

Commentary: Revisiting the primipaternity theory of pre-eclampsia

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Pre-eclampsia is characterized by abnormal implantation of the trophoblast in the placenta and poor placental perfusion, followed by sustained hypertension and proteinuria. While the disease has been recognized for centuries, the aetiology of pre-eclampsia is unknown and is likely multifactorial. Clues about the aetiology of pre-eclampsia might be derived from the risk factors that have been identified. However, to date, the only well-accepted risk factor for pre-eclampsia is primiparity. Recently, it has been suggested that primipaternity rather than primiparity is the relevant risk factor.¹ That is, that not only are primiparas at high risk but so are multiparas having a first child with a new father.^{2–6}

One current aetiological theory of pre-eclampsia proposes that incomplete implantation associated with pre-eclampsia is an immunologically mediated response and that exposure to paternal antigen protects against the disease. In 1975, Need⁶ reported severe pre-eclampsia in a woman who previously had an uncomplicated twin pregnancy; the two pregnancies were with separate fathers. Immunological studies of the woman and the two fathers demonstrated greater histo-incompatibility between the mother and the second father. Subsequent small studies also showed a higher number of new fathers among multiparas with severe pre-eclampsia.² In support of this theory, a higher risk for pre-eclampsia has also been observed in women who had artificial insemination by an unknown donor,⁷ women who had a shorter duration of sexual cohabitation before pregnancy,⁸ and women who exclusively used barrier contraceptives.⁹ The article by Trogstad *et al.*¹⁰ in the current issue of *International Journal of Epidemiology* is the first to demonstrate a *reduced* risk of pre-eclampsia associated with a change in paternity, and consequently presents a challenge to the paternal antigen theory of pre-eclampsia.

To date, only four large epidemiological studies have examined the role of paternity in risk of pre-eclampsia. The first study, by Trupin *et al.*,³ found the prevalence of pre-eclampsia in multiparous women with new partners was almost as high as in nulliparous women (3.2% versus 3.0%). When several confounders were controlled for, a new father was associated with an odds ratio for pre-eclampsia of 1.4 (95% CI : 0.8–2.4). However, this study did not differentiate between women with and without a history of pre-eclampsia.

Two subsequent studies suggested that a previous history of pre-eclampsia was an effect modifier in the relationship between

changing paternity and risk of disease.^{4,5} Both Lie *et al.*⁵ and Li and Wi⁴ found that among women with no history of pre-eclampsia, a new father increased the risk of pre-eclampsia by 30%. However, in women who had had pre-eclampsia in a previous pregnancy a new father was associated with a non-significant 10–30% decrease in risk. A possible explanation is that a mother with a non-pre-eclamptic first pregnancy may develop a tolerance to the paternal antigen she is exposed to during that pregnancy. Changing the father will expose the mother to new paternal antigen to which she may not be tolerant. Thus, changing the father, for a woman with no history of pre-eclampsia, may increase her risk to the same level that she would have had as a primipara. On the other hand, a woman who experienced pre-eclampsia in her first pregnancy may have manifested an incompatibility with the first father's antigens and changing partners might actually reduce her risk. Thus, these studies indicate that changing paternity plays a different role in women with and without a history of pre-eclampsia and that analyses must be stratified by history of disease.

Like the previous studies, the current study by Trogstad *et al.*¹⁰ also found that a new father was associated in crude analysis with an increased risk among women with no history of pre-eclampsia, but not among those with a history. However, when the authors controlled for possible confounders, including time between deliveries, a new father was associated with a decreased—not an increased—risk among women with no history of disease, and no relationship among those with a history. The authors suggest that previous results showing increased risk with a new father in women with no history of disease were confounded by insufficient control for time interval between deliveries. However, while neither Lie *et al.*⁵ and Li and Wi⁴ report odds ratios controlling for time interval between deliveries, both groups reported that time interval was examined and was not a confounder. Furthermore, time between deliveries is unlikely to be a confounder in the Li and Wi study,⁴ given that the authors restricted their population to births that were between 1 and 3 years apart.

Thus, the current study by Trogstad *et al.*¹⁰ introduces a third variable, time interval between pregnancy, into the complex relationship of changing paternity and previous history of disease. Increasing time between pregnancies was found to increase risk in women with no history of disease, but had no significant effect in women with a history of disease. Further complicating the relationship, the authors report an interaction between paternity and time between deliveries in those with no history of pre-eclampsia, but no interaction in those with a history. Nevertheless, in those with no history of pre-eclampsia, the odds of disease is always higher in those with the same partner than those with a new partner.

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The findings of the current study, if correct, seriously question the current theories implicating the role of the father in pre-eclampsia risk. A reduced risk of pre-eclampsia with a change in paternity (among women with previously healthy pregnancies) goes against the findings of all other studies and seems to refute the theory that increased exposure to paternal antigen is protective. The results of the Trogstad *et al.*¹⁰ study are divergent from the epidemiological studies that preceded it, although no other studies have examined the role of time between pregnancies as thoroughly as the current study. Clearly the effect of time between pregnancies on pre-eclampsia risk needs to be re-examined in additional studies. In the meantime, the jury is out about the impact of primipaternity on pre-eclampsia risk and the aetiological role of paternal antigen.

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