Sperm DNA fragmentation index and cumulative live birth rate in a cohort of 2,713 couples undergoing assisted reproduction treatment

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Objective: To study how the choice of the first assisted reproductive technology treatment type affects the cumulative live birth rate (CLBR) in couples with high sperm DNA fragmentation index (DFI).
Design: Longitudinal cohort study.
Setting: University-affiliated fertility clinic.
Patient(s): A total of 2,713 infertile couples who underwent assisted reproductive technology treatment between 2007 and 2017 were included in the study. All in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatments (up to three fresh treatments and all associated frozen-thawed embryo transfers) offered to the couples by the public health care system were included, in total 5,422 cycles.
Intervention(s): None.
Main Outcome Measure(s): The primary outcome was the CLBR. The secondary outcomes were the fertilization rate and the miscarriage rate. The IVF and ICSI groups were defined according to the method applied in the first treatment cycle.
Result(s): In the IVF group, the CLBR values were higher for couples with normal DFI compared with those for couples with high DFI ($\geq$20%) (48.1% vs. 41.6% for conservative CLBR estimate and 55.6% vs. 51.4% for optimal CLBR estimate after adjustment for female age, respectively). No DFI-dependent difference was seen in the ICSI group.
Conclusion(s): Our results demonstrated that a high DFI predicts a statistically significantly lower CLBR if IVF and not ICSI is applied in the first cycle of assisted reproduction. (Fertil Steril® 2021;116:1483-90. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Sperm DNA fragmentation, sperm chromatin structure assay, assisted reproduction, cumulative live birth rate, fertilization rate

Approximately 4% of all children in Sweden are conceived by assisted reproductive technology (ART)—either as standard in vitro fertilization (IVF) or as intracytoplasmic sperm injection (ICSI) (1, 2). Apart from being associated with significant physical and psychological stress, IVF/ICSI treatments are resource-consuming, both because of the costs of the treatments as well as the loss of working hours (3–6). Therefore, to minimize the burden on patients as well as on society, it is important to make the ART treatments as efficient as possible in terms of the live birth rate (LBR) (7, 8).

Today, the choice between ICSI and standard IVF is mainly based on the results of a conventional semen analysis, the concentration and motility of the spermatozoa in the raw semen sample as well as after gradient centrifugation or a swim-up procedure (9). Other factors, such as poor fertilization/outcomes by standard IVF, may lead to a switch to ICSI in subsequent cycles (10–14).

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Several studies showed that a high sperm DNA fragmentation index (DFI) was associated with a poor ART outcome (15–19). We reported that—for first ART treatment cycles—the odds ratio (OR) of live birth was approximately 0.6 if the DFI, as assessed by the sperm chromatin structure assay (SCSA), was >20% compared with treatments with a DFI of ≤20% (20). We found no such effect for ICSI treatments, which is in agreement with some, but not all, published data (8, 21).

It is still a matter of debate whether DFI testing should be routinely performed in patients undergoing ART (22, 23). One of the obstacles to making cost-benefit analyses in relation to applying DFI measurements as a standard procedure is that the available data are based on single cycles, not taking into consideration the complexity of ART procedures with multiple cycles and mixing of IVF and ICSI as well as fresh and frozen embryo transfers offered to a couple. Therefore, the cumulative LBR (CLBR), including all treatments offered to a couple, may be a better measure for the outcome of ART (7, 24).

In our center, SCSA DFI analyses of the ejaculated sperm used for IVF and ICSI have been performed as a clinical routine since 2007. The primary aim of the study was, therefore, to investigate the impact of a high DFI on the CLBR depending on whether the first ART treatment was IVF or ICSI. As secondary aims, we investigated the impact of the DFI on fertilization rates (FRs) in IVF and ICSI treatments and, additionally, on the miscarriage rate.

MATERIALS AND METHODS

The data were derived from a longitudinal cohort study of ART cycles between 2007 and 2017 at the tertiary fertility Reproductive Medicine Centre (RMC), Skåne University Hospital in Malmö, Sweden. The research protocol was reviewed and approved by the Ethical Board in Lund, and the couples signed a written informed consent before being included or were contacted by letter after treatment and offered an opt-out in case they did not wish to have their clinical data included in the analysis. All procedures were performed according to the relevant guidelines and regulations.

Cohort Characteristics

Couples with infertility, defined as at least one year of unsuccessful attempts to achieve pregnancy, who had undergone IVF/ICSI at RMC, Malmö, between 2007 and 2017 and had at least one DFI value for an ejaculate used for IVF/ICSI treatment were asked to participate in the study. The inclusion criteria were the same as the requirements for being allowed to undergo ART treatment at RMC. The woman must be ≤40 years, have a body mass index <30 kg/m^2 or achieve a 10% weight reduction in case of a body mass index of 30–35 kg/m^2, both partners must be nonsmokers, and the male partner must not be >55 years and must have a sperm concentration of $\geq 1 \times 10^6$/mL. According to the Swedish rules for the public health care system, complete reimbursement is offered for up to three fresh cycles to couples fulfilling the previously mentioned criteria.

The invitation was accepted by 2,995 of 3,240 couples. Initially, we excluded 27 couples who were enrolled under ongoing treatment and, therefore, were missing baseline data. Additional exclusion criteria were applied for the complete cycles of each couple and are shown in a flow chart (Fig. 1). Finally, we included 2,713 couples with their 5,422 fresh and frozen cycles.

The most frequent treatment pattern during the period from 2007 to 2010 initially was giving three consecutive fresh treatments followed by frozen embryo transfers (FETs) using the collected cryopreserved embryos. After 2010, the treatment strategy was slightly changed, the FETs being applied directly after each fresh cycle from which the frozen embryo was derived. The total number of treatments was still up to three complete cycles. We defined an IVF/ICSI complete cycle as ovarian stimulation and the resulting fresh as well as all FETs.

The couples were observed until the delivery of one live infant (primary outcome) or discontinuation of treatment because of use of all three complete cycles offered or for other reasons. All patients without a live birth in an ART cycle were eligible for the subsequent cycle, including patients with cancelled cycles and those with a pregnancy that did not result in a live birth. The criterion for performing standard IVF in the first cycle was the yield of $\geq 5 \times 10^6$ spermatozoa after gradient centrifugation of the ejaculate.

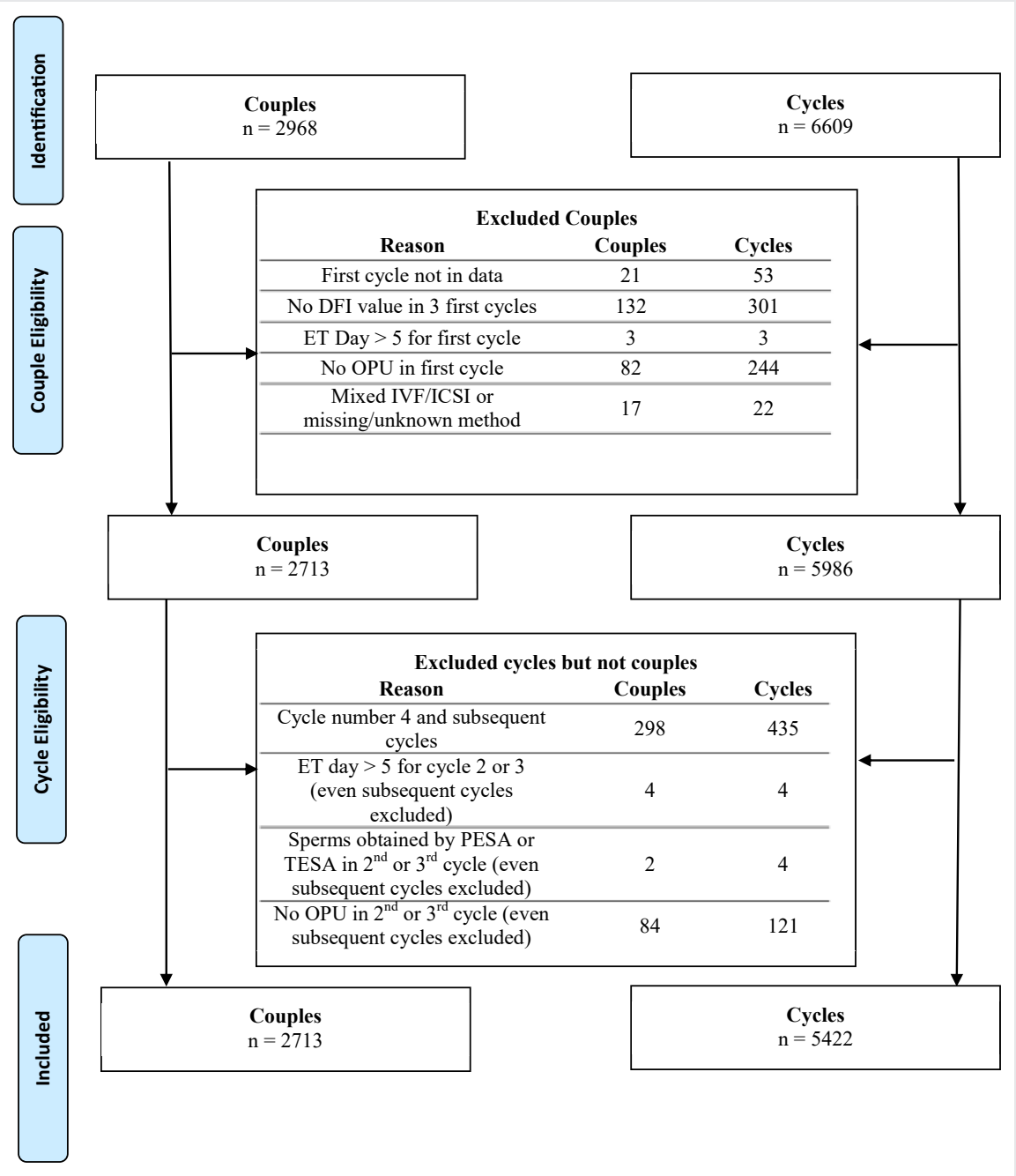
Fertilization and Embryo Morphology Classification

Fertilization was determined 18 ± 2 hours after the IVF/ICSI procedure, and the oocytes with two distinct pronuclei were considered to be fertilized. Cleavage and morphology were assessed on days 2 and 3. Embryos were assessed according to the scoring criteria for blastocysts on day 5 (25). Good quality embryos (GQEs), including those selected for transfer, were those that on day 2 were 4–6 cells, grade 1 or 2, on day 3 were 8–10 cells, grade 1 or 2, or on day 5 were blastocysts with good expansion, inner cell mass, and trophectoderm (A or B). One GQE was selected for embryo transfer on day 2, 3, or 5 after oocyte retrieval and if there were any remaining GQE, they were cryopreserved.

Stimulation Protocol

Controlled ovarian stimulation was performed using one of the following protocols: gonadotropin-releasing hormone (GnRH) antagonist suppression protocol (ganirelix; Orgalutran; Organon, Stockholm, Sweden) or luteal-phase GnRH agonist (nafarelin [Synarela; Pfizer Inc., New York, NY] or buserelin [Suprefact or Suprecur; Cheplapharm, Greifswald, Germany]) downregulation. Recombinant follicle-stimulating hormone (GONAL-f, Puregon, Bemfola, or Elonva) or urinary human menopausal gonadotropin (Menopur; Ferring, Saint-Prex, Switzerland) was started during the early follicular phase of the cycle. The protocols were previously described (26).

FIGURE 1



Flow chart illustrating the details of the procedure for inclusion/exclusion of couples/treatment cycles for the study. DFI = DNA fragmentation index; ET = embryo transfer; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OPU = ovum pickup; TESA = testicular sperm aspiration; PESA = percutaneous epididymal sperm extraction.

Vončina. Sperm DFI and cumulative birth rate. Fertil Steril 2021.

A patient-tailored dose according to age, antimüllerian hormone level, and antral follicle count was applied. The final oocyte maturation was triggered with recombinant human chorionic gonadotropin (250 μg, Ovitrelle) when 2–3 follicles reached 18 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval was performed 36 hours after trigger. Subsequently, fertilization of the oocytes by standard IVF or ICSI was attempted. Intravaginal progesterone supplementation (Lutinus; Ferring, Saint-Prex, Switzerland) or Crinone gel 8%; Merck, Darmstadt, Germany) was given as luteal-phase support from the day after the oocyte retrieval and continuing until 12 days after the embryo transfer.

The FET was performed in either a natural or a stimulated cycle. Luteal-phase support was given by intravaginal administration of progesterone (Crinone gel 8%) until 14 days after transfer and continued until 12 weeks of gestation if a pregnancy test was positive. No luteal supplementation was given in natural FET cycles.

Miscarriage

Pregnancy was defined as either a plasma human chorionic gonadotropin concentration >10 IU/L on the 12th day after embryo transfer or a positive result on a commercially available urine pregnancy test on the 17th day. Miscarriage was defined as pregnancy loss until the 18th week of gestation, verified by gynecologic ultrasound.

Sperm Preparation

A standard density gradient centrifugation method, PureSperm, 45% and 90% (Nidacon Ltd; Nidacon, Mölndal, Sweden) diluted in SpermRinse (Vitrolife, Gothenburg, Sweden), was used for sperm preparation. A 200 μL aliquot of raw semen was frozen at -80^{o}C and stored for subsequent SCSA analysis.

Sperm Chromatin Structure Assay

The SCSA was performed as previously described (27–29). A total of 1–2 $\times$ 10^{6} sperm cells were treated for 30 seconds with a detergent solution (pH 1.2) containing 0.1% Triton X-100, 0.15 M NaCl, and 0.08 M HCl and then stained with 6 mg/L of purified acridine orange (AO; Molecular Probes, Eugene, OR) in a phosphate buffer (pH 6.0). The stained cells were analyzed by a florescence-activated cell sorter scan flow cytometer equipped with an air-cooled argon ion laser. A minimum of 5,000 events were accumulated for each measurement. After excitation with a 488-nm light source, AO bound to double-stranded DNA emits green fluorescence, and AO bound to single strands emits red fluorescence. Sperm DNA damage was quantified by flow cytometry measurements of the emission shift from green (native, double-stranded DNA) to red (denatured, single-stranded DNA). They displayed as red (fragmented DNA) vs. green (DNA stainability) fluorescence intensity cytogram patterns. The extent of DNA denaturation was expressed by the DFI, ratio of red to total (red + green) fluorescence intensity, and the abnormally high DNA stainability. The first available DFI was in 87% of the cases measured on ejaculate used for the first ART cycle, in 11% for the second, and in 2% for the third cycle.

Statistical Analysis

The couples were divided into two groups according to their first available method (IVF or ICSI). The descriptive statistics for the treatment groups and subgroups were compared using the Student's *t* test. When categorizing the DFI, the couple's first available DFI value was used. To explore the DFI's influence on the FR, we used generalized linear mixed models adjusting for the women's age and repeated measures. For the FR, a linear link for normally distributed data was used. For live birth, we used a logistic link for binomially distributed data. In all models, an autoregressive covariance structure was used. The models were created for the whole cohort and for the IVF and ICSI groups, respectively.

The conservative and optimal CLBRs were calculated. The *conservative CLBR* assumed that the couples not advancing to the next cycle will have zero probability to have a live birth. The *optimal CLBR* assumed that the couples not advancing to the next cycle will have the same probability for live birth as that of the couples advancing to the next cycle. For each cycle, the number of couples having a live birth up to and including that cycle were divided by the total number of couples in the actual group. For assessment of the *conservative CLBR,* Wald confidence intervals were calculated, and to compare these rates between different levels of DFI, the chi square test was used. To be able to adjust for the women's age, the Cochran-Mantel-Haenszel test for general association was performed. The *optimal CLBRs* and their confidence intervals were estimated using the Kaplan-Meier method and compared for different levels of DFI using the log rank test. Subsequently, a sensitivity analysis based on the 87% of the DFI values that were measured on the ejaculate from the first ART cycle was done.

The miscarriage rate was calculated as the number of miscarriages divided by the number of pregnancies. The DFI's influence on this rate was modeled using a generalized linear mixed model with a logistic link for binomially distributed data and autoregressive covariance structure. In addition, for this calculation, the women's age was included as a covariate.

Previous findings showed a decreased chance of live birth in standard IVF treatments when the DFI was >20% (20). According to this, we categorized DFIs <20% as normal and DFIs $\geq$20% as high. Miscarriage was seen to be significantly increased when the DFI was >40% (20). Therefore, a DFI of 40% was used as a cutoff level when analyzing the miscarriage rate. All analyses were performed in SAS version 9.4 and the significance level was set to 5%.

TABLE 1

Baseline characteristics of couples at the first treatment cycle according to the treatment type.

Variables	Total	ICSI	IVF
Couples (n)	2,713	995	1,718
Age women (y)	32.4 (4.1)	31.8 (4.1)	32.8 (4.1)
BMI women	23. 6 (3.3)	23.7 (3.3)	23.5 (3.3)
DFI (%)	15. 9 (9.8)	19.7 (11.3)	13.7 (8.1)
FR (%)	53.0 (28.0)	59.65 (26.7)	49.3 (28.0)
Good quality embryo (n)	2.0 (1.7)	1.9 (1.7)	2.0 (1.7)

Note: The group characteristics are expressed as mean (SD). The DFI is the first available value in the database for a couple. BMI = body mass index; DFI = DNA fragmentation index; FR = fertilization rate.

Vončina. Sperm DFI and cumulative birth rate. Fertil Steril 2021.

RESULTS

Among all included couples, 36.0% completed one cycle, 28.1% completed two, and the remaining 35.9% completed three cycles. Table 1 presents the baseline characteristics of the couples at the start of the first complete cycle grouped by first treatment.

In the IVF group (n = 1,718), 71.2% (n = 1,224) couples had IVF for all cycles and 27.7% (n = 476) switched to ICSI. The mean (±SD) DFI values for these groups were 12.9% (±7.46%) and 15.7% (±9.12%), respectively.

DFI, Type of Treatment, and FR

The FR was 49% for IVF and 59% for ICSI. There was a negative statistically significant association between the DFI and the FR for IVF (–0.34; 95% confidence interval [CI]: −0.49, −0.19; $P<.001$) which meant 0.34 percentage points reduction in FR for each percentage point increase in DFI. For ICSI, there was no significant association (0.002; 95% CI: −0.106, 0.11; $P = .973$).

DFI, Type of Treatment, and CLBR

When comparing the two DFI categories in the IVF group, the CLBR values were higher for the normal group compared with those for the high DFI group (48.1% vs. 41.6% for conservative CLBR; 55.6% vs. 51.4% for optimal CLBR, respectively), reaching the level of statistical significance for both estimates ($P = .042$ and .019, respectively) in an unadjusted model. This difference remained statistically significant only for the optimal CLBR estimates after adjustment for female age ($P = 0.115$ and $P = .045$ for conservative and optimal estimates, respectively). No DFI-dependent difference was seen for the ICSI treatment categories (45.0% vs. 46.5%, $P = .638$ normal vs. high DFI for conservative CLBR estimates; 53.7% vs. 52.9%, $P = .973$ normal vs. high DFI for optimal CLBR estimates) (Table 2). A sensitivity analysis based on the 87% of the DFI values measured on the ejaculate from the first ART cycle showed no changes in the risk estimates presented previously.

DFI and Miscarriage Rate

The calculated overall miscarriage rate estimates of the cohort after completing three cycles are presented in Table 3. When a DFI of 40% was used as the cutoff value, the miscarriage rate was 31.3% in the group in which the first DFI value was <40% in comparison with 39.1% in the group in which the DFI was ≥40% (OR = 1.44; 95% CI 0.83–2.51; $P = .195$) (Table 3).

DISCUSSION

We found that couples with a sperm DFI ≥20%– compared with those with lower DFI values–obtained a lower CLBR when standard IVF was used as the ART method for the first treatment cycle, whereas this was not true for ICSI treatment. The relative difference of 16% for the *conservative* calculation model and 8% for the *optimal* estimate was statistically significant in unadjusted models and remained so for the latter calculation method even after adjustment for female age.

We in addition found that this difference can–at least partly–be explained by a negative association between the DFI and the IVF fertilization rate in IVF but not in ICSI procedures. We found–in relative terms–a 25% higher miscarriage rate for a DFI ≥40%; this difference, however, was not statistically significant.

This is, to our knowledge, the first report looking at the CLBR and not the outcome of a single cycle in relation to the DFI and adds to the ongoing debate on the usefulness of DFI testing in the context of ART. Although several studies have shown that a high DFI may be associated with a poorer ART outcome (19, 20, 30), the clinical use of this method is still questioned (15, 22). An obvious limitation of the previous studies was the fact that they were based on a single treatment only, whereas from the patient's and the society's point of view, the cumulative outcome of all treatments was of a significantly greater importance (7).

Usually, the method of fertilization applied in the first ART cycle is to a high degree decided by a standard semen analysis performed on the raw ejaculate and after swim-up or a gradient centrifugation procedure (30, 31). In the case

TABLE 2

Cumulative live birth rate according to sperm DNA fragmentation index (< 20% vs. ≥20%) and method of fertilization (IVF vs. ICSI).

			Cumulative live birth rate % (95% CI)				
			DFI < 20%			DFI ≥20%	
Group	Cycle	Couples[a] (live births)	Conservative	Optimal	Couples[a] (live births)	Conservative	Optimal
IVF	1	1,413 (376)	26.6 (24.3; 28.9)	26.6 (24.4; 29.0)	305 (54)	17.7 (13.4; 22.0)	17.7 (13.9; 22.4)
	2	856 (205)	41.1 (38.6; 43.7)	44.2 (41.5; 47.0)	210 (45)	32.5 (27.2; 37.7)	35.3 (30.0; 41.3)
	3	479 (98)	48.1 (45.5; 50.7)[b]	55.6 (52.7; 58.6)[c]	113 (28)	41.6 (36.1; 47.2)[b]	51.4 (44.9; 58.2)[c]
ICSI	1	580 (137)	23.6 (20.1; 27.1)	23.6 (20.4; 27.3)	415 (99)	23.9 (19.8; 28.0)	23.9 (20.0; 28.2)
	2	372 (72)	36.0 (32.1; 39.9)	38.4 (34.4; 42.7)	279 (59)	38.1 (33.4; 42.7)	40.0 (35.3; 45.0)
	3	209 (52)	45.0 (41.0; 49.1)[d]	53.7 (49.0; 58.6)[e]	163 (35)	46.5 (41.7; 51.3)[d]	52.9 (47.6; 58.3)[e]

Note: CI = confidence interval; CLBR = cumulative live birth rate; DFI = DNA fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

[a] Couples with at least one live birth per complete cycle.

[b] Unadjusted/adjusted comparison of DFI<20% vs. DFI ≥20% for the conservative CLBR, $P = .042/.115$.

[c] Unadjusted/adjusted comparison of DFI<20% vs. DFI ≥20% for the optimal CLBR, $P = .019/.045$.

[d] No statistical significance in either the unadjusted or adjusted comparison of DFI<20% vs. DFI ≥20% for the conservative CLBR.

[e] No statistical significance in either the unadjusted or adjusted comparison of DFI<20% vs. DFI ≥20% for the optimal CLBR.

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TABLE 3

Overall miscarriage rate and association with sperm DNA damage extent.

Cycle	Group	No. of pregnancies	No. of miscarriages	Miscarriage rate (%)
All three cycles	Overall	1,926	607	31.5
Cycle 1		996	313	31.4
Cycle 2		592	184	31.1
Cycle 3		338	110	32.5
All three cycles	DFI <40%	1,862	582	31.3[a]
	DFI ≥40%	64	25	39.1[a]

Note: DFI = DNA fragmentation index.
[a] No statistically significant difference between groups.

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of treatment failure in the first or any subsequent cycle, the standard IVF can be altered to ICSI, e.g., because of poor fertilization and/or on patient request. Thus, an important question is whether introducing a new criterion for selecting the optimal method for the first ART procedure will have any impact on the CLBR.

Our study indicated that including a DFI analysis in the decision-making before the first ART attempt may improve the overall treatment results. In the 18% of couples with a DFI ≥20% in whom, based on traditional criteria, standard IVF was done, the CLBR was lower than that in those with a DFI <20%, whereas the level of the DFI did not play any role for the couples treated by ICSI. The difference remained statistically significant, after adjustment for female age, after applying the *optimal* but not the *conservative* calculation method. The latter was based on the assumption that the couples discontinuing treatment had a zero probability of live birth in the subsequent cycle. Although this may be true for some poor prognosis couples, British and Scandinavian studies have indicated that only 25%–30% of all ART-treated couples belong to this category (32, 33).

Although a 4% difference in CLBR—between 51.4% and 56.6%—might be considered relatively small, as stated in a recently published systematic review, even 1% improvement would amount to many thousands of additional live births globally every year (34). Furthermore, many couples consider the LBR to be of primary importance when selecting an IVF clinic, and reported differences between centers are frequently <5% (35). Furthermore, the investigators concluded that the largest trials in reproductive medicine were unlikely to detect plausible improvements in the LBR, and meta-analyses do not make up for this shortcoming (34). Therefore, we consider our findings to be clinically significant.

The difference in miscarriage rate between the couples with a DFI ≥40% and <40% was close to 8% but was not statistically significant. With 64 cycles and 25 miscarriages in the high DFI group, the risk of a type II error must be considered.

The major strength of our study was the inclusion of >5,000 treatment cycles and the possibility to use the CLBR as a clinical end point. Additionally, all treatments were performed in one center and >90% of the ART cycles were done as single-embryo transfers. The calculations were based on the method applied for the first ART cycle, but only in 87% of the cases was the DFI value for the ejaculate used for this treatment available. Although significant intraindividual variation in DFI was reported, we found that only a small proportion of men switched from high to low DFI values and vice versa (36). Furthermore, misclassification because of a significant change in the DFI from the first to one of the subsequent ART treatments would tend to reduce the difference in CLBR between the high and the low DFI groups. The sensitivity analysis showed that the results remained stable when only looking at couples who had DFI measurement at their first cycle.

We did not take into consideration the change in the type of ART treatment in the second and third cycles applied for some of the couples. Although this might be considered a weakness, the advantage was that our setup mirrors a real-life situation, in which decisions regarding a change of treatment strategy are based on a variety of possible prognostic factors. Interestingly, poor fertilization or fertilization failure was a common cause of switching from standard IVF to ICSI and our study—similar to earlier findings—showed a negative association between the DFI and the FR in IVF but not ICSI treatments (20).

CONCLUSION

In conclusion, our data indicated that the use of standard IVF in the first ART cycle—in a setup of three complete treatment cycles offered to a couple—implied a lower CLBR in cases with a DFI ≥20% compared with that of those with a DFI below this level.

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Índice de fragmentación del ADN espermático y tasa acumulada de nacidos vivos en una cohorte de 2.713 parejas sometidas tratamiento de reproducción asistida.

Objetivo: Estudiar cómo la elección del primer tipo de tratamiento de reproducción asistida afecta la tasa acumulada de nacidos vivos (CLBR) en parejas con alto índice de fragmentación del ADN espermático (DFI).

Diseño: Estudio de cohorte longitudinal.

Lugar: Clínica de fertilidad afiliada a la universidad.

Paciente (s): Un total de 2.713 parejas infértiles que se sometieron a tratamiento de reproducción asistida entre 2007 y 2017 fueran incluidas en el estudio. Todos los tratamientos de fertilización in vitro (FIV) / inyección intracitoplasmática de espermatozoides (ICSI) (hasta tres tratamientos frescos y todas las transferencias de embriones congeladas-descongeladas asociadas) ofrecidas a las parejas en el sistema público de salud fueron incluidas, en total 5.422 ciclos.

Intervención (es): Ninguna.

Medida (s) de resultado principal: El resultado principal fue el CLBR. Los resultados secundarios fueron la tasa de fertilización y el índice de aborto espontáneo. Los grupos de FIV e ICSI se definieron según el método aplicado en el primer ciclo de tratamiento.

Resultado (s): En el grupo de FIV, los valores de CLBR fueron más altos para las parejas con DFI normal en comparación con los de las parejas con DFI alto ($\geq$ 20%) (48,1% frente a 41,6% para la estimación de CLBR conservadora y 55,6% frente a 51,4% para la estimación de CLBR óptima después del ajuste por edad en mujeres, respectivamente). No se observó ninguna diferencia dependiente de DFI en el grupo de ICSI.

Conclusión (es): Nuestros resultados demostraron que un DFI alto predice un CLBR estadísticamente significativamente más bajo si se aplica FIV y no ICSI en el primer ciclo de reproducción asistida.