

Association between gamete source, exposure and preeclampsia: A review of literature

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Abstract

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality. The pathologic mechanisms are well described but despite decades of research, the exact etiology of preeclampsia remains poorly understood. For years it was believed that the etiology of preeclampsia was the result of maternal factors, but recent evidence suggests that preeclampsia may be a couple specific disease where the interplay between both female and male factors plays an important role. Recent studies have suggested a complex etiologic mechanism that includes genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction. The immunological hypothesis suggests exaggerated maternal response against fetal antigens. While the role of maternal exposure to new paternal antigens in the development of preeclampsia was the initial focus of research in this area, studies examining pregnancy outcomes in pregnancies from donor oocytes provide intriguingly similar findings. The pregnancies that resulted from male or female donor gametes or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of

preeclampsia. The primary goal of the current review is the role of exposure to new gametes on the development of preeclampsia. The objective was therefore to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

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Key words: Preeclampsia; Donor embryos; Donor oocytes; Donor sperm; Primipaternity

Core tip: Preeclampsia is a potentially life threatening complication of pregnancy, etiology remains unresolved. For decades it was believed to be a disease of mainly maternal origin with many pathologic mechanisms being described, however evidence suggests that an interplay between maternal and paternal factors may play an important role in pathogenesis. The aim on this publication therefore was to provide review of current literature on association of gamete source, exposure and the risk of preeclampsia.

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INTRODUCTION

Preeclampsia complicates 3%-5% of pregnancies and is one of the major causes of maternal morbidity and mortality in both developed and low income countries^[1]. While the physical manifestations of preeclampsia have been well characterized and may include hypertension, proteinuria and intrauterine growth restriction, the primary etiology remains unknown^[1-3]. The pathologic

mechanisms described include impaired cytotrophoblast invasion of spiral arteries, exaggerated inflammatory response and endothelial cell damage with subsequent impairment of multiple organs^[3,4].

Despite decades of research, the exact etiology of preeclampsia remains unclear with several proposed hypotheses that include genetic imprinting, immune maladaptation, placental ischemia and generalized endothelial dysfunction^[5]. The immunological hypothesis suggests that an exaggerated maternal response against fetal antigens precipitates the pathological findings^[6]. Evidence for this hypothesis stems in part from studies examining duration exposure to paternal antigens and a correspondingly lower incidence of preeclampsia in subsequent pregnancies^[7,8].

Studies focused on the outcomes of pregnancies from donor oocytes confirmed the observations of initial research examining the role of maternal exposure to new fetal antigens in the development of preeclampsia. The studies on pregnancies that resulted from donor gametes (or either male or female origin) or donor embryos bring new insight into the role of immune response to new antigens in pathogenesis of preeclampsia^[9-12]. The immunologic hypothesis explaining the etiology of preeclampsia is complex and beyond the scope of this article. Experimental studies shown presence of major and minor histocompatibility antigens in human semen, it is therefore seminal priming prior to pregnancy can induce maternal tolerance to paternal alloantigens and thus protect from preeclampsia^[13]. These experiments focus on the expression of transplantation antigens [human leukocyte antigen (HLA)] by human trophoblast and their potential to induce maternal immunologic responses where regulatory T cells and cellular signals indolamine 2,3-dioxygenase, and transforming growth factor- β play important roles. Autoimmune mechanisms have also been with emphasis on the role of maternal antiphospholipid antibodies and anti-angiotensin II type I receptors^[14-17]. For interested readers we recommend the more comprehensive reviews of immunology and preeclampsia^[17,18].

The objective of this paper is to provide a review of current literature on the role of cohabitation length, semen exposure and gamete source in development of preeclampsia.

PRIMIPATERNITY AND NULLIPARITY

The risk of preeclampsia among nulligravid women is three times higher than for multiparous women and a history of prior normal pregnancy has long been considered “protective” for the risk of preeclampsia^[3,19]. The incidence of preeclampsia was higher for nulliparas in their first pregnancy, than it was subsequent pregnancies in the same women with a subsequent pregnancy, provided that it was fathered by the same partner (OR = 2.96, 95%CI: 1.80-4.88)^[8].

It was thought that, in contrast to multiparas whose subsequent pregnancy is fathered by the same man, the

risk of recurrence remains as high for woman with interval partner change as it is for nulliparas. These findings prompted researchers to investigate the role of a new father (or “primipaternity” a term first introduced by Robillard *et al*^[20] in 1993) rather than nulliparity in the development of preeclampsia^[21-23]. Subsequent investigations by Robillard *et al*^[20], reviewing cases in a Caribbean population showed increased risks of preeclampsia in multiparous women after changes in paternity. Similarly, Tubbergen *et al*^[24] showed prevalence of having severe preeclampsia or HELLP syndrome to be significantly higher among multiparous women who conceived with new partner. Li *et al*^[25] in a large retrospective cohort study showed that change in paternity increased the risk of hypertensive disorders of pregnancy for women who were normotensive during their previous pregnancy. The results presented by Trupin *et al*^[26] also support immunological hypothesis of preeclampsia. They showed that 29% of preeclampsia cases in multiparous women with an interval partner change were attributable to primipaternity, however the risk of preeclampsia remained lower in these women comparing to nulliparae. These findings imply that any previous pregnancy, even after change of partner may provide some protection. The association between preeclampsia and primipaternity was further confirmed by Bandoli *et al*^[27] in the study on risk factors for preeclampsia and small for gestational age fetuses. The investigators evaluated the number of potential confounding factors, including maternal diseases, alcohol and tobacco use, history of preeclampsia and race and found that primipaternity remained a significant risk factor for preeclampsia (Table 1).

Some of the discrepancies in studies looking at new male partners may also relate to the duration of sexual cohabitation with a new partner, or duration of antigenic exposure preceding a pregnancy. Verwoerd *et al*^[28] found that primipaternity was not a significant risk factor for preeclampsia. However, analysis of their results in the light of duration of sexual cohabitation, suggested that a duration of sexual cohabitation of 6 mo or fewer months was associated with increased risk of preeclampsia in multigravid group (OR = 3.9, 95%CI: 1.2-13.4). A recent prospective study by Chigbu *et al*^[29] in southern Nigeria population also showed that woman who changed their partners before next pregnancy did not have increased risk for preeclampsia. In contrast to the first study investigators did not find any difference in duration of sexual cohabitation (7.9 ± 1.3 mo *vs* 7.5 ± 2.1 mo, $P = 0.531$) between women with preeclamptic and uncomplicated pregnancies. This latter study is limited by the fact that there were only 11 patients with change in paternity, which may explain the conflicting findings (Table 1).

Further evidence to support a hypotheses of immune tolerance and the documented protective effects of pregnancy, stems from the observation that women with history of miscarriage like multiparas have reduced risk of preeclampsia. Saftlas *et al*^[30] evaluated 4589 nulliparous woman enrolled in Calcium for Preeclampsia Prevention

Table 1 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to change of paternity

| Ref. | Design | Sample size | Main outcome measures | Findings |
|--|----------------------------------|--|--|--|
| Robillard <i>et al</i> ^[20] | Case control | 74 hypertensive cases 60 controls | Change of paternity | Change of paternity was 61.7%, 10% and 16.6% inn PIH group, chronic hypertension group and controls respectively ($P < 0.0001$) |
| Feeney <i>et al</i> ^[21] | Matched case control | 47 cases with preeclampsia 47 normotensive controls | Change of paternity | 13 cases with paternity change <i>vs</i> 3 controls with paternity change ($P < 0.01$) |
| Ikedife ^[22] | Case series | 46 eclamptic multiparous patients | 74% of subjects had paternity change | |
| Chng ^[23] | Case report | Case of severe preeclampsia in the patient with prior history of uneventful first pregnancy | after change of paternity | |
| Tubbergen <i>et al</i> ^[24] | Retrospective case control study | 333 multiparous subjects with hypertensive disorder 182 multiparous normotensive subjects | Change of paternity | 22.6%-preeclamptic multiparas with change of paternity; 27.0%-HELLP multiparas with change of paternity; 3.3%-change of paternity among normotensive multiparas OR for preeclampsia among subjects with new partner was 8.6 (95%CI: 3.1-23.5) and for HELLP 10.9 (95%CI: 3.7-32.3) comparing to normotensive subjects |
| Li <i>et al</i> ^[25] | Retrospective cohort | 140147 pregnancies | Incidence of preeclampsia/eclampsia | OR for preeclampsia among women with previous normal pregnancy and change of paternity was 1.3 (95%CI: 1.1-1.6) |
| Trupin <i>et al</i> ^[26] | Prospective cohort | 5800 pregnancies | Incidence of preeclampsia | Adjusted OR for preeclampsia among multiparas with change of paternity 1.4 (95%CI: 0.8-2.4) |
| Bandoli <i>et al</i> ^[27] | Prospective cohort | 1396 pregnancies | Incidence of preeclampsia | OR for preeclampsia 2.75 (95%CI: 1.33-5.68) among women with change paternity |
| Verwoerd <i>et al</i> ^[28] | Case control | 60 multigravidae with preeclampsia 60 normotensive multigravidae | Change of paternity | Change of paternity was 38.3% <i>vs</i> 21.7% (cases <i>vs</i> controls) Uncorrected OR for preeclampsia with primipaternity 2.3 (95%CI: 0.9-5.5) |
| Chigbu <i>et al</i> ^[29] | Prospective cohort | 732 pregnancies | Incidence of preeclampsia | Preeclampsia in 3.5% of cases <i>vs</i> 3.1% controls (NS) |
| Saftlas <i>et al</i> ^[30] | Retrospective cohort | 4589 pregnancies | Incidence of PIH and preeclampsia | Adjusted OR for preeclampsia among women with history of abortion who conceived again with same partner 0.55 (95%CI: 0.21-0.97) |
| Olayemi <i>et al</i> ^[31] | Prospective cohort | 2630 | Incidence of hypertension in pregnancy | History of same paternity abortion was protective against preeclampsia (HR = 0.46, 95%CI: 0.22-0.96) |

PIH: Pregnancy induced hypertension; NS: Non significant.

trial and found that prior abortion fathered by the same partner reduced the risk of preeclampsia by 50%. These results were replicated by Olayemi *et al*^[31] as well as Eras *et al*^[32] who evaluated the risk associated with preeclampsia and found that women with an aborted pregnancy of the same paternity experienced the same protective effect against preeclampsia (Table 1).

DONATED GAMETES

Pregnancies that result from donor gametes provide another controlled opportunity to study immunologic aspects of preeclampsia. Need *et al*^[33] in 1983 were the first to suggest a higher incidence of preeclampsia in pregnancies resulting from insemination with donor sperm. Although their study was an uncontrolled descriptive case series, further studies demonstrated a similarly increased risk of preeclampsia in the pregnancies that result from donor inseminations^[34-36]. A retrospective study by Hall *et al*^[37] however, failed to demonstrate increased risk of preeclampsia in donor sperm recipients. Although no differences were observed, the control group in this study had a higher baseline incidence of preeclampsia (11.5%) than

is typically reported in the general population, perhaps accounting for the inability to detect an increased risk in the donor sperm cohort (Table 2).

Given the increased risk seen with donor sperm, one would similarly expect that pregnancies in donor oocyte or donor embryo recipients would be associated with similar risk of preeclampsia. Initial studies using an assisted reproductive technology model looking at women receiving embryos derived from donor oocytes would have similarly increased risks of preeclampsia. Studies demonstrated an increased risk to that seen in some donor sperm and primipaternity cases^[10,11,38]. Although these findings were intriguing, the patients using donor oocytes were older than their controls. Klatsky *et al*^[9] provided the largest in a retrospective cohort study of 158 pregnancies including aged matched controls and found an increased risk of both preeclampsia and pregnancy induced hypertension in donor oocyte recipients (OR = 4.0, 95%CI: 1.5-13.8; OR = 4.2, 95%CI: 1.5-11.9 respectively). These findings were recently confirmed again by Tranquilli *et al*^[12] (Table 2).

Of note a small study of 26 donor embryo recipients failed to detect a difference, but was likely underpow-

Table 2 Studies reporting preeclampsia and pregnancy-induced hypertension in donor oocytes, donor sperm and donor embryos pregnancies

| Ref. | Design | Sample size | Main outcome measures | Findings |
|---|---|--|---|--|
| Donor oocytes | | | | |
| Söderström-Anttila <i>et al</i> ^[11] | Retrospective cohort | 51 oocyte donation pregnancies 97 IVF age matched controls | The incidence of PIH and preeclampsia | The incidence of PIH in primiparae was 30% in oocyte donor recipients and 13% in IVF controls ($P < 0.05$), no difference in preeclampsia incidence between two groups |
| Salha <i>et al</i> ^[10] | Retrospective cohort | 27 donor oocytes pregnancies 27 age-and parity matched controls | The incidence of preeclampsia | Preeclampsia incidence 16% <i>vs</i> 3.7% (cases <i>vs</i> controls), $P < 0.05$ |
| Keegan <i>et al</i> ^[38] | Retrospective anonymous questionnaire study | 199 oocyte donor recipients 488 autologous IVF controls | The incidence of PIH | Rate of pregnancy induced hypertension in < 35 years old was 42% <i>vs</i> 12%, $P < 0.001$ (cases <i>vs</i> controls) and > 40 years old 26% <i>vs</i> 14%, $P = 0.003$ (cases <i>vs</i> controls) |
| Klatsky <i>et al</i> ^[9] | Retrospective matched cohort | 77 donor oocytes recipients 81 autologous IVF controls | The incidence of PIH and preeclampsia | 16.9% of cases with preeclampsia <i>vs</i> 4.9% controls 24.7% of cases with PIH <i>vs</i> 7.4 % controls Adjusted OR for preeclampsia with donor oocytes OR = 4.0 (95%CI: 1.2-13.8) and for gestational hypertension OR = 4.2 (95%CI: 1.5-11.9) |
| Tranquilli <i>et al</i> ^[12] | Retrospective matched cohort | 26 donor oocytes recipients 52 autologous ICSI pregnancies 52 AMA controls | Prevalence of preeclampsia | Prevalence of preeclampsia 19.2% in donor oocyte recipients <i>vs</i> 0% in autologous ICSI and AMA controls ($P < 0.001$) |
| Donor sperm | | | | |
| Need <i>et al</i> ^[33] | Case series | 584 AID pregnancies | The incidence of preeclampsia | Preeclampsia incidence 9.3% |
| Smith <i>et al</i> ^[35] | Retrospective cohort | 37 donor insemination pregnancies 44 controls | The incidence of preeclampsia | 24.3% of cases with preeclampsia <i>vs</i> 6.8% controls RR for preeclampsia with donor insemination RR = 1.85 (95%CI: 1.20-2.85) |
| Hoy <i>et al</i> ^[34] | Retrospective cohort | 1552 donor insemination pregnancies 7717 controls | The incidence of preeclampsia | 8.4% of cases with preeclampsia <i>vs</i> 5.2 % controls Adjusted OR for preeclampsia with donor insemination OR = 1.4 (95%CI: 1.2-1.8) |
| Salha <i>et al</i> ^[10] | Retrospective cohort | 33 donor sperm pregnancies 33 age-and parity matched controls | The incidence of preeclampsia | Preeclampsia incidence 18.2% <i>vs</i> 0% (cases <i>vs</i> controls), $P < 0.05$ |
| Hall <i>et al</i> ^[37] | Retrospective cohort | 45 donor insemination pregnancies 173 controls | The incidence of proteinuric hypertension | No difference in incidence of proteinuric hypertension between cases and controls (13.3% <i>vs</i> 11.0%) |
| Kyrou <i>et al</i> ^[36] | Retrospective cohort | 438 donor insemination pregnancies 275 partner sperm | The incidence of preeclampsia | Preeclampsia incidence 10.9% <i>vs</i> 7.2% (cases <i>vs</i> controls), difference 3.7%; 95%CI: -0.8 to 7.8 |
| Donor embryos | | | | |
| Porreco <i>et al</i> ^[39] | Retrospective cohort | 23 donor embryos pregnancies 24 age matched IVF controls | The incidence of preeclampsia | 26% of cases with preeclampsia <i>vs</i> 29% controls OR for preeclampsia with donor embryos OR = 0.86 (95%CI: 0.24-3.09) |
| Salha <i>et al</i> ^[10] | Retrospective cohort | 12 donor embryos pregnancies 12 age-and parity matched controls | The incidence of preeclampsia | Preeclampsia incidence 25% <i>vs</i> 0% (cases <i>vs</i> controls), NS |

AMA: Advanced maternal age; AID: Artificial donor insemination; IVF: *In vitro* fertilization; ICSI: Intracytoplasmic sperm injection; PIH: Pregnancy induced hypertension; NS: Non significant.

ered^[39]. Pregnancies that result from surgically obtained sperm for *in vitro* fertilization (IVF) are similar, immunologically to donor sperm pregnancies, as their partners have not had sufficient antigenic exposure to their husband's sperm. In these cases maternal exposure to paternal sperm antigens prior to embryo transfer is limited, a situation that could be of a key importance if the sperm antigens, not semen antigens were responsible for mounting immunologic tolerance. Wang *et al*^[40] evaluated the outcomes of pregnancies that resulted from regular

IVF or intracytoplasmic sperm injection (ICSI) cycles with ICSI pregnancies were surgically obtained sperm was used. They observed that risk for pregnancy induced hypertension was doubled (OR = 2.1, 95%CI: 1.30-3.62) and risk for preeclampsia tripled (OR = 3.10, 95%CI: 1.59-6.73) in the latter group (Table 2).

LENGTH OF SEXUAL COHABITATION

Marti *et al*^[41] observed that woman with preeclampsia had

Table 3 Studies reporting preeclampsia and pregnancy-induced hypertension in relation to length of sexual cohabitation and use of barrier contraception

| Ref. | Design | Sample size | Main outcome measures | Results |
|---|--|--|--|--|
| Robillard <i>et al</i> ^[27] | Retrospective cohort | 1011 pregnancies | Incidence of PIH | Incidence of PIH was 10.6% (entire cohort) and 5.1% among women with > 12 mo of sexual cohabitation (11.9% and 3.3% for primigravidae, respectively) |
| Verwoerd <i>et al</i> ^[28] | Case control | 60 cases with preeclampsia 60 normotensive controls | Length of sexual cohabitation | Unprotected sexual cohabitation of > 6 mo was a negative predictor for preeclampsia (coefficient -0.57, SE 0.62, <i>P</i> = 0.03) |
| Olayemi <i>et al</i> ^[31] | Prospective cohort | 2630 pregnancies | Incidence of hypertension in pregnancy | Length of sexual cohabitation before pregnancy was protective against hypertension in pregnancy (HR = 0.96, 95%CI: 0.93-0.99) but not preeclampsia (HR = 1.07, 95%CI: 0.00-1.15) |
| Kho <i>et al</i> ^[42] | Prospective cohort | 2507 pregnancies | Incidence of preeclampsia | OR for preeclampsia were 2.32 (95%CI: 1.03-5.25) and 1.88 (95%CI: 1.05-3.36) for short sexual relationship of less than 3 mo and less than 6 mo respectively |
| Klonoff-Cohen <i>et al</i> ^[43] 1989 | Case control | 110 preeclamptic cases 115 normotensive controls | Contraceptive and reproductive history of subjects | OR for preeclampsia for barrier contraceptive users was 2.37 (95%CI: 1.01-5.58) |
| Mills <i>et al</i> ^[44] | Merge data from two prospective cohort studies | 13914 pregnancies (total) | Incidence of preeclampsia | OR for preeclampsia in barrier contraceptive users were 0.85 (95%CI: 0.71-1.12) (one study) and 0.85 (95%CI: 0.49-1.45) (second study) |
| Saftlas <i>et al</i> ^[46] | Case control | 258 cases 182 controls | Length of sexual cohabitation | OR for preeclampsia among women with long (> 90%) sexual relation-OR = 0.3 (95%CI: 0.1-0.9) |

PIH: Pregnancy induced hypertension.

three times shorter length of sexual cohabitation with their partners than did women with normal pregnancies and thus proposed that spermatozoal HLA can either induce maternal tolerance to conceptus or cause maternal immunologic enhancement. The inverse relationship between length of sexual cohabitation and pregnancy induced hypertension was later demonstrated by Robillard *et al*^[7]. They interviewed 1011 woman regarding paternity and length of cohabitation and found that a duration of sexual cohabitation of greater than 12 mo prior to pregnancy decreased the incidence of pregnancy induced hypertension from 10.6% to 5.1%, and that difference was even more pronounced in the primigravidae subgroup (11.9% to 3.3%). Another study documented a protective effect after only 6 mo^[28] (Table 3).

Two large prospective cohort studies showed that women diagnosed with preeclampsia and gestational hypertension were more likely to have history of recent initiation of sexual relations with their partners than women with uncomplicated pregnancies^[31,42]. The short duration of sperm exposure prior to pregnancy has been postulated to be a factor responsible for higher prevalence of preeclampsia in younger populations (Table 3).

Other studies have shown that the use of barrier contraception and thereby limiting the exposure to paternal sperm antigens was associated with an increased risk of preeclampsia. Such an association was first documented by Klonoff-Cohen *et al*^[43] in a case control study. Authors showed that women who used barrier contraception were over twice as likely to develop preeclampsia. These results however could not be reproduced in later study by Mills *et al*^[44] in 1991 (Table 3).

The role of semen exposure and its effect on development of preeclampsia has been subject of many studies.

It seems that not only duration of sperm exposure plays role. It has been hypothesized that vaginal and oral sperm exposure prior to pregnancy may exert different effects.

Vaginal exposure is not the only posited mechanism for immunologic exposure. Koelman *et al*^[45] showed in a small study (41 preeclamptic patient, 44 controls) that women with preeclampsia were less likely to have been engaged in oral sex with their partners prior to index pregnancy. In their study preeclamptic women were also less likely to swallow sperm during oral sex with the father of their pregnancy. Using enzyme-linked immunosorbent assay they were able to detect soluble HLA in seminal plasma and showed that its levels were not different between men that fathered normal and preeclamptic pregnancy. The investigators postulated that oral exposure in particular, through exposure of maternal gastrointestinal tract mucous membranes to paternal soluble HLA induced a tolerance to future pregnancies with the same partner. The Koelman study, however, did not control for length of sexual relation before pregnancy. A similar case-control study of 440 pregnancies, examined the association between seminal fluid exposures and the development of preeclampsia, using detailed questionnaires about sexual practices, failed to find an association with reduced rates of preeclampsia. Increasing vaginal exposure to paternal semen, however, was significantly associated with a lower incidence of preeclampsia, with 70% reduction rate for women with the highest 10th percentile exposure^[46].

CONCLUSION

Preeclampsia is a syndrome that involves both multiple organs and is associated with many risk factors. Currently,

both experimental and clinical studies support a role for immune dysfunction in the etiology of preeclampsia. We reviewed the evidence that gamete source and prior exposure may be associated with the risk of preeclampsia. Non-autologous gametes, both donor oocytes and donor sperm, as well as exposure to new paternally derived antigens appear to play an important role in development of the disease. Most studies support the hypothesis that maternal exposure to male antigens either in sperm or through prior pregnancies has some protective effect. Available data support hypothesis that incidence of preeclampsia and pregnancy induced hypertension decrease with increasing length of sexual cohabitation. Examination of the pregnancy outcomes resulting from assisted reproduction using donor gametes contribute clinical evidence to evaluate the hypothesis that preeclampsia may be causally related to novel antigenic exposure in the conceptus.

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