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Review article

Type of paternal sperm exposure before pregnancy and the risk of preeclampsia: A systematic review

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ABSTRACT

Objective: The aim of this systematic review was to evaluate the role of paternal sperm exposure before pregnancy on the risk of preeclampsia.
Study design: The search was conducted using electronic databases from inception of each database through October 2019. Review of articles also included the abstracts of all references retrieved from the search. Only studies evaluating exposure to paternal sperm before pregnancy on the risk of preeclampsia in the subsequent pregnancy were included. Exposure group was defined as significant exposure to paternal sperm, either measured by sexual cohabitation, oral sex habit, or by absence of barrier methods. Control groups was defined as minimal exposure to paternal sperm, either measured by lack of sexual cohabitation or oral sex habit, or by use of barrier methods. Sperm exposure identifiable before pregnancy that may be suspected to modify the risk of preeclampsia was examined. The primary outcome was the incidence of preeclampsia. Subgroup analyses by parity and type of sperm exposure were planned. All analyses were carried out using the random effects model. The pooled results were reported as the OR with 95 % confidence interval (CI). Heterogeneity was measured using I-squared (Higgins I^2).
Results: Seven studies including 7125 pregnant women were included in this systematic review. Overall, the incidence of preeclampsia was similar in women with a higher overall sperm exposure compared to controls, 774/5512 (14 %) vs 220/1619 (13.6 %); OR 1.04, 95 % CI 0.88–1.22, respectively. The incidence of preeclampsia was significantly reduced in women with a higher overall sperm exposure when including only nulliparous women, 643/3946 (16.1 %) vs 170/725 (23.4 %); OR 0.63, 95 % CI 0.52 to 0.76. Significant lower rate of preeclampsia was also found for ≥12-month sexual cohabitation, 494/3627 (13.6 %) vs 123/691 (17.8 %); OR 0.73, 95 % CI 0.59–0.90. Significantly higher rate of preeclampsia was reported in women not using barrier methods, 315/1904 (16.5 %) vs 103/962 (10.7 %); OR 1.65, 95 % CI 1.30–2.10.
Conclusions: Paternal sperm exposure in nulliparous women and sexual cohabitation ≥ 12 months before pregnancy are associated with a decreased risk of preeclampsia.

Contents

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Introduction

Preeclampsia is a disorder of pregnancy usually associated with new-onset hypertension and proteinuria, occurring most often after 20 weeks of gestation and frequently near term, which complicates approximately 5–8 % of pregnancies in the United States. Preeclampsia is associated with short- and long-term consequences for both the fetus, such as intrauterine growth restriction, and the mother, including subsequent hypertension, and cardiovascular disorders [1,2]. According to the World Health Organization, preeclampsia is the second global cause of maternal mortality after hemorrhage [3].

The pathophysiology of preeclampsia has not been completely elucidated yet and many theories have been proposed to explain the complex mechanisms associated with the disease [1]. Defective placentation has been the major, long-standing hypothesis, with abnormal remodeling of spiral arteries and trophoblastic invasion leading to placental chronic hypoxia and ischemia [4,5], but recent research has reported that an abnormal maternal cardiovascular system could not only be the trigger of abnormal placentation, but also play a causative role in the pathogenesis of the condition [6–8]. Moreover, other mechanisms such as genetic imprinting, imbalances of angiogenic factors and immunological factors have all been considered to be involved in case of preeclampsia [1,4]. The immune maladaptation theory involves a maternal alloimmune reaction triggered by a rejection of the fetal allograft that could be prevented through paternal sperm exposure before pregnancy, by initiating a type-2 immune response towards paternal antigens that may inhibit the induction of type-1 responses against the semi-allogenic fetal unit [1,9]. This hypothesis seems to be confirmed also from evidence of a significantly increased risk of preeclampsia in in-vitro fertilization (IVF) pregnancies achieved with sperm donor. A meta-analysis including 10,898 women showed that conception using donor sperm was associated with an increased risk of preeclampsia compared with using paternal sperm [10].

Objective

The aim of this systematic review was to evaluate the role of paternal sperm exposure before pregnancy on the risk of preeclampsia.

Methods

Search strategy

This review was performed according to a protocol designed a priori and recommended for systematic review [11]. Electronic databases (Medline, Scopus, Embase, Web of Sciences, the Cochrane library, clinicaltrials.gov) were searched from the inception of each database to October 2019. Review of articles also included the abstracts of all references retrieved from the search. No restrictions for language or geographic location were applied.

The articles were identified with the use of a combination of the relevant heading term, key words, and word variants for: “sex” OR “coitus” OR “sexual relationship” OR “sexual cohabitation” OR “oral sex” OR “contraception” OR “condom” OR “sperm” OR “seminal fluid” [Mesh/Emtree] AND “preeclampsia”. The electronic search and the eligibility of the studies were independently assessed by two of the authors (DDM, AV). A manual search of reference lists of studies was performed to avoid missing relevant publications. Differences were discussed with a third reviewer (VB).

Study selection

Only studies evaluating exposure to paternal sperm before pregnancy on the risk of preeclampsia in the subsequent pregnancy were included. We excluded papers comparing two groups of women who were both exposed to sperm before pregnancy. Only full text articles were considered eligible for the inclusion. Randomized, cohort and case-control studies were accepted study designs.

Studies without a control group (e.g. case reports, case series) were excluded. Studies investigating the onset of preeclampsia after assisted conception procedures (i.e. in vitro fertilization, intracytoplasmic sperm injection, intra-uterine insemination) were also excluded.

Definitions of sperm exposure

Exposure group was defined as significant exposure to paternal sperm, either measured by sexual cohabitation, oral sex habit, or by absence of barrier methods. Control groups was defined as minimal exposure to paternal sperm, either measured by lack of sexual cohabitation or oral sex habit, or by use of barrier methods. Exposure to paternal sperm was self-reported by women with telephone or face to face interviews and questionnaires.

Sperm exposure identifiable before pregnancy that may be suspected to modify the risk of preeclampsia was examined.

We planned to analyze the following sperm exposures before pregnancy:

- overall sperm exposure (either sexual cohabitation, oral sex or lack of use barrier methods);
- sexual cohabitation ($\geq$12 months);
- oral sex (either with or without sperm ingestion);
- lack of use of barrier methods.

Primary and secondary outcomes

Primary and secondary outcomes were defined before data extraction. The primary outcome was the incidence of preeclampsia, as defined in the original studies. The secondary outcomes were gestational hypertension (GH), defined as blood pressure values higher than 140/90 mm Hg in pre-gestational normotensive women, preterm birth (PTB) at less than 37 weeks of gestation, and perinatal outcomes, including small for gestational age (SGA), defined as birth weight lower than 10th percentile for gestational age, admission to neonatal intensive care unit (NICU), and perinatal mortality.

Risk of bias assessment

Two reviewers (DDM, GS) independently assessed the risk of bias of the included studies via the Methodological Index for Non-Randomized Studies (MINORS). Seven domains related to risk of bias were assessed in each study: 1) *Aim* (i.e. clearly stated aim), 2) *Rate* (i.e. inclusion of consecutive patients and response rate), 3) *Data* (i.e. prospective collection of data), 4) *Bias* (i.e. unbiased assessment of study endpoints), 5) *Time* (i.e. follow-up time appropriate), 6) *Loss* (i.e. loss to follow-up), 7) *Size* (i.e. calculation of the study size). Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk of bias" [12]. Discrepancies were resolved by discussion.

Data extraction

Data extraction was completed by two independent investigators (DDM, GS). Each investigator independently extracted data about study features, population, and risk factors for preeclampsia. Information of adjusting for confounders and adjusted risk estimates were collected when available. Differences were resolved by consensus.

Data analysis

Data analysis was performed with Review Manager Version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark). All analyses were carried out using the random effects model (of DerSimonian and Laird, assuming that the data being analyzed was drawn from a hierarchy of different populations). The pooled results were reported as the OR with 95 % confidence interval (CI). Heterogeneity was measured using I-squared (Higgins I^2).

Subgroup analyses according to type of paternal sperm exposure, such as sexual cohabitation $\geq$ 12 months, oral sex, and lack of use of barrier methods, were planned to evaluate the risk of preeclampsia. We also planned to evaluate the primary outcome by parity.

The systematic review was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses

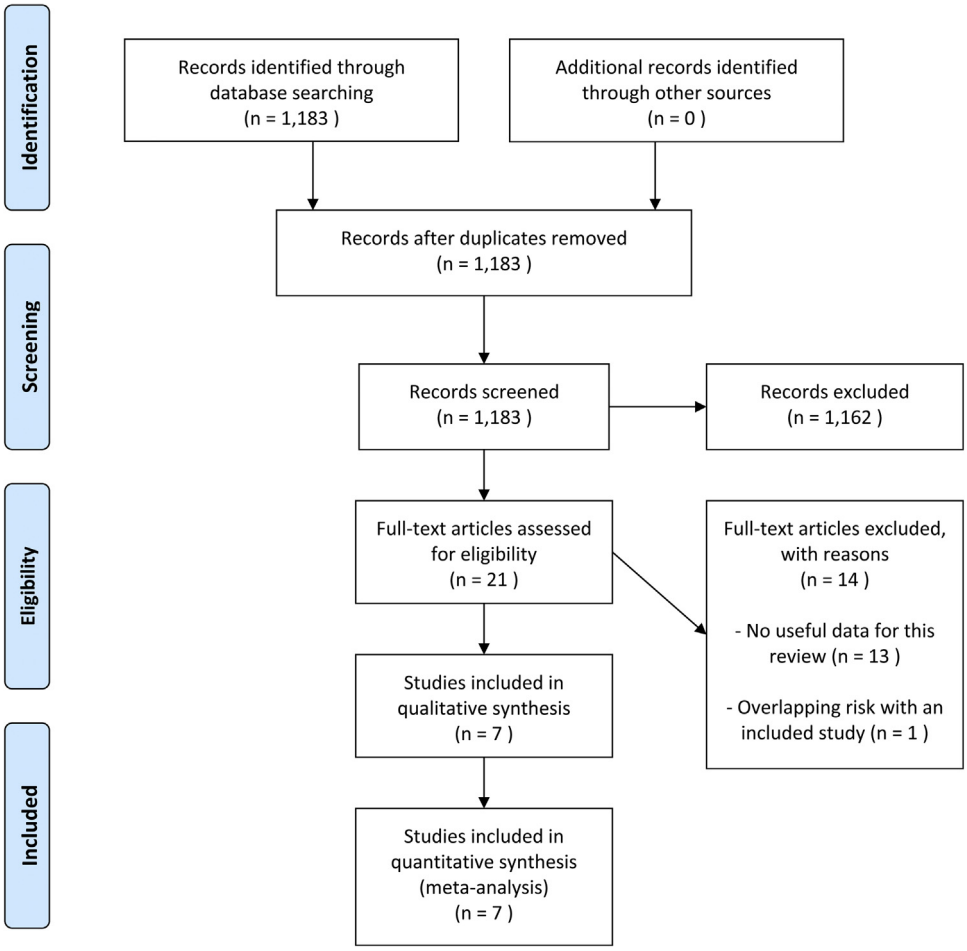

Fig. 1. Study flow chart.

Table 1
General characteristics of the included studies.

	Andraweera 2018 [14]	Saftlas 2013 [15]	Ness 2004 [16]	Einarsson 2003 [17]	Verwoed 2002 [18]	Koelman 2000 [19]	Klonoff-Cohen 1989 [20]
Study Location	Australia, UK, Ireland	USA	USA	USA	South Africa	The Netherlands	USA
Sample size	277 vs 3334	258 vs 182	85 vs 2126	113 vs 226	110 vs 110	41 vs 44	107 vs 112
Period considered	2004–2011	2002–2005	1997–2001	2000–2001	2000–2001	NR	1984 vs 1987
Type of study	Cohort study	Case control study	Case control study	Case control study	Case control study	Case control study	Case control study
Maternal age (mean)	27.7±5.7 vs 28.8±5.4	26.4±0.3 vs 26.4±0.4	26.6±6.0 vs 25.1±6.0	26.3 vs 25.9	20.2±3.0 vs 20.9±4.0	NR	NR
Parity	Nulliparous	Nulliparous	Nulliparous and multiparous	Nulliparous and multiparous	Nulliparous and multiparous	Nulliparous women	Nulliparous women
Nulliparous women (%)	100 % vs 100 %	100 % vs 100 %	NR	60.2 % vs 62.8 %	45.5 % vs 45.5 %	100 % vs 100 %	100 % vs 100 %
Definition of sperm exposure	Sexual relationship ≥ 12 months	Sexual cohabitation ≥ 12 months; oral sex before pregnancy	No barrier methods at 6 month or less before pregnancy	No barrier methods; sexual cohabitation >12 months	No barrier methods at 6 month or less before pregnancy	Oral sex before pregnancy	No barrier methods before pregnancy
Control group	Sexual relationship < 12 months	Sexual cohabitation < 12 months; no oral sex before pregnancy	Barrier methods at 6 month or less before pregnancy	Barrier methods; sexual cohabitation < 12 months	Barrier methods at 6 month or less before pregnancy	No oral sex before pregnancy	Barrier methods before pregnancy
Definition of PE	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation with proteinuria (24-h urinary protein 300 mg or spot urine protein: creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥ 2+) or any multisystem complication of PE	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation with proteinuria (24-h urinary protein 300 mg or spot urine protein: creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥ 1+)	Repeated systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and proteinuria ≥1+ on a catheterized, ≥2+ on a voided or ≥300 mg on a 24 h urine specimen, or a protein/creatinine ratio of 0.3	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation with proteinuria (24-h urinary protein 300 mg or spot urine protein: creatinine ratio ≥30 mg/mmol creatinine or urine dipstick protein ≥ 1+)	At least two diastolic BP ≥ 90 mmHg taken at least 4 h apart or at least one diastolic BP ≥ 110 mmHg and repeated proteinuria of ≥ 2+ on dipsticks)	Diastolic BP ≥ 90 mmHg or more and an increase of at least 20 mmHg compared to the diastolic BP in the first trimester plus proteinuria of at least 300 mg/24 h	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg on two or more measurements 6 h apart after 20 weeks of gestation with repeated proteinuria ≥ 300 mg and edema of the face or hands of > 1 = or a gain of ≥ 5 lb in 1 week
Main outcome	Adverse obstetrical outcomes	PE	PE	PE	PE	PE	PE

NR, not reported; BP, blood pressure; PE, preeclampsia. Data are presented as women affected by preeclampsia (cases) vs normotensive women (controls).

(PRISMA) statement [13]. The study was registered with the PROSPERO database (registration number CRD42020148320).

Results

Study selection and study characteristics

Fig. 1 shows the flow diagram of information derived from our review of potentially relevant articles (Fig. 1, Supplementary Table 1). Seven studies [14–20] including 7125 pregnant women were included in this systematic review. The majority of the included women were nulliparous, although three studies [16–18] also included multiparous women (Table 1). Sperm exposure was defined as: sexual cohabitation ≥12 months [14]; either sexual cohabitation ≥12 months or oral sex before pregnancy [15]; either sexual cohabitation ≥12 months or no use of barrier methods before pregnancy [17]; no use of barrier methods before pregnancy [16,18,20]; oral sex before pregnancy [19].

The quality of the studies included in our meta-analysis was assessed by the MINORS' tool for assessing the risk of bias (Fig. 2A, B). All studies had low risk of bias in "aim," and the majority in "rate". Six studies were case-control studies comparing women affected by preeclampsia with normotensive women [15–20], while one was a multicenter, prospective cohort study [14].

Synthesis of results

Overall, the incidence of preeclampsia was similar in women with a higher overall sperm exposure compared to controls, 774/5512 (14 %) vs 220/1619 (13.6 %); OR 1.04, 95 % CI 0.88–1.22 (Table 2). The incidence of preeclampsia was significantly reduced in women with a higher overall sperm exposure when including only nulliparous women, 643/3946 (16.1 %) vs 170/725 (23.4 %); OR 0.63, 95 % CI 0.52 to 0.76 (Table 3). Conversely, no difference was found when including only multiparous women, although this analysis was limited to two studies (Table 4).

When stratifying according to the type of sperm exposure, significantly lower rate of preeclampsia was found for ≥12-month sexual cohabitation, 494/3627 (13.6 %) vs 123/691 (17.8 %); OR 0.73, 95 % CI 0.59 to 0.90 (Table 5), while no differences were found for oral sex before pregnancy (Table 6). Significantly higher rate of preeclampsia was reported in women not using barrier methods, 315/1904 (16.5 %) vs 103/962 (10.7 %); OR 1.65, 95 % CI 1.30–2.10 compared with the other included studies (Table 7) [16,17,18,20].

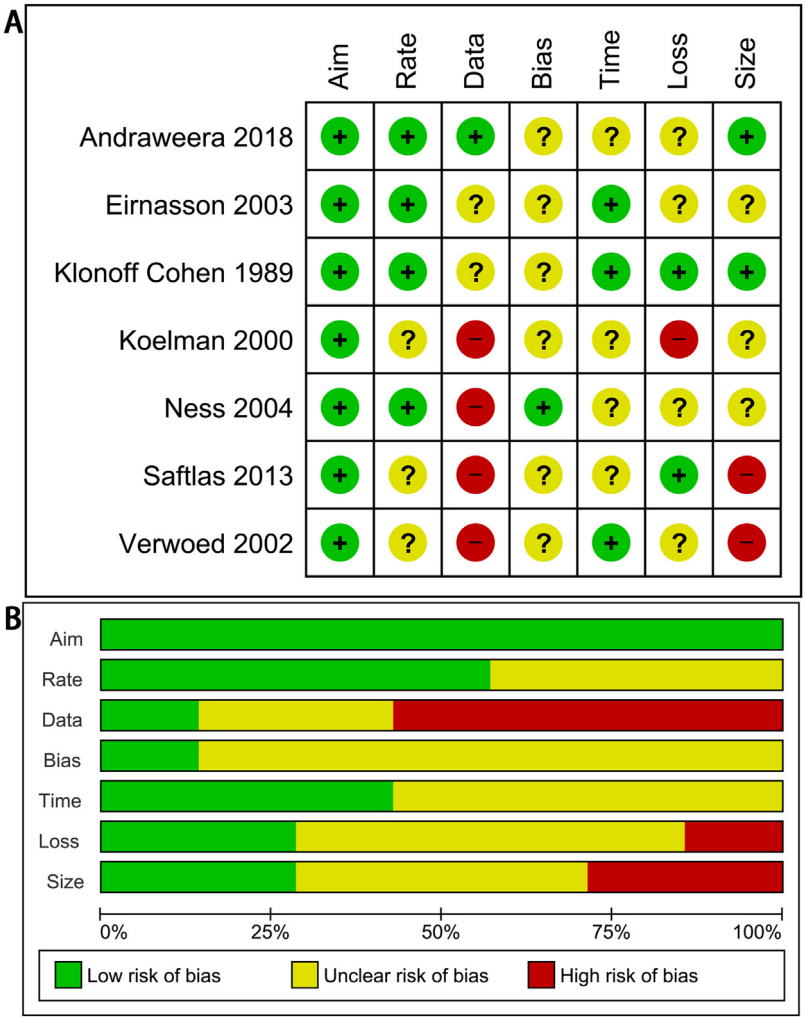

Fig. 2. Assessment of risk of bias. *Aim, clearly stated aim; Rate, inclusion of consecutive patients and response rate; Data, prospective collection of data; Bias, unbiased assessment of study end points; Time, follow-up time appropriate; Loss, loss to follow-up; Size, calculation of the study size.* (A) Summary of risk of bias for each study. *Plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias.* (B) Risk of bias graph about each risk of bias item presented as percentages across all included.

Table 2
Overall effect of sperm exposure on the incidence of PE.

	Andraweera 2018 [14]		Saftlas 2013 [15]		Ness 2004 [16]		Einarsson 2003 [17]		Verwoed 2002 [18]		Koelman 2000 [19]		Klonoff-Cohen 1989 [20]		TOTAL		
	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	OR (95 % CI)
PE	228/3092 (7.4 %)	49/519 (9.4 %)	213/364 (58.5 %)	45/76 (59.2 %)	54/1362 (4.0 %)	31/849 (3.7 %)	82/267 (30.7 %)	31/72 (43.1 %)	90/179 (50.3 %)	20/41 (48.8 %)	18/54 (33.3 %)	23/31 (74.2 %)	89/194 (45.9 %)	21/31 (67.7 %)	774/5512 (14.0 %)	220/1619 (13.6 %)	1.04 [0.88–1.22]

PE, preeclampsia; OR, odds ratio; CI, confidence interval.

Table 3
Subgroup analysis on nulliparous women.

	Andraweera 2018 [14]		Saftlas 2013 [15]		Einarsson 2003 [17]		Verwoed 2002 [18]		Koelman 2000 [19]		Klonoff-Cohen 1989 [20]		TOTAL		
	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	OR (95 % CI)
PE	228/3092 (7.4 %)	49/519 (9.4 %)	213/364 (58.5 %)	45/76 (59.2 %)	51/169 (30.2 %)	17/41 (41.5 %)	35/73 (47.9 %)	15/27 (55.5 %)	18/54 (33.3 %)	23/31 (74.2 %)	89/194 (45.9 %)	21/31 (67.7 %)	634/3946 (16.1 %)	170/725 (23.4 %)	***0.63 [0.52–0.76]***

PE, preeclampsia; OR, odds ratio; CI, confidence interval. Boldface data, statistically significant.

Table 4
Subgroup analysis on multiparous women.

	Einarsson 2003 [17]		Verwoed 2002 [18]		TOTAL		
	Exposure	No exposure	Exposure	No exposure	Exposure	No exposure	OR (95 % CI)
PE	31/98 (31.6 %)	14/31 (45.2 %)	55/106 (51.9 %)	5/14 (35.7 %)	86/204 (42.2 %)	19/45 (42.2 %)	1.00 (0.52–1.92)

Table 5
Subgroup analysis on sexual cohabitation (≥ or < 12 months).

	Andraweera 2018 [14]		Saftlas 2013 [15]		Einarsson 2003 [17]		TOTAL		
	≥ 12 months	< 12 months	≥ 12 months	< 12 months	≥ 12 months	< 12 months	≥ 12 months	< 12 months	OR (95 % CI)
PE	228/3092 (7.4 %)	49/519 (9.4 %)	213/364 (58.5 %)	45/76 (59.2 %)	53/171 (31.0 %)	29/96 (30.2 %)	494/3627 (13.6 %)	123/691 (17.8 %)	***0.73 [0.59–0.90]***

PE, preeclampsia; OR, odds ratio; CI, confidence interval. Boldface data, statistically significant.

Table 6
Subgroup analysis on oral sex.

	Saftlas 2013 [15]		Koelman 2000 [19]		TOTAL		
	Oral sex	No oral sex	Oral sex	No oral sex	Oral sex	No oral sex	OR (95 % CI)
PE	217/360 (60.3 %)	41/80 (51.3 %)	18/54 (33.3 %)	23/31 (74.2 %)	235/414 (56.8 %)	64/111 (57.7 %)	0.96 [0.63–1.47]

PE, preeclampsia; OR, odds ratio; CI, confidence interval.

Table 7
Subgroup analysis no barrier vs barrier use before pregnancy.

	Ness 2004 [16]		Einarsson 2003 [17]		Verwoed 2002 [18]		Klonoff-Cohen 1989 [20]		TOTAL		OR (95 % CI)
	No barrier	Barrier	No barrier	Barrier	No barrier	Barrier	No barrier	Barrier	No barrier	Barrier	
PE	54/1362 (4.0 %)	31/849 (3.7 %)	82/169 (48.5 %)	31/41 (75.6 %)	90/179 (50.3 %)	20/41 (48.8 %)	89/194 (45.9 %)	21/31 (67.7 %)	315/1904 (16.5 %)	103/962 (10.7 %)	***1.65 [1.30–2.10]***

PE, preeclampsia; OR, odds ratio; CI, confidence interval.

None of the secondary outcomes were reported in the included studies.

Comment

Main findings

The findings from this systematic review showed that paternal sperm exposure before pregnancy is associated with a decreased risk of preeclampsia in nulliparous women, but not in all women. Significant lower rate of preeclampsia was also found for sexual cohabitation ≥ 12 months.

Comparison with existing literature

The theory of paternal factors playing a role in the development of preeclampsia is based on the observation of both a decreased risk of preeclampsia after prolonged exposure to the paternal seminal fluid [14–20] and a higher incidence of preeclampsia in pregnancies conceived with a new father, leading to the hypothesis of an immunological role for sperm in producing a mucosal immune tolerance-like status at the level of the uterus that could be significant in the subsequent implantation [21]. These data seem to be supported also by the evidence that preeclampsia is less common in nulliparous women having longer sexual relationship with the biological father [22]. Similarly, another prospective study on the risk of hypertension in nulliparous women found a 4% decrease in the risk of developing GH for every month increase in sexual cohabitation [23]. In addition, evidence from assisted reproductive technology seems to show similar associations, as pregnancies achieved by sperm donor significantly increase the risk of preeclampsia [10,24], while pregnancies after double gamete donation are at about 3 times higher risk of developing preeclampsia compared with oocyte donation alone [25] and with standard IVF [26].

Strengths and limitations

There are no other comprehensive, up-to-date systematic reviews exploring the role of paternal sperm exposure before pregnancy on the risk of developing preeclampsia in the subsequent pregnancy. There are also no reviews on the type of sperm exposure, and analysis by parity. Inclusion of non-randomized studies, their retrospective design and small sample size represent the major limitations of the present review. The heterogeneity in the baseline population as well as in the definition of sperm exposure, and the lack of some other key confounders such as history of hypertension, body mass index, aspirin use or ethnicity could make it difficult to find an adequate causal link between sperm exposure and subsequent preeclampsia. Moreover, the rate of preeclampsia in both exposed and not exposed group is higher than usually reported [1,2]. Furthermore, an inherent limitation of this study is that information about sperm exposure before pregnancy was self-reported by the included women - either by telephone interview, personal interview or questionnaire - leading to possible reporting bias and recall bias, potentially affecting our study findings. Finally, the reported rate of

non-paternity (i.e. discrepant biological versus social fatherhood) of 2–3 % could have affected our results [27].

Implications and conclusion

The findings from this systematic review have many clinical, ethical, religious and social implications. The evidence that nulliparity is significantly associated with higher risk of developing preeclampsia is closely related to the hypothesis that nulliparous women have a reduced immune tolerance to paternal sperm antigens, and this is also supported by epidemiological data showing higher risk of preeclampsia associated with any change in paternity [21]. In our study, we found a significant decrease in the rate of preeclampsia in nulliparous women with longer exposure to paternal sperm and in all women reporting sexual cohabitation for more than 12 months.

In this review a significantly higher rate of preeclampsia was found in non-barrier users, compared to barrier users. This result stems mostly from 2 studies [17,20] which had a very high rate of preeclampsia in their small non-barrier groups (Table 7). This finding may appear surprising and in contrast with the lower rate of preeclampsia reported in women with sexual cohabitation $\geq$ 12 months. Moreover, a prior IUD use has been shown to be associated with an overall reduction of preeclampsia that was higher when removal occurred within one year before pregnancy [28], but persisted even in case of pregnancies conceived with IUD in situ [29,30]. Therefore, the choice of the method for contraception is a complex and personalized decision and based on these data, we cannot advocate for a given method with the sole purpose of decreasing the risk of preeclampsia in a subsequent pregnancy.

We acknowledge that these concepts might involve also ethical and religious issues. Nonetheless, since the time of Leonardo da Vinci, it's important that scientific research informs traditional beliefs, inducing from experiments rather than deducing from theoretical principles [31].

In conclusion, paternal sperm exposure in nulliparous women and sexual cohabitation $\geq$ 12 months before pregnancy are associated with a decreased risk of preeclampsia.

Financial support

No financial support was received for this study

Declaration of Competing Interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.05.065.

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