Maternal anxiety and ultrasound markers for aneuploidy in a multiethnic population†

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Objective Discussion of isolated ultrasound (US) markers for fetal aneuploidy can provoke significant patient anxiety. The objective of this study is to quantify maternal anxiety associated with the detection of these markers.

Methods All patients undergoing routine second-trimester US examination for fetal anatomical survey over a one-year period were administered the State-Trait Anxiety Inventory (STAI) for Adults before and after the procedure. Women with isolated fetal markers for aneuploidy were notified of the findings but discouraged from pursuing amniocentesis. Rates of normal US examination, aneuploidy markers, anomalies, amniocentesis, and pregnancy outcomes were assessed across the ethnic groups. Pre- and post-ultrasound STAI surveys were scored and standardized with previously established norms. Student t-tests, Chi-square, and analysis of variance (ANOVA) were used where appropriate.

Results Among the 798 patients tested, 57% were Hispanic, 30% were Asian, 6% were Black, and 7% were White. Maternal anxiety level was decreased in women after a normal US. The anxiety level increased with aneuploidy markers and was the highest with anomalies. Aneuploidy markers were more common among Hispanic and Asian fetuses, without any associated aneuploidy. Women with isolated aneuploidy markers underwent amniocentesis as often as women with advanced maternal age.

Conclusion The detection and communication of isolated aneuploidy markers is associated with increased maternal anxiety and unnecessary amniocentesis. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS: ultrasound; pregnancy; prenatal diagnosis; maternal anxiety; markers

INTRODUCTION

Over the past decade, several fetal ultrasound (US) abnormalities have been associated with an increased risk of carrying a fetus with chromosomal aneuploidy. These sonographic markers for aneuploidy—combined with a patient’s age, presence of structural malformations, and second-trimester maternal serum screening results—play an important role in determining the need for more invasive prenatal testing such as amniocentesis. Recent editorials, however, have debated whether physicians should disclose the presence of isolated US markers for aneuploidy since these findings can, in the absence of the other risk factors for aneuploidy, unnecessarily increase maternal anxiety (Doubilet et al., 2004; Filly, 2004; Filly et al., 2004).

The psychological impact of both abnormal maternal serum alpha-fetoprotein levels and sonographically diagnosed fetal structural malformations has previously been studied and was found to be associated with increased maternal anxiety levels (Keenan et al., 1991; Rona et al., 1998). Genetic counseling has been shown to decrease maternal anxiety levels in patients with abnormal maternal serum alpha-fetoprotein (MSAFP) screening (Keenan et al., 1991; Lai et al., 2004). However, the psychological impact of discovering US markers for aneuploidy, the manner in which this information is disclosed by healthcare providers, and the way women use this information have been highly controversial and poorly elucidated (Watson et al., 2002; Learman et al., 2005; Teixeira et al., 1999). The essence of the debate regarding whether healthcare providers should discuss these questionable US findings with women from a variety of cross-cultural backgrounds was recently reviewed by Getz and Kirkengen (Getz and Kirkengen, 2003).

In order to quantitatively assess the psychological impact of this information, we used a validated psychometric tool, the State-Trait Anxiety Inventory (STAI) to measure maternal anxiety in women undergoing routine second-trimester fetal anatomical survey (Spielberger, 1983). The full version of the STAI comprises a method for quantifying the subject’s anxiety ‘state’ and consists of 20 items to rate an individual’s response to a situation. The utility of the STAI and other similar psychometric tools in prenatal genetic screening are reviewed in a monograph by Green and colleagues (Green et al., 2004). The objectives of this study were (1) to quantify and compare anxiety levels in women carrying fetuses with normal US examinations, those with US markers...
for aneuploidy, and those with structural birth defects, and (2) to evaluate how women from various ethnic backgrounds use this information to make different decisions regarding amniocentesis.

MATERIALS AND METHODS

Subjects

All pregnant women between 14 and 24 completed weeks’ gestation undergoing routine fetal anatomic US examinations in the OB/GYN US Unit at Bellevue Hospital in New York city between June 2000 and July 2001 were approached by study personnel for participation in this study. The women were asked to self-identify themselves as Black, White, Asian, or Hispanic at the initial administration of the STAI. Patients referred to this center for a second opinion regarding a previously diagnosed fetal malformation were excluded from analysis. This study protocol was approved by the Institutional Review Board at Bellevue Hospital.

STAI testing

Patients were offered the STAI before and after sonogram evaluation in the waiting area of the US unit. Because our cohort consisted of new immigrants from various ethnic backgrounds, the STAI tool was obtained from the test developer in 11 different languages that were previously standardized and validated (Form Y, Spielberger 1983, Mind Garden Inc., Redwood City, California) (Spielberger, 1983). The written languages included English, Spanish, Chinese, French, Hindi, Bengali, Nepalese, Russian, Polish, German, and Swedish. The STAI is a well-standardized psychometric tool for assessing both ‘state’ anxiety (measurement of acute anxiety, S-anxiety) and ‘trait’ anxiety (measurement of chronic anxiety, T-anxiety). The STAI instrument that was used to measure acute stress/anxiety consisted of 20 statements that elicited a response on the basis of the degree of agreement to the stated feeling. Norms for adult men and women have been published elsewhere (Spielberger, 1983). The standardized mean score for the STAI is 35 in nonpregnant women, 36 in women with a history of abnormal biochemical marker screening did not demonstrate an increased risk for aneuploidy. The women of advanced maternal age (35 or older at the time of expected delivery), who had a history of abnormal biochemical marker screening, were found to have a fetal structural malformation, or were carrying a fetus with two or more US markers for aneuploidy were encouraged to undergo genetic counseling and amniocentesis if desired.

For the purpose of this analysis, the patients were categorized into one of three groups: (1) normal US findings, (2) US markers for aneuploidy, or (3) US evidence of structural malformation. A normal US was defined as a study in which all the major structures, as defined by AIUM criteria (AIUM, 2003), were visualized and no markers for aneuploidy or structural malformation were detected. A patient was classified as having an US marker for aneuploidy if no structural malformation was detected but one or more of the following markers was seen: choroid plexus cysts (CPC), echogenic intracardiac focus (EIF), renal pyelectasis (RP), or echogenic bowel (EB). Choroid plexus cysts were defined as well-circumscribed anechoic areas within the substance of the fetal choroid plexus, unilateral or bilateral (Benacerraf et al., 1994). Echogenic intracardiac focus was considered present when a small structure within the fetal heart with similar or greater echogenicity to the surrounding bone was detected on standard 4-chamber view (Sepulveda and Romero, 1998). Unilateral or bilateral pyelectasis was identified if the anteroposterior diameter of the renal pelvis measured 4 mm or more (Benacerraf et al., 1994). Fetal echogenic bowel was considered if the bowel appeared at least as echogenic as the surrounding bone regardless of minimization of the US gain controls (Vincoff et al., 1999). Patients were classified as having a fetus with an isolated US marker for aneuploidy if they had no other risk factors for aneuploidy, including maternal age greater than 35 years at delivery, and those with structural birth defects.
and serum markers for aneuploidy were negative. Structural fetal anomalies were also recorded and confirmed by the sonologist.

Data analysis

The US data, patient demographic data, pregnancy outcome data, and pre- and post-test scores were entered into a database/statistical software computer program (JMP for Windows, Version 4.0.3, Copyright 1989–2000, SAS Institute Inc.). The raw STAI scores from the pregnant women participating in this study were compared with standardized scores from previously identified populations of patients undergoing other stressful life events (Spielberger, 1983). Continuous variables were analyzed with the Student t-test. Chi-square analysis was used for categorical data. Analysis of variance (ANOVA) was utilized when comparing multiple groups of data. Post hoc analysis of significant ANOVA comparisons using the Tukey–Kramer test was performed to determine the individual groups that demonstrated significant differences.

RESULTS

Eight hundred and seven women underwent routine second-trimester fetal anatomy surveillance during the study period. Seven hundred and ninety-eight patients received the STAI, of whom 777 adequately completed the STAI and fulfilled the inclusion criteria for this study (96% of the total population undergoing routine US screening). Thirty of the original 807 women who underwent fetal anatomy US during this period were excluded from the analysis because of the following reasons: refusal to participate in the STAI (n = 9), incomplete filling of the STAI (n = 8), and more than 24 completed weeks’ gestational age of the fetus at the time of initial US (n = 13). Demographic information is shown in Table 1. Of the 246 women who self-identified as ‘Asian,’ 216 (88%) were Chinese, 25 (10%) were South Asian, and 5 (2%) were Nepalese. Ninety-three (12%) of the women who completed the STAI were considered to be of advanced maternal age.

Sixty-nine (9%) of the fetuses scanned in our cohort had at least one US marker. The distribution of US marker findings is shown in Table 2. Echogenic intracardiac focus was the most commonly detected marker. None of the 30 women excluded from the STAI study analysis had an US marker or structural fetal anomaly. None of the study patients with US markers was found to have a fetus with an abnormal karyotype. Nine women were found to have fetuses with structural anomalies during the US screening. These included anencephaly (1 patient), congenital cystic adenomatoid malformation (CCAM) of the lung (1), cleft lip (1), fetal hydrops (1), ventriculoseptal defect (2), multicystic kidney (1), and hydrocephaly (2). No other major structural anomalies were detected postnataally in this cohort.

Baseline maternal anxiety level prior to US was similar in all subjects across racial/ethnic backgrounds (Table 3). Overall, the women demonstrated decreased anxiety levels following the report of a normal US examination of the fetus when compared with pre-test anxiety levels. The magnitude of this change was particularly noticeable in Black women in comparison to Asian and Hispanic women (Table 4). Patients who were informed of US markers for aneuploidy and structural fetal malformations demonstrated significantly increased anxiety levels compared to pre-test levels (Table 3). Black women tended to show a greater rise in anxiety level than other groups following the finding of an US marker, but the difference was not statistically significant. The increased anxiety associated with US markers did not correlate with maternal age or parity (data not presented).

Forty-two of the 777 patients (6%) in the study underwent amniocentesis to rule out aneuploidy. Among the women with isolated markers for aneuploidy, 33% of the women with isolated markers for aneuploidy, 33%

Table 1—Demographic information (n = 798)

<table>
<thead>
<tr>
<th>Race/Ethnic background</th>
<th>Mean age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>26.3 years (5.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>26.2 years (5.7)</td>
</tr>
<tr>
<td>White</td>
<td>26.2 years (5.7)</td>
</tr>
<tr>
<td>Black</td>
<td>26.2 years (5.7)</td>
</tr>
</tbody>
</table>

Table 2—Incidence of ultrasound markers

<table>
<thead>
<tr>
<th>Marker for aneuploidy</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIF</td>
<td>48 (6.2)</td>
</tr>
<tr>
<td>CPC</td>
<td>12 (1.5)</td>
</tr>
<tr>
<td>RP</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>EB</td>
<td>3 (0.4)</td>
</tr>
</tbody>
</table>

*Five fetuses had more than one marker.

Table 3—STAI scores by ethnicity [Mean (SD)]

<table>
<thead>
<tr>
<th>Race/Ethnic background</th>
<th>Pre-US</th>
<th>Post-US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>34 (10)</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Asian</td>
<td>35 (10)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>White</td>
<td>34 (10)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>37 (10)</td>
<td>31 (8)</td>
</tr>
</tbody>
</table>

*Data not presented.*

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Table 4—Change in STAI score following ultrasound results [Mean (SD)]

<table>
<thead>
<tr>
<th></th>
<th>Hispanic</th>
<th>Asian</th>
<th>White</th>
<th>Black</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>−1.2 (8.2) n = 407</td>
<td>−0.7 (7.6) n = 201</td>
<td>−2.3 (9.3) n = 49</td>
<td>−5.5 (8.2) n = 42</td>
<td>0.0047*</td>
</tr>
<tr>
<td>US Marker</td>
<td>3.5 (13.1) n = 30</td>
<td>5.4 (9.5) n = 32</td>
<td>5.3 (6.7) n = 3</td>
<td>8 (7.7) n = 4</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*For women with normal fetal ultrasound findings, Black women demonstrated a significant decrease in STAI Score in comparison to Hispanic women and to Asian women, using the Tukey–Kramer post hoc analysis.

(23/69) underwent amniocentesis. Over 50% (5/9) of the women with fetal anomalies underwent amniocentesis, and 2% (15/699) of the patients with normal US examinations underwent amniocentesis for other unspecified indications (e.g. maternal Sickle Cell anemia). Rates of amniocentesis in women with isolated markers of aneuploidy (23/69, 33%) approached the rates in women with advanced maternal age (44/93, 47%) (Chi-square analysis, p = NS).

The STAI scores of the pregnant patients in this study were compared with previously published scores of other populations undergoing stressful life events such as hospitalization, military recruitment, college student examinations, and prison incarceration (Spielberger, 1983). In general, an STAI score of 34 is considered ‘normal.’ A score of 48 is considered an ‘acute anxiety response’ to a stressful situation (Green et al., 2004). The baseline STAI score of 36 in our cohort is comparable to those of ‘normal’ pregnant women (Shennan et al., 2005). Women with fetal markers for aneuploidy had a mean STAI score of 40, which approaches the diagnosis of a generalized anxiety disorder (Shennan et al., 2005) and is similar to the scores of hospitalized patients undergoing major surgery and college students undergoing academic examinations (Spielberger, 1983). Women with fetal anomalies had stress scores similar to those of young prison inmates (Spielberger, 1983) and pregnant women who have received abnormal genetic test results (Green et al., 2004).

DISCUSSION

In many cultures, pregnancy is considered a natural extension of the normal state of wellness, not an illness or disability that requires extensive surveillance. However, as more sophisticated testing and screening are developed and incorporated into the routine care of the pregnant woman, a presumption is often made that all women desire fetal testing without regard to the potential for elevated anxiety and stress, especially when poorly characterized US markers are found. We have also neglected to consider the broad biopsychosocial ramifications of our actions. Previously, US examination during pregnancy was reserved for the detection of major congenital fetal anomalies that might require surgical repair or were deemed incompatible with life. However, over the past decade, US technology has become so refined that previously undetected variations in fetal anatomy are being discovered, in which the implications are not well characterized. The most commonly detected ‘markers’ or ‘borderline’ findings include CPC, EB, EIF, and RP. In a karyotypically normal fetus, these ‘markers’ for aneuploidy are not associated with long-term sequelae.

We recognize that the presence of these controversial markers has been associated with Down syndrome and other aneuploidies in as many as 5% of the fetuses (Wickstrom et al., 1996; Bromley et al., 1994; Bromley et al., 1998; Nadel et al., 1992). However, recent data also demonstrate that the EIF can be found in up to 30% of karyotypically normal Asian fetuses (Shipp et al., 2000). If this marker is detected in such a high frequency in a particular minority group without an associated increase in aneuploidy, perhaps the marker might instead be considered a normal variant rather than a marker for aneuploidy.

These high-resolution screening sonograms, termed ‘genetic sonograms,’ (Bromley et al., 2002) go beyond merely looking for physical birth defects and are being used routinely on patients as a genetic screening test without proper ‘pre-test’ patient counseling or assessment of their understanding of potential implications. A recent meta-analysis has even demonstrated the poor positive predictive values of these US findings for aneuploidy (Smith–Bindman et al., 2000). If this marker is detected in such a high frequency in a particular minority group without an associated increase in aneuploidy, perhaps the marker might instead be considered a normal variant rather than a marker for aneuploidy.

The crux of the current debate is whether the health care provider is obligated to inform the patient about the marker if one is detected in a woman with no other risk factors for aneuploidy, such as advanced maternal age, abnormal biochemical marker screening, or other associated markers or anomalies, if this finding can be considered a normal variant in certain populations of women.

Our study is an attempt to quantify maternal anxiety in a commonly encountered situation in which patient counseling has been ambiguous and vague. This study also examines some of the cross-cultural responses associated with prenatal fetal US screening that has become so routine in Western culture (Getz and Kirkenden, 2003). We have demonstrated that the mere discussion of US markers with patients generates anxiety and increased requests for amniocentesis for fetal karyotyping. Traditionally, algorithms for prenatal diagnosis involve offering amniocentesis only to women whose risk of carrying a fetus with an abnormal karyotype outweighs the risk of complications of miscarriage from the procedure itself. In general, women are offered amniocentesis if they are aged 35 years or more at the time of delivery or when biochemical marker screening levels demonstrate an increased risk for aneuploidy that
is beyond the risk for pregnancy loss from the procedure itself (Kuppermann et al., 1999). Serum marker screening is not without its limitations; 98 unnecessary amniocenteses (and its associated increase in iatrogenic miscarriage) are required to be performed in order to diagnose two cases of Down syndrome (Phillips et al., 1992). As per the traditional principles of genetic counseling, patients are required to sign a consent form before undergoing serum marker screening tests in order to minimize patient anxiety and to avoid being coerced into an amniocentesis when there is a high likelihood for normal results, as well as to avoid the potential complications of the invasive procedure itself.

However, the use of 'genetic' sonograms for fetal anatomy have not followed the general principles of other genetic tests. Many women in the U.S. undergo prenatal US for nonmedical reasons (ACOG Committee Opinion, 2004). Women from other countries may undergo US without any understanding of its limitations. They may be unaware that potential fetal anomalies can be diagnosed via US, so explaining the concept of US ‘markers’ and ‘aneuploidy’ is an even more awkward and difficult task for the healthcare provider, even when a foreign language translator is available.

There has been limited research into the prevalence of various prenatal US markers in various racial groups, and none addressing the psychological implications of notifying a patient about such an abstract concept of ‘markers.’ In 2000, Shipp and colleagues demonstrated a significantly higher rate of EIF in Asian pregnancies (30.4% in Asian versus 10.5% in White patients), without any increase in associated aneuploidy (Shipp et al., 2000). This suggests that EIF may represent a normal variant, particularly in the Asian population. Using the psychological data from our study, it can be seen that Asian patients may be unfairly targeted for discussions of aneuploidy markers, and unnecessarily alarmed and compelled to undergo an excessive number of amniocenteses.

The need for cultural sensitivity in genetic counseling and prenatal diagnosis is important in our multi-ethnic nation of immigrants (Punales–Morejon, 1997; Rapp, 1997). Currently, research into how women of different educational, racial, and ethnic backgrounds access prenatal diagnosis and use the information is limited. Kuppermann and colleagues have determined that, when given the choice, Hispanic and African–American women are less likely to undergo testing than Caucasians and Asians (Kuppermann et al., 1996). They also noted a racial difference in women giving birth to Down syndrome affected neonates but did not comment on the rates of pregnancy termination. The ethnic attitudes toward termination of ‘abnormal’ fetuses when there are differing rates of finding these ‘markers’ will have important implications for genetic counseling; i.e. high rates of detecting EIF in Asian patients who otherwise have very low rates of aneuploidy. In our series, it was particularly a matter of concern to find that women with isolated US markers for aneuploidy were undergoing amniocentesis as often as women with advanced maternal age, despite discouragement from counselors to pursue further testing. Furthermore, none of the Asian women in our study with an isolated marker of aneuploidy had an aneuploid fetus.

Overall, the population who delivered at our institution during the period of this study (2209 obstetrical discharges in the year 2002) consisted of 28.4% Asian, 51.2% Hispanic, 7.7% Black, 4% White, and 8.6% ‘others.’ Although the educational status of our cohort was not directly assessed, an inference of educational background can be made from the study of another large published cohort of women with similar demography who enrolled in prenatal care at Bellevue Hospital from 1996 to 1997, which reported that 71% of pregnant women had attended at least 12 years of school in their countries of origin (Dijkstra et al., 1999). This suggests that the population in our study was relatively well educated and capable of comprehending the concept of a genetic marker if not hindered by the limitations of foreign language translation.

The psychological impact of prenatal marker screening has not been evaluated as much as those related to alpha-fetoprotein screening and amniocentesis (Keenan et al., 1991; Lai et al., 2004; Earley et al., 1991; Evans et al., 1988; Ng et al., 2004; Georgsson Ohman et al., 2004). Previous studies have utilized the State–Trait Anxiety Scale and other Likert model-based surveys (Green et al., 2004). The studies demonstrated increased anxiety in patients with abnormal screening results compared to controls; one study showed that abnormal screening results engendered more anxiety than that in women who were considered ‘high risk’ on the basis of advanced maternal age alone. Interestingly, these studies demonstrated that pre- and post-test genetic counseling was able to reduce maternal anxiety in the setting of abnormal biochemical marker screening (Keenan et al., 1991; Ng et al., 2004; Georgsson Ohman et al., 2004). The pre-ultrasound STAI scores in our patient cohort were similar to the pre-ultrasound scores reported by Lai et al. (Lai et al., 2004). The STAI scores in our cohort’s post-normal US findings were also similar to the post-ultrasound scores in the Lai study. When comparing the anxiety generated by discussions of aneuploidy markers in our pregnant patients with cohorts of patients in other populations undergoing stressful life events, we found that women with fetal aneuploidy markers had similar stress scores as hospitalized patients undergoing major surgery or receiving abnormal test results (Shennan et al., 2005).

CONCLUSIONS

In conclusion, given the amount of maternal anxiety generated with detection of aneuploidy markers, serious consideration should be given to offering pre- and post-ultrasound genetic counseling, or otherwise, nothing should be mentioned about US markers that may be normal variants in patients who have no other risk factors for aneuploidy. Furthermore, there is variation in the way women from various ethnic backgrounds will interpret and act on positive, negative, and indeterminate findings on prenatal US examinations.
REFERENCES


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