Original Article
Comparison of sperm retrieval and reproductive outcome in azoospermic men with testicular failure and obstructive azoospermia treated for infertility

Sandro C Esteves\textsuperscript{1}, Christina Prudencio\textsuperscript{1}, Bill Seol\textsuperscript{1}, Sidney Verza Jr\textsuperscript{1}, Christopher Knoedler\textsuperscript{2}, Ashok Agarwal\textsuperscript{2}

\textsuperscript{1}ANDROFERT, Center for Male Reproduction, Campinas 13075-460, Brazil.

\textsuperscript{2}Center for Reproductive Medicine, The Cleveland Clinic Foundation, Cleveland 44195, USA.

Correspondence: Dr. SC Esteves (s.esteves@androfert.com.br)

Running title: Reproductive potential of men with testicular failure

Abstract: We assessed the sperm retrieval rates and intracytoplasmic sperm injection outcomes, including the neonatal profile of infants conceived, in men with testicular failure. Three-hundred and sixty-five men with testicular failure who underwent microdissection testicular sperm extraction were included. We compared their outcomes with those of 40 men with testicular failure who used donor sperm for injections due to failed retrievals, and 146 men with obstructive azoospermia who underwent percutaneous sperm retrievals. The retrieval rate in testicular failure was 41.4\%, and the results were lower than obstructed azoospermia (100.0\%; adjusted odds-ratio: 0.033; 95\% CI: 0.007 – 0.164; \(P<0.001\)). Live birth rates after sperm injections were lower in men with testicular failure (19.9\%) compared with donor sperm (37.5\%; adjusted OR: 0.377 (95\% CI: 0.233 – 0.609, \(P<0.001\))) and obstructive azoospermia (34.2\%; adjusted OR: 0.403 (95\% CI: 0.241–0.676, \(P=0.001\))). Newborn parameters of infants conceived were comparable among the groups. We concluded that the chances of obtaining sperm at retrievals and achieving a live birth after intracytoplasmic sperm ICSI are reduced in men with testicular failure. The profile of infants conceived after sperm injection does not seem to be negatively affected by testicular failure.

Keywords: infant; intracytoplasmic sperm injection; obstructive azoospermia; pregnancy outcome; sperm retrieval; testicular failure

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Introduction
Azoospermia is a relatively common condition affecting infertile males.\textsuperscript{1} Many couples with azoospermia-related infertility rely on assisted reproductive techniques (ART) as the first line treatment for achieving biological parenthood.\textsuperscript{1,2} In such cases, sperm retrieval (SR) is performed in an attempt to obtain viable sperm for
intracytoplasmic sperm injection (ICSI).³ Men with azoospermia are broadly categorized as having either a mechanical obstruction along the seminal tract or an intrinsic testicular impairment of sperm production (nonobstructive azoospermia).⁴ Despite being well preserved in obstructive azoospermia (OA), spermatogenesis is either minimal or absent in men with testicular failure, thus lowering the success rates of SR in the latter.³

Several studies have examined the outcomes of ICSI using non-ejaculated sperm.⁵-⁹ However, reports comparing both SR and ICSI results by making a clear distinction between the type of azoospermia are scarce.¹⁰,¹¹ Still, ICSI data concerning the reproductive potential of non-ejaculated gametes from men with testicular failure with ejaculated sperm from fertile donors are lacking. Moreover, children conceived after ICSI using non-ejaculated sperm from fathers with normal and abnormal spermatogenesis are poorly studied,⁵,¹⁰-¹² and concerns exist as to whether or not these spermatozoa impact the health of offspring.¹⁴ Hence, a detailed assessment that combines: (i) data on sperm retrieval, (ii) clinical outcomes of sperm injection, and (iii) profile of infants conceived from such treatments can help doctors better counsel azoospermic patients before embarking on SR and assisted reproductive techniques.

In this study, we assessed the sperm retrieval rates (SRR) and ICSI outcomes of azoospermic men with testicular failure who underwent microdissection testicular sperm extraction (micro-TESE). Neonatal outcomes of pregnancies originated from such interventions are provided. We compared these results with those of men with testicular failure who used donor sperm for injections, due to failed SR by micro-TESE, and men with normal spermatogenesis and azoospermia caused by obstruction.

### Materials and methods

**Patient Selection**

We retrospectively studied 365 consecutive men with testicular failure who underwent SR by micro-TESE in an attempt to find sperm for ICSI, over a 7-year period. Azoospermia was confirmed on at least two different centrifuged ejaculates. A thorough evaluation, including history, physical examination, hormone profile (serum FSH, LH and total testosterone) and genetic testing (Yq microdeletions and karyotyping) were available for all patients.⁴ Testicular failure was confirmed by histologic evaluation of testicular biopsy specimens taken at the study center prior or during SR. Histology patterns were Sertoli cell-only, maturation arrest and hypospermatogenesis in 205 (57.6%), 67 (18.8%), and 84 (23.6%) men, respectively. Patients with hypogonadotropic hypogonadism and those with Yq microdeletions involving the AZFa and/or AZFb subregions were excluded. Eight patients (2.2%) had karyotyping abnormalities (47,XXY) and were included. We used our previously reported data on 146 consecutive men with obstructive azoospermia for comparison, in which SR for ICSI were accomplished in the same period by the same surgeon.⁹ Only the first treatment cycle of each patient using fresh sperm for ICSI was included. None of the patients received medication such as clomiphene, aromatase inhibitors, and human chorionic gonadotropin preoperatively. Our institutional review board approved this study.

**Sperm acquisition**

Microdissection testicular sperm extraction, as described by Schlegel, was the method of sperm acquisition.¹⁵,¹⁶ Patients were asked to collect a semen specimen by masturbation immediately before SR. In all cases, azoospermia was confirmed after
analysis of centrifuged specimens. If we failed to retrieve sperm by micro-TESE in one testis, the method was used contralaterally in the same operation. We performed retrievals on an outpatient basis under local anesthesia combined with intravenous propofol infusion. The extracted testicular fragments were immediately examined in the in vitro fertilization (IVF) laboratory. Successful retrievals were defined as the presence of sperm. The same senior urologist (SE) performed all retrievals. Percutaneous aspirations were used in our previously reported group of men with OA.

**Sperm injections**

Our methods for ovarian stimulation, oocyte collection, sperm injection, embryo culture and embryo transfer were previously described. In brief, we used recombinant gonadotropins for ovarian stimulation, in association with either gonadotropin-releasing hormone agonist or antagonist for LH surge suppression. Oocyte retrievals were performed prior to, but in the same day of SR. We offered sperm from donors with proven fertility to all patients with testicular failure as a back up for ICSI before treatment started. If we failed to retrieve sperm, ICSI would be carried out using donor sperm for couples that accepted the donation. Sperm injections and embryo culture were carried out in a clean room IVF laboratory. Ultrasound-guided embryo transfer was performed on the third day of embryo development. There was no considerable difference in laboratory techniques during the study period. Embryologists and physicians performing procedures were also unchanged. Clinical pregnancy was confirmed by ultrasound at weeks 5 to 7. Miscarriage was determined by the presence of a nonviable clinical pregnancy on ultrasound in the first 20 weeks. The live birth rate was the ratio between the numbers of deliveries resulting in at least one live born infant and initiated ICSI cycles. Twin and triplets were deliveries resulting in two or three live births, respectively. Gestational age, weight and sex of newborns were registered at birth. Perinatal mortality included stillbirths and neonatal deaths.

**Statistical analysis**

Comparisons were performed with chi-square, Wilcoxon rank sum and Fisher’s exact tests. Multivariate logistic and Poisson regression models were constructed for dichotomous outcomes and number of deliveries, respectively. For sperm retrieval the covariates included male age and hormone levels. For embryonic and clinical outcomes the covariates included male and female age, infertility duration, associated female infertility, and number of transferred embryos. Significance was considered at $P<0.05$. Analyses were performed using R version 2.14.2 (Free Software Foundation, Boston, MA, USA).

**Results**

The SRR by micro-TESE in men with testicular failure was 41.4%. Among men with testicular failure, those with Sertoli cell-only and maturation arrest had lower SRR (SCO: 19.5%, $n=40/205$; MA: 40.3%, $n=27/67$) than the ones with hypospermatogenesis (100.0%; $n=84/84$) on testicular histology ($P<0.001$). Compared to men with MA those with SCO had a lower SRR ($P=0.007$). After adjusting for age and hormone levels, the odds-ratio at obtaining sperm between the groups of testicular failure and OA was 0.033 (95% confidence interval: 0.007 to 0.164, Wald $P<0.001$). The overall complication rate following micro-TESE was 6.3%, and was not different from the 5.5% rate in percutaneous retrievals. Pain was the most common complaint (8 patients), followed by
swelling (2 patients), and infection (2 patients). None of the patients required interventions but the use of analgesics and/or antibiotics. Cryopreservation of excess sperm retrieved by micro-TESE was carried out in 22.5% of cases, and the results were similar to those obtained in OA (Table 1).

Sperm injections using testicular sperm retrieved from men with testicular failure were performed for 151 couples. We failed in obtaining sperm for 214 men with testicular failure (58.6%). Of these men 40 used donor sperm for ICSI while the others had their treatments cancelled. In the latter, the retrieved oocytes were frozen (104 patients), donated (36 patients) or discarded (34 patients). The patient characteristics and ICSI outcomes are presented in Table 2. Female age, endocrine profile and duration of infertility were not different in the groups of testicular failure, donor sperm, and OA. There were no significant differences in the number and maturity of oocytes retrieved among the groups. The normal 2PN fertilization and high quality embryos rates were lower in the testicular failure (47.0% and 43.3%, respectively) than donor sperm (61.0% and 66.5%, P<0.001) and OA (64.0% and 60.9%, P<0.001) groups. The mean number of transferred embryos was similar among the groups. Live birth rates were lower in the testicular failure (19.9%) than donor sperm (37.5%; P=0.003) and OA (34.2%, P<0.001) groups, whereas miscarriage rates did not differ among them. The adjusted odds-ratios for clinical pregnancy and live birth by ICSI were 0.360 (95% CI: 0.176 - 0.736, Wald P = 0.005) and 0.377 (95% CI: 0.233 - 0.609, Wald P <0.001) between testicular failure and donor sperm, and 0.388 (95% CI: 0.184 - 0.817, Wald p=0.013) and 0.403 (95% CI: 0.241 - 0.676, Wald P =0.001) between testicular failure and OA groups.

A total of 48 infants was delivered after ICSI with testicular sperm retrieved from men with testicular failure. Gestational age, birth weight and sex ratio of these children were comparable to those reported in the donor sperm and OA groups (Table 3). A total of 2 deliveries involved either a perinatal death or a malformation (cleft lip and palate) in the group of men with testicular failure, resulting in an overall adverse neonatal outcome of 4.1%.

Discussion

We report sperm retrieval rates and sperm injection outcomes, including the profile of neonates conceived, of men with testicular failure. The chances of obtaining sperm were markedly reduced in men with testicular failure compared with OA, even when micro-TESE was used as the method of sperm acquisition. The odds ratio estimate represented the approximate doubling in the testicular failure retrieval rate up to almost certain success in the OA patients. The high magnitude of the OR estimate in the multivariable model demonstrated that covariate adjustment did not explain the large difference in retrieval rates between the testicular failure and OA. Sperm injections were carried out in all cases where SR had been successful. ICSI using donor sperm was also performed in a subgroup of men with testicular failure who had no sperm retrieved by micro-TESE. Zygote formation, embryo development and pregnancy rates were reduced when sperm from men with testicular failure were used in ICSI compared with donor sperm. Similarly, the outcomes were lower when ICSI was performed with non-ejaculated gametes obtained from men with testicular failure compared with OA. For live birth, the covariate adjusted-OR estimates of approximately 0.4 were consistent with the approximate halving in the success rates from roughly 35% to 20% in OA/donor sperm.
compared with testicular failure patients. Nevertheless, the neonatal profile of children conceived was not affected by testicular failure.

Azoospermia is a descriptive term for ejaculates that lack spermatozoa without implying a specific underlying cause. In the clinical setting, patients presenting with azoospermia are classified with either nonobstructive azoospermia (NOA) or OA. Men with NOA have dysfunctional testes resulting from several conditions, including genetic and congenital abnormalities, post-infectious diseases, gonadotoxin exposure, trauma, endocrine disorders, and idiopathic causes. Although the fertility might be restored in the rare cases of spermatogenesis failure due to lack of appropriate stimulation by pituitary gonadotropins, the vast majority of these individuals have irreparable testicular failure. Since there are no treatment options in such cases, the alternative is to attempt SR and find viable testicular sperm for ICSI. The rationale of this approach relies on the fact that rare foci of sperm production exist in up to 60% of men with testicular failure.

The recommended method for SR in men with testicular failure is testicular sperm extraction (TESE), which yields variable success rates of 25% to 60%. Because the presence and geographic location of islets of normal spermatogenesis are unpredictable, several authors have proposed micro-TESE as a better method for SR in such cases. Micro-TESE allows the identification of enlarged seminiferous tubules more likely to harbor sperm production. The minimal tissue extraction and preservation of intratesticular blood supply are important features of micro-TESE, thus reducing the risk of testicular devascularization. In controlled series, micro-TESE performed better than TESE and percutaneous aspirations. For these reasons, micro-TESE was our preferred method for sperm acquisition in testicular failure. Given the fact that micro-TESE is an invasive procedure, we used strict criteria to classify a patient as having testicular failure. Our method included semen analysis results, history and physical examination findings, endocrine profiles, and genetic testing. In addition, we confirmed the diagnosis by histologic evaluation. The combination of these parameters was shown to be highly accurate to diagnose testicular failure. In this series, the SRR of 41.4% and complication rate of 6.3% are comparable to those reported in the literature.

Unlike testicular failure, obstructive azoospermia is the endpoint of a mechanical blockage along the reproductive tract involving the vas deferens, epididymis, or ejaculatory duct. Treatment options in OA include microsurgical reconstruction and SR for ICSI. The SRR in OA is practically 100%, and are not influenced by the sperm collection method and cause of obstruction. In this study, we performed a logistic regression analysis to assess the odds of retrieving sperm by micro-TESE in testicular failure, and by percutaneous retrieval in obstructive azoospermia. For this purpose, we used our published dataset of 146 men with normal spermatogenesis and azoospermia caused by obstruction, provided the procedures were performed by the same surgeon over the same period of time. Not surprisingly, we found that the odds of finding sperm with the aforesaid methods were significantly reduced given the presence of testicular failure ($P <0.001$).

Testicular failure is considered to be an unfavourable prognostic condition for SR because spermatogenesis is disrupted. Intracytoplasmic sperm injection is widely used for patients with severe male infertility. However, few studies have addressed ICSI outcomes by making a distinction between the type of azoospermia and taking into account the health of offspring. These aspects are important for evaluating the
impact of spermatogenesis on ICSI outcomes. Our results of lower fertilization, embryo quality, and impaired pregnancy rates, using testicular sperm of men with defective spermatogenesis, were corroborated by others. They are also in agreement with a previous report from our group which assessed 835 infertile couples who underwent ICSI using either non-ejaculated or ejaculated sperm. In this aforementioned study, live birth rates were lower for azoospermic men with NOA (21.4%) compared with both azoospermic men with OA and men with severe male factor infertility whose ejaculated sperm was used for ICSI (37.5% and 32.3%, respectively; \( P = 0.003 \)). Despite similar sperm injection outcomes, the present series substantially adds to the previous one. Of note, the studies differ in the population being assessed, albeit we acknowledge that some overlap exists. Here, we assessed SRR and defined micro-TESE as a selection criteria. Although the sperm acquisition method might not have influenced the ICSI outcomes for men with testicular failure, it would certainly have impacted the SRR. Hence, the effect of spermatogenesis on SR could be properly assessed by our logistic regression model. In addition, we controlled for co-variates that might have influenced the SR and ICSI outcomes. Male and female age, hormone profile, duration of infertility, associated female infertility factor and number of transferred embryos were taken into account in the logistic regression analysis. Some of these factors reflect ovarian function and are robust predictors of pregnancy in ART. Importantly, we included a subgroup of men that used donor sperm for ICSI. To our knowledge, none of the published series have compared ICSI outcomes between azoospermic patients and fertile donors. In this series, men with OA achieved similar results than fertile donors thus indicating that sperm integrity is not differentially affected by OA. In contrast, the sperm injection outcomes were negatively affected by testicular failure. These findings may be related to an increased risk of gametes extracted from men with severely impaired spermatogenesis to carry deficiencies involving centrioles and genetic material, which have been associated to decreased zygote formation and embryo development. Nevertheless, some investigators reported similar ICSI outcomes regardless of the azoospermia classification, which contrast to ours and others observations. The reasons for these conflicting results, however, remain unclear.

To date, only five studies compared the neonatal profile of babies born after ICSI by making a systematic distinction of obstructive and nonobstructive azoospermia. Similar to our findings, no major difference was noted in the neonatal outcomes and congenital malformation between the groups. Notwithstanding, a tendency towards lower gestational age and increased prematurity was observed for NOA in our previous study and in the series of Vernaeve et al. In this series, however, we could not confirm our previous results after controlling for the co-variates such as number of babies born and maternal age. Nevertheless, we add to the existing literature by comparing the neonatal outcomes of children conceived after ICSI from azoospermic fathers and fertile donors. From the limited group of 137 neonates born, we concluded that gestational age, birth weight, perinatal death and malformation rates do not seem to be affected by testicular failure. Although the current data on pregnancy and postnatal ICSI outcomes using non-ejaculated sperm is reassuring, the limited population analyzed calls for continuous monitoring. Moreover, studies on the physical, neurological, and developmental outcomes of children conceived are still lacking. Future research should focus not only on the long-term outcomes of such children but also on collaborative multi-center studies.
that include large patient cohorts in an attempt to estimate the risk of less common outcomes, such as congenital malformations and imprinting disorders.

Conclusions

The results from this study serve as a counseling tool for doctors treating azoospermia-related infertility. Azoospermic patients with testicular failure should be advised that their chances of having sperm retrieved, even when the best possible SR method is used, and of achieving a live birth with ICSI after a successful retrieval are negatively affected by their type of azoospermia. Once a live birth is achieved no major differences are noted in the offspring’s neonatal profile.

Author contributions

SCE designed the study, performed data analysis and prepared the manuscript. CP, BS, SV Jr, and CK participated in the acquisition of data, and helped to draft and revise the manuscript. AA participated in the design of the study, revised the manuscript and helped in coordination. All authors read and approved the final manuscript.

Competing interests

All authors declare no competing interests.

Acknowledgments

We thank Jeff Hammel performed the statistical analyses, and Fabiola Bento assisted with language revision.

References


Table 1. Sperm retrieval rates (SRR) in azoospermic men with testicular failure and obstructive azoospermia

<table>
<thead>
<tr>
<th></th>
<th>Testicular failure</th>
<th>Obstructive Azoospermia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>365</td>
<td>146</td>
<td>-</td>
</tr>
<tr>
<td>Male age (year)</td>
<td>36.9±7.6</td>
<td>42.6±9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male endocrine profile:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSH (mIU ml(^{-1}))</td>
<td>16.7±10.7</td>
<td>4.8±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (mIU ml(^{-1}))</td>
<td>7.9±5.5</td>
<td>3.9±1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total testosterone (ng dl(^{-1}))</td>
<td>412.6±168.1</td>
<td>542.1±186.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combined left and right testicular volume (ml)</td>
<td>28.7±8.1</td>
<td>37.4±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Successful sperm retrieval(^a), n (%)</td>
<td>151 (41.4)(^b)</td>
<td>146 (100.0)(^b)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complication, n (%)</td>
<td>12 (6.3)</td>
<td>8 (5.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Excess retrieved sperm cryopreservation, n (%)</td>
<td>34 (22.5)</td>
<td>39 (26.7)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Data are means ± s.d. unless otherwise indicated; Wilcoxon Rank Sum Test, Pearson chi-square test and Fisher exact test were used for comparisons.

\(^a\)Defined at obtaining sperm.

\(^b\)P<0.001 when adjusting for male age and serum levels of FSH, LH, and testosterone in a logistic regression model.
Table 2. ICSI outcome in azoospermic men with testicular failure, stratified by successful and failed sperm retrieval (donor sperm), and obstructive azoospermia

<table>
<thead>
<tr>
<th></th>
<th>Testicular failure</th>
<th>Donor sperm</th>
<th>Obstructive azoospermia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles</td>
<td>151</td>
<td>40</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>32.7±5.4</td>
<td>31.4±3.5</td>
<td>32.5±5.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Basal serum FSH (IU l⁻¹)</td>
<td>5.6±2.7</td>
<td>4.6±1.8</td>
<td>5.8±3.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Infertility duration (year)</td>
<td>4.3±3.1</td>
<td>3.6±2.2</td>
<td>5.1±4.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of oocytes Retrieved</td>
<td>13.7±4.4</td>
<td>12.7±6.7</td>
<td>12.3±7.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Metaphase II</td>
<td>10.0±5.7</td>
<td>11.5±4.2</td>
<td>9.9±6.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Two pronuclei fertilization (%)</td>
<td>47.0±30.0</td>
<td>61.0±17.0</td>
<td>64.0±22.0</td>
<td>&lt;0.001³</td>
</tr>
<tr>
<td>Embryos</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High quality (%)</td>
<td>43.3±35.0</td>
<td>66.5±24.3</td>
<td>60.9±39.2</td>
<td>&lt;0.001³</td>
</tr>
<tr>
<td>Transferred (n)</td>
<td>2.7±1.4</td>
<td>2.6±1.5</td>
<td>2.8±1.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Clinical pregnancy, n (%)</td>
<td>42 (27.8)</td>
<td>20 (50.0)</td>
<td>67 (46.9)</td>
<td>0.002⁵,⁶</td>
</tr>
<tr>
<td>Miscarriage, n (%)</td>
<td>12 (28.6)</td>
<td>5 (25.0)</td>
<td>16 (23.9)</td>
<td>0.88</td>
</tr>
<tr>
<td>Live birth, n (%)</td>
<td>30 (19.9)</td>
<td>15 (37.5)</td>
<td>50 (34.2)</td>
<td>0.004⁵,⁶</td>
</tr>
</tbody>
</table>

Data are means ± s.d. unless otherwise indicated; Kruskal-Wallis, Pearson chi-square test, and Fisher’s exact test were used for comparisons; Donor sperm vs OA not significant in all pairwise comparisons.

³Testicular failure vs donor sperm (P =0.003; Wilcoxon Rank Sum Test) and OA (P<0.001; Wilcoxon Rank Sum Test);
⁴Testicular failure vs donor sperm and OA (P<0.001; Wilcoxon Rank Sum Test);
⁵Testicular failure vs donor sperm (P =0.008; Fisher’s exact test) and OA (P =0.002; Pearson chi-square test);
⁶Testicular failure vs donor (P=0.001; Pearson chi-square test) and OA (P=0.003; Fisher’s exact test);
⁷P<0.01 when adjusting for co-variates including female and male age, male endocrine profile, duration of infertility, associated female infertility factor and number of transferred embryos.
Table 3. Outcome of neonates born after ICSI in azoospermic men with testicular failure, stratified by successful and failed sperm retrieval (donor sperm), and obstructive azoospermia

<table>
<thead>
<tr>
<th></th>
<th>Testicular failure</th>
<th>Donor sperm</th>
<th>Obstructive azoospermia $^9$</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deliveries (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.49$^b$</td>
</tr>
<tr>
<td>Singletons, $n$ (%)</td>
<td>18 (58.1)</td>
<td>10 (62.5)</td>
<td>39 (76.5)</td>
<td></td>
</tr>
<tr>
<td>Twins, $n$ (%)</td>
<td>9 (29.0)</td>
<td>4 (25.0)</td>
<td>10 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Triplets, $n$ (%)</td>
<td>4 (12.9)</td>
<td>2 (12.5)</td>
<td>2 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Neonates born ($n$)</td>
<td>48</td>
<td>24</td>
<td>65</td>
<td>--</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>36.1±3.6</td>
<td>36.7±2.6</td>
<td>36.3±3.0</td>
<td>0.94</td>
</tr>
<tr>
<td>Birth weight (gram)</td>
<td>2,962±390</td>
<td>2,954±498</td>
<td>2,978±447</td>
<td>0.99</td>
</tr>
<tr>
<td>Proportion male</td>
<td>0.56±0.45</td>
<td>0.58±0.44</td>
<td>0.55±0.457</td>
<td>0.97</td>
</tr>
<tr>
<td>Perinatal death$^a$, $n$ (%)</td>
<td>1 (2.1)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Malformation, $n$ (%)</td>
<td>1 (2.1)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Data are means ± s.d. unless otherwise indicated; Kruskal-Wallis and Fisher’s exact test were used for comparisons.

$^a$Includes stillbirth and neonatal deaths with frequency calculated as number of perinatal deaths/number of neonates born.

$^b$In a Poisson regression model for the number of babies born and adjusting for male and female age, duration of infertility and serum levels of FSH, LH and testosterone in addition to female factor infertility and number of transferred embryos, the overall comparison among the groups continued to demonstrate no statistically significant difference.