High sperm deoxyribonucleic acid fragmentation index is associated with an increased risk of preeclampsia following assisted reproduction treatment

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Objective: To study the association between sperm deoxyribonucleic acid fragmentation index (DFI) and the odds of preeclampsia and other adverse perinatal outcomes after in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment.
Design: A prospective cohort study including infertile couples undergoing conventional IVF or ICSI treatment and their children. Data regarding preeclampsia and perinatal outcomes were derived from the Swedish National Birth Register.
Patient(s): A total of 1,594 infertile couples undergoing IVF or ICSI treatment and their 1,660 children conceived by assisted reproduction.
Exposure: Sperm DFI measured by Sperm Chromatin Structure Assay.
Main Outcome Measure(s): The primary outcome was preeclampsia. The secondary outcomes were preterm birth (PTB), low birth weight, low Apgar score, and small for gestational age.
Result(s): With a DFI level of <20% as a reference, the odds ratio (OR) of preeclampsia statistically significantly increased in the group with a DFI level of ≥20% when IVF was used as the fertilization method (OR, 2.2; 95% confidence interval, 1.1–4.4). Already at the DFI levels of ≥10%, in IVF pregnancies, the OR of preeclampsia increased in a dose-response manner, from a prevalence of 3.1% in the reference group to >10% among those with a DFI level of ≥30%. The DFI was not associated with the OR of preeclampsia in the ICSI group. In the entire cohort, a DFI level of ≥20% was associated with an increased OR of PTB (OR, 1.4; 95% confidence interval, 1.0–2.0).
Conclusion(s): High DFI level was associated with increased odds of PTB and, in IVF pregnancies, also increased odds of preeclampsia. (Fertil Steril® 2025;123:97–104. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Sperm DNA fragmentation, male factor infertility, in vitro fertilization, preeclampsia, perinatal outcomes

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An increased level of sperm deoxyribonucleic acid (DNA) fragmentation is associated with male subfertility and has been found in 25% of men from couples with unexplained infertility (1). It has been shown that a high sperm DNA fragmentation index (DFI) level is associated with decreased pregnancy rates, in vivo and in vitro, impaired embryo development, and an increased risk of miscarriage (2). Because it has been demonstrated that a spermatozoon with DNA damage can fertilize an oocyte (3), there is a concern about how this affects maternal health and perinatal outcomes. A study, on the basis of 131 pregnancies, found no association between a high DFI level and gestational age and birth weight after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (4). A study recently published by Hervás et al. (5) showed that in IVF/ICSI pregnancies, a higher but nonsignificant incidence of preeclampsia was found in women from the high sperm DNA fragmentation group. Another study on 713 pregnancies did not show any difference in prematurity or birth weight between different DFI groups after ICSI treatments (6). However, no studies have investigated how DFI affects perinatal outcomes and the risk of preeclampsia in a larger cohort of couples treated with IVF or ICSI.

Assisted reproductive technology (ART) pregnancies imply an increased risk of preeclampsia as well as preterm birth (PTB) and low birth weight (LBW) (7–9). Several known risk factors for these complications, such as advanced age and primiparity, are overrepresented among women undergoing ART. However, reliable prediction models are still lacking. Women with preeclampsia are high-risk obstetric patients, with an increased risk of delivering children with PTB and LBW and being small for gestational age (SGA) (10).

Several paternal factors are also known to affect perinatal outcomes. Advanced paternal age and paternal obesity are associated with not only an increased risk of PTB and LBW (11, 12) but also having a high DFI level (2). There are also paternal characteristics that seem to contribute to the risk of preeclampsia (13). A large Swedish cohort study identified significant importance of couple effect related to genetic interaction between the mother and father as determinants of susceptibility for preeclampsia (14). A change of male partner may reduce subsequent preeclampsia risk in a female experiencing this condition in her first pregnancy (15). On the other hand, in women not experiencing preeclampsia in their first pregnancy, change of partner may imply an increased risk at their subsequent childbearing (16). This knowledge has led to a hypothesis of the "dangerous father"—however, it is not clarified how to identify those men and which biologic paternal mechanisms are involved.

In this study, we hypothesized that a high DFI level could increase the risk of preeclampsia as well as adverse other perinatal outcomes. Therefore, in a prospective single-center study including 1,594 couples and their 1,660 ART-conceived children, combining clinical data with follow-up in Swedish national registries, the association between DFI and odds of preeclampsia, PTB, LBW, low Apgar score, and being SGA was investigated.

MATERIALS AND METHODS

Study design and setting

This longitudinal cohort study was conducted at Reproductive Medicine Center (RMC) at Skåne University Hospital in Malmö, Sweden. The study was approved by the Regional Ethical Review Board in Lund, Sweden (Dnr. 2015/006 and 2018/24).

Study population

All couples included in this study were patients at RMC undergoing ART treatment, either fresh IVF or ICSI cycle, or frozen embryo transfer (ET). Preimplantation genetic testing was not performed. Because RMC is tax-funded, there is a political decision with a few requirements that should be met to receive treatment at the clinic. These are as follows:

- Failure to conceive after at least 12 months of unprotected intercourse or previously known severely impaired male or female fertility.
- Both partners being nonsmokers.
- Females aged <40 years.
- Males aged <56 years.
- Female BMI between 18 and 30 kg/m^2 or achieving 10% weight loss if BMI is 30–34 kg/m^2.
- No common child. Exceptions were made if a couple had a child after a successful treatment and there were remaining frozen embryos. Those embryos could be transferred; however, no new fresh treatments were made.

Furthermore, the couples needed to fulfill the following inclusion criteria:

- Use of own gametes.
- Sperm concentration above 1 million/mL (necessary for DFI analysis).
- Assisted reproductive technology treatment leading to childbirth in a gestational age of $\geq 22 + 0$ weeks.

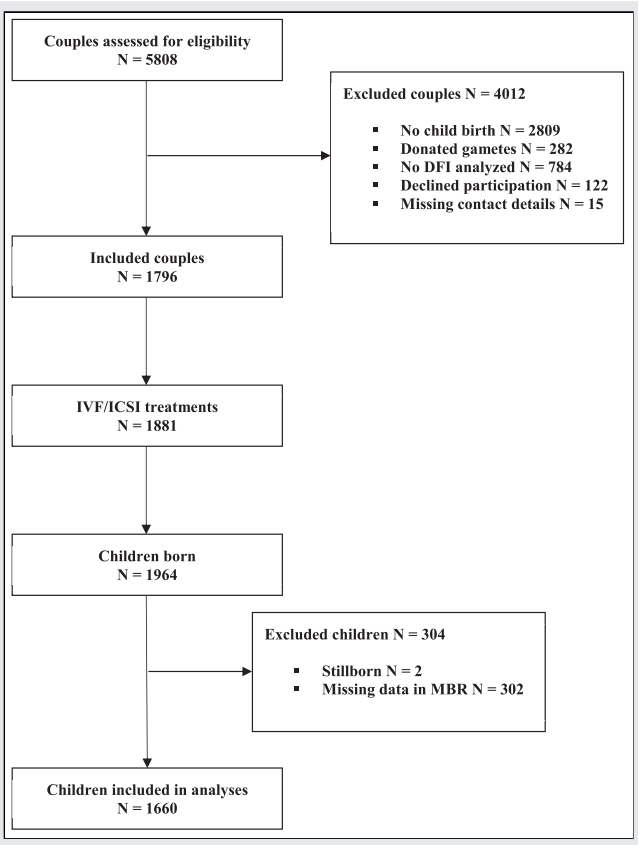
All couples who underwent ART treatment between 2007 and 2018 and fulfilled the inclusion criteria were eligible for the study. Participants were either included before treatment and signed a written informed consent before inclusion or were contacted by letter after treatment and offered opt-out if they did not wish to participate (Fig. 1).

Study outcomes

Preeclampsia was identified in the registries using the International Classification of Diseases, 10th Revision, Swedish Version, codes (O140-O149). Small for gestational age was defined as a birth weight 2 standard deviations lower than the mean weight for the gestational age (17). Multiple births were excluded from the SGA classification. Preterm birth was defined as <37 gestational weeks. Low Apgar score was defined as <7 Apgar points at 5 minutes of age (18). Low birth weight was referred to birth weight of <2,500 g.

All semen samples were collected by masturbation on the same day as the ART treatments were performed, except in frozen ET cycles, where the semen sample was collected at the time of the corresponding fresh cycle. From these samples, which were used for the ART treatments, 200 μL was saved for

FIGURE 1



Flowchart describing the inclusion of couples and their children born after assisted reproductive technology treatment. DFI = deoxyribonucleic acid fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; MBR = Medical Birth Register.

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DFI analysis. The 200-μL raw semen was frozen directly and thawed on the day of the DFI analysis. The DFI was measured using the Sperm Chromatin Structure Assay, previously described in detail (19).

Data sources

Information on birth weight, gender, gestational age, SGA, Apgar score, and preeclampsia diagnosis were collected from the Swedish Medical Birth Register (MBR). This register was established in 1973 and has almost 100% degree of coverage of births in Sweden (20). When data were retrieved from MBR, the register was updated until December 31, 2017, which means that ART treatments leading to births after 2017 were not included in the analysis (Fig. 1). The age of the mother and father, BMI of the mother, ART method, and DFI were retrieved from the medical records at RMC, Malmö.

Statistical analysis

Sample characteristics are presented as means (standard deviations) or numbers (percentages). Logistic regression was used to assess the association between DFI and odds of preeclampsia, PTB, LBW, low Apgar score, and SGA, respectively. The odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for paternal age were used.

The aim of this study was to compare outcomes between the groups with normal and high DFI levels. There were, however, no data on the level of DFI having an impact on the outcomes considered in this study. Previous studies have shown that the chance of pregnancy in vivo as well as by standard IVF is decreased for DFI level of $\geq$20% (21–24). In our primary analysis, the group with a DFI level of <20% was, therefore, compared with that with a DFI level of $\geq$20%. Patterns of the prevalence of preeclampsia across groups categorized by 10 percentiles of DFI indicated that other cutoffs may provide additional information about the association between DFI and preeclampsia as well as the perinatal characteristics. Therefore, for all outcomes the results on the basis of 5 10-percentile groups of DFI (<10% [reference], 10%–20%, 20%–30%, 30%–40%, and $\geq$40%) and specifically for preeclampsia, comparison of the DFI levels of <10% vs. $\geq$10% was also presented.

The total sample and subsamples on the basis of the method of fertilization (IVF and ICSI) were analyzed. In 12 cases, a combination of IVF and ICSI was used. These cases were included in the analysis of the total sample but not in the subsample analysis. Specification of missing cases is shown in Tables 1 and 2. There were two cases of intrauterine fetal death that were excluded from the analysis (Fig. 1).

Furthermore, the results were evaluated for the sensitivity to the potentially confounding effect of multiple births by excluding multiple birth children and their parents from the analysis. In the analysis of perinatal outcomes, where the unit of observation is the child, this strategy had the additional purpose of avoiding multiple observations per couple.

A power calculation was performed before enrollment in the study. On the basis of the estimation that approximately 25% of all included men would have a DFI level of >20%, the inclusion of at least 1,488 childbirths was needed to detect an increase in the preeclampsia risk from 5% to 10% with an α error of 0.05 and power of 90%. All analyses were performed with Stata Statistical Software, Release 16 (StataCorp LLC, College Station, TX).

RESULTS

Study population

Of the 5,808 couples who were assessed for eligibility for the study, 1,933 met the inclusion criteria, and 1,796 agreed to participate. After exclusion due to missing data, 1,594 couples and their 1,660 live-born children were included (Fig. 1). Table 1 shows the descriptive statistics of the children and parents who were included in the study cohort. In the group with a DFI level of $\geq$20%, the proportion of ICSI cycles was higher than that in the group with a DFI level of <20%. Apart from this, there were no clinically significant differences between the 2 DFI groups. Most ETs were performed as single ETs; however, double ETs were performed in 11% of cases. In total, 4% of the included pregnancies were multiple pregnancies.

TABLE 1

Characteristics of children and couples in total and by deoxyribonucleic acid fragmentation index (< 20% vs. ≥20%).

Variables	Total	DFI level of < 20%	DFI level of ≥20%
Children	N = 1,660	N = 1,268	N = 392
Boys	841 (50.7%)	644 (50.8%)	197 (50.3%)
Multiple birth children	137 (8.3%)	94 (7.4%)	43 (11.0%)
Birth weight[a] (g)	3,321 (672)	3,322 (678)	3,318 (653)
Gestational age (d)	275 (18)	275 (18)	275 (17)
Couples	N = 1,594	N = 1,222	N = 372
ICSI	741 (46.5%)	484 (39.6%)	257 (69.1%)
IVF	841 (52.8%)	727 (59.5%)	114 (30.6%)
ICSI-IVF combination	12 (0.8%)	11 (0.9%)	1 (0.3%)
FET	275 (17.3%)	205 (16.8%)	70 (18.2%)
BMI of the mother[b]	23.3 (3.1)	23.3 (3.1)	23.4 (3.0)
Age of the mother	32.2 (4.0)	32.2 (4.0)	32.4 (4.0)
Age of the father	34.1 (5.2)	33.9 (5.1)	34.8 (5.7)
DFI (%)	15.3 (9.3)	11.3 (4.3)	28.6 (8.8)

Note: Data are presented as means (standard deviations) or numbers (percentages). BMI = body mass index; DFI = deoxyribonucleic acid fragmentation index; FET = frozen embryo transfer; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.
[a] Data on birth weight were missing for eight children.
[b] Data on BMI were missing for 263 mothers.

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DFI and preeclampsia

With a DFI cutoff of 20%, for the entire cohort, there was no statistically significant difference in the odds of preeclampsia. However, when separately examining IVF and ICSI treatments, the OR of preeclampsia was 2.2 (95% CI, 1.1–4.4; *P*=.02) in the IVF-treated women (Table 3), with 10.5% of them being diagnosed with preeclampsia if the DFI level was ≥20% compared with 4.8% in the DFI < 20% group. No statistically significant difference between the 2 DFI groups was noted in the ICSI-treated women.

When the couples were categorized into five groups according to the DFI value, with a DFI level of <10% as a reference, the OR of preeclampsia statistically significantly increased at DFI levels of ≥ 10% and <20%, with a successive increase in the OR for each 10% DFI category. This phenomenon was observed in the IVF group but not in the ICSI group (Supplemental Table 1, available online).

With a DFI level of <10% as a reference, the OR of preeclampsia statistically significantly increased in the high DFI group, both in the total cohort (OR, 2.1; 95% CI, 1.2–3.8; *P*=.01) and in the IVF group (OR, 2.3; 95% CI, 1.1–4.8; *P*=.02) but not in the ICSI group (OR, 1.8; 95% CI, 0.61–5.1; *P*=.29) (Table 3). These statistically significant increases in the OR of preeclampsia, in both the total cohort and IVF group, were robust to exclusion of all multiple births when a DFI cutoff of 10% was used but not if 20% was used.

TABLE 2

Perinatal outcomes by deoxyribonucleic acid fragmentation index (< 20% vs. ≥20%) and method of fertilization.

Outcome	DFI level of < 20%	DFI level of ≥20%	Adjusted OR (95% CI)	*P* value
Preterm birth				
Total (N = 1,660)	10.8% (137/1,268)	15.1% (59/392)	1.4 (1.0–2.0)	.03
IVF (N = 871)	10.8% (81/748)	15.4% (19/123)	1.5 (0.84–2.5)	.18
ICSI (N = 776)	10.8% (55/509)	15.0% (40/267)	1.5 (0.94–2.3)	.10
Low birth weight				
Total (N = 1,652)	10.0% (126/1,261)	8.7% (34/391)	0.85 (0.57–1.3)	.44
IVF (N = 867)	9.9% (74/744)	8.1% (10/123)	0.75 (0.38–1.5)	.42
ICSI (N = 772)	10.3% (52/506)	9.0% (24/266)	0.88 (0.53–1.5)	.63
Small for gestational age[a]				
Total (N = 1,518)	4.0% (47/1,169)	2.3% (8/349)	0.56 (0.26–1.2)	.13
IVF (N = 806)	4.6% (32/701)	3.8% (4/105)	0.83 (0.29–2.4)	.72
ICSI (N = 701)	3.3% (15/457)	1.6% (4/244)	0.49 (0.16–1.5)	.20
Low Apgar score				
Total (N = 1,652)	1.7% (21/1,262)	2.6% (10/390)	1.6 (0.76–3.5)	.20
IVF (N = 868)	1.6% (12/745)	4.1% (5/123)	2.7 (0.91–7.8)	.07
ICSI (N = 771)	1.6% (8/506)	1.9% (5/265)	1.4 (0.41–4.0)	.67

Note: The odds ratios were adjusted for paternal age. The unit of observation was the child. CI = confidence interval; DFI = deoxyribonucleic acid fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio.
[a] Data on small for gestational age were unavailable for multiple birth children.

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TABLE 3

Odds of preeclampsia by deoxyribonucleic acid fragmentation index groups (< 10% vs. ≥10% and < 20% vs. ≥20%) and method of fertilization.

Outcome	DFI level of < 10%	DFI level of ≥10%	DFI level of < 20%	DFI level of ≥20%
Total (N = 1,594)				
Preeclampsia	3.1% (14/450)	6.5% (74/1,144)	5.1% (62/1,222)	7.0% (26/372)
Adjusted OR (95% CI)	Ref.	2.1 (1.2–3.8)	Ref.	1.4 (0.85–2.2)
IVF (N = 841)				
Preeclampsia	3.1% (10/325)	7.2% (37/516)	4.8% (35/727)	10.5% (12/114)
Adjusted OR (95% CI)	Ref.	2.3 (1.1–4.8)	Ref.	2.2 (1.1–4.4)
ICSI (N = 741)				
Preeclampsia	3.3% (4/122)	5.7% (35/619)	5.4% (26/484)	5.1% (13/257)
Adjusted OR (95% CI)	Ref.	1.8 (0.61–5.1)	Ref.	0.94 (0.47–1.9)

Note: The odds ratios were adjusted for paternal age. The unit of observation was the couple. CI = confidence interval; DFI = deoxyribonucleic acid fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; Ref. = reference category.

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DFI and perinatal outcomes

In the entire cohort, a DFI level of ≥20% was associated with an increased OR of PTB (OR, 1.4; 95% CI, 1.0–2.0; $P=.03$). Similar odds estimates, without reaching the level of statistical significance, were seen in both the IVF and ICSI groups. There were no significant differences between the two DFI groups in the ORs of LBW, SGA, or low Apgar score (Table 2). This was the case both when exploring the total cohort and when looking separately at the IVF and ICSI groups. All findings remained unchanged after exclusion of multiple births. When the couples were divided into five groups according to DFI value (<10% [reference], 10%–20%, 20%–30%, 30%–40%, and ≥40%, respectively), none of the ORs of PTB, LBW, SGA, or low Apgar score reached the level of statistical significance.

DISCUSSION

This study shows that a high DFI level in IVF pregnancies is associated with increased odds of preeclampsia. A dose-response effect starting at DFI levels of >10% was observed. Furthermore, regardless of the type of ART used, there was a statistically significant association between the level of DFI and odds of PTB. For SGA, LBW, and low Apgar score, the odds seemed not to depend on the DFI level.

It is well known that paternal factors contribute to the onset of preeclampsia (13). Some men appear to confer a higher risk than others; however, it is unclear by what mechanism this paternal impact occurs (8). A study by Harlap et al. (25) showed an association between advanced paternal age and preeclampsia risk. It has been discussed whether increased sperm DNA damage could be an explanation for this finding (26).

Paternal obesity (27) and metabolic syndrome (28) were also reported as being associated with an increased preeclampsia risk. Association between obesity and sperm DNA damage has been reported (29, 30). One could, therefore, speculate whether the link between paternal overweight and preeclampsia is mediated by a high DFI level.

To our knowledge, this is the first study to report an association between DFI and preeclampsia, thus bringing us closer to a better understanding of the underlying mechanisms linking paternal factors and this serious pregnancy-related pathology. The placenta, which is genetically derived from both the mother and father, plays a major role in the pathophysiology of preeclampsia. The link between DFI and preeclampsia is supported by studies that suggest that increased levels of sperm DNA damage are associated with lower placental weight (31, 32).

Our study shows an association between high DFI level and preeclampsia in IVF cycles. A potential explanation for why we see this association in the IVF group and not in the ICSI group could be that a spermatozoon with normal morphology is chosen by the embryologists for fertilization in ICSI cycles (33). This active selection may lead to fertilization with a spermatozoon with less DNA damage. In IVF, the oocyte is coincubated with spermatozoa, which makes it at higher risk of being exposed to increased levels of reactive oxygen species, metabolic end-products, and microbes. Because the reactive oxygen species levels increase with a high DFI level (34), a hypothesis is that these elevated levels of harmful products affect the oocyte and that this could be a contributing factor in the development of the placenta and, thereby, increasing the risk of preeclampsia and PTB. Furthermore, in Sweden, ICSI is preferably used in cases with decreased male fertility. Therefore, it can be anticipated that the quality of the oocytes is generally better when ICSI is performed than that when IVF is performed. Good-quality oocytes may have a better DNA repair capacity and, thus, alleviate the effect of sperm DNA fragmentation on embryonic and placental development (35).

Preeclampsia increases the risk of PTB (10) and may be the mechanism linking PTB to high DFI level. However, such an explanation is contradicted by finding similar odds estimates for PTB in both the IVF and ICSI groups, whereas a high DFI level was associated with preeclampsia only in IVF pregnancies.

A limitation of this cohort study is that the participants were not randomized to IVF or ICSI. The treatment type was chosen according to clinical practice. Furthermore, there is a lack of information regarding the women's previous medical history because the MBR only contains information about

pregnancy-related diagnoses. However, the strength is the large study cohort and low dropout rate. Mandatory registration in the medical registers in Sweden also ensures good-quality data with few cases of missing data. Furthermore, the large cohort enabled subgroup analyses.

A DFI cutoff of 20% was used in our primary analyses, a threshold on the basis of the knowledge that fertility is adversely affected at the levels above this threshold (21–24). However, the levels of DFI may vary in their impact on a number of biologic mechanisms. In our study, there seemed to be different DFI thresholds for increased odds of preeclampsia and PTB.

CONCLUSION

In conclusion, we found that in ART-conceived children, a DFI level of $\geq$20% is associated with increased odds of PTB and a DFI level of $\geq$10% is associated with increased odds of preeclampsia in IVF pregnancies. This finding is of clinical importance. The benefits of routinely testing DFI are still under debate. Our findings suggest that to reduce the risk of preeclampsia, it may be preferable to perform ICSI instead of IVF in the case of a DFI level above 10%–20%. The prophylactic use of acetylsalicylic acid during pregnancy can reduce the risk of preeclampsia in a selected group of high-risk ART women (36). A DFI-based risk assessment and screening of the high-risk group can be clinically implemented for an individualized risk assessment to reduce the risk of preeclampsia.

It has been suggested that varicocele repair (37), the use of testicular instead of ejaculated spermatozoa (38), and/or ZyMot-IVF (39) add to obtaining gametes with lower DFI levels. However, the final evidence for clinical use of these methods is still lacking. If our finding is confirmed, the importance of developing strategies to reduce DFI becomes even more warranted.

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CRediT Authorship Contribution Statement

Amelie Stenqvist: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Mona Bungum:** Writing – review & editing, Methodology. **Anja Bisgaard Pinborg:** Writing – review & editing, Methodology. **Jeanette Bogstad:** Writing – review & editing, Methodology. **Anne Lis Englund:** Writing – review & editing, Methodology. **Marie Louise Grøndahl:** Writing – review & editing, Methodology. **Anne Zedeler:** Writing – review & editing, Methodology. **Stefan R. Hansson:** Writing – review & editing, Methodology. **Aleksander Giwercman:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of Interests

A.S. has nothing to disclose. M.B. has nothing to disclose. A.B.P. has received grants (payments to institution) from Gedeon Richter, Ferring Pharmaceuticals, and Merck A/S; consulting fees from PregLem, Novo Nordisk, Ferring Pharmaceuticals, Gedeon Richter, Cryos, and Merck A/S; and payment for lectures/presentations from Gedeon Richter, Ferring Pharmaceuticals, Merck A/S, Theramex, and Organon. J.B. has nothing to disclose. A.L.E. has nothing to disclose. M.L.G. has received payments for lectures/presentations from Merck A/S. A.Z. has received grants and payments for lectures/presentations by Gedeon Richter. S.R.H. has nothing to disclose. A.G. has nothing to disclose.

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Un alto índice de fragmentación del ácido desoxirribonucleico espermático se asocia con un mayor riesgo de preeclampsia después de un tratamiento de reproducción asistida.

Objetivo: Estudiar la asociación entre el índice de fragmentación del ácido desoxirribonucleico (DFI) de los espermatozoides y las probabilidades de preeclampsia y otros resultados perinatales adversos después de un tratamiento de Fertilización In Vitro (FIV) e Inyección Intra Citoplasmática de Espermatozoides (ICSI).

Diseño: Estudio de cohorte prospectivo incluyendo parejas infértiles sometidas a un tratamiento convencional de FIV o ICSI y sus hijos. Los datos sobre preeclampsia y resultados perinatales se obtuvieron del Registro Nacional de Nacimientos de Suecia.

Entorno: Clínica de fertilidad afiliada a la universidad.

Paciente(s): Un total de 1594 parejas infértiles sometidas a tratamiento de FIV o ICSI y sus 1660 hijos concebidos por reproducción asistida.

Intervención(es): DFI de esperma medido por ensayo de estructura de cromatina del esperma.

Principales medidas de resultado: El resultado primario fue preeclampsia. Los resultados secundarios fueron parto prematuro (PTB), bajo peso al nacer, bajo puntaje de Apgar y pequeño para la edad gestacional.

Resultado(s): Con un nivel de DFI de $<20\%$ como referencia, la razón de probabilidades (OR) de preeclampsia aumentó de manera estadísticamente significativa en el grupo con un nivel de DFI de $\geq 20\%$ cuando se utilizó FIV como método de fertilización (OR, 2.2; intervalo de confianza del 95%, 1.1-4.4). Ya en los niveles de DFI de $\geq 10\%$, en los embarazos de FIV, el OR de preeclampsia aumentó de manera dosis-respuesta, desde una prevalencia de 3.1% en el grupo de referencia a $>10\%$ entre aquellos con un nivel de DFI de $\geq 30\%$. El DFI no se asoció con el OR de preeclampsia en el grupo ICSI. En toda la cohorte, un nivel de DFI de $\geq 20\%$ se asoció con un OR aumentado de PTB (OR, 1.4; intervalo de confianza del 95%, 1.0–2.0).

Conclusión(es): Un nivel alto de DFI se asoció con mayor riesgo de PTB y, en los embarazos de FIV, también aumentó el riesgo de preeclampsia.