

# Changing paternity and time since last pregnancy; the impact on pre-eclampsia risk. A study of 547 238 women with and without previous pre-eclampsia

Lill IS Trogstad,<sup>a,b</sup> Anne Eskild,<sup>a,b</sup> Per Magnus,<sup>a</sup> Sven Ove Samuelsen<sup>a,c</sup> and Britt-Ingjerd Nesheim<sup>b</sup>

<b>Background</b>	Long time interval between pregnancies has been found to increase the risk of pre-eclampsia in second pregnancy. Our aim was to investigate whether this effect is influenced by a history of pre-eclampsia or a change in paternity.
<b>Methods</b>	We studied 547 238 women with a first and second pregnancy registered in the Medical Birth Registry of Norway, 1967–1998. The relative risk of pre-eclampsia in the second delivery according to time interval between deliveries was estimated as odds ratios (OR) in logistic regression models, controlling for changing paternity, maternal age and calendar time period in women with and without previous pre-eclampsia.
<b>Results</b>	A change of paternity for the second pregnancy was associated with a reduced risk of pre-eclampsia after controlling for the time since first delivery (adjusted OR = 0.80, 95% CI : 0.72–0.90), but the interaction between change in paternity and time between deliveries was significant only for women with no previous pre-eclampsia. The interaction between history of pre-eclampsia and time interval between the two deliveries was highly significant, and for women with no previous pre-eclampsia the risk of pre-eclampsia in second pregnancy increased with increasing time interval (for intervals longer than 15 years the adjusted OR was 2.11, 95% CI : 1.75–2.53). For women with previous pre-eclampsia the risk tended to decrease with increasing time interval between deliveries.
<b>Conclusions</b>	The protective impact of a new father for the second pregnancy challenges the hypothesis of primipaternity, and implies that the increase in pre-eclampsia risk ascribed to new father by others is due to insufficient control for interpregnancy interval.
<b>Keywords</b>	Epidemiology, infection, pre-eclampsia, pregnancy, risk factors
<b>Accepted</b>	1 August 2001

Pre-eclampsia is currently regarded as a two-stage disorder: The first stage is insufficient implantation of the placenta that may cause reduced perfusion, the second is maternal symptoms such as hypertension and proteinuria, both consequences of endothelial dysfunction.<sup>1</sup> Pre-eclampsia has been found to occur mainly in first pregnancies. A previous normal pregnancy is associated

with a reduced risk of pre-eclampsia, but this protection has been assumed to be lost with change of partner.<sup>2–4</sup> In women with a history of pre-eclampsia, changing paternity has been described to reduce the risk of recurrency.<sup>5</sup> A reduction in the risk of pre-eclampsia and pregnancy-induced hypertension has been found with increasing length of sexual cohabitation before conception. Also, women using non-barrier contraceptives have lower risk compared to those using barrier contraceptives.<sup>6,7</sup>

Recent evidence points to normal pregnancy as an inflammatory process, inducing changes in peripheral leukocyte activation similar to those of sepsis.<sup>8</sup> The maternal syndrome of pre-eclampsia is described as an excessive, maternal inflammatory response to pregnancy, representing the extreme end of a general response to pregnancy rather than an intrinsically different state of

<sup>a</sup> National Institute of Public Health, Department of Population Health Sciences, Section of Epidemiology, Oslo, Norway.

<sup>b</sup> Ullevaal University Hospital, Department of Obstetrics and Gynecology, Oslo, Norway.

<sup>c</sup> University of Oslo, Department of Mathematics, Oslo, Norway.

Correspondence: Dr Lill Trogstad, Department of Population Health Sciences, Section of Epidemiology, National Institute of Public Health, PO Box 4404, Nydalen, 0403 Oslo, Norway. E-mail: lill.trogstad@folkehelsa.no

pregnancy.<sup>9</sup> These findings have been confirmed in animal models,<sup>10,11</sup> and experimental pre-eclampsia has been induced in pregnant rats by infusion of endotoxin from *Escherichia coli*.<sup>10</sup>

If pregnancy is an inflammatory process that causes an immunological response, it could be hypothesized that this response causes some kind of immunity in a new pregnancy. The immunity against infectious agents, for instance as seen after vaccination, seems to be reduced by time, hence increasing the risk of infection.<sup>12</sup> A long interval between pregnancies has been shown to increase the risk of pre-eclampsia.<sup>13</sup> To our knowledge, no studies have investigated whether this effect is related to the occurrence of previous pre-eclampsia or changing paternity. The aim of this study was to estimate the impact of time interval between the first and second delivery on the risk of pre-eclampsia in women with and without previous pre-eclampsia, controlling for change in paternity, maternal age and period to second delivery. The study population included all women with a first and second singleton delivery in Norway during 1967–1998.

## Methods

### Subjects

Since 1967 all deliveries in Norway after 16 weeks of gestation, more than 1.8 million births, have been recorded in the Medical Birth Registry.<sup>14</sup> The registration is based on standardized forms completed by midwives at the delivery ward within one week after delivery. We studied the pregnancies of 547 238 women registered with their first and second deliveries between 1967–1998 (1 094 476). Only women with singleton pregnancies both times were included.

### Variables

Information on the variables was obtained from the Medical Birth Registry.<sup>14</sup>

#### Outcome variable

*Pre-eclampsia in second pregnancy.* The diagnostic criteria for pre-eclampsia in Norway are blood pressure  $\geq 140/90$  after 20 weeks gestation, combined with proteinuria  $\geq 0.3$  g/24 h ( $\geq +1$  dipstick) on at least two occasions.<sup>15</sup> Women registered with the following ICD-8 diagnoses were defined as having pre-eclampsia: 637.4 Hypertension and proteinuria, 637.5 Hypertension, proteinuria and oedema, 637.6 Threatening eclampsia, 637.7 Pre- or intra-partum eclampsia, 637.8 Post-partum eclampsia and 637.9 Pre-eclampsia in a.

#### Independent variables

*Time interval between deliveries.* The interval between the deliveries was calculated exactly by converting the children's date of birth into numeric values before subtracting the date of the first birth from that of the second. Thereafter the time interval was categorized as:  $\leq 1$  year, 1–5 years (reference category), 6–10 years, 11–15 years and  $> 15$  years between first and second delivery.

*Previous pre-eclampsia.* Having had pre-eclampsia in first pregnancy, according to the above definition was coded 'yes' or 'no'.

*Maternal age.* The maternal age at the second delivery was categorized in the following six groups:  $< 20$ , 20–24, 25–29, 30–34, 35–39 and  $\geq 40$  years of age.

*New father.* The personal identification number of the first child's father was compared with the second child's father.

When identical, 'new father' was coded 'no', when different 'new father' was coded 'yes', and if information was missing for the first or second child 'new father' was noted as 'missing'. The father's personal identification number was not available for 12.8% of the pregnancies.

*Year of second delivery.* The variable was categorized into five 5-year periods (1967–1971, 1972–1976 etc) and one 7-year period (1992–1998).

### Statistical analyses

The relative risks of developing pre-eclampsia in the second pregnancy according to the independent variables were estimated as crude and adjusted odds ratios (OR) by applying logistic regression analyses.

## Results

### All women

The prevalence of pre-eclampsia in the first pregnancy was 3.6% ( $n = 19\ 970$ ) and in the second pregnancy 1.7% ( $n = 9535$ ). The prevalences of pre-eclampsia in second pregnancy according to all variables are presented in Table 1.

**Table 1** Number (N) and per cent (%) of pre-eclampsia according to time interval between deliveries, previous pre-eclampsia, maternal age, new father and year of second delivery in the second pregnancies of 547 238 women in Norway, 1967–1998

	Total no. of pregnancies	Pre-eclampsia 2nd pregnancy	
		N	%
<b>Time between deliveries</b>			
$\leq 1$ year	5734	99	1.7
1–5	443 533	6874	1.5
6–10	84 125	2117	2.5
11–15	9158	274	3.0
$> 15$ years	4688	180	3.6
<b>Previous pre-eclampsia</b>			
No	527 268	6721	1.3
Yes	19 970	2814	14.1
<b>Maternal age at 2nd delivery</b>			
$< 20$ years	9436	83	0.9
20–24	156 042	2039	1.3
25–29	235 486	4000	1.7
30–34	116 690	2488	2.1
35–39	26 431	813	3.1
$> 40$ years	3153	112	3.6
<b>New father</b>			
No	451 136	7695	1.7
Yes	26 093	505	1.9
Missing information	70 009	1335	1.9
<b>Year of second delivery</b>			
1967–1971	44 737	428	1.0
1972–1976	93 459	1099	1.2
1977–1981	89 598	1401	1.6
1982–1986	85 189	1795	2.1
1987–1991	95 275	1962	2.1
1992–1998	138 980	2850	2.1

After controlling for previous pre-eclampsia, change in paternity, maternal age and year of second delivery in the total study population, the OR for pre-eclampsia increased with increasing time between the deliveries. For women with intervals longer than 15 years, the adjusted OR for pre-eclampsia was 1.79 (95% CI : 1.50–2.12), compared to women having their second child 1–5 years after the first. Women with time intervals shorter than one year did not fit into this pattern. The adjusted OR of pre-eclampsia in the second pregnancy for this group was 1.44 (95% CI : 1.17–1.77), compared to women with 1–5 years intervals.

There was a close association between changed paternity and a long time interval between pregnancies. Among the women who delivered their second child within one year of the first, 2.0% (112/5734) had a new father for the second child. After 15 years the proportion of women with new father for the second child was 34.7% (1625/4688). The crude OR for pre-eclampsia in second pregnancy of women with a change in paternity was 1.14 (95% CI : 1.04–1.25), compared to women with no change in paternity. However, after controlling for the time interval between the deliveries, a new father for the second pregnancy was associated with a reduced risk of pre-eclampsia (adjusted OR = 0.84, 95% CI : 0.76–0.93).

The risk of pre-eclampsia increased by increasing maternal age for all women; the adjusted OR for pre-eclampsia for women  $\geq 40$  years was 1.66 (95% CI : 1.36–2.03) compared to the reference category (age group 25–29 years). Previous pre-eclampsia had a large impact on pre-eclampsia in second pregnancy with an adjusted OR of 12.41 (95% CI : 11.85–13.01).

In a separate logistic regression model including the total study population, we included two interaction terms. The interaction between previous history of pre-eclampsia and time interval between deliveries was highly significant ( $P < 0.001$ ). The interaction between changing paternity and time interval between deliveries was not significant ( $P = 0.07$ ).

### Women without previous pre-eclampsia

Among the women without pre-eclampsia in the first pregnancy, 1.3% developed pre-eclampsia in the second pregnancy (Table 1), accounting for 70.5% of all cases in the second pregnancy.

The prevalence of pre-eclampsia increased with increasing time between deliveries both in women with and without a change in paternity for the second pregnancy.

With intervals longer than 15 years, the risk of pre-eclampsia in women with same-paternity pregnancies was 4.5%. Women

with new-paternity pregnancies had a lower risk, but still increased by increasing time interval, 3.1% for intervals longer than 15 years (Table 2).

In the multivariate analysis including all women without previous pre-eclampsia, the adjusted OR for pre-eclampsia increased with increasing time between the deliveries (Table 3), and was higher than the estimates for the total study population. In a separate analysis, we included an interaction term between change in paternity and time interval between deliveries into the logistic regression model including women without previous pre-eclampsia. The interaction was significant ( $P = 0.04$ ).

In stratified analyses including women without previous pre-eclampsia, with and without a change in paternity, the adjusted OR for pre-eclampsia according to time interval between deliveries was 2.35 (95% CI : 1.47–3.77) after  $>15$  years time interval for women with a change in paternity, and 2.69 (95% CI : 1.89–3.83) for women without a change in paternity, after controlling for maternal age and year of second delivery (Table 4).

### Women with previous pre-eclampsia

The risk of recurrent pre-eclampsia was 14.1% (Table 1). There was no significant difference in the risk of pre-eclampsia according to time interval between deliveries in women with same- or new-paternity pregnancies (Table 2).

In the multivariate analysis including all women with previous pre-eclampsia, the adjusted OR for pre-eclampsia according to time interval between deliveries tended to decrease with increasing interval, however not significantly (Table 3). In a separate analysis, we included an interaction term between change in paternity and time interval between deliveries into the logistic regression model including women with previous pre-eclampsia. There was no significant interaction between change in paternity and time interval between deliveries ( $P = 0.36$ ) in this sub-group of women.

In stratified analyses including women with previous pre-eclampsia, with and without a change in paternity, the adjusted OR for pre-eclampsia according to time interval between deliveries was 0.52 (95% CI : 0.19–1.41) after  $>15$  years time interval for women with a change in paternity, and 0.73 (95% CI : 0.28–1.91) for women without a change in paternity after controlling for maternal age and year of second delivery (Table 4).

## Discussion

There were two main results of our study. Firstly, in contrast to other reports,<sup>2,3,5</sup> a change of paternity for the second

**Table 2** Number (N) and prevalence (%) of pre-eclampsia in second pregnancy of women with or without a change in paternity or previous pre-eclampsia, according to time interval between deliveries

	No previous pre-eclampsia		Previous pre-eclampsia	
	Same father % (N)	New father % (N)	Same father % (N)	New father % (N)
<b>Time between deliveries</b>				
$\leq 1$ year	1.1 (53/4648)	0 <sup>a</sup> (108)	13.7 (23/168)	0 <sup>a</sup> (4)
1–5	1.1 (4102/377 046)	0.8 (72/8 873)	13.9 (1987/14 276)	12.4 (42/340)
6–10	2.1 (1062/49 518)	1.6 (192/11 875)	16.3 (341/2087)	16.6 (72/435)
11–15	3.1 (78/2502)	2.2 (61/2752)	9.9 (10/101)	13.6 (11/81)
$>15$ years	4.5 (34/755)	3.1 (48/1572)	14.3 (5/35)	13.2 (7/53)

<sup>a</sup> No women in the first interval category with a change of paternity for the second pregnancy developed pre-eclampsia.

**Table 3** Stratified analyses. Crude (cOR) and adjusted odds ratios (aOR)<sup>a</sup> and 95% CI for pre-eclampsia in the second pregnancy in 527 268 women without pre-eclampsia and in 19 970 women with pre-eclampsia in their first pregnancy in Norway, 1967–1998

	No previous pre-eclampsia		Previous pre-eclampsia	
	cOR (95% CI)	aOR (95% CI)	cOR (95% CI)	aOR (95% CI)
<b>Time between deliveries</b>				
≤1 year	1.66 (0.92–1.48)	1.52 (1.20–1.93)	1.04 (0.70–1.54)	1.24 (0.83–1.85)
1–5	1.0	1.0	1.0	1.0
6–10	1.86 (1.75–1.97)	1.64 (1.54–1.75)	1.17 (1.05–1.29)	1.04 (0.93–1.16)
11–15	2.40 (2.10–2.75)	1.88 (1.62–2.17)	1.10 (0.80–1.51)	0.85 (0.61–1.19)
>15 years	3.10 (2.63–3.66)	2.11 (1.75–2.53)	1.11 (0.69–1.76)	0.78 (0.48–1.27)
<b>Maternal age at 2nd delivery</b>				
<20 years	0.49 (0.37–0.63)	0.59 (0.45–0.78)	0.65 (0.44–0.96)	0.77 (0.51–1.14)
20–24	0.76 (0.72–0.81)	0.87 (0.81–0.92)	0.80 (0.72–0.88)	0.85 (0.77–0.95)
25–29	1.0	1.0	1.0	1.0
30–34	1.28 (1.20–1.36)	1.15 (1.08–1.22)	1.20 (1.09–1.33)	1.17 (1.06–1.30)
35–39	1.91 (1.74–2.09)	1.56 (1.42–1.72)	1.44 (1.23–1.69)	1.42 (1.21–1.67)
>40 years	2.29 (1.83–2.85)	1.81 (1.44–2.27)	1.28 (0.86–1.92)	1.33 (0.88–2.00)
<b>New father</b>				
No	1.0	1.0	1.0	1.0
Yes	1.21 (1.09–1.35)	0.80 (0.72–0.90)	1.02 (0.85–1.24)	0.97 (0.79–1.18)
Missing information	1.23 (1.15–1.32)	1.02 (0.95–1.10)	0.92 (0.81–1.05)	0.94 (0.82–1.07)
<b>Year of second delivery</b>				
1967–1971	0.49 (0.43–0.55)	0.64 (0.56–0.72)	0.56 (0.46–0.68)	0.62 (0.51–0.76)
1972–1976	0.64 (0.59–0.69)	0.76 (0.70–0.83)	0.61 (0.53–0.71)	0.66 (0.57–0.76)
1977–1981	0.87 (0.81–0.94)	0.95 (0.88–1.02)	0.75 (0.65–0.85)	0.79 (0.69–0.91)
1982–1986	1.13 (1.05–1.21)	1.17 (1.09–1.26)	1.08 (0.96–1.21)	1.13 (1.00–1.28)
1987–1991	1.01 (0.94–1.08)	1.03 (0.95–1.10)	1.02 (0.91–1.13)	1.05 (0.94–1.17)
1992–1998	1.0	1.0	1.0	1.0

<sup>a</sup> Adjusted for all other variables in the Table.

**Table 4** Stratified analyses. Adjusted odds ratio (aOR)<sup>a</sup> and 95% CI for pre-eclampsia in second pregnancy of women with or without a change in paternity or previous pre-eclampsia, according to time interval between deliveries

	No previous pre-eclampsia		Previous pre-eclampsia	
	Same father aOR (95% CI)	New father aOR (95% CI)	Same father aOR (95% CI)	New father aOR (95% CI)
<b>Time between deliveries</b>				
≤1 year	1.36 (1.03–1.79)	–	1.18 (0.76–1.85)	–
1–5	1.0	1.0	1.0	1.0
6–10	1.72 (1.60–1.85)	1.55 (1.14–2.11)	1.06 (0.93–1.21)	1.02 (0.65–1.62)
11–15	2.08 (1.65–2.62)	1.90 (1.26–2.86)	0.52 (0.27–1.01)	0.63 (0.29–1.40)
>15 years	2.69 (1.89–3.83)	2.35 (1.47–3.77)	0.73 (0.28–1.91)	0.52 (0.19–1.41)

<sup>a</sup> Adjusted for maternal age and year of second delivery. No women in the first interval category with a change of paternity for the second pregnancy developed pre-eclampsia.

pregnancy was associated with a reduced risk of pre-eclampsia after controlling for the time since first delivery, but the interaction between change in paternity and time between deliveries was significant only for women with no previous pre-eclampsia ( $P = 0.04$ ).

Secondly, the interaction between history of pre-eclampsia and time interval between the two deliveries was highly significant ( $P < 0.001$ ). For women with no previous pre-eclampsia the risk of pre-eclampsia in second pregnancy increased with increasing time interval, whereas for women with previous

pre-eclampsia the risk tended to decrease with increasing time interval between deliveries.

Women with intervals ≤1 year were at increased risk of pre-eclampsia as compared to women with 1–5 years intervals. This group of women was characterized by a high prevalence of unfavourable pregnancy outcome in their first pregnancy (prevalence of perinatal deaths 17.5% versus 0.6–1.4% for the other time intervals).

The increase in risk of pre-eclampsia in second pregnancy seemed to occur approximately 5 years after the first delivery.

After 15 years, the prevalence of pre-eclampsia in women with a normal first pregnancy and no change in paternity was higher than that of primiparous women, whereas in women with a change in paternity the prevalence was lower.

Previous pre-eclampsia was a major risk factor for pre-eclampsia in second pregnancy, but women with recurrent pre-eclampsia accounted for only 29.5% of all cases in second pregnancies, thus women with no history of pre-eclampsia represent the majority of cases.

### Previous studies

To our knowledge, the impact of the time interval between pregnancies on pre-eclampsia risk has been reported only twice.<sup>5,15</sup> One of the studies found no impact of interval between deliveries, but reported for women with a change in paternity a 30% increase in pre-eclampsia risk in women with no previous pre-eclampsia (95% CI: 1.1–1.6), and a 30% reduced risk of pre-eclampsia (non-significant), in women with previous pre-eclampsia and new paternity.<sup>5</sup> The observation time in that study, however, was probably too short to detect any impact of a long time interval between deliveries, with a maximum time interval of 3 years (1989–1991). Also, the results in that study may have been biased by a selection of women with short interpregnancy interval and new father.<sup>5</sup> The other study, from the Medical Birth Registry in Norway (1967–1992), as our study, found the risk of pre-eclampsia to increase by increasing interval between pregnancies, but gave no information as to changes in risk in women with or without previous pre-eclampsia, or a change in paternity.<sup>13</sup>

Several previous studies have suggested that a change in paternity for the second pregnancy increases the risk of pre-eclampsia, and primipaternity rather than primiparity has been suggested to be a major risk factor.<sup>2,3,16</sup> In our study, women with a change in paternity for the two pregnancies seemed to have a reduced risk of pre-eclampsia in the second pregnancy after controlling for the time interval between deliveries. Our findings suggest that previous results on the impact of changing paternity on pre-eclampsia risk have been confounded by insufficient control for the time interval between the pregnancies.

### Potential sources of error

No validation of the pre-eclampsia diagnosis in the Medical Birth Registry has been performed. In Norway the diagnostic criteria for pre-eclampsia described in methods have been widely used throughout the study period.<sup>17</sup> The reported prevalences of pre-eclampsia in first pregnancy in different geographical regions in Norway (the Eastern, Southern, Western, Middle and Northern part of Norway) vary from 3.0% to 4.5%.

Inclusion of geographical region as a covariate in the multivariate analyses did not change the risk estimates according to the time interval between deliveries or a change of paternity, and was therefore not included in the final model. The prevalence and recurrence rates of pre-eclampsia in our study were comparable to those reported in other Nordic countries.<sup>18</sup>

In women with severe pre-eclampsia the delivery is more likely to be induced prematurely than in women without pre-eclampsia. Thus, the use of delivery and pre-eclampsia before 37 weeks gestation as diagnostic criteria for pre-eclampsia is likely to decrease the likelihood of misclassification of pre-eclampsia. In such sub-analysis the estimated impact of the time

interval on pre-eclampsia risk was strengthened as compared to the estimates based on all women with a diagnosis of pre-eclampsia in first pregnancy (data not shown).

Changes in body mass index and smoking habits have occurred in all age groups of women in Norway over the 30-year period studied, but are unlikely to have confounded our results.<sup>19,20</sup> The Medical Birth Registry of Norway holds no information on maternal weight/body mass index, smoking or social class, thus we have not been able to control for these potential confounders specifically. We have, however, adjusted for the year (5-year periods) of the second delivery, thus confounding by risk factors which may have changed in prevalence over this period should be at least partially accounted for.

### Possible interpretation

Our study of 547 238 women has shown a significant impact of the time interval between pregnancies on the risk of pre-eclampsia in the second pregnancy, however only in women with no history of pre-eclampsia. How can this be explained? The time interval between pregnancies could express the impact of increasing maternal age, a well known risk factor of pre-eclampsia.<sup>21</sup> We have, however, controlled for the mother's age at the second delivery in the presented results, hence, the impact of maternal age on the risk of pre-eclampsia should be accounted for. Also, the increased risk of pre-eclampsia by increasing maternal age was present in all women regardless of pre-eclampsia in the first pregnancy, whereas a long interval between deliveries only seemed to increase the risk of pre-eclampsia in women with no previous pre-eclampsia.

We speculate that the increased risk of pre-eclampsia imposed by long pregnancy interval may be due to environmental influences such as infections. A long interval between deliveries will increase the mother's risk of acquiring infections which may reactivate during pregnancy, since the cumulative risk of acquiring an infection which is prevalent in the population will increase over time.<sup>22</sup> The metabolic alterations in acute rejection in patients receiving organ transplants and in atherosclerosis share many common features with pre-eclampsia, suggesting a possible common pathophysiological pathway.<sup>1,23,24</sup> Infectious agents have been suggested to play a causal role in both acute rejection and atherosclerosis,<sup>23,24</sup> and urinary tract infections in pregnant women have been associated with pre-eclampsia.<sup>25</sup> These observations suggest there may be a possible link between infection and pre-eclampsia. Thus it may be speculated that some women, due to constitutional and immunological factors, may develop pre-eclampsia in pregnancy as a result of a coinciding infectious stimulus adding to the inflammatory burden of a normal pregnancy.<sup>8</sup> The loss of this 'immunity' demonstrated by the increase in pre-eclampsia risk according to increasing time interval between the deliveries, could be explained through such an hypothesis.

### Conclusion

The impact of time interval between deliveries demonstrated in our study may contribute to a new approach in the understanding of the causes of pre-eclampsia. The protective impact of a new father for the pre-eclampsia risk in second pregnancy challenges the hypothesis of primipaternity, and implies that the increase in pre-eclampsia risk ascribed to new father

by others is due to insufficient control for interpregnancy interval. We hypothesize that infectious agents may add to the inflammatory burden of a pregnancy, and trigger pre-eclampsia in susceptible women. Further studies are needed firstly to confirm the unexpected protective impact of changing paternity on pre-eclampsia risk in our study, and secondly to confirm the impact of interval between pregnancies on pre-eclampsia

risk and explore the possible environmental causes of such impact.

## Acknowledgments

The efforts of the staff at the Medical Birth Registry of Norway are gratefully acknowledged.

### KEY MESSAGES

- For women without pre-eclampsia in the first pregnancy the risk of pre-eclampsia in the second pregnancy increased with increasing time interval between deliveries, whereas for women with pre-eclampsia in the first pregnancy the risk tended to decrease with increasing time interval between deliveries.
- In contrast to previous reports, a change of paternity for the second pregnancy was associated with a reduced risk of pre-eclampsia in the second pregnancy after controlling for the time since first delivery, however only for women without pre-eclampsia in the first pregnancy.
- The protective impact of a new father for the second pregnancy challenges the hypothesis of primipaternity, and implies that the previous claims of an increase in pre-eclampsia risk associated with a new father are due to insufficient control for interpregnancy interval.

## References

- Roberts JM. Pre-eclampsia: What we know and what we do not know. *Semin Perinatol* 2000;**24**:24–28.
- Robillard P-Y, Dekker GA, Hulsey T. Revisiting the epidemiological standard of pre-eclampsia: primigravidity or primipaternity? *Eur J Obstet Gynecol Reprod Biol* 1999;**84**:37–41.
- Trupin LS, Simon LP, Eskenazi B. Change in paternity: A risk factor for pre-eclampsia in multiparas. *Epidemiology* 1996;**7**:240–44.
- Dekker GA, Robillard P-Y, Hulsey TC. Immune maladaptation in the etiology of pre-eclampsia: A review of corroborative epidemiologic studies. *Obstet Gynecol Surv* 1998;**53**:377–82.
- Li DK, Wi S. Changing paternity and the risk of pre-eclampsia/eclampsia in the subsequent pregnancy. *Am J Epidemiol* 2000;**151**:57–62.
- Robillard P-Y, Hulsey TC, Perianin J, Janky E, Miri EH, Papiernik E. Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception. *Lancet* 1994;**344**:973–75.
- Klonoff-Cohen HS, Savitz DA, Cefalo RC, McCann MF. An epidemiologic study of contraception and pre-eclampsia. *JAMA* 1989;**262**:3143–47.
- Sacks GP, Studena K, Sargent IL, Redman CWG. Normal pregnancy and pre-eclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol* 1998;**179**:80–86.
- Redman CWG, Sacks GP, Sargent IL. Pre-eclampsia: An excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol* 1999;**180**:499–506.
- Faas MM, Schuiling GA, Baller JFW, Visscher CA, Bakker WW. A new animal model for human pre-eclampsia: Ultra-low-dose endotoxin infusion in pregnant rats. *Am J Obstet Gynecol* 1994;**171**:158–64.
- Faas MM, Schuiling GA, Linton EA, Sargent IL, Redman CWG. Activation of peripheral leukocytes in rat pregnancy and experimental preeclampsia. *Am J Obstet Gynecol* 2000;**182**:351–57.
- Trier H, Ronne T. Duration of immunity and occurrence of secondary vaccine failure following vaccination against measles, mumps and rubella. *Ugeskrift Laeger* 1992;**154**:2008–13. (In Danish).
- Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *Br Med J* 1998;**316**:1343–47.
- Irgens LM, Bergsjø P, Lie RT. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;**79**:435–39.
- The Norwegian Society of Gynecology and Obstetrics. *Clinical Guidelines in Obstetrics*. Oslo, Norway 1998;**2**:94–95.
- Tubbergen P, Lachmeijer AMA, Althuisius SM, Vlak MEJ, van Geijn HP, Dekker GA. Change in paternity: a risk factor for pre-eclampsia in multiparous women? *J Reprod Immunol* 1999;**45**:81–88.
- Bjoro K, Molne K. Propedeutisk obstetikk. *Universitetsforlaget* 1977; 115–30. (In Norwegian).
- Makkonen N, Heinonen S, Kirkinen P. Obstetric prognosis in second pregnancy after pre-eclampsia in first pregnancy. *Hypertens Pregnancy* 2000;**19**:173–81.
- Midthjell K, Krüger Ø, Holmen J *et al*. Rapid changes in the prevalence of obesity and known diabetes in an adult Norwegian population. The Nord-Trøndelag Health Surveys: 1984–1986 and 1995–1997. *Diabetes Care* 1999;**22**:1813–20.
- Rønneberg A, Lund KE, Hafstad A. Lifetime smoking habits among Norwegian men and women born between 1890 and 1974. *Int J Epidemiol* 1994;**23**:267–76.
- Sibai BM, Ewell M, Levine RJ *et al*. Risk factors associated with pre-eclampsia in healthy nulliparous women. *Am J Obstet Gynecol* 1997;**177**:1003–10.
- Forsgren M, Skoog E, Jeansson S, Olofsson S, Giesecke J. Prevalence of antibodies to herpes simplex virus in pregnant women in Stockholm in 1969, 1983 and 1989: implications for STD epidemiology. *Int J STD AIDS* 1994;**5**:113–16.
- Sabaté M, Manito N, Cequier A *et al*. Acute rejection, cytomegalovirus infection and endothelial dysfunction early after heart transplantation. *Transplant Proc* 1995;**27**:2346–48.
- Noll G. Pathogenesis of atherosclerosis: a possible relation to infection. *Atherosclerosis* 1998;**140**(Suppl. 1):S3–S9.
- Schieve LA, Handler A, Hershow R, Persky V, Davis F. Urinary tract infection during pregnancy: its association with maternal morbidity and perinatal outcome. *Am J Public Health* 1994;**84**:405–10.