

Secondary male infertility: the importance of the urological assessment for couples who desire children in later life

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ABSTRACT

Amongst 942 out-patients who consulted our male infertility division between 2016 to 2020, 85 (9.0%) patients suffered from secondary infertility. Of these, in 59 (69.4%) subjects, the first pregnancy was achieved by natural conception. 81 subjects were evaluated for semen quality except for two subjects who at the time were undergoing cancer treatment and another of two ejaculatory dysfunction (EjD). Semen analysis revealed 16 subjects (19.8%) were azoospermic, whereas 9 (11.1%) were cryptozoospermic at median three years of infertility. Left varicocelelectomy had been undertaken in a total of 17 oligoastheno-zoospermic and cryptozoospermic cases in order to improve semen quality. For achieving natural pregnancy, microscopic vasoepididymostomy was performed in 3 subjects of obstructive azoospermia and patency was achieved in two of three. 11 azoospermic subjects and two of the EjD underwent sperm retrieval surgery for intracytoplasmic sperm injection (ICSI). Motile sperm recovery was obtained by microscopic epididymal sperm aspiration (5/5=100%), microscopic testicular sperm extraction (micro-TESE, 2/6=33.3%), and retrograde vasal sperm aspiration (2/2=100%). Natural pregnancy was obtained in two subjects following varicocelelectomy, and in one following vasoepididymostomy. Seven pregnancies were achieved by ICSI using cryopreserved sperm and surgically retrieved sperm. Even if the first pregnancy occurred naturally, 30.9% subjects showed azoospermia or cryptozoospermia at median duration of three years. We would like to emphasize that earlier urological assessment especially semen analysis is necessary if pregnancy later in life is desired.

Keywords: secondary infertility, cryptozoospermia, azoospermia

Abbreviations:

EjD: ejaculatory dysfunction

MESA: microscopic epididymal sperm aspiration

micro-TESE: microscopic testicular sperm extraction

ReVSA: retrograde vasal sperm aspiration

ICSI: intracytoplasmic sperm injection

IUI: intrauterine insemination

IVF: in-vitro fertilization

NOA: non-obstructive azoospermia

VE: microscopic vasoepididymostomy

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OA: obstructive azoospermia

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INTRODUCTION

With the general trend in industrialised societies to have children at a later age, there is also an increased awareness of the impact of male related fertility problems. At our institute, for example we have observed that the ratio of such patients was in 2006 to 2010 4%, but, in 2011 to 2015, 5.6%, and 2016 to 2020 9%. In the past, the patients who desired later-born children had a tendency not to receive a surgical treatment such as sperm retrieval. However, recently increasing number of cases desiring children in late life chose surgical treatment. We retrospectively investigated the patients who desired children in later life in our institute, and evaluated the male infertility treatments provided.

PATIENTS AND METHODS

Between 2016 and 2020, 942 subjects visited our male infertility division. Of these, 85 subjects (9.0%) were desiring to have a second or more children in later life. Five of these subjects, hoped for the third child. Median duration of infertility was three years. Patients characteristics are shown in Table 1.

Table 1 Patients characteristics

	n=85
Age (y)	36 (25–58)
Spouse age (y)	35 (24–48)
Duration of infertility (y)	3 (0.5–13)
Testis volume (right/left) mL	16 (8–28) / 14 (6–26)
LH mIU/mL	3.2 (1.0–17.9)
FSH mIU/mL	5.2 (1.2–43.8)
Testosterone ng/mL	5.20 (2.02–11.25)
Zinc µg/dL	72 (49–110)
BMI	22.3 (17.6–31.1)

The initial pregnancy was obtained by natural intercourse in 59 subjects (69.4%), intrauterine insemination in 6 (7.1%), in-vitro fertilization in 4 (4.7%), and ICSI in 16 (18.8%), respectively. One subject who had a baby by ICSI, received micro-TESE due to non-obstructive azoospermia (NOA). 51 girls and 44 boys were born, and their health condition were good except in one boy (conceived following in-vitro fertilization) having a heart and vascular disorder.

Two subjects received cancer treatment due to testicular and secondly prostate cancer. There were 3 subjects with EjD, two were retrograde ejaculation due to deteriorating diabetes mellitus,

and another was due to unexplained cause. Health condition was good for all patients except above mentioned cancer and ejaculatory dysfunction. Thus, a total for 81 subjects could be evaluated for semen quality (except for the four subjects that had prostate cancer treatment or EjD). We retrospectively evaluated treatment and subsequent pregnancy for these subjects.

RESULTS

Semen analysis revealed azoospermia in 16 subjects (19.8%), cryptozoospermia in 9 (11.1%), oligoasthenozoospermia in 41 (50.6%). On the other hand, normospermia was observed in only 15 (18.5%) subjects. Amongst the subjects with azoospermia or cryptozoospermia, initial pregnancy was achieved by natural intercourse in 16 subjects. Relationship between semen analysis and first pregnancy are shown in Table 2.

Table 2 Semen analysis and first pregnancy

Semen analysis	First pregnancy			
	natural	IUI	IVF	ICSI
Normospermia (n=15)	10	1	2	2
Oligoasthenozoospermia (n=41)	29	4	2	6
Cryptozoospermia (n=9)	5	0	0	4*
Azoospermia (n=16)	11	1	0	4
Not done	EjD (n=3)	3	0	0
	Prostate cancer (n=1)	1	0	0
Total	59	6	4	16

IUI: intrauterine insemination

IVF: in-vitro fertilization

ICSI: intracytoplasmic sperm injection

EjD: ejaculatory dysfunction

*Included one testicular cancer subject.

The 17 subjects with oligoasthenozoospermia and cryptozoospermia received left varicocelectomy in order to improve semen quality. On the other hand, 14 of the azoospermic patients received surgical treatment. Three azoospermic subjects underwent microscopic vasoepididymostomy in order to achieve natural pregnancy. In cases of microscopic vasoepididymostomy, initial pregnancy was obtained through natural intercourse (two cases) and ICSI using ejaculated sperm in one case. Sperm retrieval surgery included microscopic epididymal sperm aspiration in 5 subjects, micro-TESE in 6. In cases of microscopic epididymal sperm aspiration, clinically diagnosed as having obstructive azoospermia, initial pregnancy was obtained by natural intercourse in four subjects and intra-uterine insemination in one. In cases of micro-TESE, clinically diagnosed as having NOA, initial pregnancy was obtained by natural (three cases), using ejaculated sperm for ICSI in two, and micro-TESE for ICSI in one. Retrograde vasal sperm aspiration¹ for EjD was undertaken in 2 subjects. In cases of retrograde vasal sperm aspiration, initial pregnancy was obtained by natural intercourse. Thus, 33 subjects (38.9%) received surgical treatment to try and have a further child.

Among 17 oligoasthenozoospermic or cryptozoospermic cases who underwent left varicocelectomy, 6 showed improving semen quality post-operatively. However, only three pregnancies were achieved with natural intercourse (2) and ICSI (1).

Of the subjects who received microscopic vasoepididymostomy, two achieved patency. One subject had a natural pregnancy after microscopic vasoepididymostomy and another by ICSI using sperm which was collected during surgery. Moreover, three pregnancies were obtained by ICSI using sperm retrieval surgery. In the case of testicular cancer, the patient received right high orchiectomy due to seminoma during following left orchiectomy with seminoma. Fortunately, he had a child by ICSI using with frozen thawed sperm which was cryopreserved before operation. In the case of NOA the first pregnancy was obtained by micro-TESE-ICSI, he received 2nd micro-TESE, motile sperm was not recovered and he terminated treatment. Total of nine subjects (27.3%) achieved pregnancy related to receiving surgical treatment.

DISCUSSION

The causes of infertility are well documented to stem equally between male and female partner. Infertility is generally defined as not achieving a pregnancy within 12 months or more of regular unprotected sexual intercourse.² Secondary infertility is defined by doctors as the inability to conceive or carry to term a second or subsequent child. A US study in 1995 revealed that 1.8 million women suffered from secondary infertility which is defined as the inability to become pregnant or to carry a pregnancy successfully after previous success in delivering a child. In 2006, it has been reported to now be 3.3 million and secondary infertility now accounts for six out of ten infertility cases.³ Individuals experiencing secondary infertility are less likely to seek treatment than those who experience primary infertility. This is due in part to the perception that because they were able to conceive before, they should be able to unaided again. Although there is no clear definition regarding secondary infertility, it is can be considered to occur when a woman has completed the nursing period for the first child and did not become pregnant for one year. When it is within one year resulting in delivery, there is an increased risk of premature birth and a low birth weight child. Short interpregnancy intervals (12 > months) are associated with increased maternal and fetal and infant risks for all ages of women. Based on clinical postpartum practice and public health guidelines recommend interpregnancy intervals should be at least 18 to 24 months.^{2,4,5}

On the other hand, a Canadian large cohort study revealed that 12 to 18 months was the ideal length of time between giving birth and becoming pregnant again. This investigation indicated a shorter optimal interval than previously thought (12–24 months) for women of all ages. The result also may be reassuring particularly for older women who must weigh the competing risks of increasing maternal age with longer interpregnancy intervals (including infertility and chromosomal anomalies) against the risks of short interpregnancy intervals. Schummers et al also found that confounding does not seem to fully explain the observed association between short interpregnancy interval and increased risks of several outcomes.⁶

The median age of the spouse was 35 years-old in this study. In general, we would advocate that the spouse over age 35 or older should have their medical condition checked. Since infertility is a shared problem for both men and women, evaluating both ensures that the most effective treatments can be recommended. Secondary infertile couples may even experience resentment from other couples with infertility who are unable to even have their first child. However, about 20% of patients suffered from azoospermia for a median 3 years in this study. We would like to emphasize the need for a semen analysis even if the first child was naturally conceived.

Sperm quality deteriorates somewhat with aging, however, it generally does not become a problem before age 60. However, there may be an increase in the risk of genetic defects in sperm. Furthermore, aging men may develop medical illness that adversely affect their sexual and reproductive function.

Some infections such as chlamydial urethritis is less symptomatic, and may cause of seminal obstruction. Environmental and lifestyle factors such as smoking, excessive alcohol intake and obesity can also affect fertility. In addition, exposure to environmental pollutants and toxins can be directly toxic to sperm, resulting in their decreased sperm numbers and poor motility, leading to infertility.^{7,8} In this study normospermia was observed only 18.5% of patients. The first natural conception was detected in about 70%, however, in median three years, there were 16 azoospermic subjects (19.8%) and 9 (11.1%) cryptozoospermia. Of the 16 azoospermic patients, 10 was clinically diagnosed as obstructive azoospermia, whereas 6 as NOA. Of these subjects, they had no history of disease during the time of undergoing treatment for another child.

Causes of NOA are genetic mutations, chromosomal aberrations, hormonal disorders, maldescent of testis, the use of certain medications, radiation, and the presence of toxins. TESE is now widely applied as a method of sperm retrieval surgery, and there is no doubt that micro-TESE has become a standard technique for NOA patients.⁹ Although 6 subjects were clinically diagnosed as NOA, all subjects conceived by natural intercourse except one having TESE-ICSI. It is difficult to identify the cause of azoospermia. However, there were azoospermic patients over a relatively short period in patients with secondary infertility, therefore semen analysis is considered to be essential.

CONCLUSION

In this retrospective study, pregnancy outcomes were mainly obtained directly from patient's interviews. It is proposed that a urological evaluation is particularly important as azoospermia and/or cryptozoospermia may be present if a further pregnancy does not occur.

Although there were only three pregnancies by natural intercourse, we obtained six pregnancies by ICSI after surgical treatments. Even if the first pregnancy was obtained by natural conception, 30.9% subjects showed azoospermia (19.8%) or cryptozoospermia (11.1%) at median duration of three years. We would like to emphasize that semen analysis is necessary prior to a couple embarking upon their attempt to have further children in later life.

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DISCLOSURE STATEMENT

Informed consent

Human rights and informed consent statements. All procedures completed were done in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all individual participants included in the study.

Animal rights statements. This article does not contain any studies with animal subjects

performed by any of the authors.

Funding sources statement

Each author has no COI with regard to this manuscript.

Statement of ethics

The protocol for this research project, including its use of human subjects, was approved by a suitably constituted Ethics Committee.

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