Published in final edited form as:

Am J Obstet Gynecol. 2011 August ; 205(2): 137.e1–137.e7. doi:10.1016/j.ajog.2011.03.045.

Beta-2 adrenoceptor genotype and progress in term and late preterm active labor

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Abstract

OBJECTIVE—To evaluate whether beta-2 adrenoceptor genotype at a functional polymorphic site encoding for amino acid residue 16 influences rate of cervical dilatation in term and late preterm active labor.

STUDY DESIGN—Subjects that underwent vaginal delivery at 34 or greater weeks gestational age between May, 2006, and August, 2007, were identified. Each subject had provided venous blood from which DNA was extracted for beta-2 adrenoceptor genotyping. Digital cervical examinations with paired examination times were collected from intrapartum records. Rate of cervical dilatation in active labor was determined using linear regression and rates were compared between genotype groups.

RESULTS—Among 401 subjects with satisfactory genotype and intrapartum data, overall rate of active labor was 0.76+/-0.01 cm/hr. When labor was compared by genotype, homozygous Arg/Arg16 subjects progressed at a slower rate (0.64+/-0.03 cm/hr) than all other pooled genotypes (0.8+/-0.02 cm/hr).

CONCLUSION—Homozygous beta-2 adrenoceptor genotype encoding for Arg/Arg16 was associated with slower progress in active labor.

Keywords

Beta-2 adrenoceptor; labor progress; polymorphism

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A portion of this work was presented at the 40th annual meeting of the Society for Obstetric Anesthesia and Perinatology, Chicago, IL, April 30 - May 4, 2008

This study was conducted in New York, New York and Switzerland

Introduction

Human parturition is a complex process, with numerous factors contributing to the speed and outcome of labor and delivery. Although genetic differences between individuals are believed to contribute to intrapartum phenotype, an association between genetic variation and labor progress has yet to be demonstrated at the single-gene level.

The beta-2 adrenoceptor (β_2 AR) is the best studied of all G-protein-coupled receptors. It is ubiquitously expressed throughout the human body, including on smooth muscle of the uterine corpus and cervix^{1, 2}, and its stimulation with endogenous and exogenous agonists elicits smooth muscle relaxation. Studies suggest *ADRB2* genetic variation at nucleotides encoding amino acids 16 and 27 is associated with variability in risk of spontaneous preterm delivery, and possibly responsiveness to β -agonist therapy.³⁻⁶ In particular, *ADRB2* polymorphic variation encoding for Arg/Arg homozygosity at codon 16 appears to be strongly associated with protection against spontaneous preterm delivery. As these common polymorphisms are believed to affect down-regulation and desensitization of the β_2 AR,⁷⁻⁹ the relationship between *ADRB2* genotype and preterm delivery may involve differential maternal responsiveness to circulating endogenous catecholamines or pharmacologic β -agonist causing an altered threshold for experiencing preterm labor and delivery.

Given the compelling clinical data suggesting an association between β_2 AR genotype and myometrial activity leading to preterm delivery, and the known effects of *ADRB2* genotype on β_2 AR receptor function and response to agonist stimulation, it is biologically plausible that this putative mechanism also extends to variability in term and late-preterm labor progress. The hypothesis tested was that *ADRB2* genotype resulting in Arg/Arg16 homozygosity is associated with a slower rate of labor progress in successful term and late-preterm labor when compared to subjects possessing all other genotypes.

Materials and Methods

Approval for this investigation was obtained from the Institutional Review Board of Columbia University Medical Center.

This study was a retrospective analysis of a subset of participants in an ongoing prospective cohort designed to observe the relationship between β_2 AR genetic variation and preterm labor and delivery. Gravidas with singleton pregnancies presenting for routine obstetrical care between 8 and 20 weeks gestational age were approached for participation. Informed written consent was obtained from each subject to allow investigators to obtain and evaluate data and genetic information (genomic DNA) related to pregnancy. A 5 mL venous blood sample was obtained from each participant for genetic analysis. Demographic, medical, and obstetrical information was collected from all subjects.

Inclusion for analysis in the study cohort required vaginal delivery at Columbia University Medical Center with a gestational age greater than or equal to 34 weeks. 34 weeks was selected as a cut-off due to an institutional practice of withholding tocolytic medications to suppress late-preterm labor. Exclusion criteria included multiple gestations, major fetal malformations, and fetal demise.

For all qualifying subjects, antenatal, intrapartum, and maternal and neonatal outcomes data were collected following delivery through a review of the Columbia University Medical Center electronic medical record system (Eclipsys XA, Eclipsys Corporation, Atlanta, GA). Data were automatically extracted from archived template-based narrative notes and intrapartum flow sheets by a biomedical informatician (C.W.). To validate the electronic

extraction, all physician and nursing notes and flow charts were manually reviewed by a single investigator (R.M.).

Subjects were excluded from analysis if there was insufficient, incomplete, or inconsistent intrapartum data, or if genotyping studies were unsuccessful. Subjects lacking a documented cervical dilatation prior to 10 cm in active labor were also excluded, as a minimum of two data points in active labor are necessary to estimate a rate of cervical dilatation by linear regression. Active labor was defined as the period from 4 cm until 10 cm in a patient with regular contractions effecting cervical change.

Pregnancy dating was confirmed or revised using a standardized institutional ultrasound dating policy. All ultrasound records were reviewed by a single investigator (R.M.).

DNA was extracted and purified with a Puregene extraction kit (Gentra, Minneapolis, MN) and tested for quantity, purity, and quality by optical densitometry (ratio, 260/280 nm) and gel electrophoresis. For the identifications of the polymorphisms of the *ADRB2* gene, 60 ng DNA was amplified by polymerase chain reaction (96-well microtiter plate block; Biometra, Gottingen, Germany) using specific and validated primers for single-copy DNA regions surrounding polymorphisms Arg16Gly and Gln27Glu located in the single exon of *ADRB2*, as described in previous work.¹⁰ *ADRB2* genotype of both single-nucleotide polymorphisms at codons encoding amino acids 16 (rs1042713) and 27 (rs1042714) was determined by Sanger sequencing reaction and electrophoresis on a fluorescent DNA fragment analyzer apparatus (ABI3100; Applied Biosystems, Foster City, CA).

Subjects were categorized into two genotype groups: those with homozygous genotype encoding for Arg/Arg16 and a control group consisting of all other genotypes (encoding for either Arg/Gly16 or Gly/Gly16) based on our previous findings in preterm labor cohorts.^{3, 6} Groups were compared for selected demographic and obstetrical variables. Chi-square or Fisher's exact test were used to compare categorical variables and the unpaired student's t-test was used to compare means of continuous variables between groups. STATA 10 (StataCorp LP, College Station, Texas) was used for analysis of demographic and obstetrical data.

For a given genotype group, all timed intrapartum cervical examinations were plotted, with the ordinate representing cervical dilatation (in centimeters from 4 to 10 unless otherwise specified) and the abscissa representing hours before full dilatation. Linear regressions were created using the least squares fitting method with 95% confidence intervals using Origin 8.0 software (OriginLab Corporation, Northampton, MA). Labor rates were considered to be distinct between genotype groups if the 95% confidence bounds did not overlap. Statistical differences in labor rates among groups were calculated in PLT Tools (Plessthan.com) for NONMEM (Version 6, ICON Development Solutions, Ellicott City, MD). For each dataset, the timed cervical exams were fit with a linear equation as a naïve pooled data fit (assumption of no intra-individual variability). Random noise was treated as an additive term. Genotype was introduced as an additional variable. The model with genotype was compared to an identical model without it using the likelihood ratio test. If inclusion of the covariate decreased the log likelihood by >3.84 (χ^2 distribution, $p < 0.05$ with 1 degree of freedom), then the covariate was considered statistically justified.

Genotype groups were also created and compared as described above for genotype at codon 27. Lastly, subjects were categorized into putative *ADRB2* haplotype groups based on genotype at the two studied polymorphic sites encoding for codons 16 and 27. Haplotype groups were compared as described above for genotype groups, except that ANOVA was used for comparisons of means of continuous variables among haplotype groups.

With respect to haplotype assignments, it is well-established that there is strong linkage disequilibrium between *ADRB2* codons encoding amino acids 16 and 27, with Arg16 almost never occurring in the presence of Glu27.¹¹ Because of this relationship, haplotype can be imputed in the vast majority of cases from the genotypes at the two codons. Therefore, subjects double-heterozygous at codons encoding amino acids 16 and 27 are assumed to be haplotype Arg16Gln27 and haplotype Gly16Glu27, with a minimal chance that any subject is mis-assigned.

The sample size was determined by the number of subjects enrolled into the preterm labor trial between May 2006 and August 2007 meeting the inclusion criteria specified above. Post-hoc evaluation of effect size (defined as difference in rate of active labor based upon β_2 AR genotype) was estimated with a bootstrap analysis with replacement using 1000 iterations of our final model that included a difference in active labor rate between Arg/Arg16 subjects and subjects with all other genotypes using the available data set in PLTtools (Plessthan.com) and NONMEM (ICON Development Solutions, Ellicott City, MD).

Results

Between May, 2006, and August, 2007, 925 unselected gravidas were entered into the prospective β_2 AR-Preterm Delivery prospective cohort (figure 1). Of these, 805 (87%) subjects delivered a singleton pregnancy with gestational age of 34 or greater weeks. 293 (36.4%) were excluded due to cesarean delivery, leaving 512 subjects with vaginal deliveries. Genotype and adequate intrapartum labor data were available for 401 (78%) subjects.

For the majority (70.2%) of pregnancies, last menstrual period or in-vitro fertilization dating was consistent with first trimester sonographic biometry. 23.1% of pregnancies were assigned a revised estimated date of delivery following first-trimester ultrasound. 6.8% of pregnancies had an estimated date of delivery confirmed or reassigned following second-trimester sonogram. No pregnancy was re-dated based on third-trimester ultrasound findings.

Mean gestational age at delivery was 276 days (39 weeks, 3 days). 5% of deliveries were between 238 days (34 weeks) and 258 days (36 weeks, 6 days). 9.8% of deliveries were 287 days (41 weeks) or greater. There was no significant difference in gestational age at delivery according to genotype in this cohort.

With respect to *ADRB2*-encoding genotype, the overall study group consisted of 20% homozygous Arg/Arg16 subjects (n=80), 44.6% heterozygous Arg/Gly16 subjects, and 35.4% homozygous Gly/Gly16 subjects (n=142). When homozygous Arg/Arg16 subjects were compared to the control group of subjects with other genotypes (Arg/Gly16 or Gly/Gly16), there was no significant difference in demographic characteristics (table 1) or obstetrical outcomes (table 2) between groups.

For the entire cohort, the overall rate of active labor was 0.76 ± 0.01 cm/hr (adjusted r^2 0.92). Homozygous Arg/Arg16 subjects labored significantly more slowly (rate 0.64 ± 0.03 cm/hr, adjusted r^2 0.92) than the control group of subjects possessing all other genotypes (rate 0.8 ± 0.02 cm/hr, adjusted r^2 0.93; $p < 0.001$) (figure 2). There was suggestion of a gene-dose effect at the 16 position, with heterozygous subjects (Arg/Gly16) laboring at an intermediate rate (rate 0.78 ± 0.02 cm/hr, adjusted r^2 0.93), and Gly/Gly16 homozygous subjects appearing to labor at the fastest rate (rate 0.82 ± 0.03 cm/hr, adjusted r^2 0.93), although a statistical difference between Arg/Gly16 and Gly/Gly16 subgroups was not demonstrated.

To determine if these findings were influenced by confounding factors, selected *post-hoc* sub-group analyses were performed (figure 3). Although subgroup analyses were not planned, bootstrap analysis showed our sample size was large enough to allow for it. Given the approximate 20% occurrence of the Arg/Arg16-encoding genotype in our sample, we would have 80% power to detect a difference in rate of 0.15 cm/hr between Arg/Arg16-encoding genotype and all other genotypes at $p < 0.05$. Therefore, subgroups were created to explore potential confounders such as: nulliparity, subjects 4 cm dilated without active labor, preterm labor <37 weeks, and labor induction. The relationship between Arg/Arg16-encoding genotype at the 16 position of *ADRB2* and slower active labor was preserved in nearly all subgroups analyzed.

When the subgroup restricted to term labor ≥ 37 weeks gestational age was analyzed (figure 3a), the overall rate of labor was 0.75 ± 0.01 cm/hr (adjusted r^2 0.93). Subjects with genotype encoding for Arg/Arg16 labored significantly more slowly (0.63 ± 0.03 cm/hr, adjusted r^2 0.92) than subjects of all other genotypes (0.79 ± 0.02 cm/hr, adjusted r^2 0.93; $p < 0.001$).

A similar effect was noted when active labor was assumed to begin at cervical dilatations of 5 or greater centimeters (figure 3b). The overall labor rate was 0.78 ± 0.02 cm/hr (adjusted r^2 0.96), with the Arg/Arg16 subgroup ($n=72$) progressing at a significantly slower rate (0.71 ± 0.03 cm/hr, adjusted r^2 0.96) than all other genotypes ($n=277$, 0.8 ± 0.02 cm/hr, adjusted r^2 0.96; $p=0.02$).

When subjects were stratified based upon induction status, parturients experiencing spontaneous labor onset (figure 3c) had an overall rate of active labor of 0.74 ± 0.02 cm/hr (adjusted r^2 0.94). Within this subgroup, subjects with genotype encoding for Arg/Arg16 ($n=55$) labored significantly more slowly (0.61 ± 0.03 cm/hr, adjusted r^2 0.92) than subjects of all other genotypes ($n=220$, 0.79 ± 0.02 cm/hr, adjusted r^2 0.94; $p < 0.001$). When subjects undergoing labor inductions were analyzed (figure 3d), the overall rate of progress in active labor was 0.82 ± 0.03 cm/hr (adjusted r^2 0.92). Within this subgroup, Arg/Arg16-encoding subjects ($n=25$) exhibited progress in active labor (0.78 ± 0.06 cm/hr, adjusted r^2 0.92) that was not different from labor progress for subjects of other genotypes ($n=101$, 0.82 ± 0.03 cm/hr, adjusted r^2 0.9).

When genotype at the polymorphic site encoding for codon 27 was analyzed, homozygous Gln/Gln27-encoding subjects labored most slowly (rate 0.73 ± 0.02 cm/hr), heterozygous subjects (Gln/Glu27-encoding) labored at an intermediate rate (rate 0.76 ± 0.02 cm/hr), and homozygous Glu/Glu27-encoding subjects labored at the fastest rate (rate 0.89 ± 0.04 cm/hr; $p < 0.01$).

With respect to haplotype assignments, 99.5% of eligible subjects were assigned to six haplotype groups. 78 subjects (19.5%) were double-homozygous Arg/Arg16-Gln/Gln27 and 39 subjects (9.8%) were double-homozygous Gly/Gly16-Glu/Glu27. Two gravidas with Arg/Arg16-Gln/Glu27 haplotype were excluded from analysis due to the rarity of their Arg/Arg16-Gln/Glu27 haplotype (*vide supra*).

When labor rates were compared between the six haplotype groups (figure 4), differences in labor progress were observed. The double-homozygous Arg/Arg16-Gln/Gln27 group progressed at the slowest rate of active labor (0.63 ± 0.02 cm/hr), the double-homozygous Gly/Gly16-Glu/Glu27 group progressed at the most rapid rate of labor (0.89 ± 0.04 cm/hr), and the remaining haplotype groups progressed at varying intermediate rates (from 0.74 ± 0.03 cm/hr to 0.84 ± 0.05 cm/hr). These results suggest a genetic dose-response effect, with a “slow” haplotype (Arg/Arg16-Gln/Gln27), a “fast” haplotype (Gly/Gly16-Glu/Glu27), and “in-between” remaining pooled haplotypes ($p < 0.001$).

Comment

This study contributes to a growing body of literature implicating functional polymorphisms in the beta-2 adrenoceptor gene (*ADRB2*) with obstetrical phenotypic variation. The observation that *ADRB2* genotype influences term and late-preterm labor progress complements findings that link *ADRB2* genotype to risk for spontaneous preterm labor and delivery. In addition to our primary finding that homozygous genotype encoding for Arg/Arg16 is associated with a slower rate of labor progress when compared to other genotypes, an association appears to exist between polymorphic variation encoding for the amino acid residue at codon 27 and labor progress. Furthermore, these results suggest an association between *ADRB2* haplotype and labor progress with a pattern suggestive of a genetic dose-response effect.

These findings complement previous studies that demonstrated a protective role for *ADRB2* Arg/Arg16-encoding homozygosity in preterm delivery. Landau *et al.* performed a case-control study that strongly associated *ADRB2* Arg/Arg16 homozygosity with a decreased incidence of preterm delivery among Hispanic subjects in New York City.³ 251 subjects delivering at term and 28 subjects experiencing spontaneous preterm delivery underwent *ADRB2* genotyping. A striking difference was observed in genotype frequency between groups, with Arg/Arg16 homozygosity encountered in 78 (31%) term subjects but only one (3.6%) preterm subject (odds ratio >12). A methodologically similar study by another group independently supported a strong association of Arg/Arg16 homozygosity with protection against preterm delivery within a Hungarian cohort.⁵

Landau *et al.* conducted a follow-up investigation to examine the effect of *ADRB2* genotype on the occurrence of preterm labor and responsiveness to β -agonist tocolysis in Geneva, Switzerland.⁶ Among patients with preterm labor treated with a standardized intravenous hexaprenaline tocolytic regimen, pregnancy was significantly prolonged in patients with Arg/Arg16 homozygous genotype when compared to all other genotypes (median 69 versus 58 days).

If *ADRB2* genotype is associated with preterm labor and delivery, perhaps through differential effects of receptor regulation of uterine smooth muscle function, it is biologically plausible that the same genetically-encoded variation in β_2 AR activity at the myometrial level could influence progress in active labor. Based upon our prior work with preterm delivery, we hypothesized that homozygous Arg/Arg16 subjects would labor most slowly, as the resistance to down-regulation of β_2 ARs thought to be associated with this genotype might be expected to decrease the effectiveness of contractions in active labor just as it is believed to decrease risk for preterm delivery. Our current findings are consistent with this hypothesis. This finding is also robust, as it persisted in multiple sub-group analyses restricted to labor ≥ 37 weeks, labor ≥ 5 cm, and labor of spontaneous onset.

This study had several limitations. Due to its observational nature, intrapartum cervical examinations were neither rigorously timed nor standardized between examiners, introducing elements of random error into intrapartum data collection. However, as there is no *a priori* reason why these inconsistencies would disproportionately affect a given genotype or haplotype group, it is difficult to envision how they could significantly affect these findings.

Our definition of active labor relied upon an arbitrary initial starting point of cervical dilatation of 4 or greater cm in a patient with regular contractions effecting cervical change. On an individual basis, some gravidas may still be in early labor with this examination. Regardless, the fact that this study's findings persisted in a sub-group analysis where active labor was considered from 5 cm of dilatation suggests that the cervical dilation selected as

the transition point for active labor used in this investigation did not greatly influence its findings. Our definition of active labor starting at 4 cm may explain an overall rate of active labor for the entire study group that was slower than expected.

Our analysis of labor progress relied on a linear fit for active-phase labor. While this is a classic population-based method, it is of course possible – if not likely – that many active labors are not linear in progress.¹²⁻¹⁴ Newer sophisticated methods of analyzing labor curves should be considered when the amount and quality of data will support such analyses.

We suggest that this study should be considered strong preliminary evidence suggesting an *ADRB2* genetic effect on active labor course, awaiting confirmation with larger prospective studies. A prospective investigation into *ADRB2* and other candidate genes may serve to elucidate polymorphisms relevant to a patient's "labor genotype." These data also support *in vitro* study of myometrial contraction patterns based upon *ADRB2* genotype. These are planned directions for our group's work.

This study is novel in that it demonstrates an association between polymorphic variation in a single gene and labor progress. Each day in labor units across the country, obstetricians attempt to predict labor success based upon a patient's intrapartum performance, physical characteristics, and past success. As the national cesarean delivery rate substantiates, these predictions often prove to be flawed, with labor dystocia a leading indication for primary cesarean deliveries.¹⁵⁻¹⁷ In the future, with a more complete understanding of the multiple genetic influences that likely contribute to labor progress, it is possible that knowledge of a gravida's complete "labor genotype" during the interpretation of her intrapartum course may assist the obstetrician when determining whether labor progress is adequate for that individual, affording tolerance when conventional management would indicate the need for cesarean delivery. This finding of a genetic effect, if confirmed and shown to be causal, may also have implications for the underlying mechanism of initiation and modulation of human labor.

Acknowledgments

Financial acknowledgment: Funding for this project was received through NIH grant R01 HD048805, principal investigator Richard Smiley, M.D., Ph.D.

References

1. Hayashida DN, Leung R, Goldfien A, Roberts JM. Human myometrial adrenergic receptors: identification of the beta-adrenergic receptor by [3H]dihydroalprenolol binding. *Am J Obstet Gynecol.* 1982; 142:389–93. [PubMed: 6120652]
2. Whitaker EM, Nimmo AJ, Morrison JF, Griffin NR, Wells M. The distribution of beta-adrenoceptors in human cervix. *Q J Exp Physiol.* 1989; 74:573–6. [PubMed: 2552494]
3. Landau R, Xie HG, Dishy V, et al. Beta-2 adrenergic receptor genotype and preterm delivery. *Am J Obstet Gynecol.* 2002; 187:1294–8. [PubMed: 12439523]
4. Ozkur M, Dogulu F, Ozkur A, Gokmen B, Inaloz SS, Aynacioglu AS. Association of the Gln27Glu polymorphism of the beta-2-adrenergic receptor with preterm labor. *Int J Gynaecol Obstet.* 2002; 77:209–15. [PubMed: 12065131]
5. Doh K, Sziller I, Vardhana S, Kovacs E, Papp Z, Witkin SS. Beta-2 adrenergic receptor gene polymorphisms and pregnancy outcome. *J Perinat Med.* 2004; 32:413–7. [PubMed: 15493717]
6. Landau R, Morales MA, Antonarakis SE, Blouin JL, Smiley RM. Arg16 homozygosity of the beta-2 adrenergic receptor improves the outcome after beta-2 agonist tocolysis for preterm labor. *Clin Pharmacol Ther.* 2005; 78:656–63. [PubMed: 16338281]

7. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. *Biochemistry*. 1994; 33:9414–9. [PubMed: 7915137]
8. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. *Am J Respir Cell Mol Biol*. 1995; 13:25–33. [PubMed: 7598936]
9. Dishy V, Sofowora GG, Xie HG, et al. The effect of common polymorphisms of the beta2-adrenergic receptor on agonist-mediated vascular desensitization. *N Engl J Med*. 2001; 345:1030–5. [PubMed: 11586955]
10. Smiley RM, Blouin JL, Negron M, Landau R. beta2-adrenoceptor genotype affects vasopressor requirements during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2006; 104:644–50. [PubMed: 16571957]
11. Drysdale CM, McGraw DW, Stack CB, et al. Complex promoter and coding region beta 2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. *Proc Natl Acad Sci U S A*. 2000; 97:10483–8. [PubMed: 10984540]
12. Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. *Am J Obstet Gynecol*. 2002; 187:824–8. [PubMed: 12388957]
13. Vahratian A, Troendle JF, Siega-Riz AM, Zhang J. Methodological challenges in studying labour progression in contemporary practice. *Paediatr Perinat Epidemiol*. 2006; 20:72–8. [PubMed: 16420344]
14. Debiec J, Conell-Price J, Evansmith J, Shafer SL, Flood P. Mathematical modeling of the pain and progress of the first stage of nulliparous labor. *Anesthesiology*. 2009; 111:1093–110. [PubMed: 19858874]
15. Gregory KD, Curtin SC, Taffel SM, Notzon FC. Changes in indications for cesarean delivery: United States, 1985 and 1994. *Am J Public Health*. 1998; 88:1384–7. [PubMed: 9736883]
16. Getahun D, Strickland D, Lawrence JM, Fassett MJ, Koebnick C, Jacobsen SJ. Racial and ethnic disparities in the trends in primary cesarean delivery based on indications. *Am J Obstet Gynecol*. 2009; 201:422 e1–7. [PubMed: 19788975]
17. Lipkind HS, Duzyj C, Rosenberg TJ, Funai EF, Chavkin W, Chiasson MA. Disparities in cesarean delivery rates and associated adverse neonatal outcomes in New York City hospitals. *Obstet Gynecol*. 2009; 113:1239–47. [PubMed: 19461418]

Figure 1. Flow diagram depicting study design for subject inclusion
(*N.B.*, Full dilatation is abbreviated as FD).

Figure 2. Rate of active labor for *ADRB2* Arg/Arg16-encoding genotype compared to rate for all other genotypes

The ordinate represents cervical dilatation (in cm), the abscissa represents time until full dilatation (in hrs), and rates are displayed as linear regressions with 95% confidence intervals.

Figure 3. Subgroup analyses comparing rate of active labor for *ADRB2* Arg/Arg16-encoding genotype to rate for all other genotypes

The ordinate represents cervical dilatation (in cm), the abscissa represents time until full dilatation (in hrs), and rates are displayed as linear regressions with 95% confidence intervals. Subgroup key: (a) Term ≥ 37 weeks gestational age, (b) Active labor ≥ 5 cm, (c) Labor of spontaneous onset, (d) Induced labor.

Figure 4. Rates of active labor for study haplotype groups at *ADRB2* codons encoding amino acids 16 and 27

For each haplotype group, the first pair of letters before the backslash indicates genotype encoding for amino acid residues at codon 16, and the second pair indicates genotype encoding for amino acid residues at codon 27. Key: (before backslash) A – Arg, G – Gly; (after backslash) C – Gln, G – Glu. For example, GG/CG represents Gly/Gly-16, Gln/Glu-27 -encoding haplotype.

Table 1
Baseline characteristics

Characteristics	Arg/Arg16 (n=80)	All other genotypes (n=321)	<i>P</i>
Age (mean $\pm$ S.D. years)	29.3 $\pm$ 5.9	29.4 $\pm$ 5.8	0.87
Race			
Hispanic (%)	50	59.5	
White (%)	41.2	34.6	
Black (%)	8.8	5.9	0.27
BMI (mean $\pm$ S.D. kg/m ²)	24.7 $\pm$ 4.7	25.8 $\pm$ 5.5	0.11
Parity (% $\geq$ 1)	56.3	59.8	0.56

Table 2
Obstetrical outcomes

Outcome	Arg/Arg16 (n=80)	All other genotypes (n=321)	P
Gestational age at delivery (mean $\pm$ S.D. days)	276 $\pm$ 9	275 $\pm$ 9	0.65
Preterm (% <37 wks)	3.8	5.6	0.5
Postterm (% $\geq$ 41 wks)	11.3	9.3	0.61
Induction (%)	31.3	31.2	0.99
Oxytocin use (%)	63.8	63.6	0.97
Epidural (%)	90	81.9	0.08
Birthweight (mean $\pm$ S.D. grams)	3358 $\pm$ 375	3376 $\pm$ 478	0.76