use of gametes.

Introduction of vitrification method in oocytes banking for heterologous reproduction was induced by its remarkable implementation, thanks to efficient vitrification protocols being available and to its approval in 2013 by ASRM as non experimental technique for oocyte preservation (6-8).

Materials and methods

Study subjects, participants, setting

This study is based on 512 IVF cycles with donated oocytes performed in 512 patients. In all cases, oocytes were obtained and vitrified in a single center, afterwards, shipped to a second center where thawing, ICSI procedure and embryo transfer was performed.

A total of 3,679 oocytes was assigned and shipped to 541 recipients included in an oocyte-donation program. The mean of shipped oocytes per recipient was 6.8 ± 0.1.

A sample of 145 cases was drawn from the total; in which two different cross-border transport methods were compared; 105 cases by land carrier in liquid nitrogen and 40 cases by plane (air shipping) in vaporous phase of liquid nitrogen; both with data logger control of the temperature.

Italian centres: Recipient preparation. Oocyte thawing, ICSI and embryo transfer.

Interventions


Shipping: Cross-border shipping of biological material in liquid nitrogen by land carrier, or by plane (air shipping) in vaporous phase of liquid nitrogen; both with data logger control of the temperature.

Study design, size, duration

International multicenter, descriptive and retrospective study, with a cohort of 541 subjects included in IMEDO program from September 2015 to September 2016.

Quantitative variables are expressed as means and standard deviations and the qualitative values as percentages. The statistical analyses were performed with the SPSS® package. A p value of less than 0.05 was consider significant.

Main Outcome Measures

Results obtained were classified by total oocyte, total oocytes batches, total subjects included in the study and by shipping in the selected sample. Survival rate, fertilization rate, implantation rate and pregnancy rate were assessed.

Results

From the total of frozen oocytes in the spanish EGG-DO center and thawed oocytes in EGG-DO italians centers, the survival rate percentage after thawing was 84.8% and fertilization signs were observed in 75.6% of microinjected oocytes, with a total of 2,202 embryos obtained (Table 1).

Out of the 541 oocytes batches selected and shipped, in 512 cases (94.6%) a successful em-
bryo transfer was performed. In 3.1% of oocytes batches none of the oocytes survived after thawing, being the most common cause of treatment cancellation. Other causes for treatment cancellation are presented in Table 2, which correspond to 5.4% of all cases.

Out of the 512 embryo transfers performed, the implantation and pregnancy rate were 44.1 and 59.3%, respectively. Table 3 highlights multiple pregnancy and miscarriage data.

In the sample with 2 transport methods, when oocytes were shipped by land carrier in liquid nitrogen, survival rate after thawing was 81.1% and pregnancy rate was 50%; in air shipped in vaporous nitrogen group, oocyte survival rate and pregnancy rate were 67.4% and 25.6% respectively, with a statistically significant difference (Table 4).

### Discussion

Our preliminary data seem to suggest that competence of oocyte vitrified in one center and warmed and injected in another is comparable to that of oocytes used to complete the cycle in the same center (9).

So provided that oocytes transport is done in liquid nitrogen and not in vapors there is no evidence of clinically significant damage impairing clinical outcome of oocyte donation cycle. Notwithstanding some variability in oocytes survival rate the fertilization rate of survived oocytes was comparable to that of fresh one. Obviously these results are related to the optimal oocytes quality due to the young age of donors. Rarely (3%) oocytes warming does not produce injectable oocytes due to all gametes degeneration. This percentage seems comparable with other bank on site experience.

Our preliminary data seem to suggest that “two centers-two countries” oocyte-donation program is a safe, effective and patient friendly model for egg donation.

Direct, center to center shipping by land in a liquid medium seems to be a safer option than the international standard of courier transport by air with a dry-shipper as demonstrated by oocyte survival rate and pregnancy rate.

Our preliminary results suggest that centers in different countries can collaborate in an effective heterologous ART program provided they share vitrification protocols and Lab standards.

### Table 1 - Results by total oocytes.

<table>
<thead>
<tr>
<th>Oocytes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3,679</td>
</tr>
<tr>
<td>Survived</td>
<td>3,120 (84.8)</td>
</tr>
<tr>
<td>Fertilized</td>
<td>2,358 (75.6)</td>
</tr>
<tr>
<td>Total embryos</td>
<td>2,202</td>
</tr>
<tr>
<td>Transferred embryos</td>
<td>832</td>
</tr>
</tbody>
</table>

### Table 2 - Results by oocytes batches.

<table>
<thead>
<tr>
<th>Batches</th>
<th>%</th>
<th>Oocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thawing failure</td>
<td>17</td>
<td>3.1</td>
</tr>
<tr>
<td>Fertilization failure</td>
<td>6</td>
<td>1.1</td>
</tr>
<tr>
<td>Poor quality embryos</td>
<td>6</td>
<td>1.1</td>
</tr>
<tr>
<td>Successful transfer</td>
<td>512</td>
<td>94.6</td>
</tr>
<tr>
<td>Total</td>
<td>541</td>
<td>3.679</td>
</tr>
</tbody>
</table>

### Table 3 - Results by subjects. PR: pregnancy rate; IR: implantation rate; MR: miscarriage rate.

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer</td>
<td>512</td>
</tr>
<tr>
<td>PR</td>
<td>304 (59.3)</td>
</tr>
<tr>
<td>Single</td>
<td>241 (79.3)</td>
</tr>
<tr>
<td>Multiple</td>
<td>63 (20.7)</td>
</tr>
<tr>
<td>IR</td>
<td>367 (44.1)</td>
</tr>
<tr>
<td>MR</td>
<td>63 (20.7)</td>
</tr>
</tbody>
</table>

### Table 4 - Results by shipping. PR: pregnancy rate. *p<0.05.

<table>
<thead>
<tr>
<th>Land shipping</th>
<th>Air shipping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes batches</td>
<td>105</td>
</tr>
<tr>
<td>Total oocytes</td>
<td>697</td>
</tr>
<tr>
<td>Survival rate*</td>
<td>81.1%</td>
</tr>
<tr>
<td>Fertilization rate</td>
<td>73.4%</td>
</tr>
<tr>
<td>Transfers</td>
<td>102</td>
</tr>
<tr>
<td>PR/transfer*</td>
<td>50%</td>
</tr>
</tbody>
</table>
Conclusions

“Two centers-two countries” oocyte-donation program is a safe and effective model for patient who need egg donation.
Safe and patient friendly as the home clinician follows the whole treatment.
Effective because large scale shipping of oocytes can be achieved with no negative influence on results.
Direct, center to center shipping by land in a liquid medium seems to be a safer option than the international standard of courier transport by air in dry medium.
In this model two centers in different countries can collaborate in a treatment with good results provided they share protocols and standards.

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