
Genetic Factors in Common Obstetric Disorders

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Abstract: Genetic research of disease has recently turned from individual genes for rare but highly penetrant diseases (like cystic fibrosis) to focus on common, multigene disorders with polygenic inheritance patterns, such as preterm labor, preeclampsia, gestational diabetes, placental abruption, and thromboembolism. These conditions are characterized by multiple etiologies, chronicity, fetal involvement, adaptive clinical manifestations, and gene-environment interactions. As we understand genetic contributions to complex disease and build upon the genetic data and technology available, more effective and specific management and treatment options will become available for clinicians and their patients.

Key words: preterm labor, preeclampsia, gestational diabetes, placental abruption, thromboembolism, obstetric syndrome

As documented in this volume, obstetric practitioners now have tremendous ability to diagnose single-gene disorders,

chromosomal abnormalities, and birth defects in the fetus. Unfortunately, our ability to predict a mother's obstetric course, particularly in first pregnancies (which are now the majority of all pregnancies), lags far behind. Despite decades of research, we still cannot reliably predict who will develop common and morbid conditions such as preterm labor, preeclampsia, intrauterine growth restriction, or placental abruption. Risk-factor scoring and biochemical screening have limited utility. As a result, women are still suffering morbidity that is theoretically preventable; in a survey of US births from the mid 1990s,¹ 43% of women experienced some type of morbidity during a hospitalization for childbirth, and 28% had at least 1 obstetric complication.

All of these pregnancy disorders, or syndromes, are characterized by (1) multiple etiologies, (2) chronicity, (3) fetal involvement, (4) clinical manifestations that are often adaptive in nature, and (5) gene-environment interactions. These common obstetric disorders are best considered complex diseases, with polygenic

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TABLE 1. Genetics of Common Obstetric Complications

	Incidence	Recurrence	1st Degree	Heritability
PTL	1/8	2.5X	2.5X	17%-27%
Preeclampsia	1/15	10X	3-4X	Low
GDM	1/20	6-10X	3X	No data
Placental Abruption	1/100	10X	5X if recurrent	No data
Thromboembolism	1/400	Varies	4X	39%-68% (men)

GDM indicates gestational diabetes mellitus; PTL, preterm labor.

inheritance patterns and subject to strong environmental effects. The realization that many important obstetric complications have a genetic component (Table 1), the improvement in our understanding of the role of genes in complex disease, and the tools of the Human Genome Project may open new pathways to understanding, managing, and treating these vexing complications.

Polygenic multifactorial inheritance, in which several genetic and environmental factors must collaborate for the disease or obstetric complication to develop, usually results in "threshold" effects (Fig. 1). Only after genetic and environmental factors reach a critical point (threshold) is the clinical disorder seen. The intrinsic herit-

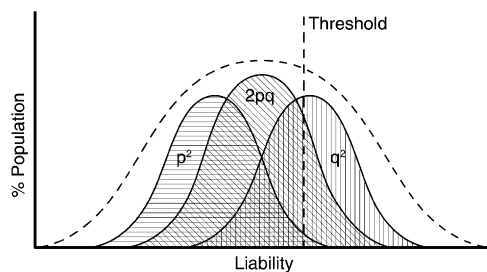


FIGURE 1. Threshold effect. The dashed line represents the distribution of susceptibilities in the population. The genotype of a disease-associated gene will usually subdivide the population into a group at a greater risk for the disease (q^2) and another group at lesser risk (p^2), with heterozygous patients ($2pq$) having an intermediate risk.

ability of the condition (genetic susceptibility) is frequently the most important factor affecting the patient's risk; however, significant clinical heterogeneity, in the form of clinical, locus, allelic, epigenetic, and environmental differences among individuals, may mask the level of penetrance of the condition. The greater the number of family members affected by a given multifactorial condition, the more likely it is that the genetic background is favorable for expression of that condition.

The risk of recurrence in an individual can be anticipated on the basis of several factors. Consanguinity increases the risk of recurrence because of the greater likelihood of disease-promoting genes being shared. Different ethnic groups will have varying population frequency for each syndrome, and the recurrence risk is higher within populations with a high incidence of the disorder. Finally, the severity of the disorder predicts the recurrence risk in some instances (eg, Hirschsprung disease), though in others (eg, neural tube defects) it does not.

Preterm Labor

Preterm labor clearly has a multifactorial etiology. Intrauterine infection, drug abuse, cigarette smoking, low pregnancy weight, utero-placental insufficiency, and multiple gestation are known causes of preterm delivery, but together these factors may account for only about 25% of

preterm births. Most of the preterm deliveries have no known cause.

Some conditions run in families because of similar diet, habits, or environment, but published reports suggest that preterm delivery is at least in part a genetic disease. Analyses of affected families suggest that relatively common alleles act as “major” genes conferring susceptibility to preterm delivery. Every ligand, every receptor, every amplification cascade in the programmed responses that orchestrate labor is under the control of either the mother’s or the fetus’ genes. It is unlikely that any particular genotype is necessary for preterm delivery to occur; rather the preterm delivery genes are susceptibility loci that lower a woman’s threshold for delivering before term. As is typical for polygenic multifactorial conditions, the number of risk factors and their relative importance will vary for each woman and for each pregnancy. In some women, numerous minor factors will combine to exceed the preterm labor threshold, whereas in others 1 or 2 major risk factors may predominate. The inheritance patterns in preterm birth can be difficult to ascertain given the heterogeneous causes of preterm labor.

Studying the genetics of preterm delivery is complicated by the fact that there are no convincing animal models of human labor, and because there are numerous difficulties in identifying and collecting human families. Until recently, preterm delivery was a fatal condition for the neonate, making familial cases rarer. Gestational age determinations can be very inaccurate, and record keeping in obstetrics was extremely limited before the last few generations. Expression of a preterm labor gene could be masked by medical care or other patient/physician decisions, including the decisions to treat a pregnancy complication or induce labor before term.

Few studies have examined the genetic basis of the duration of gestation in hu-

mans, but most of the evidence considers (1) recurrence of preterm labor, (2) ethnic and racial differences, and (3) relative risk for relatives of proband. A prior premature birth is one of the best predictors of a premature delivery. A relative risk as high as 2.5 has been associated with prior preterm birth.² Women who experience an early preterm birth (< 32 completed weeks) in their first pregnancy have the highest rate of recurrent preterm birth in subsequent pregnancies. If a woman herself was born preterm, she is also at an increased risk of spontaneous preterm labor and preterm birth, with the risks being highest for those women who themselves were born most preterm. The risk increases with 2 or more prior preterm deliveries.

Racial and ethnic differences in disease prevalence are often important clues that genes are involved in a disorder. Black women have a markedly higher risk of preterm delivery. Caution must be used when interpreting racial incidence data as showing that genes are involved. Self-described race is not genetically meaningful, and many nongenetic traits vary by race.³

Spontaneous preterm labor and preterm birth in subsequent pregnancies of a given individual also tend to recur at equivalent gestational ages. The influence of previous preterm births on future deliveries has been shown to be the highest when the gestational age of the previous preterm birth was between 23 and 27 weeks.²

The Maternal-Fetal Medicine (MFM) Network preterm prediction study by Mercer et al² studied the effect of gestational age and cause of preterm birth on subsequent obstetric outcome. The prior pregnancies of 1711 multiparous women with singleton gestations at 23 to 24 weeks’ gestation were coded for the presence or absence of a prior spontaneous preterm birth. If a prior spontaneous preterm birth had occurred, the gestation of

the earliest prior birth (13 to 22, 23 to 27, 28 to 34, and 35 to 36 wk gestation) was recorded. They found that those with a prior spontaneous preterm birth carried a 2.5-fold increase in the risk of spontaneous preterm birth in the current gestation period over those with no prior spontaneous preterm birth (21.7% vs. 8.8%; $P < 0.001$). Gravid women with a prior spontaneous preterm delivery at 23 to 27 weeks' gestation had the highest risk of recurrent spontaneous preterm delivery.

Melve et al⁴ studied the extent to which preterm birth and perinatal mortality are dependent on the gestational ages of previous births within sibships. The data for this study were collected from the Medical Birth Registry of Norway from 1967 to 1995. Newborns were linked to their mothers, yielding 429,554 pairs of mothers and first and second singleton newborns with gestational ages of 22 to 46 weeks. Siblings' gestational ages were significantly correlated ($r = 0.26$). The risk of having a second preterm birth was nearly 10 times higher among mothers whose firstborn child had been delivered before 32 weeks' gestation, compared to mothers whose first child had been born at 40 weeks.

A candidate gene association study on preterm birth using an application of high-throughput genotyping technology and advanced statistical methods found a consistent association with polymorphisms in the Factor V (*F5*) gene across ethnic groups.⁵ This large-scale, case-control study explored the associations of 426 single nucleotide polymorphisms (SNPs) in 300 mothers with preterm birth and in 458 mothers with term deliveries. Twenty-five candidate genes were included in the final haplotype analysis, and a significant association of the *F5* gene haplotype with preterm birth was revealed and remained significant after Bonferroni correction for multiple testing ($P = 0.025$). Other genes (*IL1R2*, *NOS2A*, and *OPRM1*) were as-

sociated with preterm birth in specific ethnic groups, though not at global significance level. Numerous other candidate gene studies have been published.

Wang et al⁶ reported familial clustering of low birth weight infants born to whites and blacks in the United States. Porter et al⁷ used the Utah Genealogy Database to suggest a genetic component for preterm delivery. He found that the risk for premature delivery of offspring became significantly greater in mothers who were born before 34 weeks' gestation, and that this was inversely correlated with the maternal gestation age at birth.

Large-scale population studies have been hampered primarily by the inability to obtain accurate information on the length of gestation in past generations and the heterogeneous nature of this disorder. A recent twin study in Australia estimated that the heritability was 17% for delivery before 38 weeks in the first pregnancy and 27% for premature delivery in any pregnancy.⁸ An earlier study of the Old Order Amish suggested that prematurity is related to the maternal genotype.⁹

Preeclampsia

Unfortunately, despite hundreds of studies regarding the genetics of preeclampsia, we are still at an early stage of our understanding. Dr Leon Chesley conducted the landmark studies on the genetics of preeclampsia.¹⁰ He studied 240 eclamptic women who had delivered at 1 hospital in New Jersey. He then collected outcome data on the subsequent generations, who delivered at hospitals throughout the United States. Remarkably persistent in this effort, Chesley was able to find information on 96% of all the daughters of his index cases, greatly reducing the possibility of ascertainment bias. Though the quality of the available obstetrics records varied, increasing the uncertainty that the patients he called

preeclamptic indeed had proteinuric hypertension, Chesley and his collaborators found elevated rates of preeclampsia in the mothers, sisters, daughters, and granddaughters of probands with eclampsia. Preeclampsia was not more prevalent in the in-laws of the eclamptic probands, suggesting that maternal rather than fetal genes are critical.

There have been more than 20 other family studies of preeclampsia over the past few decades. Studies in a variety of populations (eg, United States, United Kingdom, Scotland, Iceland) agree that first-degree relatives of women previously diagnosed with preeclampsia are 3 to 4 times more likely to develop preeclampsia than matched controls. Taken together, the segregation analyses suggest a polygenic, multifactorial pattern of inheritance, and several analyses also suggest a major gene effect. All models suggest that mutations conferring susceptibility to preeclampsia from the father or fetus are also relatively common.

Twin studies can be used to measure the heritability of a condition (ie, the proportion of the occurrence that is due to genetic factors, as opposed to environmental factors). One such study indicates that maternal genes do not play a major role, in contrast to the segregation data summarized above. Treloar et al¹¹ looked at Australian female twin pairs and made a retrospective diagnosis of preeclampsia from medical and hospital records. Using strict diagnostic criteria, they found no concordant female twin pairs for severe preeclampsia or eclampsia.

Over 100 genetic association studies concerning preeclampsia have now been published.¹² Genetic association studies using a case-control format are relatively easy to perform. Polymorphisms or, preferably, functional variants of the candidate gene are assayed in both populations, and χ^2 contingency tests are applied. Unfortunately, these simple studies often lead to false conclusions, as spurious as-

TABLE 2. Common Errors in Genetic Association Studies

Inadequate sample size
Nonspecific diagnoses
Subgroup analysis without corrections for multiple testing
Poorly matched control group
Hidden ethnic biases
Failure to replicate findings in a second population
Inappropriate conversion of quantitative traits to categories
Positive publication bias
Casual inferences from limited association data
Failure to consider linkage disequilibrium with neighboring loci
Failure to consider known gene-gene and gene-environment interactions
Random error

sociations can arise due to hidden biases (Table 2). Association studies cannot prove biologic causation, but if they are performed carefully, they can uncover a predisposing or causative gene that had not been suspected or a marker linked to the chromosomal region of the disease gene [ie, linkage disequilibrium (LOD)].

The candidate genes that have been tested to-date code for proteins involved in maternal adaptation, trophoblast invasion, placentation, homodynamics, blood pressure regulation, placental perfusion, oxidative stress, thrombosis, and inflammation. Unfortunately, most of the published studies lack rigor, or they are underpowered. Results are often inconsistent across populations, which may indicate that the positive associations are spurious, or they may actually support the hypothesized candidate gene if the population genetics of the candidate gene(s) are different in the study populations.

Several investigators are now studying the genetics of preeclampsia using linkage analysis in affected families and affected sibling-pairs.¹³ Polymorphic DNA markers mapped to locations that describe regular intervals in the human genome

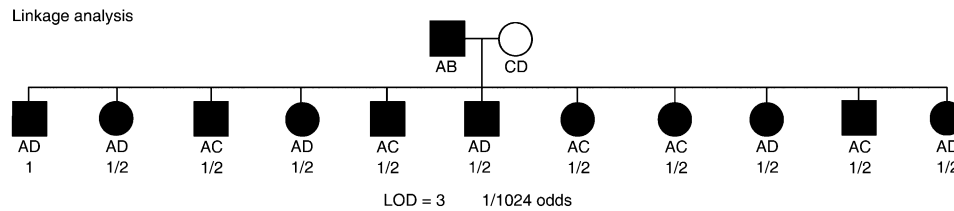


FIGURE 2. Linkage disequilibrium and its computation. In this example, a father passes on the “A” allele linked to an autosomal trait to 11 affected children. If the trait and the A allele were segregating independently, half of the children on average would have inherited the B allele. The odds of seeing this pattern by chance alone (ie, no linkage) are 1 in 1024. The LOD score is the logarithm of these odds—approximately 3.

are tested in family or affected sibling pairs. The analysis detects any violations of Mendel’s second law, which states that independent traits segregate independently. Whenever 2 independent traits are closely located on the same chromosome, Mendel’s second law is violated. Thus, linkage between preeclampsia and these reference markers can be used to map the chromosomal location of a disease gene. Linkage studies require an accurate diagnosis of the disease under study (which can be difficult with preeclampsia) and precise histories of family relationships among the study participants. Furthermore, linkage analysis of large pedigrees requires that the appropriate genetic model be used in the LOD score analysis (Fig. 2).

Gestational Diabetes

The genetics of Type I and Type II diabetes have been extensively studied, and important genetic risk factors have recently been identified. By comparison, relatively few studies have addressed the genetics of gestational diabetes. Gestational diabetes recurs in subsequent pregnancies; it occurs more frequently in African Americans, Hispanic/Latino Americans, American Indians, and people with a family history of diabetes. Obesity is also associated with higher risk.

Women who have had gestational diabetes are at increased risk for later developing Type II diabetes. It is very likely that genes that cause susceptibility to Type II diabetes will be shown to be risk factors for gestational diabetes.

Placental Abruption

Preliminary evidence for a genetic susceptibility for placental abruption comes from several observations. First, the recurrence rate of placental abruption is high, at 9% to 11%,¹⁴ and cannot be explained on the basis of known environmental risk factors such as trauma, smoking, and drug abuse. Candidate gene studies have shown a positive association between polymorphisms of both the angiotensinogen and nitric oxide synthase gene and placental abruption.¹⁵ The observed high prevalence of thrombophilia among women with placental abruption also supports the idea of a genetic background for the condition.^{16,17}

One study evaluated the rate of placental abruption in the first-degree relatives of index patients compared with that in the general obstetric population. They found that only 0.5% of the parous sisters (2/412) and 0.4% of the mothers (2/528) of the index patients had abruptions; these rates were similar to those in low-risk pregnancies. In the smaller subgroup

of women with recurrent abruption, first-degree relatives had a 5-fold risk of abruption, compared with the general obstetric population.

Thromboembolism

The risk of pulmonary embolism and deep vein thrombosis is increased during pregnancy and is further increased by the presence of inherited or acquired thrombophilias. The magnitude of the risk varies depending on the specific thrombophilia. Thirty to fifty percent of women with a thromboembolism have an inherited thrombophilia.¹⁸ Inherited thrombophilias may be associated with an increased risk of adverse events during pregnancy, including pregnancy loss, preeclampsia, placental abruption, and intrauterine growth restriction.

The risk is greater in women with more than one thrombophilic polymorphism. Initial genetic investigations focused on rare factor deficiencies for antithrombin III, protein C, and protein S. Recently common polymorphisms, particularly Factor V Leiden, the prothrombin gene, and the thermolabile variant of the methylene tetrahydrofolate reductase (*MTHFR*) gene, have been implicated.

Gene Mapping/Discovery

There are many challenges in studying pregnancy complications with genetic tools: (1) The traits may be sex-limited and expressed only during a pregnancy. (2) Onset of the condition may be delayed until the reproductive years. (3) The full expression of the disease gene may remain unobserved if it is interrupted by appropriate medical care or early delivery. (4) The definition of the obstetric phenotype may not correlate closely with the underlying genotypes. (5) Obstetric complication genes may be introduced into pedigrees in a silent manner from the paternal line. (6) Multiple genotypes—of

the mother, the fetus, or an interaction between the two—may be critical in disease manifestation. (7) Often, hundreds of genes are involved as a result of evolutionary redundancy to insure successful reproduction. (8) New/different mutations are common, on the basis of high frequency of perinatal lethality. (9) Major protective alleles may be involved because of their strong selection. (10) Animal obstetric models have limited utility because of evolutionary divergence. (11) Ethnic variation is often extreme because of “hyperevolution” of the human placenta. (12) Pleiotropy (ie, 1 gene leading to many actions) can increase the complexity of a genetic analysis.

Despite these challenges, discovery of the underlying genes should improve the classification, prediction, diagnosis, and treatment of obstetric complications. DNA is available from many clinical samples, including blood, amniotic fluid, urine, saliva, skin, and paraffin blocks. As a result of the Human Genome Project and as computing technology has continued to advance, the data composing the human genome sequence is now easily managed, distributed, and manipulated, as it requires only 6 gigabytes of storage (Fig. 3).

New technologies, such as microarrays that scan the entire genome in a single experiment, have resulted in the discovery of dozens of important disease genes over the past year. Currently, the most powerful genome-wide approach uses SNPs (ie, DNA sequence variations that occur when a single nucleotide in the genomic sequence is altered). SNPs occur every 100 to 300 bases along the 3-billion-base human genome. For instance, the Affymetrix HuSNP arrays (Affymetrix Inc, Santa Clara, CA) are composed of up to 900,000 SNPs, selected on the basis of their location, their heterozygosity, and the likelihood that they are genetically linked to each other.¹⁹ The SNP markers are < 3000 base pairs apart, on average, for the 900,000 arrays.

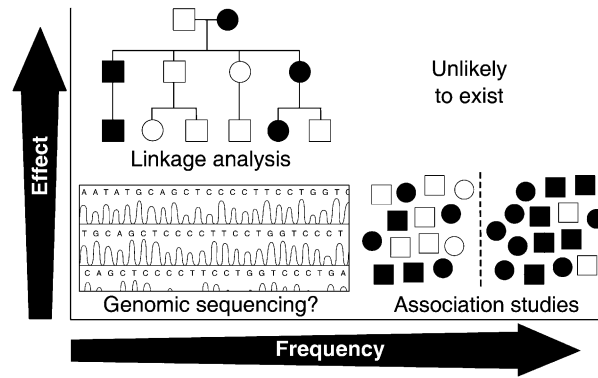


FIGURE 3. There are 3 commonly used methods for discovered disease-associated genes. The relative efficiency of these methods varies with the incidence of the disorder and the effect of the allele.

These microarrays are used to perform case-control association studies or relative pair studies. Cases and controls are matched for the most readily apparent confounding factors (age, sex, known risk factors, etc). Disease-associated alleles with modest relative risk (relative risk of 2 or more) can be detected with manageable sample sizes. A limited number of common haplotype patterns account for most of the genetic variation in any particular chromosomal region, and these blocks determine the “resolution” of this gene discovery methodology.²⁰ Current SNP chips are designed so that for every block in the human genome, there are enough SNP markers to determine the frequencies of these common haplotype patterns (Figs. 4 and 5).

When 900,000 case-control association studies are tested simultaneously, corrections for multiple testing and very stringent significance levels need to be used when analyzing the results. False positives are a risk, especially if ethnicity in the cases and controls is not well matched or if there is hidden population stratification in the cases. Founder effects reflecting the different racial or ethnic origin rather

than any link to disease alleles can also give rise to false-positive associations. Various statistical methods are being developed to deal with these issues, as we learn which of the SNPs tend to have more ethnic variation. The possibility of false associations can be diminished by using relatives as controls (ie, sibling pairs). When testing relatives, transmission disequilibrium testing (ie, testing the frequency of transmission of a specific allele from a parent to an affected child, compared with transmission of the other allele from the same parent) can also help avoid false conclusions. Ultimately, replication in additional independent samples is the best way to be certain of the findings.

Genomic sequencing—the ability to read a patient’s entire DNA sequence as a clinical tool—may be only a few years off. Estimates suggest that the very first human genome sequencing project cost about \$300 million and required hundreds of machines working 24 hours a day for 9 months. Now, prototype instruments are being developed that can sequence an entire human genome in less than a day for less than \$1000!

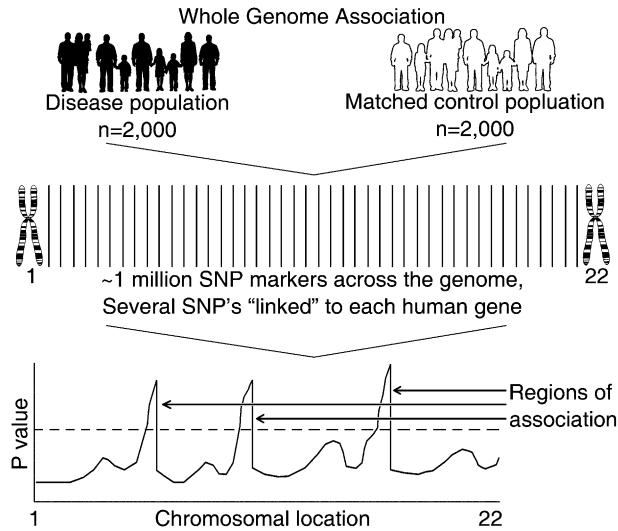


FIGURE 4. Genome-wide association studies are a powerful method for identifying susceptibility genes for common complex diseases. Genome-wide association studies involve genotyping case-control cohorts or family trios, using hundreds of thousands of SNP markers with known locations in the human genome. The frequencies of SNP genotypes and multimarker haplotypes are compared between the disease and control cohorts to identify the locations of disease-associated genes.

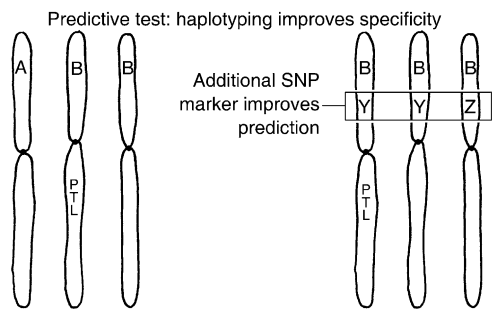


FIGURE 5. Haplotypes can be defined by a set of SNPs on a single chromatid that are statistically associated because of their proximity to one another. In this example, a pre-term labor risk allele is associated with the B genotype and the B-Y haplotype. No patients with the A genotype or the B-Z haplotype have this particular risk factor.

The Future

Upon recognizing that a given condition is genetic, researchers can use gene discovery techniques such as LOD and haplotype mapping to find the genes and the molecular pathways responsible for the condition.

Eventually, a clinically useful test for one or more of these obstetric syndromes will be developed from a panel of laboratory tests analyzed along with clinical factors such as parity, age, body-mass index, and family history. The test will be similar to the maternal serum screening tests used currently to predict the risk of Down syndrome.

This new genomic paradigm promises individualized predictive, personalized, and preemptive healthcare. In the coming

years, practitioners will be able to provide more precise counseling regarding not only birth defects, infectious disease risks, and adverse drug reactions, but also risks of developing obstetric morbidity.

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