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ARTICLE

Pregnancy outcome according to male diagnosis after ICSI with non-ejaculated sperm compared with ejaculated sperm controls

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Abstract The aim of this study was to describe pregnancy outcome in couples who had undergone ICSI using non-ejaculated sperm from men with non-obstructive azoospermia, obstructive azoospermia and aspermia compared with the outcome of ICSI with ejaculated sperm from men with severe oligozoospermia, treated during the same time period. This nationwide cohort study included all children born after ICSI with non-ejaculated sperm in Norway, from when the method was first permitted in Norway in April 2004 to the end of 2010, resulting in 420 pregnancies and a total of 359 children. In 235 of these children, the father was diagnosed with obstructive azoospermia, in 72 with non-obstructive azoospermia, in 31 with aspermia, and in 21 the male cause was unclassifiable. The control group consisted of 760 children from 939 pregnancies conceived by ICSI with ejaculated sperm. Sex ratio, birth weight, rate of pregnancy loss and congenital malformations were not significantly associated with sperm origin or the cause of male factor infertility.

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Introduction

In 1994, ICSI with spermatozoa obtained from the testicle by either testicular sperm aspiration (TESA), testicular sperm extraction (TESE) or from the epididymis by percutaneous epididymal sperm aspiration (PESA) was introduced (Tournaye et al., 1994). Indications for treatment with non-ejaculated spermatozoa are mainly azoospermia or aspermia (anejaculation) in the male partner, giving these men the ability to become genetic fathers. These conditions are found in about 5% of infertile couples (Irvine, 1998). Non-obstructive azoospermia indicates a primary testicular dysfunction, whereas obstructive azoospermia implies a transport failure caused by vasectomy, genital tract infection or congenital bilateral absence of the vas deferens. In aspermia (anejaculation), the inability to produce an ejaculate can, among others, be the result of spinal cord injury, retroperitoneal lymph node dissection, diabetic neuropathy, multiple sclerosis or trauma (Kamischke and Nieschlag, 1999).

A higher rate of malformations has been reported in children conceived through assisted reproductive technologies compared with children conceived naturally (Pandey et al., 2012). Whether this increase is attributable to patient characteristics related to infertility is uncertain, but subfertility by itself is found to be significantly associated with birth defects (Davies et al., 2012; Zhu et al., 2006). Because of the increased aneuploidy rate in spermatozoa from men with testicular failure (Bernardini et al., 2000), there is a pertinent concern as to whether or not spontaneous abortion, congenital anomaly rates, or both, are increased in children born after the use of non-ejaculated sperm. A meta-analysis reported an almost 50% increased risk of spontaneous abortion in ICSI pregnancies using sperm collected from the testis relative to sperm retrieved from the epididymis (Holte et al., 2007). Information is particularly lacking on the effect of the male diagnosis on the spontaneous abortion rate. Two systematic reviews (Holte et al., 2007; Woldringh et al., 2010) did not report any statistical difference in malformation rates in children after ICSI using non-ejaculated sperm compared with ICSI using ejaculated sperm. Many of the included studies, however, had methodological shortcomings; the study groups were small, heterogeneous, with a number of possible biases (Woldringh et al., 2010).

Most previous studies have compared pregnancy and neonatal outcome based on either the spermatozoa originating from the testicle, the epididymis or from the ejaculate (Belva et al., 2011; Woldringh et al., 2011). The possible significance of the diagnosis of the male partner (e.g. obstructive azoospermia, non-obstructive azoospermia or aspermia), however, has hardly been investigated (Belva et al., 2011; Vernaeve et al., 2003).

During 2004 and 2010, a nationwide study was conducted to assess pregnancy outcome after ICSI with non-ejaculated sperm and how it related to different causes of azoospermia or aspermia. These results were compared with a control group consisting of women undergoing ICSI with ejaculated sperm from men with severe oligozoospermia from the same time period.

Materials and methods

Patients

This nationwide cohort study included all pregnancies resulting from ICSI with the use of testicular or epididymal sperm and fresh embryo transfer during the time-period from when the method was first permitted in Norway in April 2004 to the end of 2010. All pregnancies resulting from ICSI with ejaculated sperm from men with severe oligozoospermia, defined as ≤5 million/ml on the day of oocyte retrieval, during the same period and in the same centres, were used as controls. Couples were asked to sign an informed consent form to allow the clinic to collect further data on the pregnancy, birth and neonatal outcome from the maternity hospital.

Investigation of male infertility was based on medical history and clinical examination, hormonal and genetic analyses, and histological evaluation from testicular biopsy. Men were classified into the following diagnostic categories according to the outcome of the investigations: non-obstructive azoospermia, obstructive azoospermia or aspermia (including retrograde ejaculation). Some men were unclassified because of incomplete fertility investigation. Pregnancies obtained after ICSI with fresh and frozen testicular or epididymal spermatozoa were included in the study. Pregnancies obtained by frozen embryo transfer were excluded.

Spermatozoa used for treatment were obtained by either PESA, TESA or TESE based on the routine procedure in each fertility clinic, as were the types of hormone stimulation used in woman (e.g. gonadotrophin-releasing hormone antagonist or agonist and type of gonadotrophin stimulation), testicular tissue preparation, embryo culture procedures and the distribution of single or double embryo transfer. Information about different lifestyle factors, such as smoking and alcohol intake, was not available.

The protocol for this nationwide multicentre study was approved by the Regional Committee for Medical and Health Research Ethics (REK, project number 2009/136a, on 11 March 2010), and the local data protection officer at Oslo University Hospital.

Definitions of pregnancy and spontaneous abortion

Pregnancy was verified either by urine or serum analysis of beta-HCG, not analysed uniformly but according to the different clinics routine protocols. Gestational age was calculated from the date of oocyte-aspiration and adding 14 days to convert the day of oocyte aspiration to menstrual age according to Tunon et al. (2000). A clinical pregnancy is a pregnancy that has reached a stage in which the gestation can be seen on ultrasound examination, defined here as from gestational day 42.