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Use of antihistamines before or during pregnancy and risk of early-onset pre-eclampsia in allergic women: a population-based cohort study

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ABSTRACT

Objective We have previously found that allergy is a risk factor for early-onset pre-eclampsia. The aim of this study was to assess the association between pregestational maternal use of antihistamines and early-onset pre-eclampsia.

Design A population-based cohort study.

Setting and participants All women giving birth in Norway 2004–2016, including 692 487 pregnancies. Data from the Medical Birth Registry of Norway were linked with data from the Norwegian Prescription Database. Prescriptions of antihistamines were divided into three groups: before pregnancy (<6 months), early pregnancy (<20 weeks) and late pregnancy (20–36 weeks). ORs with 95% CIs for pre-eclampsia <34 and <37 weeks by antihistamine use were estimated by logistic regression and stratified on multiple pregnancy and parity. Predicted proportions (%) with 95% CIs were estimated.

Interventions Use of antihistamines in relation to pregnancy in allergic women.

Main outcome measures Development of early-onset pre-eclampsia.

Results 2997 (0.43%) and 5769 (0.83%) women had pre-eclampsia <34 and <37 weeks, respectively. Use of antihistamines before and in early pregnancy was associated with a risk of developing early-onset pre-eclampsia that was comparable to the background population (OR 1.0, 95% CI 0.8 to 1.2 and OR 0.9, 95% CI 0.7 to 1.1, respectively). Antihistamine use only in late pregnancy was not treated as exposure, but as an indicator of allergy, and was associated with an increased risk of early-onset pre-eclampsia (OR 1.8, 95% CI 1.5 to 2.2). Predicted proportions of pre-eclampsia <34 weeks were significantly lower in women using antihistamines before (0.41%, 95% CI 0.34 to 0.49) and in early pregnancy (0.37%, 95% CI 0.31 to 0.44), compared with women using antihistamines after placentation (0.69%, 95% CI 0.57 to 0.83). Results were similar for pre-eclampsia <37 weeks.

Conclusions Antihistamine use before or during placentation was associated with reduced risk of developing early-onset pre-eclampsia in allergic women compared with women using antihistamines after placentation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a population-based cohort study using linked data from The Medical Birth Registry of Norway and the Norwegian Prescription Database.
⇒ It contains all women giving birth in Norway 2004–2016 and includes 692 487 pregnancies.
⇒ Maternal allergy is not registered with an International Statistical Classification of Diseases and Related Health Problems, 10th edition code in the Medical Birth Registry of Norway, so we used antihistamine prescription for allergy to identify women with allergies.
⇒ We have no information on what kind of allergy the participants suffer from.

INTRODUCTION

Pregestational maternal allergy is associated with early-onset pre-eclampsia.[1] This supports the hypothesis of pre-eclampsia as a disorder of immune regulation, and prompts the question if antihistamines, used to treat allergy, affect the risk of developing pre-eclampsia in allergic women. Levels of histamine in blood are altered in pregnancy, indicating its biological importance for a successful pregnancy.[2] Histamine has been assumed to contribute to embryo–uterine interactions due to its vasoactive, differentiation and growth-promoting properties[3] and elevated levels of blood histamine in pregnancy are known to lead to a variety of adverse outcomes, for example, threatened abortions, preterm labour and pre-eclampsia.[4] It is shown that histamine mediates vasoconstriction in umbilical arteries[5] and veins in human pregnancy,[6] and that severity of pre-eclampsia increases by increasing blood levels of histamine.[7] The pathogenesis of pre-eclampsia is incompletely understood, but inadequate growth of fetal cells along maternal spiral arteries is believed to be important.[8] Increased systemic inflammation leading to endothelial dysfunction

due to increased concentration of pro-inflammatory substances from a dysfunctional placenta is another important pathway.[9 10] It is also shown that sFlt-1 from the placenta is associated with activation of the complement system[11] which can cause mast cells to release histamine.

Pre-eclampsia is diagnosed in second half of pregnancy and consists of an early-onset and a late-onset entity.[12 13] Early-onset pre-eclampsia is defined as fulfilling the diagnostic criteria before 34 weeks of gestation, but also if resulting in delivery before week 37.[14] Merging early-onset and late-onset pre-eclampsia in studies will mask relevant risk factors and effects of treatment that may be specific for early-onset pre-eclampsia.[12] There are few treatment and prevention possibilities for pre-eclampsia. However, low-dose acetylsalicylic acid administered from the first trimester can prevent early-onset pre-eclampsia in women at risk for developing pre-eclampsia.[15]

The aim of this study was to assess the effect of antihistamine use for allergy on risk of early-onset pre-eclampsia, using linked data from two nationwide population-based registries. Allergy is insufficiently registered in the database, so antihistamine prescription in gestational week 20–36 was used as an indicator of allergy. Our hypothesis was that antihistamines reduce the risk of pre-eclampsia in allergic women and that by showing this we would add to the knowledge of pre-eclampsia as an immunological condition.

METHODS

Study population and data sources

A nationwide population-based cohort study with prospectively collected data from the Medical Birth Registry of Norway and the Norwegian Prescription Database from 2004 to 2016 was designed. The Medical Birth Registry of Norway was established in 1967 and is a compulsory health register with information on pregestational conditions, prenatal care, delivery and postnatal care. Pregestational conditions are registered by the general practitioner or the midwife at the first antenatal visit, and information on previous pregnancies is recorded on the personal health record form, a specific form used throughout follow-up of all pregnancies in the country. All information on live births and stillbirths are registered and sent electronically to the Medical Birth Registry of Norway by the attending midwife or obstetrician a few days after delivery. The Norwegian Prescription Database was established in 2004 and holds record of all prescribed drugs in Norway. All births in Norway during the study period were assessed. Births with gestational age >44+0 weeks or <20+0 weeks and births with missing gestational age were excluded (figure 1). In our material, each delivery counts as a separate registration, which means that twin deliveries count as two registered deliveries. Thus, the second twin and above was excluded (figure 1). Women who delivered before April 2005 were excluded because we could not assess their use of antihistamines 6 months prior to their last menstrual period.

The unique personal identification number provided to all Norwegian citizens enabled linkage of data from the two national registries.

Data on occurrence of pre-eclampsia, pre-eclampsia diagnosed before 34 weeks of gestation, gestational age at delivery in days, date of delivery, maternal age, parity, occurrence of multiple pregnancies and pre-pregnancy body mass index (BMI) were obtained from the Medical Birth Registry of Norway. The Norwegian Prescription Database provided data on all antihistamines prescribed for systemic use. The Anatomical Therapeutic Chemical Classification System (ATC) code R06, and the corresponding national refund codes from the International Classification of Primary Care (ICPC codes: F71, R97, S98) and the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10 codes: H10.1, J30, L50) were used to ensure that antihistamines were prescribed due to allergy, and not for other conditions, for example, sleep disorders

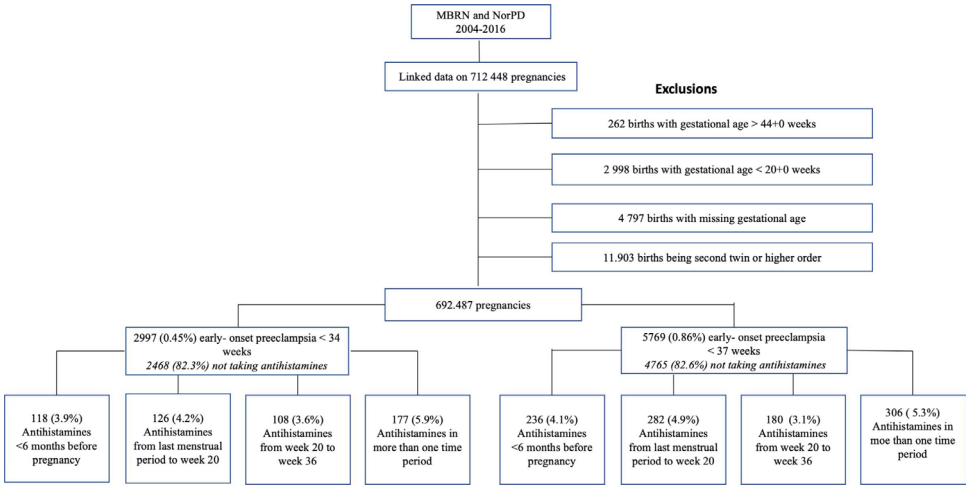

Figure 1 Flow chart for the inclusion of cases. MBRN, Medical Birth Registry of Norway; NorPD, Norwegian Prescription Database.

or hyperemesis gravidarum. For the purposes of this study, we were interested in studying women with allergies. Maternal allergy is not registered with an ICD-10 code in the Medical Birth Registry of Norway, so we used antihistamine prescription for allergy to identify women with allergies. The Norwegian Prescription Database also provided date of dispense and type of antihistamine. We identified use of antihistamines in three periods related to pregnancy: (1) before pregnancy: from 6 months prior to last menstrual period to last menstrual period, (2) early pregnancy: from last menstrual period to week 20 of gestation and (3) late pregnancy: from week 20 to week 36 of gestation. Use of antihistamines in late pregnancy was considered a proxy variable for allergy, not as exposure, as the registration of allergy in the Medical Birth registry of Norway was limited. Women that used antihistamines in more than one period were identified and treated as a separate fourth group to ensure mutually exclusive groups. We divided the antihistamines into five main groups and controlled that there was no overlap between the groups. We only included prescriptions of antihistamines that were dispensed.

Definitions

The diagnostic criteria of pre-eclampsia were proteinuria ≥+1 on a dipstick, >0.3 g urine protein loss per 24 hours or a protein/creatinine ratio >0.3 and repeated measurements of systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 after 20 weeks of gestation (ICD-10: O11, O14.0, O14.1, O14.2, O14.9). This definition by the Norwegian Society of Gynaecology and Obstetrics is in accordance with the guidelines from the National Institute for Health and Care Excellence[16 17] and the guidelines from The American College of Obstetrics and Gynecology.[18] Registration of pre-eclampsia in the Medical Birth Registry of Norway has previously been validated and found to be of high quality.[19] Early-onset pre-eclampsia was during 2004–2016 defined in the Medical Birth Registry of Norway as fulfilling the diagnostic criteria for pre-eclampsia before 34 completed weeks of gestation. However, the International Society for the Study of Hypertension in Pregnancy defines early-onset pre-eclampsia as leading to delivery before 37 weeks of gestation.[14]

Exposure

Antihistamine use in relation to pregnancy in allergic women. After week 20, antihistamines were considered a marker for allergy, not as exposure.

Outcome

Primary outcomes were early-onset pre-eclampsia, defined both as women fulfilling the criteria for pre-eclampsia before 34 completed weeks of gestation (pre-eclampsia <34 weeks), and pre-eclampsia resulting in delivery before 37 completed weeks of gestation (pre-eclampsia <37 weeks).

Statistical analysis

In our primary analysis, we used binomial logistic regression models with random effects component to account for the repeat effect of pregnancies to the same woman to estimate ORs with 95% CIs for early-onset pre-eclampsia by prescribed antihistamines in the four groups outlined above, compared with women not using antihistamines. In all analyses, we adjusted for maternal age at birth. We did four secondary analyses: stratified by parity, stratified by multiple pregnancy, separated into the five main types of antihistamines (cetirizine/levocetirizine, loratadine/desloratadine, dexchlorpheniramine, meclizine and other antihistamines) and adjusted for BMI in the women where BMI was registered. Registration of BMI in the Medical Birth Registry of Norway started in 2006 and increased successively until 2014, when the registration exceeded 70%, and BMI was therefore registered in only 309 617 women. Results from the main analyses were also presented as estimated predicted proportions of early-onset pre-eclampsia in the four groups, as well as for women not prescribed antihistamines. Average predicted proportions of early-onset pre-eclampsia were estimated and plotted using STATA (Release 17. College Station, Texas, USA: StataCorp LLC. StataCorp, 2019) functions margins and margins plot. IBM SPSS Statistics for Windows (V.26.0.0.1 Armork, New York, USA, 2019) was used for all other statistical analyses. Significance testing was two-sided, and results were considered statistically significant when $p<0.05$.

Power calculations indicated that with an anticipated 44 000 versus 22 000 pregnant women using antihistamines before and after placentation respectively, we would have a power of 82% for detecting an absolute risk reduction from 0.66% to 0.50% for developing early-onset pre-eclampsia at a one-tailed 5% significance level. In our data set, only 4797 cases had missing data. As this is less than 0.7%, we opted to exclude these cases. An exception was BMI, which was registered in about only half the pregnancies. These were handled separately.

Patient and public involvement

We gathered a Focus group with patients suffering from pre-eclampsia where we explained the background of our study and the methods we wanted to use. The group members agreed that the data protection was satisfactory in the proposed design of our study. Important elements regarding risk factors for pre-eclampsia came up, and the group's suggestion to both differentiate different forms of allergy and their effect on pre-eclampsia, and the idea that commonly used allergy medication might be used as prophylaxis or treatment against pre-eclampsia was a valuable contribution to our protocol. The group also gave us valuable insight in the use of patient and public involvement through the discussion in the group. The protocol was also assessed by the user panel at Stavanger University Hospital who agreed with the Focus group in all their comments.

RESULTS

In total 692 487 pregnancies were eligible for analyses, of which 101 287 women used antihistamines (14.6%) and

Table 1 Baseline characteristics

	No pre-eclampsia (n=670 909), No. (%)	Pre-eclampsia <34 weeks (n=2997), No. (%)	Pre-eclampsia <37 weeks (n=5769), No. (%)
Nulliparous	279 612 (41.7)	1722 (57.5)	3492 (60.5)
Mean maternal age (years)	29.9 (N/A)	30.4 (N/A)	30.1 (N/A)
Multiple pregnancy	10 540 (1.6)	299 (10.0)	820 (14.2)
Mean BMI*	24.3 (N/A)	26.5 (N/A)	26.1 (N/A)
Prescribed any antihistamine	97 566 (14.5)	529 (17.7)	1004 (17.4)
Cetirizine/levocetirizine	20 440 (3.0)	110 (3.7)	184 (3.2)
Loratadine/desloratadine	14 116 (2.1)	75 (2.5)	125 (2.1)
Dexchlorpheniramine	13 570 (2.0)	56 (1.7)	120 (2.1)
Meclizine	9954 (1.5)	44 (1.5)	100 (1.7)
Other antihistamines†	11 630 (1.7)	54 (1.8)	128 (2.2)
More than one type of antihistamine	27 856 (4.2)	190 (6.3)	347 (6.0)

Baseline characteristics and prescribed antihistamines for 692 487 pregnancies, linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016. Presented as number of pregnancies and per cent for the total population and for early-onset pre-eclampsia <34 and 37 weeks.
*In a subset of 309 617 pregnancies.
†Alimemazine, ebastine, phenoxphenidine, promethazine, thiethylperazine, cyclizine, cinarizine, clemastine, doxylamine, diphenhydramine, cyproheptadine, rupatadine, bilastine.
BMI, body mass index.

21 578 (3.1%) had pre-eclampsia. Of these, 2997 (0.43%) were diagnosed before 34 gestational weeks and 5769 (0.83%) were delivered with pre-eclampsia before gestational week 37 (figure 1, table 1). Almost 98% of pregnancies were dated by ultrasound estimates.

ORs for pre-eclampsia <34 weeks in pregnancies with prescribed antihistamines before pregnancy and in early pregnancy were 1.0 (95% CI 0.8 to 1.2) and 0.9 (0.7 to 1.1), respectively, compared with women not using antihistamines (table 2). However, in pregnancies with prescribed antihistamines in late pregnancy the OR was 1.8 (1.5 to 2.2). For pre-eclampsia <37 weeks, we saw similar associations: OR for early-onset pre-eclampsia was 1.0 (0.9 to 1.2) in women with prescribed antihistamines before pregnancy, 1.0 (0.9 to 1.2) in women using antihistamines in early pregnancy, while 1.5 (1.3 to 1.8) in women using antihistamines only in late pregnancy (table 2).

In women using antihistamines in more than one period, ORs for developing early-onset pre-eclampsia <34 and <37 weeks were 1.7 (1.5 to 2.0) and 1.6 (1.4 to 1.8), respectively.

Stratified results by nulliparous/parous pregnancies, singleton/multiple pregnancies and grouped by main types of antihistamines are presented in table 2. Effects were comparable across different strata and by types of antihistamine. BMI was recorded in 309 617 pregnancies. This group was analysed separately with maternal BMI included as a covariate, associations between use of antihistamines and early-onset pre-eclampsia were 0.9 (95% CI 0.7 to 1.2), 1.0 (0.8 to 1.3) and 2.2 (1.7 to 2.8) for pre-eclampsia <34 weeks and 1.0 (0.8 to 1.2), 1.1 (0.9 to 1.3) and 1.8 (1.4 to 2.2) for pre-eclampsia <37 weeks by antihistamine use before, early and in late pregnancy, respectively (online supplemental table S1).

Predicted proportions of early-onset pre-eclampsia <34 and <37 weeks are presented in figures 2 and 3, respectively. Women that used antihistamines before or in early pregnancy had significantly lower predicted proportions of early pre-eclampsia, 0.41% (95% CI 0.34% to 0.49%) and 0.37% (0.31% to 0.44%), respectively, compared with women using antihistamines in late pregnancy, 0.69% (0.57% to 0.83%) or in several periods (0.69% (0.59% to 0.80%) (figure 2). Results were the same for early-onset pre-eclampsia <37 weeks (figure 3). Estimated proportions for women using antihistamines before or during placentation were essentially equal to women not using antihistamines.

DISCUSSION

Allergic women using antihistamines before or in early pregnancy had reduced risk of early-onset pre-eclampsia compared with allergic women using antihistamines in late pregnancy only. It is not plausible that it is the use of antihistamines in late pregnancy itself that increases the risk of pre-eclampsia. The effect is most likely due to the known increased risk of early-onset pre-eclampsia associated with pre-existing allergy. Allergic women have an increased baseline risk for early-onset pre-eclampsia compared with non-allergic women. Women prescribed antihistamines in late pregnancy, after the formation of the placenta, do not benefit from the normalisation of risk we see in allergic women prescribed antihistamines before placental formation. Thus, we considered

Table 2 ORs for developing early-onset pre-eclampsia by antihistamine use

	Before pregnancy OR (95% CI)	Early pregnancy OR (95% CI)	Late pregnancy OR (95% CI)	Antihistamines in more than one period
Pre-eclampsia <34 weeks				
Any antihistamine	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.1)	1.8 (1.5 to 2.2)	1.7 (1.5 to 2.0)
Cetirizine/levocetirizine	1.2 (0.9 to 1.6)	0.9 (0.5 to 1.3)	1.4 (0.8 to 2.2)	2.0 (1.3 to 3.0)
Loratadine/desloratadine	0.9 (0.6 to 1.3)	1.2 (0.7 to 1.9)	1.9 (1.1 to 3.3)	2.0 (1.2 to 3.3)
Dexchlorpheniramine	0.9 (0.4 to 2.2)	0.5 (0.3 to 0.9)	1.3 (0.9 to 1.8)	1.5 (0.6 to 3.6)
Meclizine	N/A*	0.9 (0.6 to 1.3)	3.3 (1.7 to 6.3)	1.9 (0.3 to 14)
Other antihistamines†	0.8 (0.5 to 1.4)	0.8 (0.5 to 1.2)	3.1 (2.0 to 4.8)	0.7 (0.2 to 2.9)
More than one type of antihistamine in the period	0.8 (0.5 to 1.3)	1.4 (0.9 to 2.1)	2.3 (1.4 to 3.8)	1.7 (1.4 to 2.1)
Nulliparous	0.9 (0.7 to 1.2)	0.9 (0.7 to 1.2)	1.8 (1.4 to 2.3)	1.7 (1.4 to 2.1)
Parous	1.1 (0.8 to 1.4)	0.8 (0.6 to 1.1)	1.7 (1.3 to 2.3)	1.6 (1.2 to 2.0)
Singleton	1.0 (0.8 to 1.2)	0.9 (0.7 to 1.0)	1.8 (1.4 to 2.2)	1.7 (1.5 to 2.0)
Multiple pregnancy	1.1 (0.6 to 2.0)	1.1 (0.6 to 1.7)	1.2 (0.7 to 2.1)	1.6 (0.99 to 2.6)
Pre-eclampsia <37 weeks				
Any antihistamine	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.5 (1.3 to 1.8)	1.6 (1.4 to 1.8)
Cetirizine/levocetirizine	0.9 (0.8 to 1.2)	1.0 (0.8 to 1.4)	1.2 (0.8 to 1.7)	1.5 (1.0 to 2.1)
Loratadine/desloratadine	0.9 (0.7 to 1.2)	1.4 (0.98 to 1.9)	0.8 (0.5 to 1.5)	1.3 (0.8 to 2.0)
Dexchlorpheniramine	0.9 (0.4 to 1.6)	0.7 (0.5 to 0.9)	1.4 (1.1 to 1.8)	1.7 (0.9 to 3.1)
Meclizine	1.3 (0.3 to 5.2)	1.1 (0.9 to 1.3)	3.2 (2.0 to 5.2)	1.2 (0.5 to 7.9)
Other antihistamines†	1.4 (1.0 to 1.9)	1.0 (0.7 to 1.3)	2.3 (1.6 to 3.3)	2.1 (1.2 to 3.8)
More than one type of antihistamine in the period	1.1 (0.8 to 1.5)	1.3 (0.96 to 1.7)	2.1 (1.4 to 3.0)	1.6 (1.4 to 1.8)
Nulliparous	1.1 (0.9 to 1.3)	1.0 (0.9 to 1.2)	1.5 (1.2 to 1.8)	1.5 (1.3 to 1.8)
Parous	0.9 (0.7 to 1.1)	1.1 (0.9 to 1.3)	1.6 (1.2 to 2.0)	1.4 (1.1 to 1.7)
Singleton	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)	1.4 (1.2 to 1.7)	1.6 (1.4 to 1.8)
Multiple pregnancy	0.9 (0.6 to 1.3)	0.8 (0.6 to 1.2)	1.3 (0.9 to 1.8)	1.2 (0.9 to 1.7)

ORs with 95% CIs for early-onset pre-eclampsia (<34 and <37 gestational weeks, respectively) by use of antihistamines in relation to pregnancy compared with no use of antihistamines in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database 2004–2016. Estimates were obtained using binomial logistic regression with random effects component, adjusting for maternal age. Included in the table are also results for use of main types of antihistamines separately and stratified results by parous/nulliparous and singleton/multiple pregnancies.
*No women using meclizine developed early-onset pre-eclampsia <34 weeks.
†Alimemazine, ebastine, phenoxphenidine, promethazine, thiethylperazine, cyclizine, cinarizine, clemastine, doxylamine, diphenhydramine, cyproheptadine, rupatadine, bilastine.

antihistamine use in late pregnancy as an indirect indicator for allergy. These results based on the timing of antihistamine-use are consistent with studies on aspirin in the prevention of pre-eclampsia, where the drug must be initiated before 16 weeks of gestation for optimal effect.[20]

Current knowledge of histamine in pregnancy suggests an important role in trophoblastic cell differentiation and as an apoptotic cell regulator.[21 22] In normal pregnancies, the level of histamine in blood decreases from the start of pregnancy, reaching nadir around week 24, before rising and stabilising slightly below non-pregnant levels.[2] Elevated levels of blood histamine in pregnancy are known to lead to a variety of adverse outcomes, for example, threatened abortions, preterm labour and pre-eclampsia.[4] Elevated histamine levels cause vasoconstriction,[6] which might explain why high levels of histamine, either in maternal blood or at the maternal–fetal interphase, increase the risk of pre-eclampsia. Nevertheless, there is a study from 2012 that imply that that it is the hypoxia from the impaired placentation that leads to increased excretion of histamine by mast cells in the placenta.[23] One animal study of guinea pig placentas found that elevated histamine levels leads to both vasoconstriction and increased macromolecular permeability.[24] Similar effects in humans could explain the increased risk of pre-eclampsia seen in allergic women with hyperhistaminemia, as it is possible that the increased permeability for large molecules can further increase the leakage of

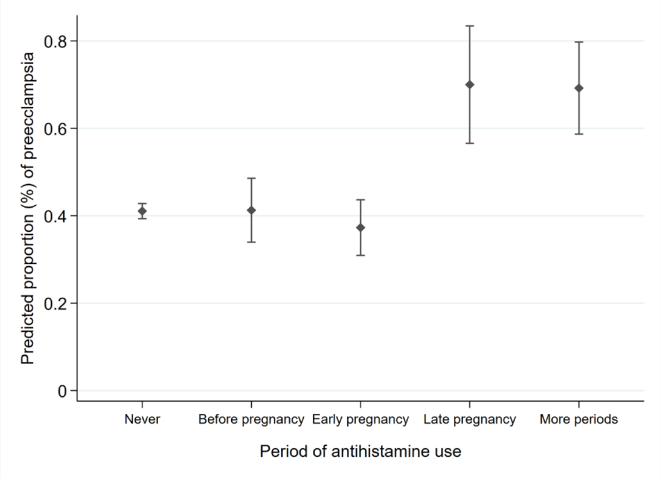

Figure 2 Predicted proportions of early-onset pre-eclampsia before 34 weeks**.** Predicted proportions with 95% CIs for pre-eclampsia (<34 gestational weeks) by no use of antihistamines (Never), use of antihistamines 6 months before pregnancy (Before pregnancy), from last menstrual period to gestational week 20 (Early pregnancy), from week 20 to week 36 (Late pregnancy) and use of antihistamines in more than one time period (More periods) in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016.

bioactive substances from the compromised placenta and thus explain the increased risk of pre-eclampsia. Diamine oxidase is the only extracellular enzyme capable of inactivating histamine in humans.[25 26] Plasma levels of diamine oxidase are almost undetectable in non-pregnant women, but increase several 100-fold during gestation.[3] A recent study has shown that levels of diamine oxidase were significantly lower in samples from women with early-onset pre-eclampsia, compared with controls,[27] indicating a crucial role of histamine in the pathophysiology of early-onset pre-eclampsia.

In the 1950s, there was some interest in the use of antihistamines in treatment of eclampsia[28] and pre-eclampsia,[29] but without any impact on clinical management. A recent case–control study from Finland estimated overall risk for pre-eclampsia by histamine use but did not differentiate between early-onset and late-onset pre-eclampsia.[30] To the best of our knowledge, the association between early-onset pre-eclampsia and antihistamine use in allergic women has not been previously studied.

In our study, associations were not restricted to any specific type of antihistamine (see table 2). The effect of antihistamine use does not differ to any significant degree between first-time mothers and in subsequent pregnancies, but findings were less pronounced in multiple gestation. Women with prescribed antihistamines in more than one period related to pregnancy had an increased risk for developing early-onset pre-eclampsia. A possible explanation could be that these women suffer more severely from allergy, and thus have a higher baseline risk, due to a more severe inflammation.[9]

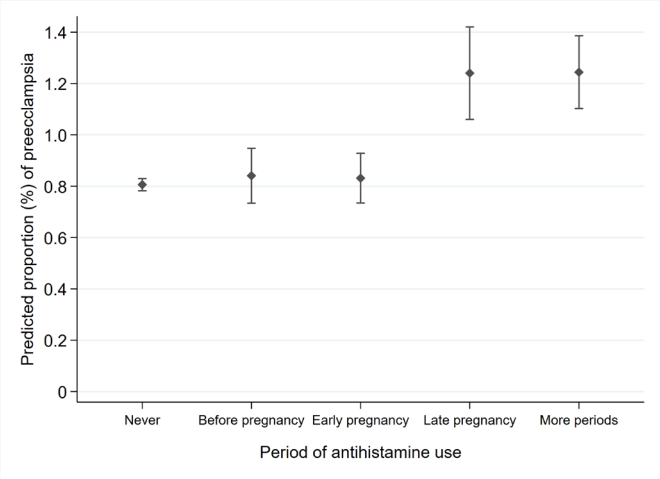

Figure 3 Predicted proportions of early-onset pre-eclampsia before 37 weeks. Predicted proportions with 95% CIs for pre-eclampsia (<37 gestational weeks) by no use of antihistamines (Never), use of antihistamines 6 months before pregnancy (Before pregnancy), from last menstrual period to gestational week 20 (Early pregnancy), from week 20 to week 36 (Late pregnancy) and use of antihistamines in more than one time period (More periods) in 692 487 Norwegian pregnancies, using linked data from the Medical Birth Registry of Norway and the Norwegian Prescription Database, 2004–2016.

Strengths

The strengths of the study are its large sample of pregnant women with linked data from two nationwide compulsory registers, accurate gestational age determination, high validity of the registered diagnosis of pre-eclampsia in the Medical Birth Registry of Norway[19] and a detailed procedure to ensure that antihistamines were prescribed due to allergy. Early-onset pre-eclampsia is a rare, but serious condition, and a large sample size is necessary to maintain sufficient power to estimate associations. In addition, the large sample of pregnant women also yielded strength to present results by the main types of antihistamines.

Limitations

Over-the-counter sale of antihistamines is not registered in the Norwegian Prescription Database, which is a possible weakness of our study. However, this only applies to cetirizine throughout the study period, which accounts for only 9% of the total sale of antihistamines in the ATC group R06A, according to official data from the Norwegian Institute of Public Health.[31] Maternal allergy is registered as a dicotome variable, and not with an ICD-10 code, in the Medical Birth Registry of Norway. Unfortunately, in our material maternal allergy was only registered in approximately 1% of the registered births, and we have therefore postulated that women suffer from allergy if they have been given a prescription containing an ICD-10 code for allergy in the Norwegian Prescription Database for reimbursement from the state. The Norwegian Institute of Public Health conclude that the

best data to estimate the prevalence of allergy among Norwegian adults are the use of the Norwegian Prescription Database.[32] We found that 14.6% of women in our population used antihistamines. There is a possibility that some women may have received antihistamines coded as allergy for other conditions by mistake. However, we do not believe that this is a large issue in our data, as quality-control measures using refund codes were used to avoid such problems.

Because the diagnosis of allergy was only available to us through the maternal use of antihistamines, the antihistamine use in late pregnancy (weeks 20–36) was considered a proxy variable in our material. As such our group of unexposed pregnancies most likely consist of both allergic and non-allergic women.

Registration of BMI in the Medical Birth Registry of Norway started in 2006, when only 0.1% of the reported pregnancies included BMI. The registration increased successively until 2014, when the registration exceeded 70%. Even in periods with poor registration, the BMI follows a normal distribution, suggesting representative registration.[33] Additional adjustment for BMI did not alter the overall findings from the main analysis. Prophylactic use of acetylsalicylic acid was implemented in Norwegian national guidelines for prevention of pre-eclampsia <34 weeks as late as 2014 and have likely had little impact on our findings.

Clinical implications

Our study sheds light on three important issues: that histamine is indeed an important biological substance necessary for the development of a successful pregnancy, that our findings add to the knowledge of pre-eclampsia as an immunological condition, and that there is no reason to recommend discontinuation of antihistamines in pregnancy for allergic women.

CONCLUSION

Antihistamines used for allergy before and during the timeframe for the formation of the placenta were associated with a reduced risk of developing early-onset pre-eclampsia in allergic women, both <34 and <37 weeks, when compared with pregnancies with use of antihistamines only in late pregnancy. Further clinical research should explore possible beneficial effects of antihistamines before and during first half of pregnancy, timing of use in pregnancy and its possible effects of reducing risk of early-onset pre-eclampsia in allergic women.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The ethics committee of the Western Norwegian regional health authorities ID 2017/292/REK vest exempted this study. This is a nationwide population-based cohort study with prospectively collected data from the Medical Birth Registry of Norway and the Norwegian Prescription Database from 2004 to 2016 and contains information on more than 700 000 women. It would not be practically feasible to obtain written consent from all these women. The Medical Birth Registry of Norway is a public register excempt for the obligation to consent and it is therefore possible for the ethics committee to allow access to these data without patient consent. Such exemption has been applied for and granted by the relevant ethics committee.

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Data availability statement Data are available upon reasonable request. Relevant anonymised data will be made available on reasonable request from the corresponding author.

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