



Maternal allergy as an isolated risk factor for early-onset preeclampsia: An epidemiological study

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ABSTRACT

Immunological mechanisms underlying the development of preeclampsia are well known, but no association to allergy has yet been demonstrated. The aim of this study was to assess the correlation between maternal pre-gestational allergy, and early-onset and late-onset preeclampsia, respectively. It was a retrospective cohort study including all women giving birth in the Norwegian cities of Stavanger (1996–2014) and Bergen (2009–2014). Pre-gestational asthma, allergy, other known risk factors for preeclampsia, maternal age and parity were obtained from the electronic medical record system. The main outcome variables were early-onset and late-onset preeclampsia (before and after 34 completed weeks of gestation, respectively). We used multinomial logistic regression to estimate odds ratios (OR) with 95% confidence intervals (95% CI) for early and late-onset preeclampsia in women with pre-gestational allergy when compared to women without allergy, adjusting for covariates. Predicted probabilities for the outcomes were also calculated. Of the 110 064 included pregnancies, 2 799 developed late-onset preeclampsia (2.5%) and 348 developed early-onset preeclampsia (0.3%). Pre-gestational allergy increased the risk of early-onset preeclampsia (OR 1.7, 95% CI 1.3–2.4), and reduced the risk of late-onset preeclampsia (OR 0.8, 95% CI 0.7–0.9). These findings add valuable information on preeclampsia as an immunological complication of pregnancy and corroborate the understanding of early- and late-onset preeclampsia as two different entities.

1. Introduction

Dysregulation of the immune system is thought to play a key role in the pathogenesis of preeclampsia. Pre-gestational exposure to paternal antigens reduce the risk for preeclampsia (Robillard et al., 1994), and pregnancies resulting from oocyte donation have a three-fold risk for preeclampsia (Blazquez et al., 2016), pointing to an immunological basis for the disease. The interaction between trophoblasts and maternal natural killer cells is thought to play a key role in the physiological regulation of the immune system during pregnancy, and the number and type of natural killer cells in the decidua is indeed altered in pregnancies complicated by preeclampsia (Rieger et al., 2009). There is also an increased number of dendritic cells in the decidua in pregnancies complicated by preeclampsia (Huang et al., 2008). Most autoimmune diseases lead to an increased risk of preeclampsia. This association is strongest for diseases with a vascular component, such as lupus erythematosus (Chakravarty et al., 2006), and less pronounced in diseases with no vascular affection, such as diabetes (Lisonkova and Joseph, 2013). However, for most of these conditions we do not know if

they affect the risk for early- and late-onset preeclampsia equally (debuting before and after 34 weeks of gestation, respectively), as few studies have stratified on early- and late-onset preeclampsia (Lisonkova and Joseph, 2013; Catov et al., 2007). To our knowledge, it is not previously shown that preeclampsia is associated with maternal allergy, although one study found increased levels of IgE in preeclamptic women (Alanen, 1984). Risk factors that only increase the risk of early-onset preeclampsia will be missed in studies not separating early-onset and late-onset preeclampsia, as the latter is a much more common condition.

Preeclampsia is a pregnancy specific disease, and occurs in 3–4 % of all Norwegian pregnancies (Vatten and Skjaerven, 2004; Klungsoyr et al., 2012). It is the leading cause of pregnancy-related morbidity and mortality worldwide (Raymond and Peterson, 2011). There are indications that early and late-onset preeclampsia are two separate conditions with different pathogenesis and clinical manifestation (Raymond and Peterson, 2011; Lisonkova and Joseph, 2013; Kucukgoz Gulec et al., 2013; Stubert et al., 2014; Salimi et al., 2014; Sezer et al., 2013, 2012; Tamas et al., 2013; van der Merwe et al., 2010; Watanabe

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et al., 2012; Villa et al., 2013). The diagnostic criteria of preeclampsia were defined by the Norwegian Society of Obstetrics and Gynecology and correspond with the NICE guidelines ((NICE), 2013a, b); proteinuria $\geq +1$ on a dipstick, > 0.3 g urine protein loss per 24 h or a protein/creatinine ratio > 0.3 and repeated measurements of systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 after 20 weeks gestational age (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). Early and late-onset preeclampsia was defined as fulfilling the criteria for preeclampsia before and after 34 completed weeks of gestation, respectively. Although late-onset preeclampsia is more common (2.8%), early-onset preeclampsia (0.4%) leads to more morbidity, in particular iatrogenic preterm deliveries (Morken et al., 2008).

We have performed a population-based study to determine if maternal allergy, an immunologically mediated condition, is an isolated risk factor for early-onset preeclampsia.

2. Materials and methods

A historic cohort with prospectively collected data from all women giving birth in the Norwegian cities of Bergen and Stavanger was designed. The annual number of deliveries were between 4000 and 5000 in both cities. We used data from the electronic medical record system (NATUS™, CSAM Health). All women giving birth in Stavanger 1996–2014 and Bergen 2009–2014 were included. Deliveries with missing information on maternal age and/or parity were excluded.

All pregnant women in Norway are offered a free-of-charge antenatal follow-up in pregnancy by a midwife and/or a general practitioner, usually starting in the first trimester. At the first consultation, information on previous pregnancies and miscarriages, chronic diseases, current or previous smoking, use of medications, drug and alcohol use, maternal age and parity are recorded at the personal health record form, a specific form used in the follow-up of all pregnancies in Norway. This information is used to differentiate pregnancies to high-risk or low-risk delivery units, either at a third trimester consultation or when the woman presents in labor. Information from the personal health record form is then registered in the electronic medical record system. In the transferal, data on medication is then limited to that which is directly related to pregnancy follow-up; intake of potentially harmful drugs in the first trimester (necessitating a first trimester scan), antithrombotic treatment, and drugs used to induce labor.

Pregnancy complications, such as preeclampsia and gestational diabetes, are also recorded. Further information is added in the electronic medical record system during delivery. After delivery, the outcome is registered by the attending midwife and all data are sent electronically to the compulsory Medical Birth Registry of Norway.

We used information on pre-gestational allergy, asthma, epilepsy, hypertension, coronary disease, recurrent urinary tract infections, kidney disease, rheumatoid arthritis, type I and type II diabetes, as recorded in the personal health record at the first consultation, and at the third trimester differentiation.

The diagnostic criteria of preeclampsia were defined by the Norwegian Society of Obstetrics and Gynecology and correspond with the NICE guidelines ((NICE), 2013a, b); proteinuria $\geq +1$ on a dipstick, > 0.3 g urine protein loss per 24 h or a protein/creatinine ratio > 0.3 and repeated measurements of systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 after 20 weeks gestational age (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). Early and late-onset preeclampsia was defined as fulfilling the criteria for preeclampsia before and after 34 completed weeks of gestation, respectively. In addition, HELLP (Hemolysis, Elevated liver enzymes, Low Platelets) syndrome, eclampsia (convulsions occurring in pregnancy, peri-partum or within one week post-partum, together with preeclampsia) and gestational hypertension, were recorded in the database.

2.1. Statistical methods

Univariate assessments of potential predictors of “early-onset preeclampsia”, “late-onset preeclampsia” and “early-onset vs late-onset preeclampsia” were done by 2×2 tables and chi-square tests. Multinomial logistic regression was used to relate all parameters with an effect on preeclampsia to early- and late-onset preeclampsia, respectively, adding each of the remaining parameters, one at a time, to see if any of these altered the *p*-value or effect size. We used multinomial logistic regression analysis to relate the predictors to the outcome variables no preeclampsia, late-onset preeclampsia, and early-onset preeclampsia. In the final model, all factors significantly altering effect size and/or statistical significance, as well as age, parity and any known confounders were added. We used this model to calculate odds ratios (OR) with 95% confidence intervals (CI) and *p*-values. The “rule of three” was used to calculate 95% CI in the cases where a predictor resulted in no occurrences of the outcome (Eypasch et al., 1995). We also calculated predicted probabilities for the most relevant predictors.

Statistical significance was set at the 5% level (*p* = 0.05). We also evaluated all effects at 1% level (*p* = 0.01), due to multiple hypothesis testing. We used SPSS (IBM SPSS Statistics for Windows, Version 23.0.2 Armork, NY), for most of the statistical analysis. We used Stata 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.) to calculate predicted probabilities for no preeclampsia, late-onset preeclampsia and early-onset preeclampsia for women with and without pre-gestational allergy, in a model adjusted for asthma, maternal age and parity.

The ethics review board of the Western Norwegian regional health authorities approved the project (2015/66/REK vest).

3. Results

A total of 110 527 pregnancies were registered at the two departments during the respective study periods (Fig. 1). Of these, 463 were excluded due to missing data. Of the 110 064 pregnancies included in the study (30 607 from Bergen, 79 457 from Stavanger), 2 799 developed late-onset preeclampsia (2.5%), and 348 developed early-onset preeclampsia (0.3%) (Table 1).

In the initial univariate analyses, we found significant effects at 1% significance level for allergy, hypertension and type 1 diabetes when comparing early-onset to no preeclampsia. We also found significant effects at 1% significance level for allergy, hypertension, type 1 diabetes and type 2 diabetes when comparing late-onset to no preeclampsia. We found significant differences in the risk of early-onset compared to late-onset preeclampsia for women with pre-gestational allergy and hypertension. There was no effect of pre-gestational asthma, epilepsy, coronary disease, recurrent urinary tract infection, kidney disease, and rheumatoid arthritis on neither early nor late preeclampsia when compared to no preeclampsia, nor between early and late preeclampsia. When adding the remaining parameters one at a time, none of these were found to alter *p*-values or effect size significantly, with the exception of asthma, which reduced the effect size and increased the *p*-value moderately for the association between allergy and early-onset preeclampsia.

In the final model including parity and maternal age we found that pre-gestational allergy significantly increased the risk of early-onset preeclampsia (OR: 1.8, 95%CI: 1.3–2.4) and significantly reduced the risk of late-onset preeclampsia (OR: 0.8, 95% CI: 0.7–0.9). There was a significantly different effect of pre-gestational allergy on early and late preeclampsia (*p*-value < 0.001) (Table 2).

Hypertension increased the risk of both early-onset preeclampsia (OR: 1.7, 95%CI: 0.9–2.9) and late-onset preeclampsia (OR: 5.0, 95%CI: 3.4–7.4) (see Table 3). Type 1 diabetes also increased the risk of both late-onset preeclampsia and early-onset preeclampsia, more so for early preeclampsia, but the difference was not statistically significant (Table 3). Type 2 diabetes increased the risk of late-onset preeclampsia.

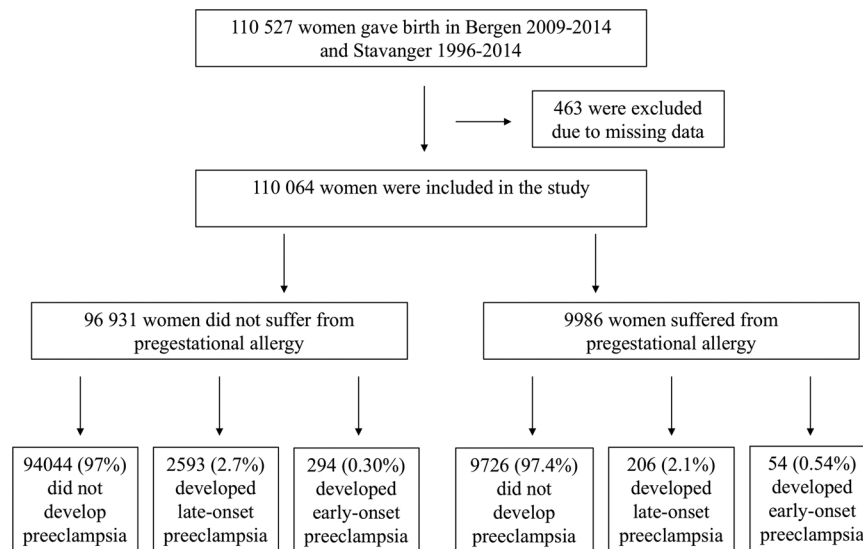


Fig. 1. Flowchart of included and excluded pregnancies. Included pregnancies are shown by predictor variable (pregestational allergy) and outcome variables (early-onset, late-onset, and no preeclampsia).

There were no patients in the group with pre-gestational type 2 diabetes who developed early-onset preeclampsia, the “rule of three” yielding a 95% CI of 0–2.21% for the incidence of early-onset preeclampsia among these patients. This corresponds to an increased risk ranging from 0 to 6.91 times the background risk. This overlaps the CI’s for the increased risk of late-onset preeclampsia in patients with pre-gestational type 2 diabetes, and so from our data we cannot conclude that there is a difference in the risk of early-onset and late-onset preeclampsia among patients with pre-gestational type 2 diabetes.

Predicted probability for early-onset preeclampsia in women with pre-gestational allergy was 0.0085, compared to 0.0048 for women without pre-gestational allergy, in the model adjusted for asthma, maternal age and parity. In the same model, predicted probability for late-onset preeclampsia in women with pre-gestational allergy was 0.032, compared to 0.040 for women without pre-gestational allergy.

Table 2

Odds ratios (ORs) with 95% confidence interval (CI) for early-onset (before 34 weeks of pregnancy) and late-onset preeclampsia (PE) by pregestational allergy, asthma, maternal age and parity in 110 064 pregnancies (348 early-onset PE, 2799 late-onset PE, and 106 917 with no PE) obtained by multinomial logistic regression. We looked at the risk for early-onset PE compared to women without PE, the risk for late-onset PE compared to women without PE, and *p*-values for the difference between early- and late-onset effects.

	Early-onset vs no PE		Late-onset vs no PE		Early- vs late-onset PE <i>p</i> -value
	OR	95% CI	OR	95% CI	
Allergy	1.8	1.3–2.4 ^a	0.8	0.7–0.9 ^a	< 0.001
Asthma	1.1	0.6–2.0	0.9	0.7–1.2	0.510
Age/10 yrs	1.5	1.2–1.9 ^a	1.1	1.0–1.2	0.004
Primipara	3.0	2.4–3.8 ^a	2.6	2.4–2.9	0.317

^a Indicate significance also at the 1% level.

Table 1

Population characteristics and pregestational morbidity by early-onset, late-onset and no preeclampsia in 110 064 pregnancies, Stavanger (1996–2014) and Bergen (2009–2014). Chi-square test *p*-value for the proportional difference between early-onset, late-onset and no preeclampsia for each factor listed.

	No preeclampsia		Late preeclampsia		Early preeclampsia		Chi-square test <i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Total	106917	100	2799	100	348	100	N/A
Maternal age							
< 20 years	2561	2.4	84	3.0	11	3.2	0.916
20–35 years	85430	80	2262	81	270	78	0.916
> 35 years	18926	18	453	16	67	19	0.085
Parity							
Nulliparous	44270	41	1801	64	225	65	> 0.001
Multiparous	62647	59	998	36	123	35	> 0.001
Predisposing factors							
Epilepsy	456	0.43	11	0.39	1	0.29	0.864
Asthma	2712	2.5	58	2.1	13	3.7	0.108
Allergy	9726	9.1	206	7.4	54	16	> 0.001
Recurring UTI	1251	1.2	28	1.0	6	1.7	0.445
Kidney disease	149	0.14	8	0.29	2	0.57	0.014
Hypertension	221	0.21	31	1.1	15	4.3	> 0.001
Rheumatoid arthritis	183	0.17	5	0.18	0	0	0.739
Cardiac disease	440	0.41	9	0.32	3	0.86	0.320
Type 1 diabetes	357	0.33	32	1.1	10	2.9	> 0.001
Type 2 diabetes	120	0.11	16	0.57	0	0	> 0.001

Table 3

Odds ratios (ORs) with 95% confidence interval (CI) for early-onset (before 34 weeks of pregnancy) and late-onset preeclampsia (PE) by pregestational hypertension, type 1, and type 2 diabetes, maternal age and parity in 110 064 pregnancies (348 early-onset PE, 2799 late-onset PE, and 106 917 with no PE) obtained by multinomial logistic regression. We looked at the risk of early-onset PE compared to women without PE, the risk of late-onset PE compared to women without PE, and *p*-values for the difference between early- and late-onset preeclampsia effects. No women with early-onset preeclampsia had pregestational type 2 diabetes.

	Early-onset vs no PE		Late-onset vs no PE		Early- vs late-onset PE <i>p</i> -value
	OR	95% CI	OR	95% CI	
Hypertension	17	9.5–29 ^a	5.0	3.4–7.4 ^a	0.001
Type I diabetes	5.8	2.9–12 ^a	3.0	2.1–4.4 ^a	0.079
Type II diabetes	n/a	n/a	4.6	2.7–7.9 ^a	n/a
Age/10 yrs	1.4	1.1–1.8 ^a	1.1	1.0–1.1	0.013
Primipara	0.6	0.5–0.6 ^a	0.6	0.6–0.6 ^a	0.317

^a Indicate significance also at the 1% level.

4. Discussion

Pre-gestational maternal allergy was an isolated risk factor for early-onset preeclampsia in this study. This novel finding offers possibilities for further research that in the future may open alleys for prevention and treatment of this common and serious condition.

This study has several strengths. Data were obtained from a population-based comprehensive database, with detailed clinical information recorded for every delivery. We had a large sample of women giving birth at two delivery departments serving two major cities in Norway as first, second and third level clinical departments. Information on pre-gestational conditions was obtained in an interview and supplied with information noted at the personal health record form obtained by the midwife or general practitioner from the first trimester and throughout pregnancy. The population characteristics and pre-gestational morbidity incidences are in line with previous studies (Mendola et al., 2013; Borthen et al., 2009; Yerby et al., 1985; Lin et al., 2010; Katz et al., 1980; Nevis et al., 2011; Minassian et al., 2013; Sorbye et al., 2015), and indicate good external validity of our data, enabling comparison of early-onset and late-onset preeclampsia.

Self-reported data is a limitation, thus recall bias may occur. Self-reported data in pregnancy are considered reasonably valid (O'sullivan et al., 2000; Olson et al., 1997). In addition, occurrence of the examined risk factors in our study correlated well with findings in previous studies (Lisonkova and Joseph, 2013) (Table 1). Midwives and general practitioners will, during the first consultation in the first trimester, normally perform a detailed medical history and a full clinical status as part of the examination. Information was prospectively recorded at the personal health record form, which accompanied the woman to the delivery department. The general practitioner holds records of the patient's full medical history, sometimes since early childhood. Body mass index was not available and overweight is a well-known predisposing factor for preeclampsia. Results should be interpreted with caution for conditions where body mass index may be a confounder, such as type 2 diabetes.

Allergy as an isolated risk factor of early-onset preeclampsia is a novel finding, adding to our knowledge of the disease. One possible explanation for our finding might be that maternal allergy leads to changes in the physiological regulation of the maternal immune system in pregnancy. This could then cause poor placentation, followed in turn by early-onset preeclampsia. This supports the idea that early-onset preeclampsia is a fetal condition, while late-onset preeclampsia is considered a maternal condition. (Raymond and Peterson, 2011). While new, the finding is in line with previous studies that have demonstrated different levels of some immunological factors in early-onset and late-onset preeclampsia (Zhang et al., 2013; Sezer et al., 2012). Increased

levels of IgE have been detected in women with preeclampsia (Alanen, 1984). In line with our finding, a previous study has shown that pre-gestational hypertension increases the risk of early onset preeclampsia more than of late-onset preeclampsia (Lisonkova and Joseph, 2013). Previous studies have found a moderately increased risk of preeclampsia in women suffering from asthma (Mendola et al., 2013), non-significant in one study (Tata et al., 2007). We did not confirm this association, probably a matter of sample size (both previous studies had more than twice the number of participants). We found a non-significant trend of asthma being linked to early onset preeclampsia (but not to late onset preeclampsia). This is interesting, as asthma and allergy share some pathogenic pathways (Gould and Sutton, 2008). In our study, we did not find the previously identified increase in risk of preeclampsia amongst women with pre-gestational epilepsy (Borthen et al., 2009; Yerby et al., 1985), rheumatoid arthritis (Lin et al., 2010), chronic kidney disease (Katz et al., 1980; Nevis et al., 2011), and recurrent urinary tract infections (Minassian et al., 2013). This could also be due to sample size.

Several studies have indicated that preeclampsia increase the risk of cardiovascular disease later in life (Skjaerven et al., 2012). Cardiac disease is a heterogeneous group, including both congenital heart disease and cardiovascular disease. Preeclampsia increases the risk of the latter, but few women develop cardiovascular disease while fertile. One study (Roos-Hesselink et al., 2013) show no elevated risk of preeclampsia in women with preexisting cardiovascular disease, but increased risk of preterm birth and low birth weight in the group of patients suffering from ischemic heart disease, most likely because of diffuse vasculopathy that leads to poor perfusion of the placenta and placenta insufficiency. It is shown that preeclamptic pregnancies are associated with allergic sensitization and allergic rhinoconjunctivitis in late childhood in children born after such pregnancies. The same association was not seen for other atopic diseases (Byberg et al., 2014). Other studies have shown that preeclampsia is a shared risk factor for eczema, asthma and allergy (Stokholm et al., 2017).

Maternal allergy was an isolated risk factor for early-onset preeclampsia. This adds to the understanding of the immunological pathogenesis in preeclampsia. Future studies should differentiate between early and late onset preeclampsia when looking at IgE-mediated immunological pathways in preeclamptic women. Studies should also assess the additional predictive value of anamnestic information on maternal allergy in existing predictive models of preeclampsia (Duley et al., 2007; Akolekar et al., 2011; Oliveira et al., 2014).

4.1. Conclusion

Maternal allergy was an isolated risk factor increasing the risk of early-onset preeclampsia (before 34 weeks of gestation), but reduced the risk of late-onset preeclampsia.

Conflicts of interest

None.

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Details of ethics approval

We applied to the regional ethics committee for permission to extract the relevant data from a large number of patient journals without written informed consent from each participant. This is not without ethical implications, but can be permitted if individual data safety is maintained and the proposed research is of sufficient value to science and the society. The Western Norway regional ethics committee

approved the project on 03. March 2015 in line with the revised Helsinki declaration, (2015/66/REK vest).

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