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ARTICLE

Sperm chromatin structure correlates with spontaneous abortion and multiple pregnancy rates in assisted reproduction

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Abstract The objective of this study was to determine if a relationship exists between sperm parameters, measured by sperm chromatin structure assay (SCSA), and spontaneous abortion and multiple births in couples undergoing assisted reproduction treatment. Retrospective analysis of infertility treatment outcomes and occurrence of spontaneous abortion and multiple births was conducted in 233 couples who underwent treatment by intracytoplasmic sperm injection or intrauterine insemination at the Sher Institute for Reproductive Medicine, between 2001 and 2004. Sperm samples used for treatments were analysed for sperm concentration, sperm motility and two different parameters of SCSA (DNA fragmentation index, DFI, and high DNA stainability, HDS). Pregnancy, spontaneous abortion and multiple birth rates were recorded for all couples. A statistically significant relationship ($P < 0.001$) was observed between DFI and spontaneous abortion. However, the correlation between HDS and spontaneous abortion was not statistically significant. Significantly lower levels of DFI were observed in men from couples having triplet pregnancies compared with those in the spontaneous abortion group ($P \leq 0.05$). It is concluded that the parameters of SCSA correlate significantly with spontaneous abortion and multiple birth and may provide guidance for clinical decision making (number of embryos per transfer) and management of spontaneous abortion-prone cases.

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KEYWORDS: assisted reproduction, multiple births, SCSA, sperm chromatin structure assay, spontaneous abortion

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Introduction

Between 6.5% and 21% of pregnancies in the normal population end in spontaneous abortion, with a higher frequency of spontaneous abortions being observed in infertile couples (Hamamah et al., 1997) In addition, a higher prevalence of primary and secondary infertility has been seen among repeated spontaneous aborters. Recent reports show that despite a normal fertilization rate, a higher rate of early spontaneous abortions occurred in patients with <4% morphologically normal spermatozoa as assessed by Kruger strict criteria (Hamamah et al., 1997). This observation indicates that the main problem with morphologically abnormal spermatozoa was not an impaired fertilization but rather that these spermatozoa may have resulted in a higher percentage of abnormal embryos which were aborted early in gestation.

The sperm chromatin structure assay (SCSA) detects spermatozoa with abnormal sperm chromatin structure consisting of abnormal nuclear proteins (high DNA stainability [HDS]) and sperm DNA fragmentation (DNA fragmentation index [DFI]). Both of these features are dependent on the highly precise interaction of acridine orange with histone/protamine complexed DNA and with single- and double-stranded DNA. The DFI is the proportion of spermatozoa containing fragmented DNA and is calculated from the DFI frequency histogram obtained from the ratio between the red and total (red + green) fluorescence intensity. HDS (or SCSI-2) is calculated based on the percentage of spermatozoa with high levels of green fluorescence, which are thought to represent immature spermatozoa with incomplete chromatin condensation (Giwercman et al., 2003, 2010). The DFI and HDS parameters are more repeatable than conventional, subjectively evaluated semen parameters such as sperm count, morphology and motility (Evenson and Wixon, 2006; Evenson et al., 2002; Virro et al., 2004).

Relatively few papers examined the correlation between spontaneous abortions and sperm chromatin quality, mostly pointing to male factors being the single most common cause of infertility, with sperm defects responsible for between 30% and 50% of infertility cases (Boe-Hansen et al., 2006; Larson et al., 2000). Boe-Hansen et al. (2006) have shown that DFI above 27%, 30% and 40% was related to male sub- or infertility, respectively, and that DFI >27%, while compatible with ongoing pregnancy and delivery after intrauterine insemination (IUI), IVF or intracytoplasmic sperm injection (ICSI), has a lower probability of live birth.

Recent studies show that neither DFI nor HDS correlate strongly with conventional semen parameters (Giwercman et al., 2003). However, these parameters may prove to be robust indicators of the potential for spontaneous abortions when attempting to conceive via assisted reproduction treatment (Larson-Cook et al., 2003). However, these studies are in disagreement regarding the DFI threshold at which spontaneous abortions increase. In a recent study, couples where men had HDS >15% experienced significantly higher spontaneous abortion rates; authors suggested that ICSI may be indicated for men with HDS >15% (Lin et al., 2008; Ming-Huei Lin, 2008). While DFI did not have a statistically significant trend toward increased abortion rate in the high DFI group (>27%) in the present study, a study by Virro et al. (2004) reported that 146 couples failed to have sustained pregnancies post assisted reproduction treatment when the DFI was >27% in the raw ejaculate. A study by Evenson and Wixon (2006) indicated a trend towards increased spontaneous abortions when the DFI was ≥30%; a ≥30% DFI score was associated with increased miscarriage rates and a higher rate of spontaneous abortion at 12 weeks of gestation ($P < 0.01$) in comparison to the <30% group. This same study suggested that 39% of miscarriages were related to a DFI >30% and a meta-analysis indicated that couples were 7.1 times more likely to achieve a term pregnancy if the DFI was <30% ($P = 0.0001$) (Evenson and Wixon, 2006).

Altogether, the above studies indicate a relationship between SCSA parameters and the incidence of spontaneous abortion. However, none of the above studies examined the effect of sperm chromatin quality on the occurrence of multiple births after assisted reproduction treatment. The present study, as far as is known for the first time, examines the possibility for a dual relationship between sperm chromatin structure and the incidence of spontaneous abortion and multiple birth in consenting couples undergoing assisted reproduction treatment.

Materials and methods

Patients and data collection

Sperm samples and clinical data were provided by 233 consenting couples with varied aetiologies of male/female infertility, with male partners aged 23–48 years at the time of the study. All samples were labelled with an identifier number and the treatment applied after which they were frozen by immediately submerging in liquid nitrogen. All samples were subjected to DNA Fragmentation Assay for HDS and DFI via SCSA diagnostics as described previously (Evenson and Jost, 2000). Couples in this study conceived predominantly via IVF/ICSI, with very few patients conceiving via IUI. All couples were treated with gonadotrophins and closely monitored via ultrasound to maximize follicular response to treatment. In IUI patients, ultrasound was also used to optimize timing of the human chorionic gonadotrophin trigger administration with subsequent IUI.

Statistical analysis

Statistical analysis, supervised by a professional statistician, was performed using Microsoft Excel and SAS to test for statistical significance. In addition a *t*-test was performed to check for differences between groups. A *P*-value ≤0.05 was considered significant.

Results

A retrospective analysis was performed on the data from 233 consenting couples (**Table 1**), determining that of all categories analysed, the spontaneous abortion group had the highest value for DFI (24.80 ± 3.2%), highest value for HDS (8.50 ± 0.015%) and lowest sperm concentration (55.85 ± 12.25 million/ml). In comparison, sperm motility

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