Characteristics and clinical outcomes of patients undergoing fertility treatment by double gamete donation

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ABSTRACT
The number of women receiving in vitro fertilization cycles with both oocyte and sperm donation (double donation; DD) has grown globally in the last decade. The aim of this retrospective study, which included 1139 DD cycles, was to describe the characteristics of patients receiving DD and the outcomes of this assisted reproductive treatment. A cluster analysis identified couple ‘status’ as the main variable in dividing patients into categories. Three such status groups were identified for further analysis: (i) single women (SW), that is women without a partner either male or female; (ii) women with a male partner (MP); (iii) women with a female partner (FP). SW were significantly older (43.9) than patients with a MP (40.4) and a FP (41.3). Women with a male or FP comprised fewer patients with no previous assisted reproductive technology cycles (18.4% and 25.7%, respectively) compared to SW (43.5%). The proportion of patients without children before treatment was significantly different between SW (94.7%) and women with a MP (87.2%). There were no differences in clinical outcomes among the three groups studied. Biochemical pregnancy rate was 58.2% in SW, 58.4% in women with a MP and 64.9% in women with a FP. For the same groups, clinical pregnancy rates were 50.2%, 49.4% and 55.4%, while ‘take-home baby’ rates were 36.6%, 38.9% and 40.3%. Multiple birth and caesarean section rates were not different among the groups, with twinning rates 21.1%, 30.4% and 36%, and caesarean section rates 25.6%, 24% and 26.4% for SW, women with MP and women with FP, respectively.

INTRODUCTION
With the development of assisted reproductive technology (ART) and gamete donation programs, a larger portion of the population can access advanced therapeutic options to become pregnant. One such example is double gamete donation (DD), that is the transfer to a recipient’s uterus of an embryo resulting from the fertilization of a donor oocyte with donor sperm. Although it is still comparatively rare in the assisted reproduction landscape, in the last few years DD has become the path to pregnancy for thousands of women worldwide.

Although a report has dealt with the psychological and socioeconomic characteristics of women undergoing double gamete donation (Landau, Weissenberg, & Madgar, 2008), no studies have as yet addressed the detailed characteristics of the patient population undergoing this fertility treatment to any reasonable extent, with the exception of one small case series of seven couples (Sills et al., 2010). To date, a description of the patients undergoing DD is lacking, efficiency studies and analysis of pitfalls have not been reported and no clear indication for this treatment option has been established. This study of 1139 DD cycles aims (i) to bridge this knowledge gap, as well as identify the characteristics of the cohort of patients receiving DD for fertility treatment and (ii) to report the efficiency of the technique on reproductive outcomes including pregnancy and delivery rate, in order to provide information for physicians and patients when evaluating this therapeutic option.

MATERIALS AND METHODS

Study design and ethical approval

This is a retrospective analysis of anonymized cohort data from 1139 DD cycles between January 2001 and August 2010 at a large private fertility centre. Permission to conduct the study was obtained from the Institutional Review Board.
**DD cycles inclusion criteria**

The inclusion criteria of the study were consecutive cycles of DD resulting in a fresh embryo transfer (ET) during the study period. Cycles where the woman was positive to HIV or HCV were excluded. All embryo recipients were between 18 and 50 years old. The unit of analysis for this study is the ET, with an average of 1.37 (SD 0.7) cycles per patient who reached ET. In 821 patients, the cycle reported was the first one to involve DD, while in 319 the patients had undergone at least one previous DD attempt.

**Statistical analysis**

**Recorded variables**

The following variables were recorded as binary: relationship status [single women (reference category), SW; with a male partner, MP; with a female partner, FP]; age (years); history of infertility (continuous [years] and categorical [more than 5 years]); previous ART cycles (yes/no and categorical [0, 1, 2, 3, 4+]); previous pregnancies (yes/no); previous live births (yes/no); endometrial preparation (oral/patch); biochemical pregnancy (yes/no); clinical pregnancy (yes/no); ongoing pregnancy at 12, 20 and 37 weeks (yes/no); multiple pregnancy at delivery (yes/no); caesarean section (yes/no); baby at home (yes/no).

**Cluster analysis**

A cluster analysis was undertaken designed to reveal natural groupings based on demographic [maternal age, relationship status (SW, women with MP or with FP)] and reproductive history (number of previous children, number of previous ART cycles and years of infertility) within the cohort of patients.

A two-step procedure was used. In the first step, cases were assigned to an automatically determined number of pre-clusters, which were treated as single cases in the second step. In the second step, a hierarchical algorithm based on the log-likelihood of the distances between variables was used to cluster the pre-clusters. The clustering was done by a procedure based on Bayesian Information Criteria. The analyses were performed using the statistical package SPSS 20.0 (Chicago, IL).

**Regression analysis**

Categorical variables were analysed by the Pearson chi-squared test and continuous variables by one-way ANOVA. Logistic regression models were performed for the pregnancy outcomes (biochemical pregnancy, clinical pregnancy, ongoing pregnancy and child at home) to evaluate the effect of the relationship status, adjusted by the potential confounders (age, years of infertility, previous ART cycles, endometrial preparation and previous children). The statistical software SPSS 20.0 was used for the analyses. A p value <0.05 was considered statistically significant.

**Results**

**Double gamete donation patients throughout the years**

DD cycles were analysed from 2001 to 2010 based on the relationship status of the patients. There were few cases for the years 2001 and 2002, and there was no visible trend in the patient population during the study period.

The overall number of DD cycles increased steadily throughout the study. On the one hand, there was a progressive increase in the proportion of FP couples accessing this technique (from 0% in 2001 to 9.1% in 2010). The number of SW seeking DD also increased, comprising in 2010 about 50% of those accessing the technique. The proportion of patients reaching DD as part of a MP couple therefore decreased from 2003 to 2010 to about 40% of the patients (Figure 1).

**Double gamete donation patients’ characteristics**

Patient population characteristics are reported in Table 1. On average, patients accessing DD were 42.2 (SD 4.2) years old, and reported a history of infertility...
of 3.41 years (SD 4.0; range: 0–21). Twenty-two percent (22.5%) of them had a history of more than 5 years of infertility. Most patients (91.7%) did not have a child at the time of treatment, with the notable exception of one mother of seven children. The decision to perform a DD cycle came, on average, after 3.21 (SD 3.8) previous unsuccessful ART cycles, although 31.8% of the patients underwent a DD cycle directly without having had a previous ART cycle; these patients were on average 43.3 (SD 4.1) years old, with means of 44.2 (SD 3.3) for SW, 41.0 (SD 5.1) for MP and 41.8 (SD 4.1) for FP.

Most DD patients were European (92.1%), while 3.5% were African and 0.5% from North and South America. A cumulative 3.9% of patients came from other regions of the world. Consistent with these data, the ethnicity of the patient was 91.6% non-Hispanic white, 3.9% black, 2.0% Hispanic white, 1.6% mulattos, 0.6% Asian and 0.3% of other ethnicities (Table 2).

Clusters

The clustering procedure resulted in the definition of three groups of patients, representing 34.6% (cluster I), 43% (cluster II) and 22.4% (cluster III) of the population; the clustering overall showed a ‘fair’ quality (Silhouette measure of cohesion and separation of 0.4).

Cluster I (n = 393) comprised 18.8% of women with FP and 81.2% of SW. They had no children (97.7%), despite having had previous ART cycles (95.2%). Cluster II (n = 488) was made up mainly of women with MP (97.5%); 85% of them were childless, and about half (49.6%) had had 3 or more previous ART cycles. They tended to be younger and with a longer history of infertility. Cluster III (n = 254) comprised SW (100%) with no previous ART treatment. Most were childless (94.9%) and tended to be older and with a shorter history of infertility (Table 3).

Classification by relationship status

We identified ‘relationship status’ as the most relevant variable defining sub-populations among DD patients in the cluster analysis (Supplementary Figure 1) and therefore chose to do a quantitative analysis of the three types of couple relationship in our sample: namely, SW (used as the reference category); women with MP and women with FP (Table 1).

Although MP women were younger than SW when they started a DD cycle: 40.4 (SD 4.7) versus 43.9 (SD 3.18) years, (p < 0.001), they had undergone more ART cycles: 4.3 (SD 4.1) versus 2.3 (SD 3.4) (p < 0.001), and reported a longer history of sterility: 5.2 (SD 4.2) versus 2.2 (SD 3.5) years (p < 0.001). The proportion of patients without children was lower in MP women than SW (87.2% vs. 94.7%, p < 0.001).

FP women were younger than SW when accessing DD: 41.3 (SD 3.2) versus 43.9 (SD 3.18), (p < 0.001). The proportion of FP patients with more than 5 years of infertility was lower than SW (2.7% vs. 12%, p = 0.016), as was the case for the proportion of patients without any previous ART cycle (25.7% vs. 43.5%, p = 0.030). Data on region of origin and ethnicity by relationship status are provided in Table 2.

Table 1. Demographic characteristics of patients accessing double gamete donation by relationship status.

|                      | Total | SW   | MP   | FP   |
|----------------------|-------|------|------|------|
| **N**                | 1139  | 587  | 478  | 74   |
| Age, years, mean (SD)| 42.2  | 43.9 | 40.4 | 41.3 |
| History of infertility, years, mean (SD)| 3.41 | 2.2  | 5.2  | 1.8  |
| More than 5 years of infertility, n (%)| 255 (22.5) | 70 (12) | 183 (38.4) | 2 (2.7) |
| Previous ART cycle (SD) | 3.2 | 2.3 | 4.3 | 3.0 |
| No previous ART cycle, n (%) | 363 (31.8) | 256 (43.5) | 88 (18.4) | 19 (25.7) |
| No previous pregnancies, n (%) | 471 (41.3) | 246 (41.8) | 199 (41.6) | 26 (35.1) |
| No previous children, n (%) | 1043 (91.7) | 557 (94.7) | 415 (87.2) | 71 (95.9) |

|                      | Overall | Single women | Male partner | Female partner |
|----------------------|---------|--------------|--------------|----------------|
| **Origin, n (%)**    |         |              |              |                |
| European             | 1050 (92.1) | 536 (91.4) | 443 (92.7) | 70 (94.6) |
| Africa               | 40 (3.5) | 22 (3.7) | 16 (3.3) | 2 (2.7) |
| America              | 5 (0.5) | 3 (0.5) | 2 (0.4) | 0 (0) |
| Other                | 46 (3.9) | 26 (4.4) | 17 (3.6) | 2 (2.7) |
| **Ethnicity, n (%)** |         |              |              |                |
| Non-Hispanic whites  | 1045 (91.6) | 531 (90.4) | 443 (92.6) | 70 (94.5) |
| Black                | 44 (3.9) | 25 (4.3) | 17 (3.6) | 2 (2.7) |
| Hispanic Whites      | 23 (2.0) | 17 (2.9) | 6 (1.3) | 0 (0) |
| Mulattos             | 18 (1.6) | 8 (1.4) | 9 (1.9) | 1 (1.4) |
| Asian                | 7 (0.6) | 4 (0.7) | 2 (0.4) | 1 (1.4) |
| Other                | 3 (0.3) | 2 (0.3) | 1 (0.2) | 0 (0) |

SW: single women; MP: male partner; FP: female partner. Different superscripts indicate a statistically significant difference between groups in rows (p < 0.05).

*pMP versus SW.

*pFP versus SW.
Pregnancy outcomes

Details about ET and pregnancy outcomes are reported in Tables 4 and 5. On average, 73.9% of patients used oral oestrogen in their protocol for endometrial preparation, while 26.1% used transdermal oestrogen patches. The overall rates of biochemical, clinical and ongoing pregnancy were 58.7%, 50.2% and 49.4%, respectively, with multiple delivery rates of 25.5% for twins and 0.5% for triplets. Overall, 25% of the patients gave birth by caesarean section.

There were no differences in the biochemical, clinical and ongoing pregnancy rates between the three groups (SW, MP and FP), neither in the multiple pregnancy rates nor the proportion of caesarean sections. These differences remained non-significant after adjustment for potential confounders (Supplementary Table 1).

Discussion

In the last few decades, the number of people accessing fertility treatments has been rising (Chandra & Stephen, 1998; Dyer et al., 2016; Stephen & Chandra, 1998) and DD treatments follow this trend. We have observed that the clinical profile of ART patients has shifted in the last 10 years, with more FP and SW being treated currently, as well as older patients overall.

Assisted reproductive care in general has become more widespread and socially accepted, while technical advances allow for the treatment of increasing numbers of people. The main factor for the increase in the demand for ART in developed countries is the increasing age at which women have their first child (de Graaff, Land, Kessels, & Evers, 2011; INE, 2014). In addition, more women are waiting to have children until they have completed higher education degrees, and participation of women in the skilled workforce is increasing, however, delaying motherhood can reduce the possibility of using one’s own oocytes to achieve a pregnancy (Blickstein, 2003; Pal & Santoro, 2003).

Although the number of MP couples requiring DD has risen in absolute terms over the years, the relative proportion has not. One reason for this shift is that while DD is for the moment the only successful ART treatment available for SW or FP couples experiencing ovarian failure, research has advanced such that we are now able to offset, to a great extent the influence of a mild to moderate male factor (Nangia et al., 2011; Palermo, Cohen, & Rosenwaks, 1996), thus lowering their relative need to access DD. The proportion of FP women and SW electing double gamete donation has increased over the years, which may be due to the

Table 3. Demographic characteristics and reproductive history of each cluster.

|                        | Cluster I | Cluster II | Cluster III | p     |
|------------------------|-----------|------------|-------------|-------|
| N (%)                  | 393 (34.6%) | 488 (43%) | 254 (22.4%) | <0.001|
| SW                     | 319 (81.2%) | 12 (2.5)  | 254 (100)   |       |
| Age, years, mean (SD)  | 43.1 (3.1)  | 40.5 (4.7) | 44.3 (4.2)  | <0.001|
| Years of infertility, mean (SD) | 2.7 (3.4)  | 5.2 (4.3)  | 1.04 (2.6)  | <0.001|
| SW: single women; MP: male partner; FP: female partner.|

Table 4. Endometrial preparation and pregnancy outcomes.

|                        | Total 1139 | SW 587 | MP 478 | FP 74 |
|------------------------|------------|--------|--------|-------|
| Oral endometrial preparation, n (%) | 840 (73.9) | 399 (67.9) | 286 (80.8)* | 55 (74.3) |
| Patch endometrial preparation, n (%) | 297 (26.1) | 186 (31.8) | 92 (19.2)* | 19 (25.7) |
| Biochemical pregnancy, n (%) | 669 (58.7) | 342 (58.2) | 279 (58.4) | 48 (64.9) |
| 7 weeks pregnancy, n (%) | 572 (50.2) | 295 (50.2) | 236 (49.4) | 41 (55.4) |
| 14 weeks pregnancy, n (%) | 563 (49.4) | 283 (48.1) | 242 (50.6) | 38 (51.4) |
| 20 weeks pregnancy, n (%) (total n = 1031) | 402 (39) | 205 (38.8) | 172 (39) | 25 (40.3) |
| 37 weeks pregnancy, n (%) (total n = 1030) | 383 (37.2) | 198 (37.5) | 161 (36.6) | 24 (38.7) |
| Caesarean section, n (%) (total n = 945) | 236 (25) | 125 (25.6) | 97 (24.0) | 14 (26.4) |
| Baby at home, n (%) (total n = 1030) | 400 (38.8) | 204 (38.6) | 171 (38.9) | 25 (40.3) |
| SW: single women; MP: male partner; FP: female partner. Different superscripts indicate a statistically significant difference between groups in rows (p < 0.05). |
| *MP versus SW. |
| bFP versus SW. |

Table 5. Multiple births by relationship status.

|                        | Total (400) | SW (204) | MP (171) | FP (25) |
|------------------------|-------------|----------|----------|--------|
| Singleton birth, n (%) | 296 (74)  | 161 (78.9) | 119 (69.6) | 16 (64) |
| Twin birth, n (%)      | 102 (25.5) | 9 (21.1)  | 50 (29.4) | 9 (36)  |
| Triplet birth, n (%)   | 2 (0.5)    | 0        | 2 (1)    | 0      |
| SW: single women; MP: male partner; FP: female partner. |
progressive acceptance in society of new social relationships such as lesbian and single parent families.

With the clustering procedure the aim was to divide the patients into groups, the profiles of the patients being as close as possible when they were within a group and as different as possible when between groups.

This analysis confirmed that relationship status is the best variable to analyse groups accessing DD. Situations requiring DD are: (i) SW and FP suffering from premature ovarian failure (primary ovarian insufficiency, mainly due to ovarian aging), (ii) recurrent unexplained infertility in MP couples and (iii) MP couples with a medical indication not to use their own gametes; this category can be divided further into two main groups: couples that came to DD gradually; via oocyte donation with multiple implantation failure although the sperm of partner was of acceptable quality for IVF/ICSI, and in couples who opted for DD without prior experience of single gamete donation (a health issue other than infertility that discourages the use of one’s own gametes such as cancer treatment or genetic disease, or in older women whose partner has a very severe male factor).

Women with a MP tend to be younger, with the longest history of infertility, and more previous ART cycles. Heterosexual couples therefore reach the decision to have a DD at a younger age; it is likely that they start at an earlier age than other DD patients to try and have children since their relationship is the social norm, all of which leads to an earlier request for ART if a pregnancy is not achieved spontaneously, but without an initial requirement to resort to gamete donation apart from cases of a severe male factor. Such couples experience more ART treatments and a longer duration of infertility than SW and FP women, as they start having ART treatments earlier. It is also noticeable that women in this group have had more children than SW and FP women. This could be due to their having started to have children earlier, when their fertility is still unaffected by ovarian ageing, or resuming their wish for motherhood later in their reproductive years, sometimes with a different MP.

More heterogeneity can be found among SW, although they are in general the oldest amongst the relationship groups. SW may have waited to have children within a traditional family structure before accessing ART as single parents, and are then unable to conceive with their own gametes. In the cluster analyses, they tend to distribute into two groups; in the first, some SW profiles overlap with FP couples: younger women who have had previous ART treatments, either alone or with a previous partner. Younger SW might be more open to the prospect of single parenthood as a result of shifting social norms. However, there are also some SW women who are older, have a short history of infertility and no previous infertility treatments; this subgroup of patients decide to have their first child as their reproductive age increases, and so reach DD faster.

FP women access DD earlier, possibly because lesbian patients in a stable relationship do not wait as long as SW to address the issue of maternity. A woman who is openly in a lesbian relationship and cohabiting with her partner might also live in a more accepting social environment, which in turn would offer emotional and practical support for parenthood. However, FP patients do wait slightly longer than those with a MP; again possibly due to the social acceptance of the relationship. Society might accept the homosexual relationship with more difficulty, which may slightly delay motherhood for lesbian couples.

The reproductive outcomes of DD treatments were no different among the three groups. The proportion of deliveries with twins and triplets are comparable with those reported from IVF and ICSI cycles worldwide (Sullivan et al., 2013), and the rate of caesarean section is similar to that reported for spontaneous pregnancies in the European population (OECD, 2013). Spontaneous miscarriage/abortion rate (loss of a clinical pregnancy that occurs before the 21st week of gestation) was 19.7% overall. This rate is also comparable with the general population (Wang et al., 2003; Wilcox et al., 1988) and for pregnancies achieved by ART taken as a whole in a region (FINCAT, 2011, p. 14).

To the best of our knowledge, this is the first large study reporting patients’ characteristics and reproductive outcomes of DD cycles. We recognize some limitations, the most important being that it was carried out in a single private centre, which could have skewed the patient population. The inclusion of 100% of the DD patients in the study period notwithstanding the absence of publicly available literature on the subject makes it impossible to know how representative our cohort might be of worldwide DD trends. To address this issue partially we have obtained data for all DD cycles performed in the USA in the 2000–2010 decade from the US Centers for Disease Control and Prevention (R.V. personal inquiry) from which growth of DD cycles over time, average age at access and reproductive results, are similar to those observed here (Supplementary Table 2). In conclusion, DD is a reasonable treatment option for selected patients. The results are encouraging; however, perinatal and neonatal outcomes should be reported and monitored more widely,
as has been done for outcomes of ART cycles with couples’ own or donor oocytes.

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Disclosure statement

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