

## THE INTERVAL BETWEEN PREGNANCIES AND THE RISK OF PREECLAMPSIA

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**ABSTRACT**

**Background** The risk of preeclampsia is generally lower in second pregnancies than in first pregnancies, but not if the mother has a new partner for the second pregnancy. One explanation is that the risk is reduced with repeated maternal exposure and adaptation to specific antigens from the same partner. However, the difference in risk might instead be explained by the interval between births. A longer interbirth interval may be associated with both a change of partner and a higher risk of preeclampsia.

**Methods** We used data from the Medical Birth Registry of Norway, a population-based registry that includes births that occurred between 1967 and 1998. We studied 551,478 women who had two or more singleton deliveries and 209,423 women who had three or more singleton deliveries.

**Results** Preeclampsia occurred during 3.9 percent of first pregnancies, 1.7 percent of second pregnancies, and 1.8 percent of third pregnancies when the woman had the same partner. The risk in a second or third pregnancy was directly related to the time that had elapsed since the preceding delivery, and when the interbirth interval was 10 years or more, the risk approximated that among nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the odds ratio for preeclampsia for each one-year increase in the interbirth interval was 1.12 (95 percent confidence interval, 1.11 to 1.13). In unadjusted analyses, a pregnancy involving a new partner was associated with higher risk of preeclampsia, but after adjustment for the interbirth interval, the risk of preeclampsia was reduced (odds ratio for preeclampsia with a change of partner, 0.73; 95 percent confidence interval, 0.66 to 0.81).

**Conclusions** The protective effect of previous pregnancy against preeclampsia is transient. After adjustment for the interval between births, a change of partner is not associated with an increased risk of preeclampsia. (N Engl J Med 2002;346:33-8.)

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**P**REECLAMPSIA is a transient but potentially dangerous complication of pregnancy that affects 3 to 5 percent of pregnant women.<sup>1,2</sup> Although the causes of preeclampsia remain uncertain,<sup>3</sup> epidemiologic features of the condition have led to speculation about immunologic causes. The risk of preeclampsia is at least twice as high during first pregnancies as during second or later pregnancies.<sup>4-6</sup> Recent studies have suggested that the risk

may decrease with a second pregnancy only if the mother's partner is the same.<sup>1,7</sup> The hypothesis is that the risk of preeclampsia may be reduced with repeated maternal exposure and adaptation to specific foreign antigens of the partner.<sup>3,8,9</sup> According to this hypothesis, a new partner presents new antigens, which results in a risk of preeclampsia that is similar to the risk during a first pregnancy. However, it is also possible that the increased risk of preeclampsia associated with a change of partner might be attributable to a longer interval since the previous delivery, which may also increase the risk of preeclampsia.<sup>5,10</sup> We used a large registry in Norway to evaluate the effects on the risk of preeclampsia of both the interbirth interval and a change of partner.

**METHODS****Data on Deliveries**

We used data from the Medical Birth Registry of Norway, comprising the records of more than 1.8 million births between 1967 and 1998. Stillbirths occurring after 16 weeks or more of gestation are also reported to the registry. The registry contains a unique personal identification number for all mothers, all liveborn children, and nearly all fathers.

All children born to a given woman were linked by means of the national identification number of the woman. We identified 551,478 sets (7.6 percent) of first and second singleton deliveries that occurred during this period. Of these, 509,548 of the pairs (92.4 percent) had the same father, and 31,683 pairs (5.7 percent) had different fathers; for the remaining 10,247 pairs (1.9 percent), it could not be determined whether the father was the same. Similarly, we identified 209,423 sets of first, second, and third singleton deliveries. Of these, 158,284 sets (7.6 percent) had the same father; in the case of 24,252 sets (11.6 percent), the partner had changed either between the first and second deliveries (4.6 percent) or between the second and third deliveries (7.0 percent). For the remaining 26,887 sets (12.8 percent), information on the father was missing for at least one pregnancy.

**Calculation of Interbirth Interval**

The interbirth interval was calculated as the time (in days) between two consecutive birth dates. We used birth dates (rather than approximate dates of conception) for calculating the interbirth interval because this information was virtually 100 percent complete, whereas information on the gestational age (which is necessary for estimating the date of conception) was more often missing or unreliable. The effect of using the birth date rather than the estimated date of conception was expected to be minimal for the present

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analysis, which focuses on longer interbirth intervals. The interbirth interval was categorized according to completed years (e.g., an interbirth interval of two years indicates a period of at least two years and less than three years).

### Definition of Preeclampsia

Preeclampsia was defined as an increase in blood pressure to at least 140/90 mm Hg after the 20th week of gestation, an increase in diastolic blood pressure of at least 15 mm Hg from the level measured before the 20th week, or an increase in systolic blood pressure of at least 30 mm Hg from the level measured before the 20th week, combined with proteinuria (protein excretion, at least 0.3 g per 24 hours).<sup>11</sup> A diagnosis of preeclampsia in the medical record is routinely entered on the medical registration form as a specified diagnosis by the midwife or obstetrician. In some cases, the registration form contains information on the presence of hypertension, proteinuria, or edema during pregnancy. We included as cases of preeclampsia all pregnancies with a specified diagnosis of preeclampsia and pregnancies with a combination of pregnancy-related hypertension and proteinuria.<sup>5</sup>

### Statistical Analysis

We used stratification and logistic-regression techniques to evaluate possible confounding. In these analyses, we divided the deliveries into three periods according to the year (1967 to 1976, 1977 to 1986, and 1987 to 1998) and maternal age into five categories (less than 20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, and 35 years or more). In assessing the interbirth interval, we used the mother's age at the time of the later delivery and the period during which that delivery occurred. Age and period were treated as categorical variables, and the interval between pregnancies was treated as a linear variable, categorized into 10 groups according to completed years (with <1 year included in the 1-year category and >10 years included in the 10-year category). For the interbirth interval, the main variable of interest, we report the increase in risk with each additional year between deliveries as an estimated odds ratio. For most analyses, the data were restricted to women with no history of preeclampsia during previous pregnancies and to the pregnancies of women who had the same partner for all pregnancies. We only considered pregnancies that led to a recorded birth, including stillbirths that occurred after at least 16 weeks of gestation.

## RESULTS

### Risk of Preeclampsia According to Parity

Preeclampsia occurred during 3.9 percent of first pregnancies. When subsequent pregnancies involved

the same partner, preeclampsia occurred during 1.7 percent of second pregnancies and 1.8 percent of third pregnancies (Table 1). When women with previous preeclampsia were excluded, preeclampsia occurred during only 1.3 percent of second and third pregnancies (Table 1).

### The Effect of the Interval between Deliveries

Among women with no history of preeclampsia, the median interbirth interval was 2.9 years between the first and the second deliveries and 3.6 years between the second and the third deliveries. The risk of preeclampsia during the second pregnancy was found to increase steadily as the time since the first delivery increased (Fig. 1). The estimated odds ratio for preeclampsia was 1.16 per additional year (95 percent confidence interval, 1.15 to 1.18). By 10 years after the first pregnancy, the risk of preeclampsia had more than tripled, nearly reaching the level of the risk found among nulliparous women. An increasing interval between the second and the third deliveries was similarly associated with an increasing risk of preeclampsia (Fig. 1).

The risk of preeclampsia is known to increase with maternal age,<sup>12</sup> and this relation might contribute to an apparent increase in risk with an increasing interbirth interval. Nonetheless, the increased risk of preeclampsia associated with an increasing interbirth interval remained after we controlled for maternal age (in five-year categories) (odds ratio, 1.13 per year; 95 percent confidence interval, 1.12 to 1.14). An analysis that adjusted for maternal age with the use of one-year age categories gave the same results.

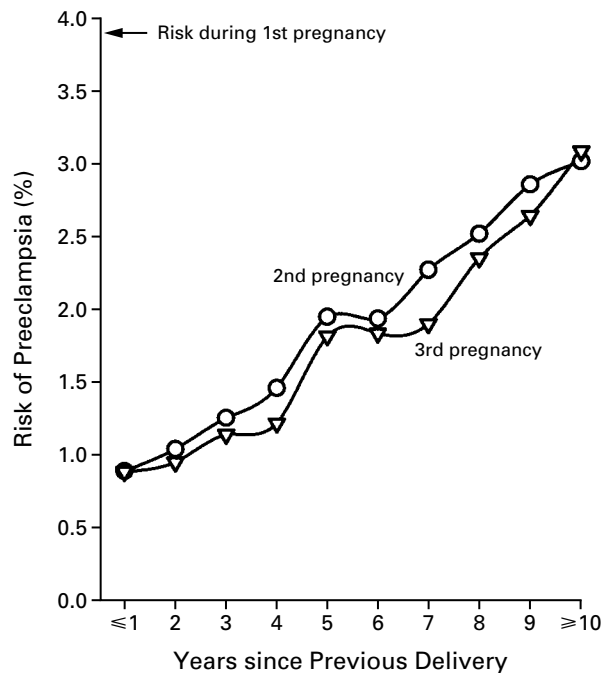
There was a moderate increase in the risk of preeclampsia during the first 15 years of the birth registry (1967 to 1982), and the risk remained stable thereafter. When we adjusted for the year of delivery, the results were essentially unchanged (data not shown).

Finally, we considered the possibility that the increase in the risk of preeclampsia with an increasing

**TABLE 1. RISK OF PREECLAMPSIA DURING FIRST, SECOND, AND THIRD SINGLETON PREGNANCIES.\***

PREGNANCY	ALL WOMEN			WOMEN WITH NO PREVIOUS PREECLAMPSIA		
	NO. OF CASES OF PREECLAMPSIA	NO. OF DELIVERIES	RISK OF PREECLAMPSIA (%)	NO. OF CASES OF PREECLAMPSIA	NO. OF DELIVERIES	RISK OF PREECLAMPSIA (%)
1st	29,507	755,112	3.9	—	—	—
2nd	8,900	509,548	1.7	6237	490,845	1.3
3rd	3,025	167,871	1.8	2134	160,210	1.3

\*First pregnancies also include only pregnancies; second pregnancies are those of women with at least two deliveries, and third pregnancies are those of women with at least three deliveries. Second and third pregnancies were included in this analysis only if the woman's partner was the same.



**Figure 1.** Risk of Preeclampsia during Second and Third Pregnancies, According to the Interval since the Previous Delivery, for Women with No History of Preeclampsia and the Same Partner for All Pregnancies.

interbirth interval could be confounded by an association between preeclampsia and subfertility. If less fertile women are at higher risk for preeclampsia, then the increase in the risk of preeclampsia with an increasing interbirth interval could be attributable to the overrepresentation of less fertile women. However,

we found no association between the risk of preeclampsia in the first pregnancy and the interval between the first and second pregnancies (odds ratio for preeclampsia in the first pregnancy, 1.01 per year; 95 percent confidence interval, 0.99 to 1.01).

#### Effect of a Change of Partner

The association between an increasing interbirth interval and an increasing risk of preeclampsia might be explained by the fact that a change of partner is more common among the women with longer interbirth intervals. In our cohort, about 6 percent of the women changed their partners between their first and second pregnancies. The median time to the second delivery when the partner remained the same was 2.9 years, as compared with 5.9 years with a change of partner (Table 2). Similarly, the median time from the second to the third delivery was 3.6 years when the partner remained the same and 7.5 years with a change of partner. Among women with no history of preeclampsia, the complication occurred during 1.3 percent of second pregnancies for which the partner remained the same and 1.5 percent of those for which there was a change of partner. This excess risk of preeclampsia for women who changed partners as compared with those who remained with the same partner was small but statistically significant (odds ratio, 1.14; 95 percent confidence interval, 1.04 to 1.26) (Table 3). The risk of preeclampsia was similarly increased for the third pregnancy if there was a different partner (odds ratio, 1.42; 95 percent confidence interval, 1.25 to 1.62).

We assessed the association between the interbirth interval and the risk of preeclampsia during the second pregnancy, stratifying the women according to whether or not their partner was the same for both

**TABLE 2.** TIME SINCE THE PREVIOUS PREGNANCY AND THE RISK OF PREECLAMPSIA AMONG WOMEN WITH THE SAME OR A DIFFERENT PARTNER.\*

VARIABLE	MEDIAN TIME BETWEEN PREGNANCIES (YR)	PREECLAMPSIA IN LATER PREGNANCY		
		NO. OF CASES OF PREECLAMPSIA	NO. OF DELIVERIES	RISK OF PREECLAMPSIA (%)
From 1st to 2nd pregnancy				
Same partner	2.9	6237	490,845	1.3
Different partners	5.9	443	30,526	1.5
Unknown	4.3	132	9,913	1.3
Total	3.6	6812	531,284	1.3
From 2nd to 3rd pregnancy				
Same partner	3.6	2134	160,210	1.3
Different partners	7.5	265	14,068	1.9
Unknown	4.0	340	25,636	1.3
Total	3.7	2739	199,914	1.4

\*The analysis is restricted to women with no reported preeclampsia in previous pregnancies. "Unknown" indicates a pair of pregnancies for one or both of which the identity of the partner was unknown.

pregnancies. A strong effect of the interbirth interval was seen regardless of change or lack of change of partner (Fig. 2). The effect of changing the partner was eliminated when the interbirth interval was taken into account. In fact, after the interval had been taken into account, the risk of preeclampsia was lower for pregnancies involving a new partner than for those involving the same partner (Fig. 2).

We also used multivariate analysis to assess simultaneously the effects of the interbirth interval and change or lack of change of partner on the risk of preeclampsia (Table 3). After adjustment for the interbirth interval, a change of partner was no longer associated with an increased risk of preeclampsia but, rather, with a significantly decreased risk of this complication. The results were essentially the same after further adjustment for maternal age and the period when the delivery occurred (Table 3).

These analyses included stillbirths that had occurred as early as 16 weeks after gestation began. Since preeclampsia typically occurs later in pregnancy, we reanalyzed the data for second deliveries excluding stillbirths that had occurred at less than 21 weeks of gestation. The associations of the interbirth interval and a change of partner with the risk of preeclampsia were materially unchanged.

### DISCUSSION

We found that multiparous women who are pregnant 10 years or more after their previous pregnancy are as likely to have preeclampsia as nulliparous women. Preeclampsia has been described as “a disease of

first pregnancy”<sup>3,13,14</sup> and is sometimes defined as occurring only among nulliparous women. Although our data confirm that the risk of preeclampsia falls sharply after the first pregnancy, we also found that the risk subsequently increases over time. This striking increase in risk with an increasing interbirth interval suggests that the benefit of higher parity in terms of the risk of preeclampsia is only transient.

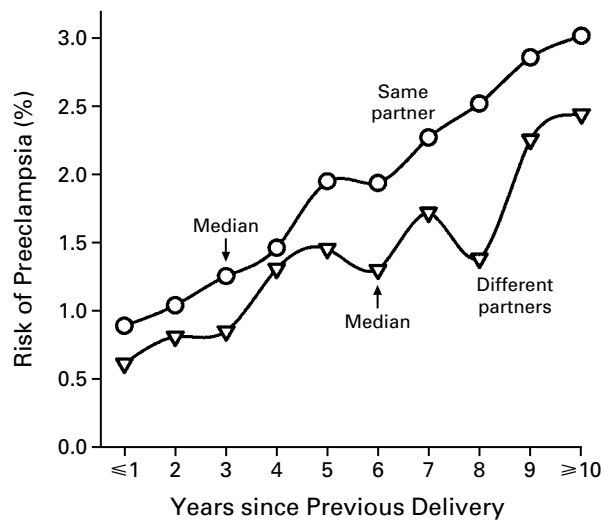
A change of partner has been thought to increase the risk of preeclampsia.<sup>1,7,13,15</sup> This observation is likely to be confounded by the effect of the interbirth interval. The apparent increase in the risk of preeclampsia with a change of partner has been interpreted as support for the hypothesis that a failure of the immune system to adapt to the partner’s antigens causes preeclampsia. This theory was proposed in 1975 in a case report of preeclampsia during the second pregnancy of a woman who changed her partner after having her first child.<sup>16</sup> This has led to extensive speculation about possible immune mechanisms related to a change of partner.<sup>3,8,9,14,16-18</sup> Our data suggest that after appropriate adjustment for the interbirth interval, there is no increased risk associated with a change of partner. The observed association between the interbirth interval and the risk of preeclampsia may be relevant in interpreting the results of other studies of risk factors for preeclampsia. For example, miscarriage has been associated with a reduction in the risk of preeclampsia in a subsequent pregnancy.<sup>4,12,19</sup> This result might be explained by the fact that the average interval between pregnancies is shorter after a miscarriage than after a live birth.<sup>20</sup> Also, artificial insemination with donor

**TABLE 3.** CHANGE OF PARTNER, INTERBIRTH INTERVAL, AND THE RISK OF PREECLAMPSIA.\*

VARIABLE	UNADJUSTED SEPARATE ANALYSES	MODEL INCLUDING BOTH VARIABLES	MULTIVARIATE MODEL†
	odds ratio (95% CI)		
From 1st to 2nd pregnancy			
Same partner	1.00	1.00	1.00
Different partners	1.14 (1.04–1.26)	0.73 (0.66–0.81)	0.75 (0.68–0.83)
Each additional year between pregnancies	1.15 (1.14–1.16)	1.16 (1.15–1.17)	1.12 (1.11–1.13)
From 2nd to 3rd pregnancy			
Same partner	1.00	1.00	1.00
Different partners	1.42 (1.25–1.62)	0.90 (0.78–1.03)	0.93 (0.81–1.07)
Each additional year between pregnancies	1.15 (1.13–1.16)	1.15 (1.14–1.17)	1.12 (1.10–1.14)

\*The analysis is restricted to women with no reported preeclampsia in previous pregnancies. CI denotes confidence interval.

†The analyses were further adjusted for maternal age at the time of the later delivery (five categories for second delivery: <20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, and ≥35 years; and four categories for the third delivery: <25 years, 25 to 29 years, 30 to 34 years, and ≥35 years) and for the period of the later delivery (three categories: 1967–1976, 1977–1986, and 1987–1998).



**Figure 2.** Risk of Preeclampsia during the Second Pregnancy, According to the Interval since the First Delivery, with the Same or a Different Partner, for Women with No History of Preeclampsia.

The median number of years since the previous delivery for each group of women is indicated.

semen and the use of donated oocytes have been reported to increase the risk of preeclampsia.<sup>21,22</sup> Women who receive these treatments have often been trying for a long time to become pregnant.

Although the influence of the time since a previous pregnancy appears to be as strong as that of any of the known risk factors for preeclampsia, the recognition of this association should not be taken as a recommendation of short intervals between pregnancies. Other adverse outcomes of pregnancy — most notably preterm delivery — are more likely with very short intervals.<sup>23</sup> In terms of these other adverse outcomes, the lower limit of the interval at which high risk is attenuated varies, ranging from 6 months between delivery and subsequent conception in developed countries to 18 months in developing countries.<sup>24</sup>

Our study has some limitations. We do not have data on the smoking status of the women, which may confound the association between a change of partner and the risk of preeclampsia. Many pregnant women in Norway smoke,<sup>25,26</sup> and smoking may be more common among women whose marriages end in divorce.<sup>27</sup> If so, smoking may be more frequent among women who later become pregnant with a new partner. Since smoking is associated with a reduction in the risk of preeclampsia,<sup>4,12,28</sup> this set of associations might explain the lower risk of preeclampsia observed among women who change partners.

Another limitation is the lack of data on obesity. Obesity is associated with an increased risk of preeclampsia.<sup>4,12</sup> The risk of obesity increases with a woman's age and parity. However, if increasing weight were contributing to the effect of the interbirth interval, we would have expected a higher risk of preeclampsia during the third pregnancy than during the second pregnancy. No such increase was seen (Fig. 1).

An extended interval between pregnancies appears to be a major risk factor for preeclampsia, with the risk after 10 years similar to that among nulliparous women. Furthermore, after adjustment for the interbirth interval, a change of partner between one pregnancy and the next is not a risk factor for preeclampsia.

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