

Pregnancy Complication and Outcome in Women with History of Allergy to Medicinal Agents

Iris Ohel¹, Amalia Levy², Aya Zweig¹, Gershon Holcberg¹, Eyal Sheiner¹

¹Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel;

²Department of Epidemiology and Health Services Evaluation, Faculty of Health Sciences, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Keywords

Allergy, intrauterine growth restriction, pregnancy outcome, preterm labor

Correspondence

Eyal Sheiner, MD, PhD, Department of Obstetrics and Gynecology, Soroka University Medical Center, PO Box 151, Beer-Sheva, Israel.

E-mail: sheiner@bgu.ac.il

Submitted December 31, 2009;
accepted February 24, 2010.

Citation

Ohel I, Levy A, Zweig A, Holcberg G, Sheiner E. Pregnancy complication and outcome in women with history of allergy to medicinal agents. *Am J Reprod Immunol* 2010

doi:10.1111/j.1600-0897.2010.00845.x

Problem

Pregnancy outcome in women with a previous history of drug allergy and the role of drug allergies in adverse pregnancy outcomes is unclear.

Method of study

A retrospective cohort study comparing pregnancies of women with and without history of drug allergy was conducted. Data were collected from the computerized perinatal database. A multiple logistic regression model, with background elimination, was constructed to control for confounders.

Results

Of 186,443 deliveries, 4.6% ($n = 8647$) occurred in patients with a history of drug allergy. The following conditions were significantly associated with a history of drug allergy: advanced maternal age, recurrent abortions, fertility treatments, hypertensive disorders, and diabetes mellitus. Using multivariate analysis, with background elimination, history of drug allergy was significantly associated with intrauterine growth restriction (OR = 1.52, CI = 1.3–0.8, $P < 0.001$) and with preterm delivery (OR = 1.26, CI = 1.14–1.38, $P < 0.001$).

Conclusion

A history of drug allergy is an independent risk factor for intrauterine growth restriction and preterm delivery. Further prospective studies are needed to investigate the nature of this association.

Introduction

Drug hypersensitivity, also known as drug allergy, is characterized by idiosyncratic and unpredictable immune-mediated reactions to drugs, affecting women more often than men.¹ Successful pregnancy requires maternal immune system adaptation to allow for the growth of an antigenically foreign fetus.² This maternal–fetal tolerance involves general reduction of the maternal immune system capability to respond to fetal antigens. A number of immuno-

suppressive factors have been recognized, which are produced by the placenta and serve as immune regulators in the maternal immune system, suggesting that the placenta has an immunosuppressive function;³ on the other hand, the altered function of the cellular response has crucial importance in the trophoblast's invasion and in the maintenance of pregnancy. For example, Breckler et al.⁴ have shown that during pregnancy, maternal responses to fetal alloantigens are altered by maternal allergic disease and/or previous pregnancies.

Aberrant immune mechanisms, specifically regarding cellular immunity, have been implicated in various gestational complications such as preeclampsia, intra-uterine growth restriction (IUGR), and recurrent abortions.^{5,6} Moreover, autoimmune diseases, such as rheumatoid arthritis,⁷ systemic lupus erythematosus (SLE),⁸ and psoriasis,⁹ are often associated with greater risk for adverse pregnancy outcomes. Drug allergy, also the result of aberrant immune function, appears to be related with autoimmunity.¹⁰

Recent studies by Romero and Garfield on the role of hypersensitivity and preterm labor demonstrate that an episode of preterm labor may be related to a type I hypersensitivity reaction. Their group showed in a retrospective study that a large proportion of eosinophils in the amniotic fluid in women with preterm labor and intact membranes represent an increased risk for spontaneous preterm delivery (PTD).¹¹ In another work, uterine and cervical contractile activity was studied in sensitized guinea pigs after challenge with ovalbumin antigen. Ovalbumin significantly increased contractility of uterine and cervical strips from sensitized versus non-sensitized animals. Furthermore, histamine H(1) receptor antagonist in uterine strips abolished these effects. Again, the authors have shown that type I hypersensitivity reactions may be important in mediating uterine contractility in pregnancy.¹²

Despite the well-characterized associations between immune dysfunction, including autoimmune phenomenon and perinatal complications, pregnancy outcome in women with a previous history of drug allergy has not been systematically studied. The purpose of this study was to examine pregnancy course and outcome in women with history of drug allergy.

Material and methods

A retrospective population-based study was conducted comparing all singleton pregnancies of women with and without a previous history of drug allergy. Data were collected from the computerized perinatal database consisting of information recorded directly after delivery by an obstetrician, and as each pregnancy poses a risk for adverse perinatal outcome, accordingly it was handled as a new case. Deliveries occurred during 1988 through 2007 at the Soroka University Medical Center. Drug allergy was a code given to women who reported during routine questioning at arrival of having previous drug

allergy. If they reported positive, then a question regarding the specific cause was asked and recorded according to the ICD-9 codes: V14.0 to penicillin, V14.1 to other antibiotics, V14.2 to sulfa, V14.3 to other infective agents, V14.4 to anesthetic, V14.5 to narcotics, V14.6 to analgesics, V14.7 to ferum, V14.8 to other medications.

The following clinical characteristics were noted: maternal age, parity, recurrent abortions, fertility treatments, and previous cesarean delivery (CD). The following obstetrical risk factors were examined: hypertensive disorders (defined as mild or severe preeclampsia and chronic hypertension), gestational and pre-gestational diabetes mellitus, IUGR, premature rupture of the membranes (PROM), and cervical incompetence. Cervical incompetence was defined as previous painless dilatation of the cervical os resulting in preterm-premature rupture of membranes and/or preterm labor, PTD, and late abortions. The following labor characteristics and perinatal outcomes were assessed: CD, placental abruption, placenta previa, meconium-stained amniotic fluid, non-progressive labor, non-vertex fetal presentation, fetal malformations, Apgar scores at 1 and 5 min <7, perinatal mortality, and PTD. Preterm delivery was defined as delivery before 37-weeks gestation. The local ethics institutional review board approved the study.

Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, IL, USA). Statistical significance was calculated using the Chi-square or Fisher exact test. A similar analysis was performed for a subgroup of women who had a history of a specific allergy to penicillin. Odds ratios (OR) and their 95% confidence interval (CI) were computed. $P < 0.05$ was considered statistically significant. Multivariate logistic regression models with backward elimination were constructed to find independent risk factors associated with a history of drug allergy and to determine whether a history of drug allergy is an independent risk factor for IUGR and spontaneous PTD.

Results

There were 186,443 deliveries during the study period, of which 8647 occurred in patients with a history of drug allergy. The characteristics of women with history of allergy to medicinal agents compared to women without such history are shown in Table I. The following conditions were significantly associated

Table I Characteristics of Women with History of Allergy to Medicinal Agents

Characteristics	Women with previous allergy (n = 8646)	Women without known allergy (n = 177,796)	OR	CI 95%	P Value
Maternal age (years)	30.5 ± 5.3	28.5 ± 5.8			<0.001
Ethnicity Jewish	8102 (93%)	92,819 (52.2%)	13.6	12.5–14.8	<0.001
Bedouin	545 (6.3%)	84,976 (47.8%)			
Parity					
1	28.6%	23.9%			
2–4	60.7%	51.2%			
>5	10.7%	24.8%			<0.001
Recurrent abortions	5.9%	5.4%	1.1	1.0–1.2	0.053
Fertility treatments	4.8%	1.8%	2.8	2.5–3.1	<0.001
Previous CD	12.5%	11.6%	1.1	1.0–1.1	0.015

Data are expressed as means ± standard deviations (S.D.) or percentage.

CI, confidence intervals and P-values for statistical significance; CD, cesarean delivery; OR, odds ratio.

with a history of drug allergy: advanced maternal age, nulliparity, and fertility treatments. The obstetric risk factors of women with history of allergy to medicinal agents compared to controls is presented in Table II. Almost all parameters that were examined – hypertensive disorders, gestational and pre-gestational diabetes mellitus, IUGR, premature rupture of the membranes (PROM), and cervical incompetence – were significantly associated with a history of allergy, except for severe preeclampsia. Cervical incompetence had an odds ratio of 2.605 in the group of women with allergy, with $P < 0.001$. Pregnancy and labor complications and outcomes of women with

history of allergy to medicinal agents compared to controls are shown in Table III. Women with previous allergy had significantly higher rates of CD in their index pregnancy, higher rates of placental abruption, meconium-stained amniotic fluid, non-progressive first stage labor, non-vertex presentation, and PTD.

Similar analysis was performed regarding a subgroup of women ($n = 4840$) with a history of allergy to penicillin. In this group too, mean maternal age was significantly elevated (30.2 ± 5.4 vs. 28.5 ± 5.8 , $P < 0.001$), the percentage of nulliparity was greater (29% vs. 24%, $P < 0.001$), and they had

Table II Obstetric risk Factors for Women with History of Allergy to Medicinal Agents

Characteristics	Women with previous allergy (n = 8646) (%)	Women without known allergy (n = 177,796) (%)	OR	CI 95%	P Value
Mild preeclampsia	4.6	3.4	1.4	1.2–1.5	<0.001
Severe preeclampsia	1.3	1.1	1.1	0.9–1.4	0.159
Chronic HTN	2.7	1.7	1.6	1.4–1.8	<0.001
Gestational HTN	8.1	5.9	1.4	1.3–1.5	<0.001
GDM	8.3	5.3	1.6	1.5–1.7	<0.001
Pregestational DM	1.2	1.7	1.3	1.1–1.6	<0.001
IUGR	3.0	2.1	1.5	1.3–1.7	<0.001
PROM	7.8	6.8	1.1	1.0–1.2	<0.001
Cervical incompetence	1.2	0.5	2.6	2.1–3.2	<0.001

Data are expressed as percentage.

CI, confidence intervals and P-values for statistical significance; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HTN, hypertension; IUGR, intrauterine growth restriction; OR, odds ratio; PROM, premature rupture of membranes.

Table III Pregnancy and Labor Complications and Outcomes of Women with History of Allergy to Medicinal Agents

Characteristics	Women with previous allergy (n = 8646) (%)	Women without known allergy (n = 177,796) (%)	OR	CI 95%	P Value
CD	19.0	12.9	1.6	1.5–1.7	<0.001
Placental abruption	0.8	0.7	1.0	0.8–1.3	0.841
Placenta previa	0.6	0.4	1.4	1.0–1.8	0.027
Meconium-stained amniotic fluid	13.4	16.2	0.8	0.7–0.8	<0.001
Non-progressive labor first stage	2.5	1.9	1.3	1.1–1.5	<0.001
Non-vertex presentation	6.9	5.3	1.3	1.2–1.4	<0.001
Preterm delivery <37 weeks	9.2	7.8	1.2	1.1–1.3	<0.001
Malformations	4.9	5.2	0.9	0.8–1.0	0.217
Apgar at 1 min <7	3.7	4.0	0.9	0.8–1.0	0.208
Apgar at 5 min <7	0.6	0.6	1.0	0.8–1.4	0.830
Perinatal mortality	1.1	1.3	0.8	0.6–1.0	0.053

Data are expressed as percentage.

CD, cesarean delivery; CI, confidence intervals and *P*-values for statistical significance; OR, odds ratio.

Table IV Independent Factors Associated with Drug Allergy: Results from a Multiple Logistic Regression Model with Backwards Elimination

Characteristics	OR	CI 95%	P Value
Jewish ethnicity (vs. Bedouins)	12.6	11.5–13.8	<0.001
Fertility treatments	1.7	1.5–1.9	<0.001
Cervical incompetence	1.5	1.2–1.8	<0.001
HTN	1.2	1.1–1.3	<0.001
Diabetes mellitus	1.2	1.1–1.2	<0.001
Previous Cesarean delivery	1.1	1.07–1.2	<0.001
Maternal age	1.035	1.031–1.039	<0.001

The initial model included, in addition, recurrent abortions and parity.

CI, confidence intervals and *P*-values for statistical significance; HTN, hypertension (hypertensive disorders); IUGR, intrauterine growth restriction; OR, odds ratio.

Nagelkerke $R^2 = 0.127$.

higher rates of infertility treatments (4.2% vs. 1.8%, OR = 2.3, CI: 2.03–2.71, $P < 0.001$). Significant differences in obstetric risk factors and labor complications were found between those with penicillin allergy and controls, and these include: hypertensive disorders (except for severe preeclampsia), gestational and pregestational diabetes mellitus, IUGR, cervical incompetence, CD, meconium-stained amni-

Table V Multiple Logistic Regression Models of Risk Factors for Preterm Delivery and Intrauterine Growth Restriction

Model	Characteristics	OR	CI 95%	P Value
Preterm delivery <37 weeks	Drug allergy	1.3	1.1–1.4	<0.001
	Maternal age	1.0	1.0–1.0	0.036
	HTN	3.5	3.3–3.7	<0.001
IUGR	Drug allergy	1.5	1.3–1.7	<0.001
	Maternal age	1.0	1.0–1.0	<0.001
	HTN	3.5	3.2–3.8	<0.001
	Fertility treatments	1.9	1.6–2.3	<0.001
	Malformations	2.4	2.1–2.6	<0.001

CI, confidence intervals and *P*-values for statistical significance; HTN, hypertension; IUGR, intrauterine growth restriction; OR, odds ratio.

otic fluid, and non-vertex presentation. No significant differences between the groups were found regarding perinatal mortality.

Independent factors associated with drug allergy were also evaluated using a multiple logistic regression model with backwards elimination (Table IV).

Using multivariable analysis, with backward elimination, history of drug allergy was significantly associated with IUGR (OR = 1.48, CI: 1.3–1.7, $P < 0.001$) and with PTD (OR = 1.26, CI: 1.14–1.38, $P < 0.001$; Table V). In the subgroup of women with history of allergy specific to penicillin, it was significantly associated with IUGR (OR = 1.52, CI: 1.3–1.8, $P < 0.001$ and OR = 1.48, CI: 1.3–1.7, $P < 0.001$, respectively),

Table VI Multiple Logistic Regression Models of Risk Factors for Preterm Delivery and Intrauterine Growth Restriction

Model	Characteristic	OR	CI 95%	P Value
Preterm delivery <37 weeks	Penicillin allergy	1.3	1.1–1.4	<0.001
	Maternal age	1.0	1.0–1.0	0.036
	HTN	3.5	3.3–3.7	<0.001
IUGR	Penicillin allergy	1.5	1.3–1.8	<0.001
	Maternal age	1.0	1.0–1.0	<0.001
	HTN	3.5	3.2–3.8	<0.001
	Fertility treatments	2.0	1.7–2.3	<0.001
	Malformations	2.4	2.1–2.6	<0.001

CI, confidence intervals and *P*-values for statistical significance; HTN, hypertension; IUGR, intrauterine growth restriction; OR, odds ratio.

but not with preterm delivery (OR = 1.02, CI: 0.99–1.17, *P* < 0.73; Table VI).

The association between drug allergy and specifically spontaneous preterm deliveries excluding indicated preterm deliveries was also investigated, using another multivariable logistic regression model (data not shown in a table). While controlling for maternal age and hypertensive disorders, drug allergy was noted as an independent risk factor for spontaneous preterm deliveries, with a similar OR of 1.26 (CI: 1.14–1.38, *P* < 0.001). Additional model investigated the risk for PTD <34 weeks gestation found an OR of 1.19 (CI: 1.1–1.28, *P* < 0.001).

Discussion

The maternal immune system has crucial importance in the success of pregnancy throughout its course from implantation, through maintenance, and outcome. Numerous alterations in the function of the immune system take place with the cellular response having a unique importance. During pregnancy, variations in maternal–fetal cellular interactions may influence the course of pregnancy and its outcome.

From this knowledge emerged the study assumption that in allergic women, in whom the immune system has ‘proved’ to respond improperly to a foreign antigen, there would also be more pregnancy complications that are known to be related to immunity. Indeed, this study demonstrates that a previous drug allergy is an independent risk factor for IUGR and spontaneous PTD.

These findings may be partially explained by the study by Breckler et al.⁴ who demonstrated that

T cells derived from peripheral blood of allergic women have an exaggerated response toward fetal antigens. Although the main question of their study was to determine the role of these responses in the development of allergic disease of the newborn, and pregnancy complications were not examined, still their findings are significant for understanding the underlying processes that may lead to our findings. Allergic women in their study were defined as women having a history of asthma, eczema, or allergic rhinitis plus a positive skin prick test to one or more common allergens, whereas our study group was defined as having a drug allergy upon routine medical history questionnaire.

Preterm labor is considered a syndrome in obstetrics with a common final pathway leading to delivery before 37 completed weeks but with various causes.¹³ Few studies support allergy as a possible pathogenesis for PTD. For example, mast cell products such as prostaglandins and histamine can cause uterus contractions in tissue culture; the uterus is rich in mast cells; and myometrium fibers of women with known allergy cultured with their specific allergen produces muscle contraction.¹⁴ Bytautiene et al.¹⁵ have shown that activation of mast cells and release of their mediators increases uterine contractility. Histamine and serotonin increased contractility of uterine strips from non-pregnant and pregnant guinea pigs, and uterine sensitivity to these agents were dependent on gestational age. They concluded that mast cells increase uterine contractility through multiple mediators, and uterine responses to these mediators are dependent on gestational age.

Accordingly, an allergic response could lead, in ways that are not yet fully understood, to a range of obstetrical syndromes, including preterm labor, and could serve as an explanation of at least part of the pathogenesis of these conditions.¹⁶

Another possible model that can explain our findings is the role of the immune system in autoimmune diseases and its previously proven effect on adverse pregnancy outcome. Perhaps the common branch in these women is the T-cell system that attacks ‘self’ or, in the context of pregnancy, attacks fetal antigens. Although the well-established connection between autoimmune diseases and adverse pregnancy outcome has been published, to the best of our knowledge, the relationship between drug allergy and pregnancy outcome has not been studied before. In this study, more women with drug allergy were found to suffer than the general population

from a range of maternal complications (hypertensive disorders, gestational diabetes mellitus) pregnancy complications (fertility treatments, PROM, PTD, cervical incompetence, CD, placental abruption), and fetal complications (IUGR). The question that these findings raise is whether this whole series of complications could be attributed to the same underlying mechanisms involved with maternal allergy. Importantly, if a common pathogenesis would be found, then a specific and problem-targeted treatment could be tailored.

Drug allergy has a genetic predisposition¹⁷ as do some obstetrical syndromes such as preterm labor and cervical incompetence; a new area studied using the genomics, proteomics, and metabolomics techniques.¹⁸ Perhaps some common genes involved in drug allergy and obstetric complications will be identified in the course of future research.

A main limitation of the study is the fact that allergy was defined based on the women's report, which was not always confirmed by objective documented doctor's diagnosis or specific skin tests. This limitation is mentioned in the literature and an objective proof of drug allergy is difficult to achieve because the tests are not standardized, the challenge tests are cumbersome and have the potential to cause harm to the patient. Also, more than half of the cases reporting a reaction attributed to a drug are actually not drug allergies.¹⁹ Still, the self report limitation of drug allergy may be non-differential and may bias results to the null. Further limitations of our study are the lack of information regarding indicator of maternal socioeconomic status, for example maternal education, information on tobacco and alcohol consumption, and use of recreational drugs in pregnancy. Unfortunately, we do not have data regarding prescription medications nor types of allergies.

Nowadays, our options as clinicians facing obstetric syndromes such as PTD and IUGR are general and focus on treatment of symptoms and observation rather than treating the underlying pathogenesis causing the syndrome. Understanding the significance of allergies as one of the possible causes for certain obstetric morbidities could lead to the development of deeper understanding of their molecular basis and perhaps in the future may guide to specific and efficient treatment.

In conclusion, some association exists between history of drug allergy and pregnancy complications. History of drug allergy was shown to be an independent risk factor for IUGR and PTD in multivariable

analysis. History of drug allergy can adversely affect the course of pregnancy but even if it does, it is not a modifiable risk factor and for now, the effect of drug therapy on reducing adverse outcome in human pregnancy is not clear. Further prospective studies are needed to investigate the nature of this association.

References

- 1 Gomes ER, Demoly P: Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005; 5:309–316.
- 2 Sargent IL: Maternal and fetal immune responses during pregnancy. *Exp Clin Immunogenet* 1993; 10: 85–102.
- 3 Hedlund M, Stenqvist AC, Nagaeva O, Kjellberg L, Wulff M, Baranov V, Mincheva-Nilsson L: Human placenta expresses and secretes NKG2D ligands via exosomes that down-modulate the cognate receptor expression: evidence for immunosuppressive function. *J Immunol* 2009; 183:340–351.
- 4 Breckler LA, Hale J, Taylor A, Dunstan JA, Thornton CA, Prescott SL: Pregnancy IFN-gamma responses to foetal alloantigens are altered by maternal allergy and gravidity status. *Allergy* 2008; 63:1473–1480.
- 5 Loke YW, King A: Immunological aspects of human implantation. *J Reprod Fertil Suppl* 2000; 55:83–90.
- 6 Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF 3rd, Petraglia F: Inflammation and pregnancy. *Reprod Sci* 2009; 16:206–215.
- 7 Mecacci F, Pieralli A, Bianchi B, Paidas MF: The impact of autoimmune disorders and adverse pregnancy outcome. *Semin Perinatol* 2007; 31:223–226.
- 8 Clowse ME, Jamison M, Myers E, James AH: A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008; 199: 127.e1–6.
- 9 Ben-David G, Sheiner E, Hallak M, Levy A: Pregnancy outcome in women with psoriasis. *J Reprod Med* 2008; 53:183–187.
- 10 Pichler WJ: Drug-induced autoimmunity. *Curr Opin Allergy Clin Immunol* 2003; 3:249–253.
- 11 Romero R, Kusanovic JP, Gomez R, Lamont R, Bytautiene E, Garfield RE, Mittal P, Hassan SS, Yeo L: The clinical significance of eosinophils in the amniotic fluid in preterm labor. *J Matern Fetal Neonatal Med*. 2010; 23:320–329.
- 12 Bytautiene E, Vedernikov YP, Maner WL, Saade GR, Romero R, Garfield RE: Challenge with ovalbumin antigen increases uterine and cervical contractile activity in sensitized guinea pigs. *Am J Obstet Gynecol* 2008; 199:658.e1–6.

- 13 Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. *Lancet* 2008; 371:75–84.
- 14 Garfield RE, Irani AM, Schwartz LB, Bytautiene E, Romero R: Structural and functional comparison of mast cells in the pregnant versus nonpregnant human uterus. *Am J Obstet Gynecol* 2006; 194:261–267.
- 15 Bytautiene E, Vedernikov YP, Saade GR, Romero R, Garfield RE: IgE-Independent Mast Cell Activation Augments Contractility of Nonpregnant and Pregnant Guinea Pig Myometrium. *Int Arch Allergy Immunol* 2008; 147:140–146.
- 16 Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassn S, Erez O, Chaiworapongsa T, Mazor M: The preterm parturition syndrome. *BJOG* 2006; 113:17–42.
- 17 Guéant JL, Guéant-Rodriguez RM, Gastin IA, Cornejo-Garcia JA, Viola M, Barbaud A, Mertes PM, Blanca M, Romano A: Pharmacogenetic determinants of immediate and delayed reactions of drug hypersensitivity. *Curr Pharm Des* 2008; 14:2770–2777.
- 18 Romero R, Espinoza J, Gotsch F, Kusanovic JP, Friel LA, Erez O, Mazaki-Tovi S, Than NG, Hassan S, Tromp G: The use of high-dimensional biology (genomics, transcriptomics, proteomics, and metabolomics) to understand the preterm parturition syndrome. *BJOG* 2006; 113:118–135.
- 19 Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P: Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004; 34:1597–1601.