• REVIEW ARTICLE •

Antenatal Screening for Down Syndrome with Special Considerations in the Puerto Rican Population

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Down syndrome is the most studied chromosomal abnormality, and the risk of having a child with Down syndrome increases as maternal age increases. The prevalence of Down syndrome has been increasing in the last decade because more women older than 35 years of age are having children. In recent decades, the rate of identification of fetal anomalies in the uterus has substantially increased. Diagnostically speaking, serious concerns yet remain within the obstetrical community regarding who should be recommended for invasive procedures. The FASTER, SURUSS, and BUN studies have attempted to address this issue. In the United States, the quadruple screen for Down syndrome (hcG, AFP, estriol, and inhibin-A) is the most commonly used test today. During the first trimester, the nuchal translucency measurement combined with serum markers hcG and PAPP-A (pregnancy-associated plasma protein-A) results in high detection rates and low false-positive rates. For Down syndrome screening, new methods of evaluation have been proposed; among these are integrated, sequential, and contingent modalities. Different trials have demonstrated that first-trimester screening for Down syndrome is very effective, but all conclude that combining screening during both trimesters allows for lower false-positive values and higher detection rates. In Puerto Rico, in spite of the fact that a large proportion of the population undergoes serum screening, the rate of Down syndrome live births remains steady. One important aspect that appears to limit prenatal diagnosis of Down syndrome in our population is a poor acceptance rate of diagnostic testing techniques such as amniocentesis. Also, a limited efficiency in the implementation of these screening methods as well as their diagnostic success has been observed for our patient population. [*P R Health Sci J 2011;30:206-210*]

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Down syndrome is the most studied chromosomal abnormality (1). This syndrome is most commonly produced by the presence of an additional copy of chromosome 21 (trisomy 21). Less common causes include chromosomal rearrangements, such as translocations. Individuals with this condition have unusual facial features, such as a flat face, epicanthal folds, small ears, and other craniofacial abnormalities. They frequently suffer from cardiac defects and are at high risk of infections, thyroid abnormalities, leukemia, and premature aging (2). The risk of a baby's being born with Down syndrome increases with maternal age, and the syndrome's prevalence has been increasing during the last decade because women are more willing to have their children at past 35 years of age (3, 4).

More than 20 years ago, the maternal serum testing approach for Down syndrome screening was introduced (5, 6), and it is still the most common method used today. In recent decades, with more advanced technologies in ultrasound and prenatal screening, the ability to identify fetal anomalies in utero has been greatly improved. Nevetheless, serious concerns remain within the obstetrical community with regard to who should be recommended for invasive diagnostic procedures, such as chorionic villus sampling (CVS) or amniocentesis, given the fact that both of these procedures are not innocuous and can, potentially, induce miscarriage. Studies such as the First- and Second-Trimester Evaluation of Risks (FASTER) trial, the Serum Urine and Ultrasound Screening Study (SURUSS), and the Serum Biochemistry and Fetal Nuchal Translucency

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Screening (BUN) study have attempted to deal with this issue. In this clinical review, the concept of screening for Down syndrome during the first and second trimesters as well as new modalities of integrated, sequential, and contingent screening will be addressed. Finally, an overall view of the Down syndrome screening methods that are used in Puerto Rico will be presented.

Medical Screening in Perspective

Medical screening refers to the concept of testing individuals who (or populations that) are at a particularly high risk of having a disease or condition. As Cuckle et al. described, screening should be applied to populations in which a diagnostic follow-up is warranted (7). Given the high incidence and morbidity that having a child with Down syndrome carries, screening for this condition is advised, and as the ACOG new guideline states, "… all women should be offered aneuploidy screening" (8). For practical purposes, a stepwise screening process should have a follow-up management alternative available, which includes termination of pregnancy if the mother so decides. Finally, an ideal screening process should maximize the positive predictive value of the test for the condition diagnosed (4), and it should also minimize the false-positive rates. Thus, detection rates, false-positive rates, and positive predictive values should all be taken into consideration when making decisions on the further management of screened individuals whose levels (in terms of the Down syndrome) are abnormal.

Second-trimester Screening

During the 1980s, newly acquired knowledge regarding the link between low levels of alpha-feto protein (AFP) and fetal anomalies led health providers to implement the regular use of this serum biomarker to screen for Down syndrome (5, 6). A combination of age-related risk and the AFP values were used to further define a given patient's risk. Unfortunately, the AFP alone was able to identify only about 23% of Down syndrome cases. After this advancement, further efforts to discover more of these markers were more active than ever. High levels of serum human chorionic gonadotropin (hCG) and, later, low levels of unconjugated estriol (uE3) were also found to be associated with higher risks of having a fetus affected with trisomy 21 (9). Therefore, the triple screen consisting of the measurement of hCG, AFP, and estriol during the second trimester was found to be a powerful tool and became the most used method for Down syndrome screening (10), with a sensitivity of approximately 65%. The later addition of a fourth serum biomarker, inhibin-A, which is found at higher levels in fetuses with this anomaly, has made possible the quadruple screening test. This is, in fact, the most common test used today in the United States (11), and it is considered the standard of care by the American College of Obstetricians and Gynecologists (8). After interpreting the results of the SURUSS trial's study of quadruple screening, Weisz and Rodeck concluded that those results clearly showed that the quad screen test was only slightly superior to the original triple screen in terms of its detection rate, but if it was positive, the quad screen test reduced the need for amniocentesis by 35% (12). However, this study differs from other works such as the FASTER trial. For example, there was a significant difference in detection rates between the triple test and the quadruple test (69% versus 81%). False-positive values also differed markedly: 14% for the triple screen and 7% for the quadruple. Both of these tests are done between the 15th and 21st weeks of pregnancy, with the greatest level of sensitivity obtained between the 16th and the 18th weeks. The greatest level of sensitivity represents a problem associated with the late identification of fetal chromosomal anomalies that may be near the age of viability. Thus, studies aimed at developing methods of earlier detection are desirable.

First-trimester Screening

Spencer et al. identified high levels of the free hCG beta chain (13) and Wald et al. described low levels of the placental product, pregnancy-associated plasma protein-A (PAPP-A) (14), in fetuses with trisomy 18, with the two metabolites being measured between the 10th and 13th week of gestation. Unfortunately, their measurement alone provides a sensitivity close to 50%, far from desirable. Nicolaides and colleagues elegantly described the direct relationship between a sonographic marker called the nuchal translucency (NT) and Down syndrome (15). The NT is measured from the fetal cervical vertebrae to the skin surface during the late first trimester, between the 9 6/7 and 13 6/7 week (Figure 1). This sonographic marker by itself reaches a detection rate of almost 60%, with low false-positive values. When combined with the serum biomarkers hCG and PAPP-A, the detection rate is 85 to 90%, with false-positive rates of 4 to 6%. Earlier screening (during gestation) with high detection rates means an earlier opportunity for diagnosis, making decisions by the parents, as well as any treatment, easier.

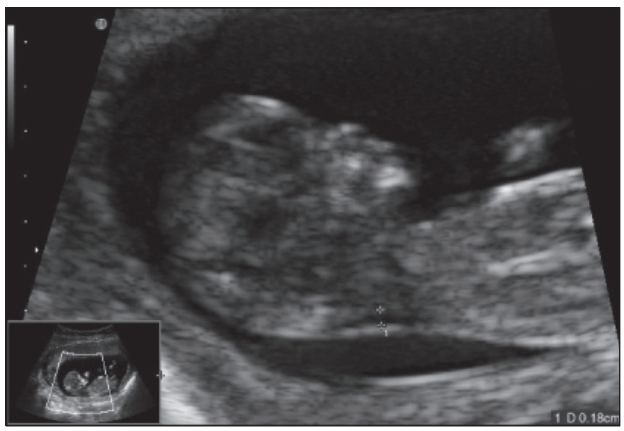

Figure 1. Nuchal translucency at 11 weeks of gestational age

Studies by Cicero and co-workers also suggest that a determination that the nasal bone is absent in a fetus (another promising first-trimester sonographic marker of the syndrome) combined with NT, hCG, and PAPP-A screening, could result in a 97% detection rate (16). Further multicentric studies are needed to corroborate this finding. Difficulty remains in terms of the availability (or lack thereof) of trained obstetricians or technicians to perform these measurements.

First- and Second-trimester Screening

Instead of choosing one evaluation over the other (that is, the first-trimester evaluation over the second-trimester evaluation or viceversa), an integrated method has been devised in which both the first- and the second-trimester screenings are evaluated together (17). The test is based on measuring serum PAPP-A and free Beta chain hCG, along with NT, during the first trimester. The interpretation is then delayed until the second trimester, when the quadruple serum testing (AFP, hCG, estriol, and inhibin-A) is done. The results of all these tests are then computed into a single risk assessment. This combination results in detection rates of over 94% with false-positive values of 5% (17); both the SURUSS and the FASTER trials had similar results. Given this low figure of false-positive results coupled with a higher sensitivity, there are clear benefits to integrated testing. Screening costs, however, are significantly higher, which limits the availability of this test for the general population.

The issue remains whether the results of first-trimester screening should be provided to the patient prior to completing the second-trimester integrated screening process. Studies by Palomaki et al. addressed this issue and reported that the majority of pregnant women undergoing integrated screening programs were more prone to wait until the second-trimester results before deciding whether or not they wanted to proceed with invasive diagnostic testing (17). When there is a lack of trained personnel to measure NT, an integrated serum approach with high detection rates can also be used, that is, measuring PAPP-A and free Beta hCG during the first trimester and integrating the results with those of the quad screen done during the second trimester. This results in an 85% detection rate, which is higher than what results when using the quad screen alone and is similar to the first-trimester integrated screening test (PAPP-A + free BhCG + NT) (18). Pregnant women should be urged to undergo a serum-only integrated test if NT sonographic measurements are not available.

Another approach to this dilemma has been proposed, i.e., sequential integrated screening. This test is offered to pregnant women who are willing to undergo invasive procedures if the first-trimester results are abnormal. For example, after the first-trimester integrated test is performed (NT + free BhCG + PAPP-A), if a high risk for Down syndrome is calculated, a patient will immediately be offered an invasive first-trimester diagnostic test (CVS) without waiting for a second-trimester quadruple screen test. If the first-trimester screening results determine that there is a low risk, the patient will then continue her regular care until the second-trimester quadruple test is done. If a positive second-trimester screening is found, then amniocentesis will be offered. If the test is negative, no further testing is required. This sequential integrated test offers immediate options in the form of diagnostic tests to patients with first-trimester screening results that are positive for Down syndrome.

Another alternate screening approach has been proposed by Wright and colleagues, in which the second-trimester assessment is contingent on the first-trimester screening results. For example, women with the lowest risks would not need to undergo second-trimester testing. On the other hand, patients with high risks, would be offered invasive testing by CVS, and those with intermediate risks would be offered integrated screening. Thus, contingency screening might be considered to be more effective than is sequential screening since high-risk patients can be diagnosed during the first trimester, and only 15% of patients would require second-trimester testing. As proposed by Nicolaides and colleagues, this approach could be even more reliable for patients with intermediate risk if combined with ultrasound markers such as nuchal translucency and others that have not been firmly established, i.e., the assessment of nasal bone, the resistance to flow in the ductus venosus, or tricuspid regurgitation (19).

Screening for Down Syndrome in Puerto Rico

As a result of maternal serum screening, the incidence of Down syndrome in live births has fallen gradually in many countries, in spite of an increase in the average maternal age. However, in Puerto Rico, in spite of a large proportion of the population undergoing serum screening, the prevalence of Down syndrome for every 10,000 live births has remained steady at approximately 14.4 (as reported by the Puerto Rico Health Department's Birth Defects Registry annual report) (20). There are some problems that are of particular importance regarding screening for Down syndrome in our population, and these problems may reduce the sensitivity of detection; in particular, late registration for prenatal care, being of Hispanic origin, the type of test used, and lastly, lack of acceptance of diagnostic methods remain significant barriers to screening.

Many of our patients register late for prenatal care. This may be due to not realizing that they are pregnant, often because the pregnancy is unplanned; over 50% of pregnancies in Puerto Rico are unplanned (21). Another possibility is that a given patient may not have medical insurance coverage or that her policy does not cover certain screening procedures. Irrespective of the cause, late registry for prenatal care usually means that first-trimester screening is unlikely.

Studies have shown that the AFP values of Hispanic patients tend to be lower than those of either Caucasian patients or African American patients; thus, there is a tendency to

overestimate the risk of Down syndrome in these populations, creating more false-positive tests.

For either economic reasons or because of lack of availability, it seems, many physicians in Puerto Rico are ordering the triple maternal serum screen and not the quadruple screen during the second trimester, and very few are ordering first-trimester screening at all. We reviewed the charts of all of the patients with positive screens for Down syndrome who had been referred to us. Of the patients referred from January 1 through June 30 of 2010 for evaluation at the University Hospital's Antenatal Evaluation Unit because of abnormal serum tests (n = 1656), 90% underwent a triple test, 8%, a quadruple, and only 2% had first-trimester tests. None underwent integrated testing. Use of a less sensitive method of evaluation will, obviously, result in fewer diagnoses of Down syndrome. The above data may not describe the experiences of all patients in Puerto Rico, but these are patients referred from all of the health regions of our island, including both those patients with private insurance and those with public health plans. A thorough evaluation of our island screening practice is needed in order to better assess its effectiveness.

One important aspect that appears to limit prenatal diagnosis of Down syndrome in our population is a poor acceptance rate of diagnostic testing techniques, such as amniocentesis. Of the patients who are found to have a significant risk (as determined by their having a positive maternal serum screen) of giving birth to a child with Down syndrome, fewer than 50% of them express an interest in proceeding with an amniocentesis. Eventually, fewer than 20% actually undergo this procedure (22). One would question the type of information given to those patients by their providers and how this information affects their decision-making. In addition, social status, type of insurance coverage, and the region in which she resides may affect the patient's decision to undergo or refuse amniocentesis. Unfortunately, these data are unavailable. Irrespective of the screening method used, its efficacy will depend on the eventual diagnosis achieved through a diagnostic method such as an amniocentesis. If the patient refuses the diagnostic test, for whatever reason, then screening has failed. This has been a constant problem that we encounter in our population. More information is needed to ascertain which elements or pieces of information affect a patient's decision to opt for an invasive procedure.

Conclusions

Different trials have demonstrated that first-trimester screening for Down syndrome is very effective, but all conclude that combining screening done in both trimesters allows for lower false-positive values and higher detection rates (23,24). Both the FASTER and SURUSS studies concluded that if nuchal translucency is not available, the serum integrated (PAPP-A and free BhCG during the first trimester and quad markers in the second trimester) test is the next best screening option and may be used as an alternative method. All physicians should inform their patients appropriately about the benefits and risks of different screening tests. Antenatal diagnosis of Down syndrome may continue improving as discoveries continue to appear. More information is needed regarding the cultural issues that might be affecting our patients' decisions regarding invasive procedures as well as the providers' perspectives and attitudes when providing their insured patients with such information as is felt to be pertinent. A limited efficacy in the implementation of these screening methods as well as their diagnostic success has been observed for our population. The fact that we base these conclusions on our experience at the University Hospital does not permit a generalization regarding the status of maternal serum screening in our entire population. However, our patients came to us as a result of islandwide referrals, which strongly suggests that they are in fact representative. Thus, further studies are needed to properly conclude whether maternal screening for Down syndrome is a succesful practice in our population. Our limited conclusions suggest that it is not.

Resumen

El síndrome de Down es la anormalidad cromosómica más estudiada, y su incidencia aumenta con la edad materna. La prevalencia del síndrome de Down ha ido en aumento durante la última década, puesto que las mujeres están más dispuestas a tener hijos pasados sus 35 años de edad. En décadas recientes, la identificación de anomalías de fetos en el útero ha aumentado sustancialmente. Dentro de la comunidad obstétrica existe una gran preocupación con respecto a quién se debe recomendar para procedimientos invasivos para obtener un diagnóstico. Estudios tales como el FASTER, SURUSS y BUN han tratado de responder a esa interrogante. En los Estados Unidos, la cuádruple prueba para el síndrome de Down (hcG, AFP, estriol e inhibina-A) es la más utilizada en la actualidad. Durante el primer trimestre la medida de translucencia nucal, cuando se combina con los marcadores de sangre hcG y PAPP-A (plasma proteína-A relacionada con el embarazo), logra tasas altas de detección y tasas bajas de falsos positivos. Para la prueba del síndrome de Down, se han propuesto nuevos métodos de evaluación, entre ellos, modalidades integradas, secuenciales y contingentes. Diferentes pruebas han demostrado que la prueba para el síndrome de Down es muy efectiva, pero todas concluyen que el combinar las pruebas durante ambos trimestres resultan en tasas más bajas de valores falsos positivos y tasas más elevadas de detección. En Puerto Rico, a pesar de una proporción alta de la población que se somete a la prueba de sangre, la tasa de nacimientos con el síndrome de Down ha permanecido estable. Un aspecto importante que parece limitar el diagnóstico prenatal del síndrome de Down en nuestra población es una tasa baja de aceptación de las técnicas de pruebas diagnósticas, tales como amniocentesis. Además, en nuestra población de pacientes se

ha observado una eficiencia limitada en la implementación de estos métodos de pruebas así como de su éxito de diagnóstico.

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