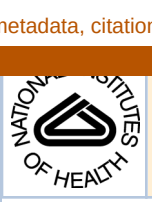

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Down syndrome serum screening also identifies an increased risk for multicystic dysplastic kidney, 2-vessel cord, and hydrocele

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Abstract

Objective—The FASTER trial compared 1st and 2nd trimester screening methods for aneuploidy. We examined relationships between maternal serum markers and common congenital anomalies in the pediatric outcome data set of 36,837 subjects.

Methods—We used nested case control studies, with cases defined by the most common anomalies in our follow-up database, and up to four controls matched by enrollment site, maternal age and race, enrollment gestational age, and infant gender. Serum markers were dichotomized to ≥ 2 or < 0.5 multiples of the median (MoM). Odds ratios and 95% confidence intervals (C.I.) were estimated.

Results—Statistically significant ($p < 0.05$) associations were found between inhibin A ≥ 2 MoM and fetal multicystic dysplastic kidney (MCDK) (odds ratio (OR) =27.5, 95% C.I.:

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2.8-267.7) and 2-vessel cord (OR=4.22, 95% CI:1.6-10.9), hCG of ≥ 2 MoM with MCDK (OR=19.56, 95% CI: 1.9-196.2) and hydrocele (OR=2.48, 95% CI: 1.3-4.6), and PAPPA ≥ 2.0 MoM with hydrocele (OR=1.88, 95% CI:1.1-3.3).

Conclusion—In this large prospective study, significant associations were found between several maternal serum markers and congenital anomalies. This suggests potential additional benefits to screening programs that are primarily designed to detect aneuploidy.

Keywords

serum screening; FASTER trial; multicystic dysplastic kidney; 2-vessel cord; hydrocele

INTRODUCTION

Noninvasive prenatal diagnosis using maternal serum markers initially focused on detection of open neural tube defects and subsequently on detection of aneuploidies such as trisomies 21 and 18. More recently, associations between abnormal levels of maternal serum markers and single gene disorders, such as Smith-Lemli-Opitz and Cornelia de Lange, have been found (Canick *et al*., 1997; Aitken *et al*., 1999; Palomaki *et al*., 2002; Craig *et al*., 2006). Few studies to date have examined the possibility of using maternal serum screening results to detect common congenital anomalies or single gene disorders other than those that are mentioned above (Celentano et al., 2005).

The objective of this study was to assess the association between abnormal levels of maternal serum markers and specific malformations and/or groups of single gene disorders in the newborn using data from the FASTER trial.

METHODS

Data source description

The FASTER (First and Second Trimester Evaluation of Risk) trial was an NIHfunded multicenter study, designed to compare first and second trimester methods of screening for aneuploidy in singleton pregnancies (Malone *et al*., 2005a). The study included over 38,033 pregnant women enrolled in 15 clinical centers across the United States. It has been described in detail and reported elsewhere (Malone *et al*., 2005a). First trimester screening included standardized sonographic measurement of the nuchal translucency (NT), maternal serum free beta subunit of human chorionic gonadotropin (fβhCG), and serum pregnancy associated plasma protein A (PAPP-A) levels. Second trimester screening included maternal serum alpha-fetoprotein (AFP), total human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin A levels. A maternal screening result was considered “positive” if the risk of Down syndrome was calculated to be 1/150 during the first trimester or 1/300 in the second trimester. The FASTER trial study design also included comprehensive pregnancy and neonatal outcome information, which were incorporated into the study database.

Study Subjects

The analytic sample for the present study included all participants in the FASTER study with pediatric outcome data available (n=36,837, 97% ascertainment). Pregnant women whose fetuses were initially noted to have cystic hygroma on a first trimester sonographic examination were excluded; their outcome data have been reported separately (Malone *et al*., 2005b). Pregnant women carrying karyotype-confirmed aneuploid fetuses were also excluded from the present study.

Pediatric Outcome Database

Research coordinators at each clinical site recorded outcome information on study subjects using a computerized tracking system designed specifically for the FASTER study to maximize protocol compliance and minimize loss to follow-up. In all cases in which a possible fetal or neonatal medical problem was suspected, copies of the fetal and pediatric medical records were obtained and reviewed by a single neonatal nurse (BLM) and a pediatric geneticist (DWB). In addition, medical records from all cases with a positive FASTER screening result and a 10% random sample of all enrolled subjects were reviewed. All structural and functional pediatric abnormalities were entered into a database, which was then cleaned to consolidate terminology and eliminate redundancy. These results were reviewed and categorized by anomaly or single gene disorder.

Case-Control Sets

Nine primary outcomes, including the five most commonly observed congenital anomalies and the four single gene disorder groups observed most commonly in the FASTER trial outcome study infants, were analyzed separately. Because each of the outcomes occurred infrequently, we used nested case control studies to efficiently control for key confounding factors. “Cases” were pregnant women carrying a fetus subsequently confirmed to have an anomaly or single gene disorder. Up to four unaffected controls for each case were derived from the FASTER cohort, selected for each outcome considered separately, and matched to cases by enrollment site, maternal age (or age of the egg if an egg donor was used), gestational age at enrollment, maternal race, and gender of the infant.

Statistical Analysis

Descriptive statistics were generated on all participants in the study sample (i.e., the full cohort from which cases and controls were drawn), including means and standard deviations for continuous variables and relative frequencies for categorical variables. To facilitate interpretation of associations between serum and ultrasound markers and anomalies, each serum and ultrasound marker was dichotomized following previous studies reporting relationships between markers and adverse pregnancy outcomes (Dugoff *et al*., 2005). Some markers were hypothesized to be positively associated with outcomes while others were hypothesized to be negatively associated with outcomes. Two parameterizations of each marker were evaluated. Specifically, markers were first dichotomized to compare values of 2 multiples of the median (MoMs) or greater with values less than 2 MoMs, and also dichotomized to compare values of 0.5 MoMs or less with values equal to or exceeding 0.5 MoMs. Crude odds ratios and 95% confidence intervals were estimated to qualify the associations between each marker and each pediatric outcome using logistic regression analysis. Due to the small number of cases we were unable to adjust for other potential confounders. All analyses were performed in SAS Version 9.1 (SAS Institute, Cary, NC). Results were considered to be statistically significant if the p value was less than 0.05.

RESULTS

A description of the sample of women with non-aneuploid fetuses and complete pediatric outcome data is shown in Table 1. Women were on average 30 years of age at enrollment into the FASTER trial, nearly 80% were married, and approximately 5% and 2% reported using tobacco and alcohol during pregnancy, respectively. More than half had a previous live birth, and over 26% had a prior history of miscarriage. Approximately 5% of enrolled subjects had a pregnancy that was conceived using assisted reproductive technology.

The numbers of observed cases and matched controls for each congenital anomaly and single gene disorder are shown in Table 2. Table 3a shows the odds ratios (OR) and 95%

confidence intervals reflecting the association between serum markers and each of the most commonly observed congenital anomalies. hCG ≥ 2 MoMs was statistically significantly associated with hydrocele (OR=2.48, 95% confidence interval (CI): 1.3-4.6) and multicystic dysplastic kidney (OR=19.56, 95% CI: 1.9-196.2). Inhibin ≥ 2 MoMs was significantly associated with two-vessel cord (OR=4.22, 95% CI: 1.6-10.9) and multicystic dysplastic kidney (OR=27.5, 95% CI: 2.8-267.6). Note that the category multicystic dysplastic kidney included both unilateral and bilateral cases. PAPP-A ≥ 2 MoMs was significantly associated with hydrocele (OR=1.88, 95% CI: 1.1-3.3).

Non-significant associations with elevated odds ratios included AFP ≥ 2 MoMs with two-vessel cord (OR=1.73 95% CI: 0.5-5.9), hydrocele (OR=1.37, 95% CI: 0.4-5.3) and undescended testicle (OR=1.72, 95% CI: 0.2-19.5); free β hCG ≥ 2 MoMs with pyloric stenosis (OR=2.31, 95% CI: 0.7-7.4), multicystic dysplastic kidney (OR=2.73, 95% CI: 0.8-9.8), and undescended testes (OR=1.38, 95% CI: 0.6-3.3); hCG ≥ 2 MoMs with pyloric stenosis (OR=1.48, 95% CI: 0.3-8.3); NT measurements of ≥ 2 MoMs with hydrocele (OR=2.74, 95% CI: 1.0-7.4), two-vessel cord (OR=3.92, 95% CI: 0.2-64.1) and undescended testicle (OR=3.84, 95% CI: 0.5-28.2); PAPP-A ≥ 2 MoMs with multicystic dysplastic kidney (OR=1.91, 95% CI: 0.3-11.8); and. uE3≥ 2 MoMs was associated with undescended testicles (OR=3.46, 95% CI: 0.2-56.6).

Non-significant associations with elevated odds ratios also included free β hCG levels of ≤ 0.5 MoMs with multicystic dysplastic kidney (OR=1.49, 95% CI: 0.3-8.8); hCG ≤ 0.5 MoMs with undescended testicles (OR=2.67, 95% CI: 0.9-7.6); inhibin ≤ 0.5 MoMs with two-vessel cord (OR=1.39, 95% CI: 0.4-4.6), pyloric stenosis (OR=7.88, 95% CI: 0.7-92.4), multicystic dysplastic kidneys (OR=1.79, 95% CI: 0.1-21.5), and undescended testicles (OR=1.38, 95% CI: 0.3-7.4); PAPP-A levels ≤ 0.5 MoMs with two vessel cord (OR=1.4, 95% CI: 0.4-4.7) and undescended testicles (OR=1.49, 95 CI: 0.4-5.0); and uE3 ≤ 0.5 MoMs with two-vessel cord (OR=7.78, 95% CI: 0.7-88.2) and undescended testicles (OR=1.38, 95% CI: 0.3-7.4).

With regard to single gene disorder groups (Table 3b), no statistically significant associations were found. Free β hCG ≥ 2 MoMs and inhibin ≥ 2 MoMs were associated with skeletal dysplasias, with elevated odds ratios of 2.76 (95% CI: 0.5-15.1) and 2.56 (95% CI: 0.3-18.9) respectively. High levels of inhibin and PAPP-A were also non-significantly associated with the craniosynostosis syndromes (OR=1.77, 95% CI: 0.1-21.1 and 3.60, 95% CI: 0.8-15.9, respectively).

DISCUSSION

Our results show that there are statistically significant associations between certain maternal screening markers and specific anomalies. Use of the FASTER trial database allowed access to one of the largest prospectively collected databases on maternal serum screen markers and pediatric outcome. Collection of medical records was extensive and curated by experts in genetics and neonatology. The database was meticulously reviewed and cleaned multiple times, which allowed for accurate classification of common malformations and single gene disorder groups.

Our results showed statistically significant associations between three common malformations (multicystic dysplastic kidney, hydrocele, and 2-vessel cord) and three commonly used maternal markers (hCG, inhibin and PAPP-A). Of these, multicystic dysplastic kidney is the malformation with the most serious postnatal consequences. Of the 13 cases of multicystic dysplastic kideney, 4 of 13 had hCG ≥ 2.0 MoMs and 5 of 13 had inhibin ≥ 2.0 MoMs. As prenatal ultrasound examination is only approximately 60%

sensitive for abnormalities, identification of pregnancies with high levels of hCG and inhibin could guide use of targeted renal sonographic studies or postnatal management that may decrease morbidity and/ or mortality in multicystic dysplastic kidney. This information may allow for enhanced prenatal counseling and monitoring of fetal renal function.

To date, relatively few studies have examined the association of maternal serum screening markers with conditions other than aneuploidy and neural tube defects. In 2005 Celentano *et al*. examined the possible association of elevated maternal serum hCG with fetal structural abnormalities. In contrast to our study, their results showed that isolated hCG elevations did not confer an increased risk for congenital anomalies other than those due to aneuploidy. However, in this report, there were 8 major anomalies in the study group, and none of them were multicystic dysplastic kidney.

Although the database used in this study was large, certain common anomalies and single gene disorders are so rare, that not even a database of this size provided sufficient numbers of outcome events to support precise statistical analysis. Thus, some of the associations with large odds ratios, such as low inhibin and pyloric stenosis, or low estriol and 2-vessel cord, failed to reach statistical significance. Despite this, some of the odds ratios observed were very large, and for that reason, deserve mention.

Several previous studies have retrospectively analyzed maternal serum screening results from cohorts of pregnant women whose children have certain single gene disorders. In 1998, Tint *et al*·, determined that an increased accumulation of fetal dehydrocholesterol in amniotic fluid was an accurate predictor of Smith-Lemli-Opitz syndrome. These data led to the observation that a low unconjugated maternal estriol serum level is associated with an increased risk for Smith- Lemli-Opitz syndrome. Estriol is a downstream product of cholesterol metabolism, which is disrupted in this syndrome (Bradley *et al*., 1999). In 1999, Aitken reviewed serum screen results of 19 pregnancies that resulted in children with Cornelia de Lange syndrome. A significant reduction in PAPP-A was seen in 18 of the 19 pregnancies, suggesting that in pregnancies with significantly low PAPP-A, there may be an increased risk for Cornelia de Lange syndrome. Most recently, Begleiter (2007) suggested a possible association between the 22q11.2 microdeletion syndrome and decreased levels of maternal serum markers in three pregnancies, a finding that deserves further study. These studies, in addition to the results presented here, suggest that software algorithms may be developed that highlight the abnormal findings and prompt consideration of the anomaly or the single gene disorder

The prospectively collected FASTER trial clinical database provided valuable pre- and post-natal information that allowed us to study the relationship between common malformations, single gene disorder groups and maternal screening results. Due to the limitations of identifying large enough cohorts of patients with rare anomalies and single gene malformations, we were unable to look at certain anomalies, such as congenital diaphragmatic hernia, that might benefit from early detection and management. The development of a large, international, prospective database would allow for further analysis of maternal serum markers with certain anomalies and single gene conditions. Despite these limitations this study has shown that certain patterns of routinely assayed maternal serum markers, such as unexplained elevated hCG and inhibin levels, might suggest consideration of a sonogram to rule out multicystic dysplastic kidney.

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Table 1

Demographic Information on pediatric outcome subset of FASTER Trial (n=35,496 pregnant women)

Characteristic	Mean (SD) or %
Mean (SD) Maternal Age (years)	30 (5.8)
Mean (SD) Education (years)	14 (2.5)
Married (%)	78.7%
Mean (SD) Body Mass Index	25 (5.2)
Tobacco use during pregnancy (%)	4.7%
Illicit Drug use during pregnancy (%) (Cocaine, Marijuana, Heroin)	1%
Alcohol use during pregnancy (%)	2.1%
Medication use during pregnancy (%)	38%
Pregestational diabetes (%)	1%
Previous Live Birth (%)	54.7%
Previous Miscarriage (%)	26.1%
Previous Preterm Birth (%)	6.6%
Current Pregnancy result of ART * (%)	4.9%
ART= Assisted Reproductive Technology	

Table 2

Numbers of cases and controls for analysis of common congenital anomalies and single gene disorder groups

Congenital Anomaly	Number of Cases	Number of Matched Controls
Hydrocele	113	425
Undescended Testicle	41	148
Two Vessel Cord	39	147
Pyloric Stenosis	19	66
Multicystic Dysplastic Kidney	13	46
Single Gene Disorder Group		
Craniosynostosis	14	50
Hemoglobinopathies	11	35
Skeletal Dysplasia /Connective Tissue Disorder	8	29
Metabolic Disorders	8	32

Table 3a

Relationship between serum markers and congenital anomalies

Serum Marker	Two Vessel Cord	Hydrocele	Pyloric Stenosis	Multicystic Dysplastic Kidney	Undescended Testicle
AFP ≥ 2 MoM	1.73 (0.5-5.9)	1.37 (0.4-5.3)	*	*	1.72 (0.2-19.5)
fβhCG ≥ 2 MoM	0.80 (0.4-1.8)	1.14 (0.7-2.0)	2.31 (0.7-7.4)	2.73 (0.8-9.8)	1.38 (0.6-3.3)
hCG ≥ 2 MoM	0.92 (0.2-3.4)	**2.48 (1.3-4.6)**	1.48 (0.3-8.3)	**19.56 (1.9-196.2)**	0.60 (0.1-2.8)
Inhibin ≥ 2 MoM	**4.22 (1.6-10.9)**	1.04 (1.3-4.6)	*	**27.5 (2.8-267.6)**	0.36 (0.0-2.9)
NT ≥ 2 MoM	3.92 (0.2-64.1)	2.74 (1.0-7.4)	*	*	3.84 (0.5-28.2)
PAPP-A ≥ 2MoM	1.00 (0.2-3.2)	**1.88 (1.1-3.3)**	1.44 (0.3-8.1)	1.91 (0.3-11.8)	0.8 (0.3-2.2)
uE3 ≥ 2MoM	*	*	*	*	3.46 (0.2-56.6)
AFP ≤ 0.5 MoM	*	*	*	*	*
fβhCG ≤ 0.5 MoM	0.93 (0.3-2.6)	0.79 (0.5-1.4)	0.7 (0.2-2.7)	1.49 (0.3-8.8)	1.18 (0.5-3)
hCG ≤ 0.5 MoM	0.92 (0.2-3.4)	0.95 (0.5-2)	*	1.17 (0.1-12.3)	2.67 (0.9-7.6)
Inhibin ≤ 0.5 MoM	1.39 (0.4-4.6)	1.22 (0.5-3)	7.88 (0.7-92.4)	1.79 (0.1-21.5)	1.38 (0.3-7.4)
NT ≤ 0.5 MoM	*	0.41 (0.1-3.3)	*	*	*
PAPP-A ≤ 0.5 MoM	1.4 (0.4-4.7)	1.05 (0.5-2)	0.99 (0.2-5.2)	1.19 (0.1-12.5)	1.49 (0.4-5)
uE3 ≤ 0.5 MoM	7.78 (0.7-88.2)	*	*	*	1.38 (0.3-7.4)
Levels that are statistically significant at p<0.05 are in **bold**.					
All entries are odds ratios with 95% confidence intervals in parenthesis.					

*Due to sample size limitations, odds ratios could not be estimated.

Table 3b

Relationship between serum markers and single gene disorder groups

Serum Marker	Craniosynostosis	Hemoglobinopathies	Skeletal Dysplasia	Metabolic Disorders
AFP ≥ 2 MoM	*	0.86 (0.1-8.7)	1.10 (0.1-12.3)	*
fβhCG ≥ 2 MoM	1.14 (0.3-4.3)	0.75 (0.1-4.2)	2.76 (0.5-15.5)	*
hCG ≥ 2 MoM	0.45 (0.1-4.0)	0.67 (0.1-6.5)	0.79 (0.1-8.2)	*
Inhibin ≥ 2 MoM	1.77 (0.1-21.1)	*	2.56 (0.3-18.9)	*
NT ≥ 2 MoM	*	*	*	*
PAPP-A ≥ 2MoM	3.60 (0.8-15.9)	0.78 (0.1-7.8)	0.86 (0.1-9.0)	1.00 (0.1-10.4)
uE3 ≤ 0.5 MoM	*	*	*	*
All entries are odds ratios with 95% confidence intervals in parenthesis.				
No values achieved statistical significance at $p < 0.05$.				

* Due to sample size limitations, odds ratios could not be estimated.