Non-obstructive idiopathic azoospermia vs azoospermia with antecedents of cryptorchidism: ways and probabilities of becoming parents

Jacques Singh Sangwan1,2, Claire Petit1, Romane Sainte Rose1, Cynthia Frapsauce1, Laura Dijols1, Jean Marc Rigot3 and Fabrice Guérif1,4,5*

Abstract

Background: Non-obstructive azoospermia (NOA) with history of cryptorchidism and idiopathic NOA are the most common forms of NOA without genetic aetiology. Of all patients with one of these two types of NOA, only a few will have a positive Testicular Sperm Extraction (TESE). Of those with positive extraction followed by sperm freezing, not all will have a child after TESE-ICSI. What are the ways and probabilities of taking home a baby for patients with NOA and a history of cryptorchidism compared with patients with idiopathic NOA?

Results: Patients with idiopathic NOA or NOA and a history of cryptorchidism who underwent their first TESE were included. The patients were divided into two groups: Group 1 was composed of 125 patients with idiopathic NOA and Group 2 of 55 patients with NOA and a history of surgically treated cryptorchidism. Our results showed that more than half of the NOA patients succeeded in becoming parents. The main way to fulfil their plans for parenthood is to use sperm or embryo donation (72%) for men with idiopathic NOA, whereas the majority of men with NOA and a history of cryptorchidism had a child after TESE-ICSI (58.8%).

Conclusions: In our centre, before considering TESE for a patient with NOA, we explain systematically TESE-ICSI alternatives (sperm donation, embryo donation or adoption). As a result, the couple can consider each solution to become parents.

Keywords: Non-obstructive azoospermia, Cryptorchidism, TESE-ICSI, Sperm donation, Embryo donation

* Correspondence: guerif@med.univ-tours.fr
1Service de Médecine et Biologie de la Reproduction, Hôpital Bretonneau, F-37044 Tours, France
4Université François Rabelais, F-37041 Tours, France
Full list of author information is available at the end of the article

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Resume

Contexte: L’azoospermie non obstructive (ANO) avec un antécédent de cryptorchidie et l’ANO idiopathique sont les causes les plus fréquentes d’ANO sans étiologie génétique. Parmi les patients présentant un de ces 2 types d’ANO, seuls quelques-uns auront une extraction positive de spermatozoïdes testiculaires (TESE). Parmi les patients ayant une extraction positive suivie d’une congélation de spermatozoïdes, tous n’obtiendront pas de naissance après TESE-ICSI. Quels sont les moyens et les probabilités de « ramener un enfant à la maison » pour les patients avec une ANO associée à un antécédent de cryptorchidie en comparaison à ceux présentant une ANO idiopathique ?

Résultats: De tels patients ont été inclus dans notre étude et divisés en deux groupes : Groupe 1 composé de 125 patients avec une ANO idiopathique et Groupe 2 de 55 patients avec une ANO associée à un antécédent de cryptorchidie traitée chirurgicalement. Nos résultats ont montré que plus de la moitié des patients atteints d’ANO ont réussi à devenir parents. Le principal moyen pour réaliser leur projet parental était le recours au don d’embryon ou l’accueil d’embryons (72%) pour les hommes avec ANO idiopathique, alors que la majorité des hommes avec ANO et antécédent de cryptorchidie (58.8%) achevaient leur projet parental par TESE-ICSI.

Conclusions: Dans notre centre, avant d’envisager une biopsie testiculaire chez un patient présentant une ANO, les alternatives (don de sperme, accueil d’embryon ou adoption) à la TESE-ICSI sont explicitées systématiquement. En conséquence, le couple peut envisager chaque solution pour devenir parent.

Mots clés: Azoospermie non-obstructive, Cryptorchidie, TESE-ICSI, Don de sperme, Don d’embryons

Introduction

The absence of spermatozoa in the ejaculate is identified in about 15% of infertile men. It can be classified as obstructive azoospermia and non-obstructive azoospermia (NOA). Thorough history-taking and physical examination are crucial in the classification of azoospermia etiology and may be accompanied by laboratory and genetic testing.

NOA, which comprises 60% of azoospermic men, includes several etiologies: abnormal testicular development (genetic causes, cryptorchidism, hypogonadism) and toxic exposures (radiotherapy, chemotherapy) [1, 2]. When no cause is found, it is termed idiopathic NOA. NOA with a history of cryptorchidism and idiopathic NOA are the most common forms of NOA [2]. Since the establishment of testicular sperm extraction (TESE) and the use of intracytoplasmic sperm injection (ICSI), patients with NOA have had an opportunity to conceive with their own spermatozoa [3]. According to previously published studies, the number of spermatozoa detected during a biopsy varies from 20% to 60% [4–6]. Of all patients with a positive TESE, only some will have a child after ICSI [4–6].

In the event of a negative TESE or after TESE-ICSI failure, many patients won’t be able to conceive a biological child. It is therefore crucial to inform couples of other procedures including sperm or embryo donation as well as adoption. Sperm donation is a technique used for couples suffering from severe male infertility, after repeated failures of ICSI fertilization or with a serious, transmissible genetic disorder. Embryo donation consists of embryos initially derived from intra-conjugal in vitro fertilization (IVF), whose owners no longer have parental plans and have decided to give them to other infertile couples. Embryo donation is preferentially offered to couples suffering from severe female and male infertility. The procedure of adoption in France is becoming increasingly difficult. The wait time is very long, and few couples will be able to adopt a child.

The aim of this study was to evaluate the chances of fathering a child (biological or not) in two populations of men with NOA (idiopathic or with a history of cryptorchidism).

Materials and methods

Patient population

This retrospective study took place in the Department of Reproductive Medicine and Biology of Tours, University Hospital, between November 2013 and December 2017 including 180 men with NOA and undergoing a conventional TESE. Azoospermia was diagnosed in all patients, due to the total absence of spermatozoa in the ejaculate of at least two sperm samples, determined by high-speed centrifugation [7]. Patients with a history of TESE were excluded.

Before surgical sperm extraction, each patient underwent a complete andrologic evaluation to determine the etiology of azoospermia. All patients underwent a thorough history-taking and physical examination including testicular volume assessment, measured manually using a Prader orchidometer. Moreover an endocrine profile (follicle stimulating hormone (FSH), inhibin B and serum testosterone levels) [8] and genetic analyses (karyotype and Y-chromosome microdeletion testing)
least one motile spermatozoon was observed in 10 fields extraction was followed by freezing for later use when at spermatozoon in the testicular cell suspension. Positive examination was defined by the presence of at least one centre, positive spermatozoa extraction after exam-

remaining sample was sent to the IVF laboratory for fur-

histologically for histological diagnosis of NOA. The was randomly taken from each specimen and examined could explain NOA.

could explain the NOA.

Our centre, positive spermatozoa extraction after exam-

would explain NOA (radiotherapy, chemotherapy and hypogonadotrophic hypogonadism).

Group 1 consisted of 125 patients with idiopathic NOA, whereas Group 2 was composed of 55 NOA pa-
tients with a history of surgically treated cryptorchidism without genetic aetiology or other antecedents that could explain the NOA.

**Ethical approval**

All participating couples gave their written informed consent for the reporting and publishing of the results of the study. The protocol for this retrospective study was approved by the Ethics Committee for research involving human subjects in our hospital (Research Project No. 2016 066).

**Hormone assays**

The serum FSH level was measured by chemiluminescent microparticle (CMIA) immunoassay with a normal concentration ranging from 0.9 to 10 IU/L. Serum testo-
tosterone levels were determined using CMIA with nor-
mal concentrations between 7.2 and 24.2 nmol/L. Serum inhibin B levels were measured using the enzyme im-
munoassay (EIA) with a detection limit of 15 pg/mL.

**Testicular sperm recovery**

All the procedures of open excisional testicular bilateral biopsy (conventional TESE) were performed by the same operator and under general anaesthesia or spinal anaes-
thesia. The TESE procedure was performed before any ovum pick-up was carried out on the female partner. One sample was taken from each testicle; the volume of the sample was determined as a function of testicular volume [10]. A very small biopsy (approximately 1/20) was randomly taken from each specimen and examined histologically for histological diagnosis of NOA. The remaining sample was sent to the IVF laboratory for fur-
ther examination, followed by spermatozoa freezing. In our centre, positive spermatozoa extraction after exam-

in the testicular cell suspension. Positive extraction was followed by freezing for later use when at least one motile spermatozoon was observed in 10 fields at 400x magnification.

**IVF procedure**

In cases of positive extraction followed by freezing, an ICSI was performed in the following months. The ovar-
ian stimulation protocol used in our medical centre has already been described elsewhere [11]. After removal of cumulus-corona cells, metaphase II oocytes were injected with motile spermatozoa. Briefly, embryo cul-
ture with sequential media and assessment were carried out as follows: fertilisation (day 0) was performed in G-
IVF medium (Vitrolife, Göteborg, Sweden). The follow-
ing morning (day 1), the oocytes were individually placed in microdrops (25 μl) in G-1 PLUS medium (Vitrolife, Göteborg, Sweden) under Ovoil (Vitrolife, Göteborg, Sweden). From day 3 to day 5/6, embryo cul-
ture was performed in microdrops in G-2 PLUS medium (Vitrolife, Göteborg, Sweden) under Ovoil (Vitrolife, Göteborg, Sweden). All cultures took place in incubators at 37°C with 6% CO₂, 5% O₂ and 89% N₂.

All the subsequent optical assessments were per-
formed using an inverted microscope with Hoffman modulation contrast (x200 and x400 magnification) [12]. All observations were performed by two experienced embryologists. Embryos were evaluated 44-46 hours post-insemination/ICSI (day 2) on the basis of the number of blastomeres, shape (regularity) of cells, fragmenta-
tion rate and the presence of multinucleated blastomeres. Embryos with one or more multinucleated blastomeres were excluded from transfer and further extended embryo culture. The outcome of extended em-

bryo culture was recorded for each individually cultured embryo. The morphological assessment was based on the expansion of the blastocele cavity (B1 to B6) and the number and cohesiveness of the inner cell mass (ICM) and trophodermal cells. One or two embryos with the best morphology were transferred on day 2 or day 5/6. Supernumerary blastocysts at the B2-B6 stages on day 5 or the B3-B6 stages on day 6 with an A/B inner cell mass and A/B trophoderm were frozen for later use.

**Pregnancy follow-up**

Clinical pregnancy was defined as the presence of a ges-
tational sac with foetal heart activity on ultrasound 5 weeks after oocyte retrieval. A birth was defined as the delivery of a living infant after 20 weeks or more of gestation.

**Donation procedure**

When sperm freezing was not possible or after several ICSI-TESE failures, couples were routinely offered the use of sperm or embryo donation in our centre. In order to be informed about the process of sperm and/or em-

bryo donation, the couple meets first the surgeon, the IVF clinician and the psychologist from our IVF center.
If necessary, the couple meets the biologist to discuss about the principles of donation in France, the rules of allocation and the waiting period. When sperm freezing was not possible or after several ICSI-TESE failures, 68 couples accepted the process of donation, while 37 couples refused in Group 1. In Group 2, 17 couples accepted the process of donation, while 17 couples refused.

Outcome measure
The study ended at least 2 years after the testicular biopsy, allowing couples to carry out their parental project through other procedures (donation or adoption). The outcome measure was taking home a baby (biological or not). Thus, at the end of the study, couples completed either a biological parental project (TESE-ICSI), either a non-biological parental project (ART with a donation or adoption) or failed.

Statistical analysis
Statistical analysis was performed using the Statview 4.1 software (Abacus Concepts, Berkeley, CA, USA). Quantitative variables were compared by analysis of variance (ANOVA) using a Student’s t-test. The data were expressed as mean ± standard deviation (SD). Qualitative data were compared using the χ² test. Fisher’s exact test was used to compare small samples. Differences were considered significant when P < 0.05.

Results
Patients
The epidemiological characteristics of patients with idiopathic NOA (Group 1) or a history of cryptorchidism (Group 2) are shown in Table 1. The values of total testicular volume (TTV), FSH, inhibin B and testosterone were similar between the two groups.

Sperm extraction
Of the 180 patients, 63(35%) had positive sperm extraction. Positive sperm extraction was significantly more frequent in Group 2 (n=29, 53%) than in Group 1 (n=34, 27%), p = 0.01. This result was consistent with an increased frequency of hypospermatogenesis in Group 2 compared with Group 1 (58% vs. 39%, respectively, p< 0.028).

Moreover, patients with NOA and a history of cryptorchidism had almost double the probability of having a positive extraction with freezing, in comparison with idiopathic NOA patients (51% vs. 26%, respectively, p = 0.01).

As outlined in Table 2, on the basis of TTV, serum levels of FSH and inhibin B, we compared patients with sperm freezing and patients without sperm freezing or negative extraction. In each group, there was no significant difference when TTV, FSH and inhibin B concentrations were considered separately. Moreover, there was no significant difference for TTV, FSH or inhibin B when we combined the two groups (data not shown).

Table 1 Epidemiological, biological and histopathological data in Group 1 (idiopathic NOA) and Group 2 (NOA with a history of cryptorchidism) patients

|                        | All Patients (n = 180) | Group 1 Idiopathic NOA (n = 125) | Group 2 NOA with History of Cryptorchidism (n = 55) | P  |
|------------------------|------------------------|----------------------------------|-----------------------------------------------------|----|
| Male age (years)       | 33.3 ± 5.9             | 33.5 ± 5.3                       | N5                                                  |    |
| Female age (years)     | 29.7 ± 4.1             | 30.3 ± 3.9                       | N5                                                  |    |
| Length of infertility (years) | 2.9 ± 1.9            | 3.4 ± 2.8                        | N5                                                  |    |
| TTV (mL)               | 19.0 ± 7.0             | 17.8 ± 7.1                       | N5                                                  |    |
| FSH (IU/L)             | 17.0 ± 9.3             | 17.2 ± 10.0                      | N5                                                  |    |
| Inhibin B (pg/mL)      | 53.3 ± 74.1            | 57.8 ± 67.6                      | N5                                                  |    |
| Testosterone (nmol/L)  | 13.6 ± 6.2             | 14.0 ± 5.7                       | N5                                                  |    |
| Fresh examination by IVF laboratory |          |                                   |                                                     |    |
| Positive extraction    | 34 (27%)               | 29 (53%)                         | 0.01                                                |    |
| Positive extraction with freezing | 32 (26%)             | 28 (51%)                         | 0.01                                                |    |
| Histological examination |                      |                                   |                                                     |    |
| Hypospermatogenesis    | 49 (39%)               | 32 (58%)                         | 0.028                                               |    |
| Spermatogenesis with maturation arrest | 22 (18%)             | 1 (2%)                           | 0.007                                               |    |
| Sertoli cell only       | 54 (43%)               | 22 (40%)                         | N5                                                  |    |

Data are presented as mean ± SD or as percentages
NOA non-obstructive azoospermia, FSH follicle stimulating hormone, IVF In Vitro Fertilization, NS not-significant, TTV total testicular volume, SD standard deviation
Different results after TESE

In Group 1 (idiopathic NOA), all couples with positive extraction followed by sperm freezing (n = 34) performed ICSI cycles (Figure 1). Of the remaining 91 couples, including those with negative extraction or non-freezable sperm extraction, 26 couples (28.6%) declined the sperm or embryo donation procedure, while 65 couples (71.4%) used a donation. In group 2 (NOA with antecedents of cryptorchidism), all couples with positive extraction followed by sperm freezing (n = 29) underwent ICSI cycles (Figure 2). Of the remaining 26 couples with negative extraction, 10 couples (38.5%) declined the sperm or embryo donation procedure, while 16 couples (61.5%) accepted a donation.

Table 2 Prediction of sperm extraction with freezing in patients with idiopathic NOA (Group 1) or NOA with a history of cryptorchidism (Group 2)

| All Patients (n = 180) | Group 1 (Idiopathic NOA, n = 125) | Group 2 (NOA with History of Cryptorchidism, n = 55) |
|-----------------------|----------------------------------|----------------------------------|
|                       | Sperm freezing | No sperm freezing* | p | Sperm freezing | No sperm freezing* | p |
|-----------------------|----------------|-------------------|---|----------------|-------------------|---|
| n                     | 34             | 91                |   | 29             | 26                |   |
| TTV (mL)              | 19.6 ± 6.8     | 18.7 ± 7.1        | NS| 19.7 ± 7.0     | 15.8 ± 6.7        | NS|
| FSH (IU/L)            | 14.9 ± 8.9     | 17.8 ± 9.4        | NS| 14.6 ± 8.9     | 20.2 ± 10.5       | NS|
| Inhibin B (pg/mL)     | 64.7 ± 77.5    | 48.8 ± 72.7       | NS| 70.0 ± 71.9    | 44.0 ± 60.9       | NS|

*Negative extraction and non-freezable sperm extraction
Data are presented as mean ± SD and numbers
FSH follicle stimulating hormone, NOA non-obstructive azoospermia, NS not significant, TTV total testicular volume, SD standard deviation

Different ways to become a father after TESE

In Group 1 (idiopathic NOA), among 99 couples undergoing an assisted reproduction procedure (ICSI with TESE, sperm or embryo donation), 72 couples (72.7%) completed a parental project (Figure 1). Successful couples became parents, mainly non-biologically, after sperm donation [49/72 (68.1%)] or embryo [3/72 (4.2%)] donation, while 27.7% of couples (20/72) became parents using the TESE procedure.

In Group 2 (NOA with antecedents of cryptorchidism), among 45 couples undergoing an assisted reproduction procedure (ICSI with TESE, sperm or embryo donation), 34 couples (75.6%) carried out their parental plans (Figure 2). In contrast to Group 1, most...
Successful couples became parents using the TESE procedure [20/34 (58.8%)], while 41.2% (14/34) of them became non-biological parents, only after sperm [12/34 (35.3%)] or embryo [2/34 (5.9%)] donation.

Altogether, in couples undergoing an assisted reproduction procedure, the rate to take home a baby was similar in Groups 1 and 2 (72/99 (72.7%) versus 34/45 (75.6%) couples, respectively, \( p = 0.37 \)). However, in successful couples, men in Group 2 had twice the chance of becoming fathers with their own spermatozoa, in comparison with men from Group 1 [58.8% (20/34)] vs. [27.7% (20/72)], respectively, \( p < 0.01 \).

**DISCUSSION**

NOA with a history of cryptorchidism and idiopathic NOA are the most common forms of NOA without a genetic aetiology [2]. Among such patients, not all of those who have their spermatozoa frozen after a positive TESE will have a child after TESE-ICSI [4–6]. However, these studies did not consider the possibility of carrying out a parental plan with alternative ART procedures (sperm and embryo donation) and adoption. To our knowledge, this is the first study evaluating the cumulative probability of taking home a baby, by combining different strategies after TESE.

The most common parameters considered to predict the probability of positive extraction in patients with NOA are total testicular volume, serum FSH and inhibin B levels. In patients with NOA, only a few studies have confirmed that total testicular volume could predict TESE results [13]. By contrast, several other studies have failed to confirm the predictive relationship with sufficient precision [14, 15]. Similarly, some studies have shown that serum FSH levels could be a valuable parameter [16, 17], while other studies did not support it [15]. Some studies have suggested that serum inhibin B could be a useful parameter alone [16, 18, 19] or in combination with serum FSH [20]. However, the serum level of inhibin B was not found to be sufficiently discriminating by other studies [15]. In our study, we found no significant difference between patients with a positive TESE followed by sperm freezing and those with a negative extraction or non-freezable sperm extraction. Previous studies analyzing biological or hormonal markers to predict sperm extraction have often larger populations allowing to reach statistical differences. In our study, as our groups are strictly defined, the size of the population is small. It could be the major explanation leading to the lack of difference about such biological parameters.

It seems that there was no consensus defining a limit below which it would be superfluous to freeze sperm from TESE, because the chances of pregnancy would be very low. In a previous study, a testicular cell suspension obtained after a wet laboratory preparation was frozen...
for later use when at least one sperm was observed [21].
Of their patients with NOA, 41% had a positive TESE
with a cumulative crude delivery rate of 37% after 6
ICSI. In our IVF centre, we applied stricter criteria for
freezing after TESE. According to this threshold, testicu-
lar spermatozoa were detected in 35% (63/180) of pa-
tients with NOA. Among our patients with frozen sperm
after TESE, the cumulative delivery rate after 4 potential
ICSI cycles was 66.7% (40/60). The difference in the cu-
mulative delivery rate between our study and that of
Vloeberghs et al. could be explained by our stricter cri-
tera for freezing testicular sperm. In our centre, back-
up TESE (i.e. rescue TESE performed on the day of o-
ocute retrieval if frozen—thawed suspensions could not be
used) was not included in the sperm exploration strat-
 egy. However, our stricter freezing criteria reduced the
risk of unnecessary oocyte retrieval due to the lack of sperm available for ICSI without decreasing the chances
of achieving a birth after TESE.

Several studies have shown that NOA patients with a
history of cryptorchidism are more likely to have positive sperm retrieval during TESE than men with idiopathic
NOA [13, 22, 23]. Our results are consistent with such
observations. In fact, in our study, NOA patients with a
history of cryptorchidism had almost double the chances
of having a positive extraction followed by freezing, in
comparison with idiopathic NOA patients (51% vs. 26%,
respectively).

When sperm extraction was positive after TESE, 63.5%
of couples (40/63) managed to have a baby using TESE-
ICSI and only 6.3% through a donation process after fail-
ure of TESE-ICSI (4/63). When sperm extraction was
negative after TESE, 53.8% of couples (63/117) managed
to have a baby only through the donation of sperm or
embryos. The originality of our study was that it
highlighted all the procedures for becoming a father (in-
cluding ART and non-ART procedures) available to
NOA patients, regardless of the results of TESE explora-
tions. Indeed, biological paternity is not the only way to
conceive a child. Of all NOA couples included in our
study, 58.9% (106/180) took home a baby, mainly after
sperm or embryo donation (36.7% = 66/180) and less
frequently using intra-conjugal spermatozoa (22.2% = 40/180).
Around seven percent of couples (13/180) initi-
at ed an adoption process. When patients with idiopathic
NOA and those with a history of cryptorchidism were
analysed separately, we observed that patients with an-te-
cedents of cryptorchidism had approximately double the
frequency of positive extraction followed by freezing.
Altogether, such results allowed them to become fathers
with their own spermatozoa more frequently in com-
parison with idiopathic NOA patients (36.4% vs. 16.0%,
respectively), and there was no difference between the
two groups in the overall rate of taking home a baby
61.8% vs. 57.6%, respectively), when alternative proce-
dures were also considered.

Failure of sperm extraction after testicular biopsy or
failures of pregnancy after TESE-ICSI are dramatic
events for couples. All couples followed in our center for
infertility with azoospermia have different consultations
with our clinician andrologist, our psychologist and an
IVF physician in order to prepare the course of IVF and
possibly the use of sperm donor. Indeed, even after these
times of explanations and exchanges, sperm donation
procedure for parenthood is experienced very differently
by couples treated for infertility with azoospermia. Rea-
sons are mainly psychological. Some explanations put
forward by couples (both men and women) are: the loss of "transmission of the genetic heritage", fear of the
family gaze, feeling of adultery through the technique of
sperm donation. Religious reasons are also sometimes
put forward. However, often the couple concludes not to
use donation without indicating clearly what the reasons
are for this. We did not note any differences in the rea-
sons given by the couple refusing recourse to donation
after TESE failure or ICSI-TESE failure.

In embryo donation although the intended mother car-
ries the baby until the birth, neither the woman or the
man from the recipient couple will be genetically related
to the resulting child. Thus, from a genetic point of view,
families issued from embryo donation do resemble to
families issued from adoption. However, legally, practic-
ally and psychosocially, there are differences between
embryo donation and adoption. A key question for such
couples is how to tell to their child the mode of concep-
tion which is fundamentally different between both pro-
cedures. For some parents, before planning to disclose in
the future, their child should have first some knowledges
about physiological reproduction. Professionals from
Assisted reproduction technologies as well as form adop-
tion procedure, initially advocated secrecy. However, a
spirit of openness has emerged among professionals of
assisted reproduction.

Some couples refuse the use of sperm or embryo do-
nation to fulfill their parental project, while other split
up after the announcement of such failures. In such situ-
ation, the medical staff has to inform the couple that
adoption, which is a non-medical way to become par-
tents, could be considered. However, the final decision is
in the hands of the affected couple. Adoption has always
been a long process. Over the past years, it tended to be-
come more and more complex. Thus, in France, the
number of adoptable children decreases years after years.
In addition, international adoption had also become
more difficult. Many countries have stopped the possi-
bility of adoption of children by foreigners. Altogether,
fewer and fewer couples manage to become parents by
this procedure or only after increasingly long delays. In
the field of the medical reproduction, the scientific literature on adoption is poor. For all this reasons (refusal of donation, split up, non-medical project of parenthood) couple are less inclined to answer to medical solicitation. In such conditions, the follow up of unsuccessful couples after initiation of an ART procedure remains quite difficult.

Conclusions
In our study, more than half of patients with NOA became parents. The majority of these patients were successful with the help of a donation and not by TESE-ICSI. Men with a history of cryptorchidism were twice more likely to become fathers with their own spermatozoa than men with idiopathic NOA. In our IVF centre, before considering TESE for a patient with NOA, we systematically explain the alternatives of TESE-ICSI (sperm donation, embryo donation or adoption) and the expected results from these processes. As a result, these couples can choose how they want to try to become parents.

Abbreviations
ART: Assisted reproductive technology; CMA: Chemiluminescent microparticle; EIA: Enzyme immunoassay; FSH: Follicle-stimulating hormone; ICSI: Intra-cytoplasmic sperm injection; IVF: In vitro fertilization; NOA: Non-obstructive azoospermia; TESE: Testicular sperm extraction; TTV: Total testicular volume

Acknowledgments
Not applicable.

Authors’ contributions
Initiation and design of the study: JSS and FG. JSS recruited patients, performed testicular biopsies and wrote the manuscript. CP and RSR wrote the manuscript. CF, LD and JMR reviewed the manuscript critically. FG wrote the final manuscript. The corresponding author on reasonable request.

References
1. Schlegel PN. Causes of azoospermia and their management. Reprod Fertil Dev. 2004;16:561–72.
2. Tüttelmann F, Werny F, Cooper TG, Klesch S, Simoni M, Nieschlag E. Clinical experience with azoospermia aetiology and chances for spermatozoa detection upon biopsy. Int J Androl. 2011;34:291–8.
3. Devroey P, Liu J, Nagy Z, Goossens A, Tournaye H, Camus M, et al. Pregnancies after testicular sperm extraction and intrauterine sperm injection in non-obstructive azoospermia. Hum Reprod. 1995;10:1457–60.
4. Tournaye H. Update on surgical sperm recovery – The European view. Hum Fertil. 2010;13:342–6.
5. Bernie AM, Ramasamy R, Schlegel PN. Predictive factors of successful microdissection testicular sperm extraction. Basic Clin Androl. 2013;23:5.
6. Thornhill JA, Fanning DM, Davis NF, Ward F, Shamsou O, Brinsden P. Testicular Sperm Extraction and Intracytoplasmic Sperm Injection: Outcomes in a specialist fertility centre. Ir J Med. 2015;108:263–5.
7. Ghef F, Michell V, Mandon-Pepin B, Vialard F. Genetic defects in human azoospermia. Basic Clin Androl. 2019;29:4.
8. Wosnitzer M, Goldstein M, Hardy MP. Review of azoospermia. Spermatogenesis. 2014;4:e28218.
9. Boitrelle F, Robin G, Marcelli F, Albert M, Leroy Martin B, Devally D, et al. A predictive score for testicular sperm extraction quality and surgical ICSI outcome in non-obstructive azoospermia: a retrospective study. Hum Reprod. 2011;26:3215–21.
10. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod. 1999;14:131–5.
11. Guerif R, Bidault R, Gassier O, Coquet ML, Gervereau O, Lansac J, et al. Efficacy of blastocyst transfer after implantation failure. Reprod BioMed Online. 2004;9:630–6.
12. Guerif F, Gouge AL, Giraudeau B, Poindron J, Bidault R, Gassier O, et al. Limited value of morphological assessment at days 1 and 2 to predict blastocyst development potential: A prospective study based on 4042 embryos. Hum Reprod. 2007;22:1973–81.
13. Raman JD, Schlegel PN. Testicular sperm extraction with intracytoplasmic sperm injection is successful for the treatment of nonobstructive azoospermia associated with cryptoorchidism. J Urol. 2003;170:1287–90.
14. Li H, Chen Y, Li M, Chen R, Lan R, et al. Predictive value of FSH, testicular volume, and histopathological findings for the sperm retrieval rate of microdissection TESE in non-obstructive azoospermia: a meta-analysis. Asian J Androl. 2018;20:30–6.
15. Tunc L, Krac M, Gurcosk S, Yucel A, Kupeli B, Alkayy T, et al. Can serum inhibin B and FSH levels, testicular histology and volume predict the outcome of testicular sperm extraction in patients with non-obstructive azoospermia? Int Urol Nephrol. 2006;38:629–35.
16. Goulis DG, Polychronou P, Mikos T, Grimbizis G, Gercou S, Pavlidou V, et al. Serum inhibin-B and follicle-stimulating hormone as predictors of the presence of sperm in testicular fine needle aspirate in men with azoospermia. Horm Athens Greece. 2008;7:140–7.
17. Chen SC, Hsieh JT, Yu HJ, Chang HC. Appropriate cut-off value for follicle-stimulating hormone in azoospermia to predict spermatogenesis. Reprod Biol Endocrinol. 2010;8:108.
18. Ballesca JL, Balasch J, Galafell JM, Alvarez R, Fabregues F, de OMJM, et al. Serum inhibin B determination is predictive of successful testicular sperm extraction in men with non-obstructive azoospermia. Hum Reprod. 2000;15:1734–8.
19. Brugo-Olmedo S, De Vincentis S, Calamera JC, Urtuia F, Nodar F, Acosta AA. Serum inhibin B may be a reliable marker of the presence of testicular spermatozoa in patients with non obstructive azoospermia. Fertil Steril. 2001;76:1243–9.
20. Böhring C, Schroeder-Printzen I, Weidner W, Krause W. Serum levels of inhibin B and follicle-stimulating hormone may predict successful sperm retrieval in men with azoospermia who are undergoing testicular sperm extraction. Fertil Steril. 2002;81:195–8.
21. Vloeberghs V, Verheyen G, Haentjens P, Goossens A, Polyzos NP, Tournaye H. How successful is TESE-ICSI in couples with non-obstructive azoospermia? Hum Reprod. 2015;30:1790–6.

22. Marcelli F, Robin G, Lefebvre-Khalil V, Marchetti C, Lemaître L, Mitchell V, et al. Results of surgical testicular sperm extractions (TESE) in a population of azoospermic patients with a history of cryptorchidism based on a 10-year experience of 142 patients. Prog Urol. 2008;18:657–62.

23. Plouvier P, Barbotin AL, Boitrelle F, Dewailly D, Mitchell V, Rigot JM, et al. Extreme spermatogenesis failure: andrological phenotype and intracytoplasmic sperm injection outcomes. Andrology. 2017;2:219–25.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.