Lower Sperm Exposure among Participants Undergoing Intrauterine Insemination Associated with Increased Incidence of Gestational Hypertensive Disorders

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ABSTRACT **Background:** Gestational hypertensive disorders remain a major obstetric problem.

Objectives: To evaluate the incidence of gestational hypertensive disorders among participants undergoing intrauterine insemination (IUI) after exposure to various levels of sperm from sperm donation (SD).

Methods: A retrospective case-control study was conducted at a single tertiary medical center between 2011 and 2019. Participants conceived via IUI using SD from a single sperm bank and had a successful singleton birth. Group 1 conceived during 1–2 cycles of IUI from the same sperm donor; whereas Group 2 after 3+ cycles.

Results: Overall 171 patients (Group 1 = 81, Group 2 = 90) met inclusion criteria. Participants showed no differences in age, chronic medical conditions, or history of pregnancy complications. The groups differed in gravidity and parity. The factors positively associated with Group 1 included either preeclampsia or gestational hypertension (GH) (11 [13.5%] vs. 1 [1.1%], $P = 0.001$) and GH alone (8 [9.9%] vs. 1 [1.1%], $P = 0.014$). Newborns from Group 1 had a statistically significant lower birth weight than those from Group 2 (3003 grams ± 564.21 vs. 3173 grams ± 502.59, $P = 0.039$). GH was more prevalent in Group 1 ($P = 0.008$) than a control group of 45,278 participants who conceived spontaneously. No significant differences were observed between Group 2 and the control group.

Conclusions: The incidence of GH and preeclampsia in participants was higher among those exposed to 1–2 cycles than those exposed to 3+ cycles of IUI.

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Gestational hypertensive disorders, including gestational hypertension and preeclampsia, are major obstetric problems [1,2] despite advances in prenatal care. Based on the protection offered by prior exposure to paternal/fetal antigens against the development of these complications, recent data underline immunologic factors as possible contributors in the development of gestational hypertension or preeclampsia [3,4]. Several retrospective studies and a meta-analysis inferred a significantly higher incidence of preeclampsia among participants who conceived by intrauterine insemination (IUI) from donor sperm when compared to participants who conceived from the sperm of their partner [5-7]. The absence of sperm exposure and a short duration of sexual cohabitation before conception is related to gestational hypertensive disorders [8-10].

The effect of sperm exposure level on pregnancy complications was reported in previous studies [11]. It was shown that prolonged exposure to sperm via IUI protects against preeclampsia development. In this study, we focused on participants with primary infertility and included both donor and partner sperm samples.

Another study [12], which included sperm donor IUI (SD-IUI), sperm donor in-vitro fertilization (SD-IVF), and egg donation, inferred no correlation between the extent of donor sperm exposure and obstetric complications.

We assessed the effect of the number of times women were exposed to SD from the same sperm donor on the incidence of gestational hypertensive disorders.

PATIENTS AND METHODS

PATIENTS

This retrospective case-control study was conducted between March 2011 and May 2019 at a single tertiary medical center in Israel that treats a heterogeneous population with over 10,000 deliveries per year. All participants were between the ages of 18–44 years with a singleton birth who conceived following SD-IUI.

The donor sperm was selected and evaluated according to the Practice Committee of the American Society for Reproductive Medicine [13,14], and all semen specimens met minimal semen parameters recommended for sperm donors according to the American Society of Reproductive Medicine [15].

The data collected included maternal age, body mass index before pregnancy and before giving birth, past medical history, smoking, gravidity, parity, and a history of obstetrics. Data regarding current pregnancy included the occurrence of gestational hypertensive disorders, gestational age at delivery, mode of delivery, and birth weight.

The data collected from the sperm bank included the number of sperm donations from each participant and the number of donations from the same donor until it resulted in a pregnancy.

The exclusion criteria included abortions, giving birth outside of Sheba Medical Center, age exceeding 44 years, having more than two previous births, having a multiple birth, and having pregnancies via IVF.

The participants were divided into two groups: Group 1 included participants who conceived during their first or second attempt from the same sperm donor and Group 2 comprised participants who conceived after using 3 or more cycles.

A diagnosis of gestational hypertensive disorders included systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 on two occasions at least 4 hours apart after 20 weeks of gestation or preeclampsia, which is defined as blood pressure ≥ 140/90 with proteinuria ≥ 0.3/g/24 hours. This group also included subgroups of hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome, and eclampsia [16].

Small for gestational age (SGA) was defined according to the Israeli national reference birth weight [17]. The primary outcome was a composite of gestational hypertension or preeclampsia in the study groups.

DATA MANAGEMENT

Clinical data regarding the number of IUI cycles from the same sperm donor and obstetrical outcomes were collected from the computerized hospital medical database. The charts were reviewed manually.

STATISTICAL ANALYSIS

Categorical variables were summarized as frequency and percentage. Continuous variables were evaluated for normal distribution and reported as mean ± standard deviation or as median and interquartile range.

Categorical variables of both groups were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using the independent samples *t*-test or Mann-Whitney test.

The standardized incidence ratio was applied as an indirect standardization method to compare the whole group as well as each group separately with a cohort of participants who had their first or second birth and conceived spontaneously.

All statistical analyses were 2-sided. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

ETHICS APPROVAL

The institutional review board approval at Sheba Medical Center waiving informed consent for this retrospective study (6225-19-SMC, 07/01/2019).

RESULTS

A total 171 participants conceived through SD-IUI from a single sperm bank between March 2011 and May 2019 and had a singleton birth at Sheba Medical Center. Of these participants, 81 conceived during the first or second IUI cycle from the same donor sperm and the other 90 conceived during the third or later IUI cycles from the same donor sperm [Figure 1].

Figure 1. Inclusion criteria for study population

IUI = intrauterine insemination

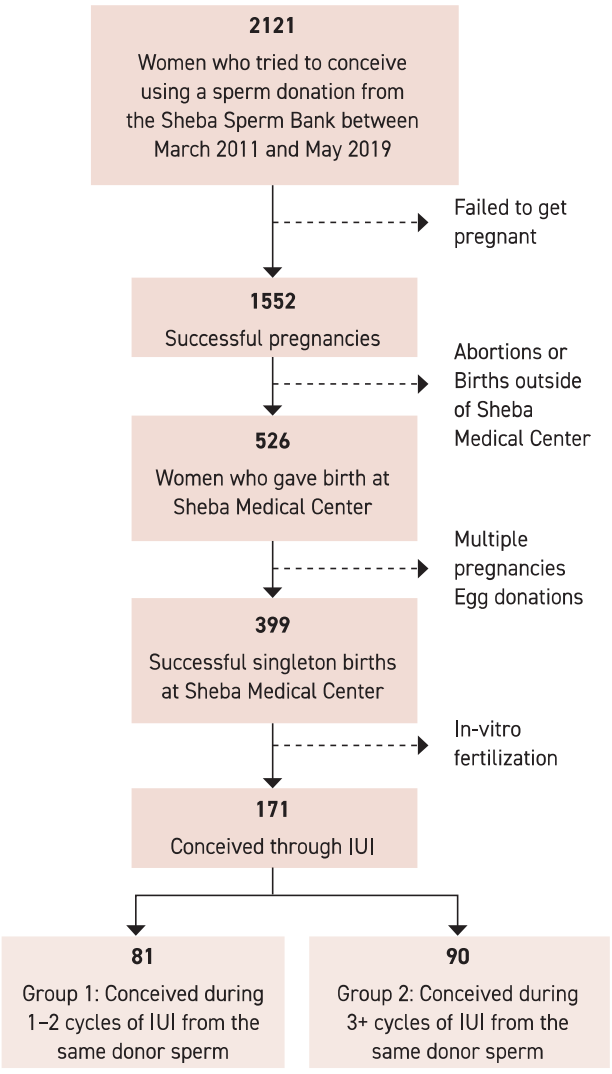

Table 1. Demographic characteristics and obstetric history of patients in relation to number of SD-IUI cycles

Characteristics	Group 1 (1–2 IUI cycles) n=81	Group 2 (3+ IUI cycles) n=90	I value
Age on date (years)	37 (34–40)	38 (34.75–40.25)	0.142
Weight before pregnancy (kg)	65 (58–79.5)	70 (59–87)	0.181
BMI before pregnancy	24.73 (22.35–29.76)	25.5 (22.63–30.36)	0.328
Smoking history	5 (6.2%)	6 (6.7%)	0.895
Alcohol or drug use	0	0	
Chronic hypertension	1 (1.2%)	4 (4.4%)	0.371
Past PET	0	0	
SLE	0	0	
APS	0 (0%)	1 (1.1%)	1
Past IUGR	0	0	
ITP	0	0	
Coagulopathy (Factor 2,5,protein S,C deficiency, MTHFR)	2 (2.5%)	5 (5.6%)	0.448
Kidney disease	0	0	
OSA	0	0	
DM type 1	1 (1.2%)	1 (1.1%)	1
DM type 2	0	0	
Number of pregnancies	1.43 (1–4)	1.73 (1–6)	0.035
Number of births	0.17 (0–2)	0.34 (0–3)	0.015
Number of abortions	0.26 (0–2)	0.38 (0–2)	0.315
Number of ectopic pregnancies	0	0	1
Number of cesareans	0.01 (0–1)	0.09 (0–1)	0.026
Number of vaginal births after cesarean	0	0	1
Number of live children	0.17 (0–2)	0.31 (0–2)	0.024

APLA = antiphospholipid syndrome, BMI = body mass index, DM = diabetes mellitus, IUGR = intrauterine growth restriction, ITP = immune thrombocytopenic purpura, IUI = intrauterine insemination, MTHFR = methylenetetrahydrofolate reductase, OSA= obstructive sleep apnea, PET = preeclampsia toxemia, SLE = systemic lupus erythematosus

Maternal characteristics are presented in Table 1. Although Group 1 did not differ from Group 2 in age, chronic medical conditions, or history of pregnancy complications, they differed in terms of gravidity and parity. In addition, no difference was shown between the groups with regard to semen parameters of sperm donations [Table 2].

Fewer IUI cycles from the same donor sperm before conception were positively associated with pregnancy complications when compared with multiple IUI cycles (11 [13.5%] vs. 1 [1.1%], $P = 0.001$) [Table 2]. While treating these pregnancy complications separately, gestational hypertension was observed more often in Group 1 (8 [9.9%] vs. 1 [1.1%], $P = 0.014$) [Table 2]. In addition, newborns from Group 1 had a statistically significant lower birth weight than those from the Group 2 (3003 ± 564.21 vs. 3173 ± 502.59, $P = 0.039$), whereas no significant difference was observed while comparing their SGA.

When Group 1 was compared with a control group consisting of same age participants with up to two previous births who conceived spontaneously and had a singleton birth at Sheba Medical Center during the same period, gestational hypertension was observed to be more prevalent in Group 1 ($P = 0.008$) than preeclampsia ($P = 0.08$) [Table 3]. No significant differences were observed when comparing Group 2 with the same control group.

DISCUSSION

According to our findings, fewer exposures to a specific SD-IUI cycles before conception were associated with a higher incidence of gestational hypertensive disorders and lower birth weight.

Furthermore, although sperm donation is a risk factor for gestational hypertension and preeclampsia, using the same donor sperm for three or more cycles showed no significant difference when compared with the general population of participants who conceived spontaneously.

The possibility of immunologic factors in contributing to gestational hypertensive disorders was based, in part, on the observation that prior exposure to paternal/fetal antigens appears to protect against preeclampsia [3,4,7,18]. Nulliparous participants and participants who change partners between pregnancies, have long interpregnancy intervals, or use barrier contraception have

Table 2. Semen parameters of sperm donations and pregnancy outcomes in relation to number of sperm donation-intrauterine insemination cycles

Characteristics	Group 1 (1–2 IUI cycles) n=81	Group 2 (3+ IUI cycles) n=90	*P* value
Semen parameters			
Volume of successful semen donation (ml)	3.3 (2.15–4.45)	3.46 (1.97–4.95)	0.431
Semen concentration (×106 motile sperm/ml)	58.9 (35.9–81.9)	57.07 (32.78–81.36)	0.614
Sperm motility (%)	59.9 (53.2–66.6)	60.5 (53.6–67.4)	0.566
Pregnancy outcomes			
Weight before birth (kg)	81.11 ± 13.21	82.56 ± 14.67	0.509
Pregnancy days overall	272 (265–279)	273.5 (265.75–282)	0.551
Birth weight of newborn (grams)	3003 ± 564.21	3173 ± 502.59	0.039
Small for gestational age	9 (11.1%)	4 (4.4%)	0.1
Cesarean section delivery	35 (43.2%)	34 (37.8%)	0.47
Gestational hypertension or preeclampsia	11 (13.5%)	1 (1.1%)	0.001
Gestational hypertension	8 (9.9%)	1 (1.1%)	0.014
Preeclampsia	3 (3.7%)	0 (0%)	0.104

IUI = intrauterine insemination

less exposure to paternal antigens and higher risks of developing preeclampsia [8-11]. Pregnancies following only 1–2 SD-IUI cycles is another example of lacking exposure to sperm before pregnancy. Although SD-IUI has been related to hypertensive disorders, this association has not been consistent in various studies [19-21]. In addition, the relationship between the number of IUIs and hypertensive disorders has not been thoroughly investigated.

Although a prior study showed that IUI with SD appeared to increase the incidence of preeclampsia and a presence of protective effect of multiple cycles, their study focused on participants with primary infertility, and the identity of the sperm donor in the different cycles was unknown [11].

The length of preconception sexual cohabitation has also been related to pregnancy complications, with a possible protective effect against previous sperm exposure. The data obtained in these studies were based on personal questionnaires that may not accurately reflect true sperm exposure level [8,18]. The data obtained in this study were based on a computerized system that matched the dates of IUI in the sperm bank and the pregnancies that followed the IUI from that specific donor, which aided in overcoming the response bias of personal questionnaires.

In this study, we showed that the incidence of gestational hypertension or preeclampsia is significantly dependent on the level of donor sperm exposure. The use of specific donor sperm for up to two cycles is associated with a higher incidence of both gestational hypertension or preeclampsia and of gestational hypertension alone compared to three or more cycles from the same donor or the general population of participants who conceived spontaneously. These findings are consistent with the immunological hypothesis that prolonged exposure to sperm may alter the immune response and decrease the risk of gestational hypertension and preeclampsia via the mechanism of immune tolerance of the participant to paternal antigens.

Another difference in the gestational outcome was that the newborns exposed to up to two SD-IUI cycles had a significantly lower birth weight. This finding can be explained by the predominant etiologic theory that preeclampsia reduces uteroplacental perfusion, a unique pathogenic process that might lead to lower birth weight [22].

LIMITATIONS

The retrospective nature of this study carries an inherent bias. A limited sample size and the small number of observations did not allow us to perform multiple regression analysis. Last, the lack of information regarding the indication for sperm donation may have resulted in a potential bias. However, any type of indication, in contrast to previous studies that mostly focused on infertile participants, were included.

STRENGTHS

All patients received sperm donation from a single sperm bank and were delivered at the same center. The study groups were relatively homogeneous for efficient effect isolation of the level of sperm exposure on the incidence of gestational complications. The data regarding the level of sperm exposure were based on computerized medical records.

CONCLUSIONS

Lower levels of sperm exposure are associated with higher rates of gestational hypertension or preeclampsia and lower birth weight. In addition, a higher level of sperm exposure showed no differences in the complications from the general population of participants who conceived spontaneously. These risks should be evaluated in larger studies, and future studies should prospectively evaluate the influence of sperm exposure via SD-IUI on the incidence of gestational hypertensive disorders.

Table 3. Difference between the rates of gestational hypertension and preeclampsia in successful IUI pregnancies based on the previous number of IUI cycles from the same donor

	Observed	Expected*	Standardized incidence ratio	*P*-value
Gestational hypertension				
IUI from donor sperm, n=171	9	5.29	1.7	0.178
Group 1 (1–2 IUI cycles), n=81	8	2.47	3.23	0.008
Group 2 (3+ IUI cycles), n=90	1	2.81	0.35	0.456
Preeclampsia				
IUI from donor sperm, n=171	3	1.6	1.86	0.574
Group 1 (1–2 IUI cycles), n=81	3	0.74	4.02	0.08
Group 2 (3+ IUI cycles), n=90	0	0.86	0	0.845

*Expected number was calculated using incidence rate from a population of 45,278 participants who conceived spontaneously and only up to their second birth.

IUI = intrauterine insemination

IMPLICATIONS STATEMENT

If there is a statistically significant increase in the incidence of gestational hypertensive disorders when conception occurred following lower sperm exposure, then there is a correlation between those two, and based on results from previous studies, we posit that this could be related to an immune etiology.

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