

## Research Article

# The Role of the Father in the Occurrence of Preeclampsia

Shiho Nagayama, Akihide Ohkuchi\*, Rie Usui, Shigeki Matsubara, and Mitsuaki Suzuki

Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, Japan

Special Issue on

## Prediction of Preeclampsia

### \*Corresponding authors

Akihide Ohkuchi, Department of Obstetrics and Gynecology, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi, 329-0498, Japan, Tel: 81-285-58-7376; Fax: 81-285-44-8505; Email: okuchi@jichi.ac.jp

Submitted: 04 April 2014

Accepted: 09 June 2014

Published: 10 June 2014

ISSN: 2333-6439

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### Keywords

- Preeclampsia
- Risk factor
- Paternity
- Dangerous father

### Abstract

**Aims:** Our aim was to evaluate the role of the father in the occurrence of preeclampsia in the second pregnancy.

**Methods:** We searched for articles evaluating the effect of a change of paternity on the occurrence of preeclampsia in PubMed and in review articles.

**Results:** We found 5 articles evaluating the effect of a change of paternity in the second pregnancy on the occurrence of preeclampsia. In 4 articles, we could calculate the average incidence rate of preeclampsia; 629,962 women were included in these articles. In women with a normal first pregnancy, preeclampsia in the second pregnancy occurred in 1.5% (8,601/566,727) with the same father, and 2.0% (722/34,638) with a different father ( $p < 0.001$ ). In women with preeclampsia in the first pregnancy, preeclampsia in the second pregnancy occurred in 13.9% (3,729/26,797) with the same father, and 12.8% (231/1,800) with a different father ( $p = 0.198$ ).

**Conclusions:** When women had a normal first pregnancy, preeclampsia in the second pregnancy occurred more frequently in women when there was a different father than the same husband. However, when women had preeclampsia in the first pregnancy, the change of paternity was not significantly related to the occurrence of preeclampsia in the second pregnancy. Although the effect of the change of paternity on the occurrence of preeclampsia might be small, the results of our systematic review support the hypothesis of a 'dangerous father.'

## INTRODUCTION

A new partner who contributes to preeclampsia in a woman's second pregnancy is called 'dangerous father' [1]. There are several reasons why such a father is a risk for the occurrence of preeclampsia [1]. First, protection against the risk of preeclampsia by a preceding history of abortion with the same partner [2]; second, promotion of the risk of preeclampsia by a history of preeclampsia in the man's mother [3]; and third, promotion of the risk of preeclampsia by a man with a history of preeclampsia with another woman [4]. However, the risk of preeclampsia in the second pregnancy might differ according to the occurrence of preeclampsia in the first pregnancy; when a woman had changed her partner for the second pregnancy, the risk of preeclampsia increased only when the woman had had a normal first pregnancy [4]. In this review, we collected articles on the occurrence of preeclampsia according to the change of paternity, and evaluated the incidence rates of preeclampsia in the second pregnancy while stratifying subjects by the presence/absence of preeclampsia in the first trimester, and the change of paternity in the second pregnancy.

## METHODS

We attempted to search for articles evaluating the effect of a change of paternity on the occurrence of preeclampsia in PubMed on March 18<sup>th</sup>, 2014, using the following key words: preeclampsia and paternity. S.N. and A.O. checked the titles and abstracts, extracted 4 articles which evaluated the effect of a change of paternity from the first pregnancy to the second pregnancy, and confirmed the eligibility by reading the original articles [4-7]. In addition, we decided to collect articles by examining relevant references from previously published review articles evaluating the effect of a change of paternity on the occurrence of preeclampsia [1,8,9], and found another eligible article [10]. When the number of women with preeclampsia was available in the collected articles, we calculated the average incidence rate of preeclampsia.

## RESULTS

We found 5 articles evaluating the effect of a change of paternity from the first to second pregnancy on the occurrence of preeclampsia in the second pregnancy (Table 1). In 4 articles, we could calculate average incidence rates of preeclampsia.

**Table 1:** Incidence rate of PE in the second pregnancy while stratifying subjects by the presence/absence of PE in the first trimester, and the change of paternity in the second pregnancy.

First author, year [reference]	Study design	The first pregnancy	Partner in the second pregnancy (same/different)	Numbers (PE/cohort)	Incidence rate of PE	RR (95%CI)	cOR (95%CI)	aOR (95%CI)
Lie RT, 1998 [4]	Cohort	Normal	Same	4,443/351,321	1.3%	-	-	-
		Normal	Different	223/13,834	1.6%	-	-	-
		PE	Same	1,635/12,437	13.1%	-	-	-
		PE	Different	51/432	11.8%	-	-	-
Li DK & Wi S, 2000 [5]	Cohort	Normal	Same	888/123,942	0.7%	1	-	-
		Normal	Different	118/13,372	0.9%	1.3 (1.1-1.6)	-	-
		PE	Same	245/2,598	9.4%	1	-	-
		PE	Different	15/235	6.4%	0.7 (0.4-1.2)	-	-
Trogstad LI, 2001 [6]	Cohort	Normal	Same	-	-	-	1	1
		Normal	Different	-	-	-	1.21 (1.09-1.35)	0.80 (0.72-0.90)
		PE	Same	-	-	-	1	1
		PE	Different	-	-	-	1.02 (0.85-1.24)	0.97 (0.79-1.18)
Basso O, 2001 [10]	Cohort	Normal	Same	2,191/24,049	9.1%	-	-	-
		Normal	Different	279/2,547	11.0%	-	-	-
		PE	Same	1,239/7,637	16.2%	-	-	-
		PE	Different	115/764	15.1%	-	-	-
Mostello D, 2008 [7]	Cohort	Normal	Same	1,078/67,415	1.6%	-	-	-
		Normal	Different	102/4,885	2.1%	-	-	-
		PE	Same	610/4,125	14.8%	-	-	-
		PE	Different	51/369	13.8%	-	-	-
Average		Normal	Same	8,600/566,727	1.5%			
		Normal	Different	722/34,638	2.0%			
		PE	Same	3,729/26,797	13.9%			
		PE	Different	231/1,800	12.8%			

Abbreviations: PE, preeclampsia; RR, relative risk; cOR, crude odds ratio; aOR, adjusted odds ratio.

A total of 629,962 women were included in the 4 articles. In women with a normal first pregnancy, preeclampsia in the second pregnancy occurred in 1.5% (8,601/566,727) when they had the same partner, and 2.0% (722/34,638) when they had a different partner ( $p < 0.001$ ). In women with preeclampsia in the first pregnancy, preeclampsia in the second pregnancy occurred in 13.9% (3,729/26,797) when they had the same partner, and 12.8% (231/1,800) when they had a different partner ( $p = 0.198$ ). In another article where only the odds ratio was reported [6], when women had a normal first pregnancy, the crude odds ratio in the second pregnancy with a different partner was 1.21 (1.09-1.35), and the adjusted odds ratio was 0.80 (0.72-0.90); when women had had preeclampsia in the first pregnancy, the crude odds ratio in the second pregnancy with a different partner was 1.02 (0.85-1.24), and the adjusted odds ratio was 0.97 (0.79-1.18).

## DISCUSSION

When women had had a normal first pregnancy; preeclampsia in the second pregnancy occurred more frequently in women with the different partner than in those with the same partner. However, when women had experienced preeclampsia in the first pregnancy, the change of paternity was not significantly

related to the occurrence of preeclampsia. Since the effect of the change of paternity on the occurrence of preeclampsia in women with a normal first pregnancy was significant, the results of our systematic review support the hypothesis of a 'dangerous father,' although the absolute incidence rate increment of preeclampsia was very small, only 0.5% (from 1.5% to 2.0%).

The hypothesis of a 'dangerous father,' a concept indicating the role of the father in the occurrence of preeclampsia was proposed by Sibai et al. [1] proposed in 2005. Their hypothesis is based on several past studies evaluating the relationship between the occurrence of preeclampsia and the paternal role [2-4]. Saftlas et al. [2] reported that women with a history of abortion who conceived again with the same partner had nearly half the risk of preeclampsia (adjusted odds ratio: 0.54 (0.31-0.97)), when women without a history of abortion served as the reference group; in contrast, women with an abortion history who conceived with a new partner had the same risk of preeclampsia as women without a history of abortion (adjusted odds ratio: 1.03 (0.72-1.47)). These results suggested the protecting effect of a history of abortion on the occurrence of preeclampsia. Esplin et al. [3] reported that the adjusted odds ratio of preeclampsia was 2.1 (1.0-4.3) ( $P = 0.04$ ) in the group of men whose mothers

had had preeclampsia and 3.3 (1.5-7.5) ( $P=0.004$ ) in the group of women whose mothers had had preeclampsia. These results suggested the promoting effect of a history of preeclampsia in the mother of the partner on the occurrence of preeclampsia. Lie et al. [4] reported that if a woman becomes pregnant by a man who has already fathered a preeclampsia pregnancy in a different woman, her crude odds ratio of developing preeclampsia is 1.8 (1.2-2.6). These results suggested the promoting effect of men with a history of preeclampsia with a different woman on the occurrence of preeclampsia after changing partner. The results in our current review added further evidence supporting the promoting effect of a change of paternity on the occurrence of preeclampsia, although such an effect was observed only when the women had had a normal first pregnancy. Taken together, previous reports and our results supported the hypothesis of a 'dangerous father.'

In our review, when women had had preeclampsia in the first pregnancy, a change of paternity was not significantly related to the occurrence of preeclampsia. This is highly unusual because we confirmed a significant increase in the incidence rate of preeclampsia by a change of paternity in women with a normal first pregnancy. Why does the effect of a change of paternity differ according to the presence/absence of preeclampsia in the first pregnancy? Two reasons were considered. First, the promoting effect of a change of paternity in the second pregnancy might be much smaller than other known risks of preeclampsia. A past history of preeclampsia is the strongest risk of preeclampsia [11]; therefore, although the change of paternity might promote the occurrence of preeclampsia, the effect might be embedded in the very strong effect of a past history of preeclampsia in the mother, resulting in no difference in the incidence rate of preeclampsia in the second pregnancy in women with preeclampsia in the first pregnancy. Second, the effect of the change of paternity might occur as a result of several related confounding factors, although such an effect could never be determined by our simple meta-analysis. Interestingly, Trogstad et al. [6] reported that in women with a normal first pregnancy, although a different partner was a promoting factor of preeclampsia in unadjusted logistic regression analysis, a different partner was a protecting factor against preeclampsia in multivariate logistic regression analysis after adjusting for time between deliveries, maternal age at second delivery, and year of second delivery. They suggested that previous results on the impact of changing paternity on preeclampsia risk have been confounded by insufficient control of the time interval between the pregnancies [6]. Skjaerven et al. [12] also evaluated the effects on the risk of preeclampsia of both the inter birth interval and a change of partner in 551,478 women who had two or more singleton deliveries and 209,423 women who had three or more singleton deliveries; in unadjusted analyses, a pregnancy involving a new partner was associated with a higher risk of preeclampsia, but after adjustment for the inter birth interval, the risk of preeclampsia was reduced (adjusted odds ratio for preeclampsia with a change of partner: 0.73[0.66-0.81]). These results suggested that the promoting effect of a change of partner on the occurrence of preeclampsia might be false when it occurred after a long inter birth interval

accompanied by a change of paternity. If so, it is not unexpected that a change of paternity in women with preeclampsia in the first pregnancy was not significantly related to the occurrence of preeclampsia in the second pregnancy.

In conclusion, in our systematic review, we confirmed the effect of the change of paternity on the occurrence of preeclampsia, supporting the hypothesis of a 'dangerous father.' However, several past articles using multivariate analysis adjusted for a change of paternity and the inter birth interval suggested that a change of partner might be not associated with an increased risk of preeclampsia [6,12]. Is the hypothesis of a 'dangerous father' for the occurrence of preeclampsia true? We speculate that a change of paternity in women with a normal first pregnancy might slightly increase the risk of preeclampsia, but a long inter birth interval might have a greater effect on the occurrence of preeclampsia than a change of paternity [12].

## CONTRIBUTORS

S.N. and A.O. systemically searched for articles and selected eligible articles, and A.O. wrote the manuscript. R.U, S.M. and M.S. critically reviewed the manuscript.

## FINANCIAL DISCLOSURE

This work was supported by Grants-in-Aid (24390383 and 24592482 to A.O.) from the Ministry of Education, Culture, Sports, Science and Technology in Japan and a research grant (3-2417-011 to S.M.) from the Japan Association of Obstetricians and Gynecologists Ogyaa Donation Foundation.

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**Cite this article**

Nagayama S, Ohkuchi A, Usui R, Matsubara S, Suzuki M (2014) The Role of the Father in the Occurrence of Preeclampsia. *Med J Obstet Gynecol* 2(2): 1029.