Published in final edited form as:
Am J Obstet Gynecol. 2013 March ; 208(3): 215.e1–215.e6. doi:10.1016/j.ajog.2012.12.031.

The impact of glucocorticoid polymorphisms on markers of neonatal respiratory disease following antenatal betamethasone administration

David M. Haas, MD, MS, **Jessica Dantzer**, **Amalia S. Lehmann**, **Santosh Philips**, **Todd C. Skaar, PhD**, **Catherine L. McCormick, RN**, **Scott J. Hebbring, PhD**, **Jeesun Jung, PhD**, and **Lang Li, PhD**
The Indiana University School of Medicine, Indianapolis, IN

Mayo Clinic, Rochester, MN (SJH)

Abstract

OBJECTIVE—We previously demonstrated that maternal and fetal genotypes are independently associated with neonatal respiratory distress syndrome (RDS). The objective of the current study is to determine the impact of maternal and fetal single nucleotide polymorphisms (SNPs) in key betamethasone (BMZ) pathways on respiratory outcomes that serve as markers for severity of disease.

STUDY DESIGN—DNA was obtained from women given BMZ and their infants. Samples were genotyped for 73 exploratory drug metabolism and glucocorticoid pathway SNPs. Clinical variables and neonatal outcomes were obtained. Logistic regression analysis controlling for relevant clinical variables to determine SNP impact on bronchopulmonary dysplasia (BPD), need for respiratory support, and surfactant therapy use was performed.

RESULTS—109 women delivering 117 infants were analyzed. 14.5% of the infants developed BPD, 70.8% needed some respiratory support after birth, and 27.5% needed surfactant. In a multivariable regression analysis, gestational age at delivery was associated with most neonatal respiratory outcomes ($p \leq 0.01$) and chorioamnionitis was associated with BPD ($p < 0.03$). Genotypes associated with respiratory severity outcomes were as follows: BPD- Fetal *IPO13* (rs4448553; OR 0.01, 95% CI 0.00–0.92); Surfactant use- Maternal *IPO13* (rs2428953 and 2486014; OR 13.8, 95%CI 1.80–105.5 and OR 35.5, 95% CI 1.71–736.6, respectively).

CONCLUSIONS—Several discrete maternal and fetal SNPs in the Importin 13 gene (*IPO13*) may be associated with neonatal respiratory outcomes after maternal antenatal corticosteroid treatment for anticipated preterm birth.

Corresponding author: David M. Haas, MD, MS, Department of OB/GYN, 550 N. University Blvd, UH 2440, Indianapolis, IN 46202, (317) 630-7837, dahaas@iupui.edu.

DISCLOSURE: The authors report no conflict of interest.

This research to be presented at the 2012 Annual Meeting of the Central Association of Obstetricians and Gynecologists in Chicago, IL, October 2012

Keywords

antenatal corticosteroids; pharmacogenetics; preterm birth

Introduction

Antenatal corticosteroids are one of the most significant interventions to improve neonatal morbidity and mortality.[1] While they are administered to essentially all women with threatened early preterm delivery, it has been documented that not all neonates experience the same benefits. Differences in neonatal respiratory outcomes are seen in different ethnic groups, independent of gestational age, weight, and other socio-demographic factors.[2–4] Additionally, respiratory distress syndrome (RDS)-related mortality has a racial disparity that cannot be explained by demographic characteristics.[3]

Pharmacogenetics is one potential explanation for some of the differences seen in therapeutic response.[5] Genetic polymorphisms in drug metabolizing enzymes (such as the cytochrome P450 (CYP) families), transporters, and receptors have been able to explain differences in drug response and side effects for several drugs.[6–8] We have previously described genetic polymorphisms in both maternal and fetal genotype for drug metabolizing enzymes such as *CYP3A5* and *CYP3A7,* and for steroid pathway genes such as adenylate cyclase 9 (*ADCY9*) that were associated with the development of respiratory distress syndrome (RDS) in infants born to mothers after administration of betamethasone (BMZ) to enhance fetal maturity in situations of anticipated preterm delivery.[9] These associations were present after controlling for several key maternal and delivery variables including maternal race, infant gender, and gestational age at delivery. We are unaware of any study on the pharmacogenetic impact of SNP variants in other markers of severity of respiratory disease in newborns after administration of BMZ.

The objective of this project was to determine the impact of genetic polymorphisms in the drug metabolism and glucocorticoid pathways of BMZ on neonatal respiratory outcomes that serve as markers for severity of disease. Additionally, as pregnancy is a unique environment where both the maternal and fetal/placental compartments play a role in drug metabolism, we sought to determine the impact on these outcomes analyzing both the maternal and fetal genotypes.

Materials and Methods

Subjects and Samples

This was a planned secondary analysis of our BMZ pharmacogenetics cohort study. The full details of study recruitment, sample acquisition and processing, and analysis plans are contained in the original report.[9] Briefly, women admitted to the hospital with threatened preterm delivery who received at least one dose of BMZ were recruited to the study. Informed consent was obtained for all women enrolled and the governing Institutional Review Board approved the study. Participants had to be at least 18 years old and at least 23 weeks gestation. Exclusion criteria included known fetal anomaly or inability to provide consent. Standard clinical care at the providers' discretion was provided to the woman and standard neonatal resuscitation and care practices were provided by the pediatric/neonatal services. Clinical care was not guided by this observational cohort study. The outcome of need for any respiratory support included oxygen use more than "blow-by" oxygen at initial resuscitation, any ventilator support or respiratory support including continuous positive airway pressure (CPAP) or nasal cannula. Surfactant use was extracted from the neonatal chart. Surfactant was administered per general clinical guidelines by the neonatal care

providers. For babies not breathing at during the resuscitation, surfactant is usually given soon after delivery. For those babies who are breathing but are getting respiratory support, if the work of breathing is moderately or very high or if the FiO2 is over 30–40% on CPAP, then surfactant is given to the neonate. The diagnosis of bronchopulmonary dysplasia (BPD) was made by the pediatricians following standard NICHD Neonatal Research Network criteria.[10]

Maternal DNA was obtained from whole blood or from a salivary sample if unable to obtain blood. Neonatal DNA was obtained from umbilical cord blood or from buccal swabs if unable to obtain umbilical cord blood at the time of delivery. Salivary or buccal samples were collected and processed using the Oragene® saliva kit (DNA Genotek). DNA isolation was done according to manufacturer instructions. Samples were frozen at −80° C until quantification. DNA was extracted from blood samples using the QIAamp® DNA mini kits (Qiagen Inc., Valencia, CA). Manufacturer spin protocol instructions were followed for all kits. When manufacturer protocols listed steps for highly concentrated DNA those steps were followed. Isolated DNA was transferred into cryovials and all samples were stored at −80° C until quantification.

Genotyping

Seventy-three SNPs were genotyped using a combination of methods specific to the desired SNP. Genotypic designations assigned from assayed SNPs in *CYP 3A4, CYP3A5, CYP3A7,* Sulfotransferase (*SULT*), Multi-Drug Resistance gene-1 (*ABCB1*), Glucocorticoid Receptor (GR) and associated pathway gene assays are fully listed in the previous report.[9] The SNPs were selected based on known metabolism pathways of glucocorticoids and prior work on relevant SNPs for glucocorticoid response in asthma.[11–15] The individuals were genotyped for the majority of SNPs using the OpenArray™ TaqMan™ genotyping platform (Applied Biosystems, Foster City, CA, USA). A high throughput genotyping 32 SNP chip was utilized for some of the SNPs. For SNPs that did not have valid OpenArray™ assays, predesigned and commercially available Taqman or fragment analysis real-time polymerase chain reaction (PCR) assays were used following manufacturer published methods (Applied Biosystems, Foster City, CA, USA). For other SNPs that did not have predesigned assays (namely *CYP3A7* and GR), Sanger dideoxy-DNA bidirectional sequencing using high throughput capillary sequencing instrumentation was performed (http://polymorphicdna.com/reeqvardisc.html). *SULT1A1* copy number variation was determined using semi-quantitative PCR followed by fragment analysis. For each SNP, once a platform was chosen, all samples were genotyped using the same platform.

Analysis

Clinical variables of maternal age, maternal race, diabetes, estimated gestational age (EGA) at delivery, birth weight, infant gender, cesarean delivery (vs. vaginal delivery), EGA at first dose of BMZ, and the presence of chorioamnionitis were recorded as potential cofactors. EGA and the woman's due date were determined by last menstrual period confirmed by ultrasound measurements of the fetus as per routine clinical care. Neonatal outcomes of any respiratory or oxygen support after birth, surfactant use, bronchopulmonary dysplasia (BPD) were all recorded as outcomes. The outcomes of "any respiratory support after birth" did not include short amounts of oxygen or pressure support immediately after delivery. These infants were excluded from this outcome to keep the outcome representative of more significant respiratory difficulty after birth and the initial neonatal resuscitation. A single SNP association analysis was initially performed to assay for any one-on-one SNP to outcome associations. Since many clinical variables may influence the development and severity of neonatal respiratory outcomes, we rigorously tested our genetic hypothesis

through multivariate analysis. Demographic and delivery information listed above were analyzed as covariate variables in a multivariate analysis. Odds Ratios (ORs) and 95% Confidence Intervals (CI) were calculated for each SNP. Adjustment for multiple comparisons was not performed due to the small sample size.

Genotype was analyzed in the model in different ways. Genotypic models assess each of the 3 possible allele combinations separately. The dominant model assumes that one or two copies of the risk allele (variant) lead to increased risk. The recessive model assumes that the two copies of risk variant develop risk of the neonatal respiratory outcome. The trend model (or additive model) looked at an "allele-dose" effect where the more variant alleles that were present were tested for associations with risk of disease. For the analyses reported, the dominant model is reported below as it consistently performed best in this analysis and our prior analysis.[9] This means that when a listed SNP is given, the presence of at least one minor allele (Aa or aa) is compared to the homozygous wild type (AA). The full results of the recessive and additive models are not displayed due to space considerations and are available from the authors upon request. A *CYP3A5* genotype score was calculated based on the individual SNPs to categorize the mothers as either expressing or not expressing CYP3A5. Women who possess two *3 allele do not express CYP3A5 where as those who are *CYP3A5*1/*1,*1/*3 *1/*6*, or *1/*7* do demonstrate some CYP3A5 activity.[16]

Our initial sample size was calculated based on the incidence of RDS. As this is a secondary analysis, a sample size calculation was not performed for the outcomes reported here.

Results

Full details regarding the overall subject population recruited can be found in the earlier report.[9] After excluding subjects with missing DNA, the final cohort analyzed included 109 women and 117 neonates with adequate DNA and outcome data. The mean maternal age was 26.5±5.7 years. The median gravidity was 3 and median parity was 1. There were four sets of twins included. Nineteen women (16.4%) were Hispanic ethnicity. Racial distribution was white (n=58, 54%), black (36, 33%), other (11, 10%), mixed (2, 2%), and Indian (1, 1%). Paternal ethnicity was Hispanic for 17 (16%) of subjects. Paternal race was white (46, 41%), unknown (29, 26%), black (27, 24%), other (9, 8%), and Indian (1, 1%). Thirteen women had gestational diabetes (11%). The gestational age at receiving the first dose of BMZ was 28.8±3.3 weeks gestation and the mean gestational age at delivery was 32.2±3.9 weeks. The admission diagnoses were preterm labor (37%), preterm premature ruptured membranes (35%), preeclampsia (15%), other (10%), and placenta previa (3%). Tocolytic medications were given to 35% of the women, with nifedipine and magnesium sulfate being the most commonly used (45% and 42% respectively of those receiving tocolytics). "Rescue" doses of BMZ were used in 8 women. The mean number of days from first dose of BMZ to delivery was 23.4±22.2. All but four subjects received two doses of BMZ. Sixty-four (55%) women delivered babies vaginally.

The mean birth weight of the babies was 1913±785 grams. Half of the babies were male (51%). Median 1 and 5 minute Apgars were 7 and 8 respectively. Sixty-four babies were diagnosed with RDS (49%) and subsequently 19 were diagnosed with BPD (14.5%). Necrotizing enterocolitis developed in 9 (7%) babies, IVH in 10 (7.6%), and neonatal death occurred in six (4.6%) of the babies. The gestational age at birth of the babies who died ranged from 24–29 weeks. Neonatal sepsis occurred in 23 (17.6%) of the babies. 39 babies (30%) were intubated, 70 (53.4%) placed on CPAP, 34 (26%) on high-flow nasal cannula, and 38 (29%) treated with nasal cannula room air (FiO2 of 0.21) for respiratory support. Thus, there were 80 infants who required some form of respiratory support beyond the initial

newborn resuscitation (70.8%). Surfactant was given to 36 (27.5%) of the babies. Mean total hospital days was 40±39 and mean total days of respiratory support in hospital was 19±33.

All SNPs assayed were in Hardy-Weinberg equilibrium ($p \geq 0.00083$) after correction for multiple comparison. The overall SNP frequencies can be found in the original report.[9] Maternal carriers of at least one copy of the minor allele in *CYP3A7* and *CRHR1* were associated with BPD (*CYP3A7:* rs113874418, p=0.006; novel *CRHR1* sequence: Chr. 17-43895531, p=0.006; *CYP3A7*1E*: rs28451617, OR 4.97, 95% CI 1.12–22.05, p=0.02). Fetal SNP in the glucocorticoid receptor was associated with BPD (*NR3C1*: rs41423247, OR 2.56, 95% CI 1.11–5.95, p=0.02). No maternal single SNPs were associated with the outcome of any respiratory support although several had p values just above 0.05. The exon 12 SNP in the *ABCB1* gene was associated with the need for respiratory support in the newborns (rs1128503, OR 2.23, 95% CI 1.05–4.74, p=0.03). A fetal SNP in *OLR1* was associated with surfactant replacement therapy (rs3736233, OR 0.35, 95% CI 0.17–0.71, p=0.003).

Table 1 displays significant genetic analysis results from the multivariable logistic regression analysis for the three outcomes marking severity of neonatal respiratory disease. In a multivariable regression analysis, gestational age at delivery was associated with most neonatal respiratory outcomes ($p \leq 0.01$) and chorioamnionitis was associated with BPD ($p < 0.03$). Genotypes associated with non-RDS respiratory outcomes were as follows: Surfactant use- Maternal *IPO13* (rs2428953 and 2486014; OR 13.8, 95%CI 1.80–105.5 and OR 35.5, 95% CI 1.71–736.6, respectively); BPD- Fetal *IPO13* (rs4448553; OR 0.01, 95% CI 0.00–0.92). Trends were seen for independent associations of maternal *ABCB1* exon 26 with the need for respiratory support (p=0.05), fetal *OLR1* with surfactant use (p=0.07), and maternal *CYP3A7*1E* and *TRAPPC5/FCER2* with BPD (p=0.07 for both).

Comment

This study demonstrates that genetic variations in key BMZ pathway genes may be associated with severity of respiratory morbidity after BMZ administration for anticipated preterm delivery. Carrying minor alleles in these genes may be responsible for some of the outcome differences seen in other larger trials. As providers search for ways to improve therapy for anticipated preterm delivery, understanding the role of pharmacogenetics in pregnancy therapeutics is important.

Some of these significant SNPs were also found to be associated with the incidence of RDS.[9] The fact that in the present secondary analysis that several SNPs are associated with severity of respiratory distress indicates that there may be a set of key pathway enzymes, transporters, and receptors responsible for severity of outcomes and/or the degree of response of the fetal lung tissue to maternally administered BMZ. As we are unaware of other genetic association studies with BMZ response or severity of newborn respiratory outcomes, these findings can serve to generate hypotheses for future confirmatory pharmacogenetic studies.

Importin-13 (IPO-13) genetic variations have been associated with improved airway responsiveness to glucocorticoids in children with asthma.[12] We found that babies with any rs4448553 variant allele had a greatly reduced incidence of BPD (OR 0.01). Neonates with this genotype were not found to have an association with the diagnosis of RDS in the primary study.[9] Thus, it is possible that while babies with this SNP allele may be diagnosed with RDS just as frequently as those who do not carry it, babies who do not have this SNP have a much higher chance of their RDS being severe and persisting to BPD. It is unclear,

however, why the maternal *IPO-13* minor alleles would be conversely associated with more surfactant use. This will be explored in future studies.

The CYP3A family of enzymes is responsible for the majority of drug metabolism in humans and demonstrates increased activity in pregnancy.[17, 18] CYP3A7, primarily a fetal enzyme that regresses in soon after birth, has known polymorphisms that allow its expression to persist even into adulthood.[19] Thus, more drug metabolizing enzyme may be present to metabolize drugs. As seen in this study, infants born to women with the *CYP3A7*1E* SNP have a higher rate of BPD, potentially indicating that less BMZ is able to act on the fetus. Our prior report demonstrated that this same polymorphism in the fetus was strongly associated with RDS (OR 23.68) and that the SNP in the mother similarly showed a trend toward a strong association with RDS (p=0.09).[9] This combination of findings may lead to further study to better understand the role of drug metabolizing enzyme genotypes on fetal effects of drugs given to mothers. Having pharmacokinetic data in addition to this genetic data would allow for a more detailed analysis of drug metabolizing enzyme polymorphism's potential impact.

The glucocorticoid receptor and pathways have been well characterized in the asthma literature.[13–15] We are unaware of any other investigation into the genetics of this pathway and BMZ response from antenatal corticosteroids. The polymorphism identified in *FCER2* to be strongly associated with BPD has also been found to be robustly associated with asthma exacerbations in children taking inhaled corticosteroids.[20, 21] Thus, this polymorphism may be a marker for lack of ability to respond to exogenous steroids. While this preliminary finding of BPD possibly associating with this SNP after antenatal corticosteroid use needs to be replicated, it may serve to be a potential marker for mother-infant pairs who may not respond to the usual dosage and formulation of antenatal corticosteroids. More work needs to be done in this area.

Oxidized low density lipoprotein receptor 1 (OLR1) has been shown to have associations[22] with cardiovascular and endothelial dysfunction. The neonatal SNP allele association with having less need for surfactant use is novel and will be explored further in future studies.

The *ABCB1* gene encodes for p-glycoprotein efflux transporter. The exon 26 SNP was found to be protective against needing respiratory support after birth. The haplotype analysis for the three *ABCB1* exons has been performed for other drugs with mixed associations.[8, 18, 23] In general, the more variant alleles, the less p-glycoprotein activity.[18] Thus a woman having a variant allele could have diminished activity of the placental efflux transporter. In turn, more of the drug would be allowed to cross the placenta to act on the fetus to stimulate lung maturation. While this may be somewhat oversimplified, it has physiologic plausibility and should be further studied.

As a planned secondary analysis of an initial investigation into pharmacogenetic impact on BMZ therapy, this study has some limitations. While the sample size was large enough to demonstrate significant genotype effects in the multivariate analysis, the p values would not stand up to adjustments for multiple comparisons with the number of genotypes analyzed. However, controlling for the most important clinical predictors of severe respiratory morbidity and other adverse outcomes allows for isolation of the genotype effect. A larger trial is being designed to overcome this limitation. A larger study would also allow for more meaningful analysis of the less frequent outcomes. We do not have pharmacokinetic data on all of these subjects. As most of them (93%) delivered > 48 hours after the BMZ was given, the concentrations of BMZ would be expected to be undetectable.[24] It is also possible that the polymorphisms identified in the glucocorticoid pathway as being protective against BPD and other markers of respiratory morbidity severity exert an effect on these outcomes

independent of BMZ administration. As independent genetic associations with BPD, need for respiratory support, and need for surfactant administration have not been reported in the literature to our knowledge, replication or analysis of this question in an existing data set is needed. There was also no control group of preterm deliveries for women who did not receive BMZ. As very few women deliver at less than 34 weeks gestation without receiving BMZ in our institution, obtaining this control group would be difficult and it would be unethical to withhold BMZ from these women.

Expanding the pharmacogenetic knowledge base in this and other areas of obstetrics can serve to be clinically used. Knowing someone's genetic profile for drug metabolizing enzymes, transporters, and receptors before administering a drug like BMZ may allow for more individualized dosing of the drug or better prediction of effectiveness or toxicity. While this pharmacogenetically-informed therapy is still far off in obstetrics, some modeling techniques have been utilized to develop dosing strategies for other medications in pregnancy.[25]

In conclusion, this study identified potential individual candidate polymorphisms in drug metabolizing enzymes and steroid pathway genes that may be associated with BPD, the need for respiratory support, or surfactant use after birth after antenatal corticosteroid use. It is possible that future studies may confirm the pharmacogenetic potential for pregnancy therapeutics in areas such as antenatal corticosteroids. While more research is necessary, obstetricians should pursue integrated translational research on drugs in pregnancy so we can truly optimize therapy for pregnant women and their babies.

Acknowledgments

This work was supported by grants 5K23HD055305 (Haas) and 5U01HD063094.

The authors wish to acknowledge the support and guidance of Dr. Richard Weinshilboum (Mayo Clinic), Scott Weiss (Harvard), David Flockhart (Indiana), and Kelan Tantisira (Harvard) for their expertise in designing the study.

References

1. ACOG practice bulletin. Management of preterm labor. Number 43, May 2003. Obstet Gynecol. 2003; 101:1039–1047. [PubMed: 12738177]
2. Frisbie WP, Forbes D, Pullum SG. Compromised birth outcomes and infant mortality among racial and ethnic groups. Demography. 1996; 33:469–481. [PubMed: 8939419]
3. Frisbie WP, Song SE, Powers DA, Street JA. The increasing racial disparity in infant mortality: respiratory distress syndrome and other causes. Demography. 2004; 41:773–800. [PubMed: 15622954]
4. Kavvadia V, Greenough A, Dimitriou G, Hooper R. Influence of ethnic origin on respiratory distress syndrome in very premature infants. Arch Dis Child Fetal Neonatal Ed. 1998; 78:F25–F28. [PubMed: 9536836]
5. Ensom MH, Chang TK, Patel P. Pharmacogenetics: the therapeutic drug monitoring of the future? Clin Pharmacokinet. 2001; 40:783–802. [PubMed: 11735602]
6. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy. Clin Pharmacol Ther. 2011; 90:328–332. [PubMed: 21716271]
7. Grossniklaus D. Testing of VKORC1 and CYP2C9 alleles to guide warfarin dosing. Test category: pharmacogenomic (treatment). PLoS Curr. 2010; 2
8. Crettol S, Venetz JP, Fontana M, Aubert JD, Pascual M, Eap CB. CYP3A7, CYP3A5, CYP3A4, and ABCB1 genetic polymorphisms, cyclosporine concentration, and dose requirement in transplant recipients. Ther Drug Monit. 2008; 30:689–699. [PubMed: 18978522]

9. Haas DM, Lehmann AS, Skaar T, et al. The impact of drug metabolizing enzyme polymorphisms on outcomes after antenatal corticosteroid use. Am J Obstet Gynecol. 2012; 206(447):e17–e24. [PubMed: 22445700]
10. Stoll BJ, Hansen NI, Bell EF, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010; 126:443–456. [PubMed: 20732945]
11. Hawkins GA, Lazarus R, Smith RS, et al. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. J Allergy Clin Immunol. 2009; 123:1376–1383. e7. [PubMed: 19254810]
12. Raby BA, Van Steen K, Lasky-Su J, et al. Importin-13 genetic variation is associated with improved airway responsiveness in childhood asthma. Respir Res. 2009; 10:67. [PubMed: 19619331]
13. Tantisira K, Weiss S, Tantisira K, Weiss S. The pharmacogenetics of asthma treatment. Curr Allergy Asthma Rep. 2009; 9:10–17. [PubMed: 19063819]
14. Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet. 2004; 13:1353–1359. [PubMed: 15128701]
15. Weiss ST, Lake SL, Silverman ES, et al. Asthma steroid pharmacogenetics: a study strategy to identify replicated treatment responses. Proc Am Thorac Soc. 2004; 1:364–367. [PubMed: 16113459]
16. Lamba JK, Lin YS, Schuetz EG, Thummel KE. Genetic contribution to variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev. 2002; 54:1271–1294. [PubMed: 12406645]
17. Cholerton S, Daly AK, Idle JR. The role of individual human cytochromes P450 in drug metabolism and clinical response. Trends Pharmacol Sci. 1992; 13:434–439. [PubMed: 1293869]
18. Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005; 192:633–639. [PubMed: 15696014]
19. Smit P, van Schaik RH, van der Werf M, et al. A common polymorphism in the CYP3A7 gene is associated with a nearly 50% reduction in serum dehydroepiandrosterone sulfate levels. J Clin Endocrinol Metab. 2005; 90:5313–5316. [PubMed: 15985487]
20. Koster ES, Maitland-van der Zee AH, Tavendale R, et al. FCER2 T2206C variant associated with chronic symptoms and exacerbations in steroid-treated asthmatic children. Allergy. 2011; 66:1546–1552. [PubMed: 21958076]
21. Tantisira KG, Silverman ES, Mariani TJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. J Allergy Clin Immunol. 2007; 120:1285–1291. [PubMed: 17980418]
22. Hou XW, Wang LF, Wang N, et al. The G501C polymorphism of oxidized LDL receptor gene [OLR-1] is associated with susceptibility and serum C-reactive protein concentration in Chinese essential hypertensives. Clin Chim Acta. 2008; 388:200–203. [PubMed: 18054331]
23. Hebert MF, Easterling TR, Kirby B, et al. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. Clin Pharmacol Ther. 2008; 84:248–253. [PubMed: 18288078]
24. Ballard PL, Granberg P, Ballard RA. Glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy to prevent respiratory distress syndrome. J Clin Invest. 1975; 56:1548–1554. [PubMed: 1202085]
25. Hebert MF, Ma X, Naraharisetti SB, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther. 2009; 85:607–614. [PubMed: 19295505]

Table 1

Multivariable analysis of genetic predictors of selected neonatal respiratory outcomes

Genetic SNP and outcome	OR (95% CI)	p value
Respiratory Support		
Maternal *		
ABCB1 ex26 (rs1045642)	0.18 (0.03–1.02)	0.05
Fetal- none significant in this model		
Surfactant use		
Maternal		
IPO13 (rs2428953)	13.8 (1.80–105.5)	0.01
IPO13 (rs2486014)	35.5 (1.71–736.6)	0.02
Fetal		
OLR1 (rs3736233)	0.26 (0.05–1.16)	0.07 **
Bronchopulmonary dysplasia		
Maternal		
*CYP3A7*1E* (rs28451617)	11.5 (0.85–156.9)	0.07
TRAPPC5/FCER2 (rs28364072)	11.4 (0.84–153.9)	0.07
Fetal		
IPO13 (rs4448553)	0.01 (0.00–0.92)	0.04

OR= Odds Ratio, CI= Confidence Interval, Results of the dominant model are displayed. Comparisons are for the presence of any minor allele (Aa or aa) to wild type homozygous (AA). Analyses controlled for maternal age, maternal race, diabetes, estimated gestational age (EGA) at delivery, birth weight, infant gender, cesarean delivery (vs. vaginal delivery), EGA at first dose of BMZ, and the presence of chorioamnionitis.

* NR3C1 glucocorticoid receptor (rs41423247) had an OR=0.27, p=0.05 in the additive model only

** This SNP was significant with p<0.05 in the additive and recessive regression models