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SECOND-TRIMESTER SERUM CHORIONIC GONADOTROPIN CONCENTRATIONS AND COMPLICATIONS AND OUTCOME OF PREGNANCY

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ABSTRACT

Background Maternal serum chorionic gonadotropin is measured to screen for fetal chromosomal abnormalities. Whether the results can also be used to predict the risk of complications or an adverse outcome of pregnancy is not known.

Methods We reviewed the medical records of 28,743 girls and women in whom chorionic gonadotropin was measured during the second trimester of pregnancy (between July 1, 1995, and January 31, 1997), seeking information about the complications and outcome of their pregnancies. We excluded girls and women who had preexisting risk factors for complications or an adverse outcome of pregnancy.

Results Higher serum chorionic gonadotropin concentrations were associated with higher rates of stillbirth (odds ratio for every increase in chorionic gonadotropin of 1 multiple of the median, 1.4; 95 percent confidence interval, 1.1 to 1.9). There was no relation between higher serum chorionic gonadotropin concentrations and the risk of gestational diabetes, premature rupture of membranes, or intrauterine growth retardation or small size for gestational age (odds ratio, 1.1; 95 percent confidence interval, 0.9 to 1.2). Higher serum chorionic gonadotropin concentrations were associated with a risk of placental abnormalities (odds ratio, 1.5; 95 percent confidence interval, 1.3 to 1.7), pregnancy-induced hypertension (odds ratio, 1.4; 95 percent confidence interval, 1.3 to 1.5), and preterm delivery without pregnancy-induced hypertension (odds ratio, 1.1; 95 percent confidence interval, 1.0 to 1.2). Inclusion in certain racial or ethnic categories (black, Filipino or Pacific Islander, unknown race or ethnic group, and "other," which included those of Middle Eastern descent and Native Americans) was a better predictor of the risk of an adverse outcome than serum chorionic gonadotropin values.

Conclusions Measurements of serum chorionic gonadotropin are of little clinical value for predicting the risk of complications and the outcome of pregnancy. (N Engl J Med 1999;341:2033-8.)

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MATERNAL serum biochemical screening at 15 to 20 weeks of gestation is increasingly being used to identify fetal abnormalities such as neural-tube defects, Down's syndrome, and other chromosomal abnormalities. In California, maternal serum alpha-fetoprotein, chorionic gonadotropin, and unconjugated estriol are measured to aid in the diagnosis of these fetal abnormalities (triple-marker screening). Some studies have suggested that high serum chorionic gonadotropin concentrations, independently of serum alpha-fetoprotein concentrations, are associated with an increased risk of such complications of pregnancy as preeclampsia, preterm delivery, placental abnormalities, intrauterine growth retardation or small size for gestational age, and stillbirth.¹⁻⁴ However, the definition of a high serum chorionic gonadotropin concentration has varied,^{2,5,6} the data concerning the value of the measurement for predicting pregnancy outcome have varied,^{1,3,7} and the practical clinical value of the measurement has been questioned.⁷⁻⁹ We undertook this study to determine the clinical utility of second-trimester measurements of maternal serum chorionic gonadotropin in predicting adverse pregnancy outcome in women with no preexisting risk factors who might benefit from obstetrical intervention.

METHODS

Subjects

From July 1, 1995, through January 31, 1997, a total of 33,493 pregnant girls and women who were members of the Kaiser Per-

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manente Medical Care Program in northern California underwent triple-marker screening at 15 to 20 weeks of gestation through the state screening program. We obtained demographic information and test results for these girls and women from California state records. We obtained pregnancy and delivery information and diagnoses coded according to the *International Classification of Diseases, 9th Revision*,¹⁰ for the mothers and their babies from the Kaiser Permanente data base or their medical records. To rule out the possibility of fetal abnormalities, a special Kaiser Permanente genetic data base was used. For 733 of the 33,493 girls and women, either no data were stored in the data base or the medical records were missing; for an additional 1067 girls and women, test results were invalid because of errors in dating.

To eliminate confounders and to limit the study population to pregnant girls and women with no preexisting risk factors for complications or adverse outcome of pregnancy, we excluded from the remaining 31,693 girls and women those who had any of the following: a preexisting condition, including diabetes mellitus before pregnancy, seizure disorder, chronic hypertension, or congenital uterine abnormalities (606 girls and women); a serum alpha-feto-protein concentration that was at least 2.5 multiples of the median (278); a therapeutic abortion (142); evidence of a fetus with chromosomal or ultrasonographic abnormalities (348); and multiple pregnancies (511). In addition, 1120 girls and women were unavailable for follow-up because of a change in residence or insurance coverage, 76 were tested twice during the same pregnancy (only the later test was included); 131 of these subjects fit multiple exclusion criteria and were counted twice.

The population of the enrollees of the health plan racially and ethnically reflects the general population of California, although people with very low incomes and levels of education are somewhat underrepresented.¹¹ Ninety-three percent of pregnant girls and women sign up for prenatal care within the first trimester. In 62.5 percent of the girls and women, ultrasonography was used for gestational dating to minimize the possibility of incorrect gestational age as an explanation for a high serum chorionic gonadotropin concentration. The results of triple-marker screening were interpreted by the Genetic Disease Branch of the California State Health Department.

Race or ethnic group was classified into eight categories: white, black, Hispanic (all persons identified as ethnically Hispanic, regardless of race), Asian (including Chinese, Japanese, and Korean), Southeast Asian (including Indian, Southeast Asian, Laotian, and Vietnamese), Filipino and Pacific Islander (including Guamanian, Hawaiian, and Samoan), other (including Middle Eastern and Native American), and unknown.

Outcomes

The study protocol was approved by the institutional review board of the Kaiser Permanente Medical Care Program. The main adverse outcome of pregnancy that we studied was stillbirth, defined as fetal death at or after 24 weeks of gestation. To analyze instances in which intervention might have been effective, we considered separately stillbirths occurring at or after 28 weeks of gestation. The medical records of all stillborn infants and infants who died during the neonatal period were reviewed by one investigator to determine the cause. Neonatal deaths were excluded from the analysis because a chart review failed to reveal a relation between such deaths and any preventable antenatal events except extreme prematurity.

In addition to our primary outcome of stillbirth, we studied the following seven complications of pregnancy: preterm delivery (defined as delivery of a live-born infant before 37 weeks of gestation); placental abnormalities, including placenta previa, abruptio placentae, and vasa praevia; pregnancy-induced hypertension, including transient hypertension of pregnancy, eclampsia, and preeclampsia; gestational diabetes; uterine complications, including cervical incompetence, uterine rupture, and uterine inversion; premature rupture of the membranes (before 37 weeks of gestation); and intrauterine growth retardation or small size for gestational age (estimated fetal weight or actual birth weight below the 10th

TABLE 1. CHARACTERISTICS OF THE 28,743 PREGNANT GIRLS AND WOMEN.

CHARACTERISTIC	PERCENT
Race or ethnic group	
White	42.3
Hispanic	24.5
Black	9.0
Filipino or Pacific Islander	6.8
Unknown	5.4
Asian	5.1
Southeast Asian	3.9
Other	3.0
Age*	
10–14 yr	0.1
15–19 yr	8.8
20–24 yr	18.8
25–29 yr	32.4
30–34 yr	31.8
35–39 yr	7.1
40–44 yr	0.9

*Percentages do not total 100 because of rounding.

percentile for age, as defined by Williams et al.¹² for births at sea level in California).

Statistical Analysis

Our primary regression analysis was used to predict the odds of stillbirth, and seven additional analyses were performed to predict the odds of each of the various complications of pregnancy as a function of the serum chorionic gonadotropin concentration. In each of these analyses, serum chorionic gonadotropin concentration, race or ethnic group, and the mother's age at the expected date of delivery were included as independent variables. The serum chorionic gonadotropin concentration was analyzed as a continuous variable.

RESULTS

The racial and ethnic composition and the age spectrum of the 28,743 girls and women are shown in Table 1. Among the 28,446 girls and women whose pregnancies lasted to at least 24 weeks of gestation, there were 79 stillbirths, yielding an overall stillbirth rate of 2.8 per 1000 pregnancies. As a result of chart review, these stillbirths were categorized into four groups: possibly preventable (27 cases), cord-related (20), unknown cause (16), and other causes, including trauma, drug use, and other events unrelated to the placenta (16). Of the 27 possibly preventable cases of stillbirth (34 percent of the total), all had evidence of placental failure or infection, but 12 of the 27 (44 percent) occurred before 28 weeks of gestation.

The relation between the serum chorionic gonadotropin concentration and the risk of stillbirth at or after 24 weeks of gestation is shown in Figure 1. Higher serum chorionic gonadotropin concentrations were associated with higher rates of stillbirth, although the total number of stillbirths was small — only 79 (0.28 percent). Among the 28,446 girls and women who were still pregnant at or after 24 weeks

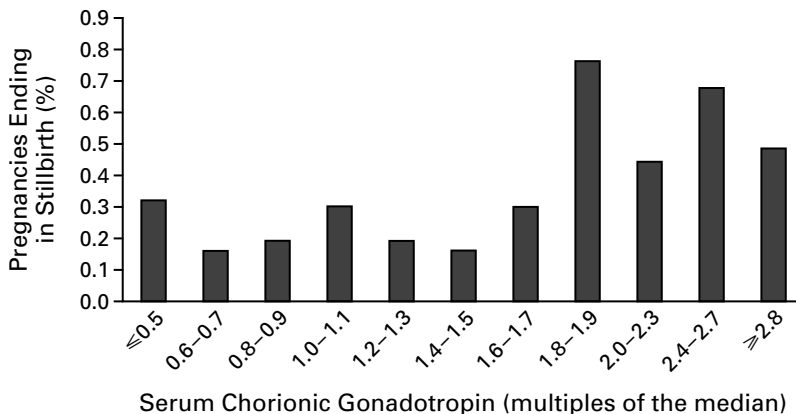


Figure 1. Relation between the Serum Chorionic Gonadotropin Concentration and the Risk of Stillbirth at or after 24 Weeks of Gestation among 28,446 Girls and Women.

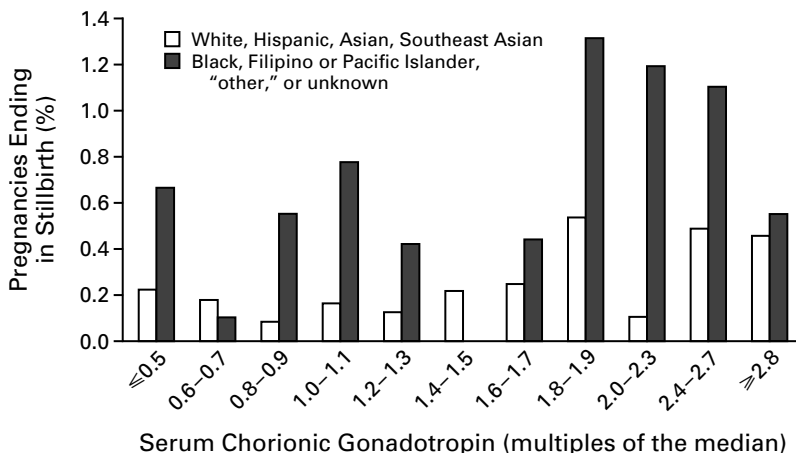


Figure 2. Relation between the Serum Chorionic Gonadotropin Concentration and the Risk of Stillbirth at or after 24 Weeks of Gestation among 28,446 Girls and Women, According to Race or Ethnic Group. Girls and women who were white, Hispanic, Asian, or Southeast Asian were considered to be at low risk, and those who were black, Filipino or Pacific Islander, or from the "other" group or those whose race or ethnic group was unknown were considered to be at high risk.

of gestation, 2561 (9 percent) had high serum chorionic gonadotropin concentrations (defined as concentrations that were at least 2 multiples of the median) at the time of delivery.

There was also a strong relation between race or ethnic group and the risk of stillbirth (Fig. 2). The rate of stillbirth was substantially higher at nearly every serum chorionic gonadotropin concentration for blacks, Filipinos and Pacific Islanders, girls and women of races or ethnic groups categorized as "other," and those whose race or ethnic group was not known. The rates in these groups ranged from 4 to 7 per 1000 pregnancies, as compared with a rate of less than 2 per 1000 for whites.

The serum chorionic gonadotropin concentration was a positive predictor of stillbirth, with an odds ratio of 1.4 for every increase of 1 multiple of the median (95 percent confidence interval, 1.1 to 1.9). The rate of stillbirth among girls and women whose serum chorionic gonadotropin concentrations were at least 2 multiples of the median at 24 or more weeks of gestation was 5.1 per 1000 pregnancies. Given the low incidence of adverse events, the odds ratios can also be interpreted as risk ratios.

Four racial or ethnic groups were statistically significant positive predictors of the risk of stillbirth, as compared with the risk among white girls and women: blacks (odds ratio, 3.9), Filipinos or Pacific Is-

TABLE 2. RELATION OF SERUM CHORIONIC GONADOTROPIN CONCENTRATION AND RACE OR ETHNIC GROUP TO THE RISK OF STILLBIRTH.

INDEPENDENT VARIABLE	ODDS RATIO (95% CI)*	P VALUE
Chorionic gonadotropin concentration†	1.4 (1.1–1.9)	0.01
Race or ethnic group‡		
Asian	1.1 (0.3–3.4)	0.83
Black	3.9 (2.0–7.5)	<0.001
Hispanic	1.4 (0.7–2.8)	0.27
Other	4.1 (1.4–10.1)	0.01
Filipino or Pacific Islander	2.7 (1.2–5.7)	0.01
Southeast Asian	1.0 (0.2–3.5)	0.97
Unknown	2.6 (1.0–6.0)	0.03

*Only the 28,446 girls and women who were still pregnant at or after 24 weeks of gestation were included in the analysis. CI denotes confidence interval.

†The odds ratio represents the odds of stillbirth associated with an increase in the serum chorionic gonadotropin concentration of 1 multiple of the median.

‡The odds ratio represents the odds of stillbirth as compared with the odds for white girls and women.

TABLE 3. COMPLICATIONS AND ADVERSE OUTCOMES OF PREGNANCY IN 28,743 PREGNANT GIRLS AND WOMEN.

COMPLICATION OR OUTCOME	ODDS RATIO (95% CI)*	P VALUE
Placental abnormalities	1.5 (1.3–1.7)	<0.001
Pregnancy-induced hypertension	1.4 (1.3–1.5)	<0.001
Preterm delivery without pregnancy-induced hypertension	1.1 (1.0–1.2)	0.03
Uterine complications	0.8 (0.6–1.0)	0.07
Premature rupture of membranes	0.9 (0.7–1.0)	0.08
Intrauterine growth retardation or small size for gestational age	1.1 (0.9–1.2)	0.37
Gestational diabetes	1.0 (0.9–1.1)	0.81

*The odds ratio represents the odds of an adverse outcome or complication associated with an increase in the serum chorionic gonadotropin concentration of 1 multiple of the median. CI denotes confidence interval.

landers (odds ratio, 2.7), girls and women of “other” races or ethnic groups (odds ratio, 4.1), and those whose race or ethnic group was unknown (odds ratio, 2.6) (Table 2).

The results of the analyses of the relation between complications of pregnancy and serum chorionic gonadotropin concentrations are shown in Table 3. There was no association between serum chorionic gonadotropin concentrations and the risk of gestational diabetes, intrauterine growth retardation or small size for gestational age, or premature rupture of membranes. Higher serum chorionic gonadotropin concentrations were associated with a higher risk of placental abnormalities, pregnancy-induced hyperten-

sion, and preterm delivery without pregnancy-induced hypertension, but the increases in risk were slight.

DISCUSSION

In our study population of girls and women who were at low risk for complications of pregnancy, when the serum chorionic gonadotropin concentration was treated as a continuous variable, we found that higher concentrations were associated with a statistically significant increase in the risk of stillbirth. However, given the extremely low frequency of stillbirths, the potential benefits of intervention in such cases would have been very small.

The Genetic Disease Branch of the California State Health Department has notified health care providers that a maternal serum chorionic gonadotropin concentration that is at least 2 multiples of the median “has been associated with adverse pregnancy outcomes.” Without evidence of the benefits and risks of intervention, the selection of any cutoff value can only be speculative. Thus, the statement is of doubtful value to health care providers — not only because it is clinically misleading, but also because methods of intervention (e.g., serial ultrasonography and antenatal fetal monitoring) that have been used in similar situations (e.g., in women with high serum alpha-fetoprotein concentrations) do not affect the clinical outcome.¹³

The stillbirth rate of 5.1 per 1000 pregnancies among women whose serum chorionic gonadotropin concentrations were at least 2 multiples of the median at 24 weeks or more of gestation contrasts with the higher perinatal mortality rate among the infants of women who receive no antenatal testing and who have conditions such as insulin-dependent diabetes mellitus (perinatal mortality rate, 28 to 62 per 1000 pregnancies),¹⁴ pregnancy-induced hypertension (perinatal mortality rate, 20 to 40 per 1000 pregnancies),¹⁵ drug addiction (perinatal mortality rate, 32 to 35 per 1000 pregnancies),^{16,17} and prolonged (more than 42 weeks) pregnancy (perinatal mortality rate, 50 to 70 per 1000 pregnancies).¹⁸ For these high-risk women, in whom placental failure is usually the cause of pregnancy loss, antenatal testing of the fetal heart rate can reduce the perinatal mortality rate to 1 to 3 per 1000 pregnancies.¹⁹ In our population, using as a cutoff level a chorionic gonadotropin concentration that was at least 2 multiples of the median, it would have been necessary to treat 197 girls and women in order to prevent 1 stillbirth, assuming that such interventions would be effective in girls and women selected in this way. Because only 34 percent of the 79 stillbirths in the study were considered potentially preventable, it would have been necessary to treat 576 girls and women in order possibly to prevent 1 stillbirth. There is, however, no evidence that intervention would improve outcome in this low-risk group.

The results of other studies relating high serum chorionic gonadotropin concentrations to complications and adverse outcome of pregnancy are conflicting, but the study designs were inconsistent, multiple confounding variables were present, and relatively few women were studied.¹⁻⁹ Moreover, the definition of a high serum chorionic gonadotropin concentration varied widely (from ≥ 2 to 5 multiples of the median).^{2,5,6}

Our findings illustrate the problem with the use of an arbitrary cutoff value for serum chorionic gonadotropin instead of a continuum for analyzing outcome. In our cohort, girls and women with serum chorionic gonadotropin concentrations that were 1.8 to 1.9 multiples of the median had a relatively large number of stillbirths, as compared with the other girls and women (Fig. 1), and this was apparently the result of random variation. The potential bias introduced by selecting an arbitrary cutoff point is reduced by analyzing the serum chorionic gonadotropin value as a continuous variable. When events are rare, as is the case with stillbirth in low-risk pregnant women, the selection of an arbitrary cutoff point can obscure moderate trends or incorrectly indicate statistical significance because the cutoff value can be selected to "fit" the data.

In some cases, the identification of a statistically significant relation, such as that between second-trimester serum chorionic gonadotropin concentrations and the risk of some complications and adverse outcomes of pregnancy, may not be clinically useful. We believe that the use of an intervention with a potentially marginal benefit is not warranted when the odds ratio is low and adverse events are rare. In our study of 28,446 low-risk women, 2561 (9 percent) had serum chorionic gonadotropin concentrations that were at least 2 multiples of the median. Intervention on the basis of this cutoff value with the aim of preventing stillbirth would result in unnecessary intervention in many women, even if the intervention had proven efficacy. Furthermore, false positive results of prenatal screening tests cause anxiety and stress in many women and their families.²⁰⁻²² These psychological effects can persist and may lead to a negative attitude toward the pregnancy and the baby.^{21,22}

Even with our large data base, serum chorionic gonadotropin concentrations of at least 4 multiples of the median were so uncommon that we cannot draw conclusions about interventions in these rare and extreme cases. We did find a small increase in the risk of placental abnormalities and pregnancy-induced hypertension in women with high serum chorionic gonadotropin concentrations. The high values might serve to alert clinicians to these problems and consequently lead to earlier detection, but whether that would affect outcome is not known. Furthermore, as was the case for stillbirth, the increase in risk was very small.

Women of low socioeconomic status and those in high-risk racial or ethnic groups have much higher stillbirth rates than do low-risk women with high serum chorionic gonadotropin concentrations. Antenatal monitoring of women in these high-risk groups, regardless of their serum chorionic gonadotropin values, might have a far greater potential for improving pregnancy outcomes than using precious health resources to intervene in low-risk women on the basis of their serum chorionic gonadotropin concentrations.¹⁴⁻¹⁹

In conclusion, we do not recommend using serum chorionic gonadotropin concentrations that are at least 2 multiples of the median as a determinant for intervention in low-risk pregnant women.

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