A Review of Biochemical and Ultrasound Markers in the Detection of Down Syndrome

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ABSTRACT

Childbirth educators need to understand existing prenatal care opportunities and current information for expectant women. This article reviews several testing options that are available during the second trimester of pregnancy to detect the risk of Down syndrome. Educators can help expectant women develop their own specific plan of care according to their special situations and needs. Pregnancy outcomes can be improved when women are informed and educated about the testing available to them.

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The purpose of this article is to assist perinatal educators to understand the etiology of Down syndrome, recognize the population of women who are at risk for having an affected fetus, remain informed of the available screening procedures for second-trimester pregnancies, and understand the efficacy of these prenatal screening tests. With this understanding, educators will be better prepared to assist expectant women with the choices available to them.

Down syndrome is the most frequent genetic cause of mild to moderate mental retardation in newborn infants and occurs in 1 out of 800 live births. The diagnosis of Down syndrome in pregnancy is an increasing concern for today's practitioners because more women are delaying pregnancy until they are over the age of 35 years,

and Down syndrome has a higher incidence of occurrence in older mothers. In the past, a Maternal Serum Alpha-Fetoprotein (MSAFP) or triple screen performed in the second trimester of pregnancy was the most reliable, noninvasive test available to practitioners. However, the MSAFP test provides only a 60–70% chance of identifying Down syndrome and, because some positive results are false, a positive screening only suggests an increased risk of Down syndrome. An amniocentesis is generally offered to all women over the age of 35 years and to women with abnormal MSAFP tests between the 15th and 20th weeks of pregnancy. Due to the risk to the fetus during the invasive amniocentesis procedure and to the incidence of both false-negative and false-positive results of the MSAFP screening test, researchers continue to investigate

Lamaze International has created an independent study based on this article. Please visit the Web site of Lamaze International (www.lamaze.org) for detailed instructions regarding completion and submission of this independent study for Lamaze contact hours.

other methods for the detection of Down syndrome.

HISTORY AND INCIDENCE OF DOWN SYNDROME

In 1866, John Langdon Down, an English physician, discovered a set of children with common features that were distinct from those of other children with mental retardation. His documentation of specific facial and physical features placed these children in a classification known today as *Down syndrome* (DS). Nearly a century later, in 1959, a French physician, Jerome Jeune, discovered that an extra chromosome caused the syndrome. Clinicians now know that the extra chromosome appears as a third chromosome attached to the 21st of the 23 pairs of chromosomes normally present in the human genome (*The Columbia Encyclopedia*, 2001–2005). This condition, in which three copies of chromosome 21 are present in all cells, is called *Trisomy-21* and occurs in 92% of DS cases. In approximately 2–4% of cases, DS is due to *mosaic Trisomy-21* and 3–4% have a third form called *translocation Trisomy-21* (National Institute of Child Health and Human Development [NICHD], 2005). Although DS is caused by an abnormality of the 21st chromosome, the reason this abnormality occurs remains unclear.

DOWN SYNDROME AND MATERNAL AGE

Down syndrome is the most common karyotypic abnormality in live-born infants (1 per 800 live births) and is one of the leading causes of mental retardation (Thompson, McInnes, & Willard, 1991). The risk of the occurrence of DS increases dramatically with maternal age, as shown in Table 1. However, women at any age can have a baby with DS. Studies show that the majority of DS babies are born to women under the age of 35 years because many more babies are born to younger women than to older women (Canick & Messerlian, 2005). Only about 9% of the nation's total pregnancies occur in women 35 years or older each year; however, about 25% of babies with DS are born to women in this age group (NICHD, 2005).

Because of the risk associated with age, maternal age can be viewed as the first "screening test" for

TABLE 1
Relationship of Down Syndrome Incidence to Mother's Age*

Mother's Age	Incidence of Down Syndrome
20 years	1:1,500
30 years	1:800
35 years	1:270
40 years	1:100
45 years and older	1:50 and greater

*From Cuckle, H. S., Wald, N. J., & Thompson, S. G. (1987). Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and alpha-fetoprotein level. *British Journal of Obstetrics and Gynaecology*, 94, 387–402.

fetal chromosome abnormalities (Newberger, 2000). When women reach the age of 35 years and become pregnant, the second-trimester prevalence rate of DS approaches the estimated risk of fetal-loss rate due to amniocentesis (Kuller & Laifer, 1995). Given the cost/benefit ratio, since the 1970s in the United States, a woman's age of 35 years during birth has been used as the cutoff age for routinely offering chorionic villi sampling or amniocentesis for DS detection (Mennuti & Driscoll, 2003). However, due to the risk to the fetus from these invasive procedures, less invasive but reliable testing is continually being sought. Today, due to rapid progress in new testing development, constantly changing protocols are in use.

ALPHA-FETOPROTEIN AND DOWN SYNDROME

Alpha-fetoprotein (AFP) is an oncofetal protein produced by the yolk sac and fetal liver. It is present in the fetal circulation in amounts measured in milligrams per milliliter, with values peaking at 12–14 weeks' gestation (Luthy, 1999). In the 1970s, researchers discovered that AFP levels were elevated in cases with open neural tube defects and it was used as the first biochemical marker for prenatal risk screening (Killingsworth, 2001). Later, in the 1980s, researchers recognized that a lower-than-normal pregnancy level of AFP in the mother's serum was more common in pregnancies that resulted in babies with certain chromosomal abnormalities. Use of the AFP screening test was extended to younger women when a low serum AFP concentration was recognized as a marker of risk for DS. The sensitivity of this marker is low at 25–35% when used to modify age-related risk alone, but showed to be a simple

A karyotype is the complete set of all chromosomes of a cell of any living organism.

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testing measurement for younger women (DiMaio, Baumgarten, Greenstein, Saal, & Mahoney, 1987).

TRIPLE SCREEN

Researchers discovered that by adding tests for levels of human chorionic gonadotropin and estriol to the screening test, the accuracy of the screen increased to 65% sensitivity and, at the same time, decreased the number of false-positive results (Killingsworth, 2001). The combination-screening test is called *the triple screen* or *Maternal Serum Alpha-Fetoprotein* (MSAFP) and is usually performed in the second trimester between 15 and 20 weeks' gestation.

The triple screen measures levels of normal substances called *markers*, which are secreted by the placenta or the fetus and are present in the mother's blood. Typically, serum chorionic gonadotropin concentrations are high, and alpha-fetoprotein and serum unconjugated estriol concentrations are low in women whose fetuses are at risk for Trisomy-21 (Luthy, 1999). A computer program analyzes this maternal blood test, factoring in weight, race, maternal age, and diabetic status to calculate patient-specific risk factors for DS, as well as neural tube defects and Trisomy-18. Women whose MSAFP tests screened positive are then offered amniocentesis for further prenatal diagnosis. However, because the triple screen is not a diagnostic test but only a screening test, many women have a false-positive screen for DS and some cases are missed (Saller & Canick, 1996). False-positive tests have caused much prenatal anxiety for mothers and have led to higher numbers of invasive amniocentesis or chorionic villi sampling, with the risks these diagnostic procedures carry for the fetus.

QUADRUPLE TEST

Researchers continue to study DS detection and work to improve screening tests. Today, another biochemical marker, called *Dimeric Inhibin-A*, has been incorporated into a quadruple test and found to improve the detection rates of DS and reduce false-positive rates (see Tables 2 and 3).

In a recent study, researchers used a large population of pregnant women to investigate the sensitivity of the quadruple test (Benn, Fang, Egan, Horne, & Collins, 2003). Subjects included 23,740 women with unaffected pregnancies and 45 women with affected pregnancies. All of the study's subjects had quadruple tests performed at the University of Connecticut Health Center during a 32-month pe-

riod beginning in November 1999. The study reviewed all quadruple tests performed on singleton pregnancies with gestational ages of 14–21.9 weeks. When the combination of four analytes (alpha-fetoprotein, human chorionic gonadotropin hormone, unconjugated estriol, and Dimeric Inhibin-A) was tested, the overall sensitivity of the quadruple test screening was 86%, and the false-positive rate was reduced to 8.2% after correcting for gestational age. Researchers concluded that the quadruple test meets or exceeds performance expectations and appears to represent an improvement over the widely used triple test (Benn et al., 2003).

Wald, Huttly, and Hackshaw (2003) also conducted a study on the efficacy of the quadruple test. Carried out over a 5-year period in 14 hospitals, their study assessed the performance of antenatal serum (double and triple tests) screening for DS with the quadruple test in 46,193 pregnancies. Expectant women with a positive screen were offered amniocentesis or chorionic villi sampling. The researchers reported that the detection rate with the quadruple test was 81%, and the false-positive rate was 7%. Their study confirmed that in the second trimester, the quadruple test is sufficiently more effective than the double or triple tests and that it should now be regarded as the blood test of choice during this time of pregnancy (Wald et al., 2003). Although the quadruple screen is an improvement over the triple screen, it is not diagnostic, and a positive test continues to indicate a recommendation for further diagnostic testing (Graves, Miller, & Sellers, 2002; Killingsworth, 2001). However, the screen is now accurate enough that women who are 35 years of age or older increasingly opt to undergo serum screening plus ultrasonography before deciding about the risk/benefit ratio for having an amniocentesis (Mennuti & Driscoll, 2003).

ULTRASONOGRAPHIC MARKERS

The second trimester remains an important screening time because patients may have their first sonographic assessment at this time (Bromley, Lieberman, Shipp, & Benacerraf, 2002). In the mid-1980s, many groups reported that a number of ultrasound markers of DS could be recognized

Oncofetal antigens are produced by fetal tissues and in much lower levels in adult tissues.

Researchers continue to study Down syndrome detection and work to improve screening tests.

TABLE 2
Second Trimester Prenatal Screening Options for Detecting Down Syndrome

Blood Tests	Report	Sensitivity	False-Positive Rates
Triple screen (MSAFP, hCG, Estriol)	Killingsworth (2001)	65%	5%
Quad screen (MSAFP, hCG, Estriol, Dimeric Inhibin-A)	Benn, Kaminsky, Ying, Borgida, & Egan (2002)	81.5%	6.9%
	Benn, Fang, Egan, Horne, & Collins (2003)	86%	8.2%
	Wald, Huttly, & Hackshaw (2003)	81%	7%
Ultrasonographic Findings	Report	Sensitivity	False-Positive Rates
Nuchal translucency	Crane & Gray (1991)	75%	1.0%
Isolated markers:	Nyberg, Souter, El-Bastawissi, Young, Luthhardt, & Luthy (2001)		
		39.4%	0.6%
		20.6%	0.6%
		31.6%	5.2%
		21.9%	1.4%
		27.7%	4.4%
Nuchal translucency & long- bone measurement	Benn, Kaminsky, Ying, Borgida, & Egan (2002)	79.9%	6.7%
Nuchal translucency, quad screen, proximal long-bone length	Benn, Kaminsky, Ying, Borgida, & Egan (2002)	90%	10%
Nasal bone length	Bromley, Lieberman, Shipp, & Benacerraf (2002)	81%	11%

during a routine ultrasound at 18–20 weeks' gestation (Benacerraf, Gelman, & Frigoletto, 1987). Second-trimester ultrasonography has the additional advantage of potentially being able to detect fetal anomalies (Copel & Bahado-Singh, 1999). Today, systematic use of multiple sonographic markers to detect fetal aneuploidy is commonly referred to as a *genetic sonogram* and is increasingly being used as a screening test for Trisomy-21 (Souter et al., 2004). Studies show that neonates with DS have a variety of physical features that are potentially detectable by prenatal sonography, including redundant skin on the neck, cardiac abnormalities, short stature, and gastrointestinal anomalies (Bromley et al., 2002).

Nuchal Thickening

Nuchal-skinfold thickness on the fetal neck was first reported by Dr. John Langdon Down in 1866 and is a characteristic clinical feature of infants with Trisomy-21. Nuchal thickening, as seen on sonograms, remains one of the most sensitive and important markers of Trisomy-21 during the second trimester (Nyberg & Souter, 2001). Benacerraf, Frigoletto, and Laboda (1985) were the first to report the sonographic correlation of this clinical feature in terms of nuchal thickening and, thus, began the search for other ultrasound markers. In an article published in the *American Journal of Obstetrics and Gynecology*, Benacerraf and Frigoletto (1987) reported collecting data showing that, regardless of gestational age, nuchal-fold thickness of 303 normal fetuses measured between 1 and 5 mm.

Crane and Gray (1991) provided further testing on the measurement of nuchal-skinfold thickness. The technique of measurement was tested in a study of 3,338 consecutive pregnancies at 14–21 weeks' gestation. A nuchal-skinfold thickness of 6 mm or greater was identified in 47 fetuses (1.4%), only 12 of whom—either by amniocentesis or postnatal follow-up procedures—were proved subsequently to have DS. Thus, when used alone, this measure has a high rate of false positives.

TABLE 3
Scoring Index for Sonographic Markers in Detecting Down Syndrome

Report	Sensitivity	False-Positive Rates
Benacerraf, Neuberg, Bromley, & Frigoletto (1992)	81%	4.4%
Bromley, Lieberman, & Benacerraf (1997)	86.8%	27.1%

W
Aneuploid: having a chromosome number that is not a multiple of the haploid number for the species. The haploid number for humans is 23 chromosomes in reproductive cells.

W
Nuchal pertains to skin at the nape of the neck.

More recently, Benn, Kaminsky, Ying, Borgida, and Egan (2002) reported a study that evaluated the efficacy of DS screening by combining second-trimester maternal serum analytes and the ultrasound measurements of nuchal-skinfold thickness plus proximal long-bone length. The information was collected from January 1992 through March 2001 from a database of 7,063 referrals. The results showed that, by ultrasound findings alone, 79.9% sensitivity was found with a false-positive rate of only 6.7%. The blood quadruple tests alone showed a sensitivity of 81.5% and a false-positive rate of 6.9%. However, when the ultrasound findings (nuchal-skinfold thickness and long-bone measurements) were combined with the quadruple test, a sensitivity of 90% detection was achieved, with a 3.1% false-positive rate. Thus, this combined modality of screening is substantially more effective than either serum screening or ultrasound alone. Even so, 90% sensitivity means 10% of DS cases will be missed. Thus, the search for more ideal screening measures continues.

Other Nonstructural and Structural Markers

From March 1990 to March 1999, Nyberg and colleagues (2001) identified DS among 186 fetuses that had second-trimester sonography between 14 and 20 weeks' gestation. The affected fetuses were compared with a control group of 8,728 unaffected fetuses. The researchers used six potential markers in this study: nuchal thickening, hyperechoic bowel, shortened femur, shortened humerus, echogenic intracardiac focus, and renal pyelectasis. The results showed some type of abnormal sonographic finding in 68.8% of the fetuses with DS. As isolated markers, nuchal thickening and hyperechoic bowel showed the strongest association with DS, followed by shortened humerus, echogenic intracardiac focus, shortened femur, and pyelectasis. The researchers concluded that at least one single marker is commonly encountered during the second trimester among fetuses with Trisomy-21 (Nyberg et al., 2001). Their 68.8% finding is less than the 79.9% sensitivity found by Benn and colleagues (2002).

Scoring Index for Sonographic Markers

Benacerraf, Neuberg, Bromley, and Frigoletto (1992) continued research in second-trimester testing by devising a scoring index to optimize interpretation and clinical management of sonographic markers. Their research incorporated the

sonographic features of 588 normal second-trimester fetuses and 43 trisomic fetuses. Femur and humerus lengths, nuchal fold, renal pelvic dimension, and major structural defects were compared between the two groups. The researchers formulated a scoring index: nuchal fold = 2 points; major structural defect = 2 points; and short femur, short humerus, and pyelectasis = 1 point. Fetuses with a score ≥ 2 would identify 81% of DS fetuses. To evaluate the accuracy of the scoring index, Bromley, Lieberman, and Benacerraf (1997) performed a study that included maternal age. They determined that the scoring index system could be modified to incorporate maternal age by giving 1 point for women 35 years of age or older and 2 points for women 40 years of age or older. The age-adjusted modification resulted in the identification of 86.8% of fetuses with DS, with a false-positive rate of 27.1%.

Nasal-Bone Measurements

Recently, the nasal bone has been shown to be absent in 73% of fetuses with DS in the first trimester, compared to 8.3% of control fetuses, which suggests a promising new sonographic marker at an earlier time in the pregnancy (Cicero, Curcio, Papageorgiou, Sonek, & Nicolaides, 2001). Bromley and colleagues (2002) evaluated 239 fetuses referred to their facility between 15 and 20 weeks' gestation because screening tests suggested an increased risk of aneuploidy. A structural survey, biometric measurements, and measurement of the nasal bone were obtained at the time of the amniocentesis. The results were compared with the karyotype testing from the amniocentesis. The researchers found that 16 fetuses had DS, and 6 of the 16 did not have detectable nose bones. Detectable but shorter nasal bones were seen in the remaining 10 fetuses with DS, suggesting an increased likelihood for fetal DS in the study's high-risk population. Data showed that, during the second trimester, fetuses with DS tend to have absent or shorter nasal bones than euploid fetuses. Bromley and colleagues (2002) agreed with the conclusions of an earlier study conducted by Stempfle, Hutten, Fredouille, Brisse, and Nessmann (1999): The absence of the nasal bone, even as an isolated finding, should serve as a warning for the clinician to suspect DS, and amniocentesis for karyotype should be recommended as an option for the patient if prenatal diagnosis is desired.

Pyelectasis is a collection of fluid in the fetal kidneys that causes them to dilate. It can occur in any pregnancy, but increases the chance of DS.

Hyperechoic or echogenic conditions are sonogram observations of bright areas that suggest tissues more dense than usual.

Euploid fetus: a fetus having the normal number of chromosomes for its species.

Researchers have improved the efficacy of screening for Down syndrome by adding new serum testing, creating advances in ultrasound techniques, combining serum screenings and ultrasounds, and working to develop tests that can be administered earlier and include the highest sensitivity and lower rates of false positives.

CONCLUSION

Researchers have improved the efficacy of screening for DS by adding new serum testing, creating advances in ultrasound techniques, combining serum screenings and ultrasounds, and working to develop tests that can be administered earlier and include the highest sensitivity and lower rates of false-positive results. Screening advances may decrease losses related to invasive procedures. The testing available in the recent past for pregnant women no longer provides the best options for prenatal screening.

Today, advanced prenatal screening offers opportunities for pregnant women to participate in individual choices for their testing. For example, maternal age alone need not be the determining factor for an amniocentesis procedure. The type of maternal serum testing being offered has changed. Expectant women may not be aware of the choices available for prenatal testing during their first or second trimester. Women may benefit from receiving detailed information on testing options and on the likely risks for each testing method. (See the Box for a list of Down syndrome resources for childbirth educators to share with expectant parents.) Caregivers and educators should provide support for the expectant mother's personal input regarding her choice of testing. Women are more likely to be satisfied with their prenatal care when they know screening options are available and when they are able to participate in the decision-making process of their care. Women vary in their desire to identify problems prenatally or their interest in terminating a DS infant. A woman who has become pregnant after infertility may weigh the risks of a missed DS case against the risk of an amniocentesis differently than a woman with an unplanned pregnancy.

Prenatal screening of some type for fetal defects such as DS has become a standard offering in almost every pregnant woman's obstetric care. Research shows that testing performed during the first or second trimester of pregnancy is capable

BOX

DOWN SYNDROME RESOURCES FOR CHILDBIRTH EDUCATORS AND EXPECTANT PARENTS

National Down Syndrome Society

666 Broadway, 8th Floor
New York, NY 10012-2317
Telephone: (212) 460-9330
Web site: <http://www.ndss.org/>

National Down Syndrome Congress

7000 Peachtree-Dunwoody Road, N.E.
Lake Ridge 400 Office Park
Building #5 – Suite 100
Atlanta, GA 30328-1655
Telephone: (770) 604-9500
Web site: <http://www.ndscenter.org/>

National Association for Down Syndrome

P.O. Box 4542
Oak Brook, IL 60522
Telephone: (630) 325-9112
Web site: <http://www.nads.org/>

of revealing a wide range of possible genetic disorders. Practitioners should respect pregnant women's abilities to make educated choices about their prenatal care and support their decisions concerning their pregnancy and unborn child. The aim of genetic screening programs and prenatal diagnosis should be to maximize the options available to families rather than to reduce the prevalence of genetic diseases (Rowley, 1984).

Perinatal educators who see women in their first trimester for early classes should be able to explain the risks and benefits of available choices, while recognizing that the available testing is continually changing. Perinatal educators who work with couples in their last trimester should be able to answer any remaining questions couples have about the screening choices they made earlier related to DS.

REFERENCES

- Benacerraf, B. R., & Frigoletto, F. D. (1987). Soft tissue nuchal fold in the second trimester fetus: Standards for normal measurements compared to the fetus with Down syndrome. *American Journal of Obstetrics & Gynecology*, 157, 1146–1149.
- Benacerraf, B. R., Frigoletto, F., & Laboda, L. (1985). Sonographic diagnosis of Down syndrome in the second trimester. *American Journal of Obstetrics & Gynecology*, 153, 49–52.
- Benacerraf, B. R., Gelman, R., & Frigoletto, F. D. (1987). Sonographic identification of second trimester fetuses

- with Down's syndrome. *The New England Journal of Medicine*, 317, 1371–1376.
- Benacerraf, B. R., Neuberger, D., Bromley, B., & Frigoletto, F. D. (1992). Sonographic scoring index for prenatal detection of chromosomal abnormalities. *Journal of Ultrasound in Medicine*, 11, 449–458.
- Benn, P. A., Fang, M., Egan J. F. X., Horne, D., & Collins, R. (2003). Incorporation of Inhibin-A in second-trimester screening for Down syndrome. *The American College of Obstetricians and Gynecologists*, 101, 451–454.
- Benn, P. A., Kaminsky, L. M., Ying, J., Borgida, A. F., & Egan, J. F. X. (2002). Combined second-trimester biochemical and ultrasound screening for Down syndrome. *The American College of Obstetricians and Gynecologists*, 100, 1168–1176.
- Bromley, B., Lieberman, E., & Benacerraf, B. R. (1997). The incorporation of maternal age into the sonographic scoring index for the detection at 14–20 weeks of fetuses with Down's syndrome. *Ultrasound in Obstetrics and Gynecology*, 10, 321–324.
- Bromley, B., Lieberman, E., Shipp, T. D., & Benacerraf, B. R. (2002). Fetal nose bone length. *Journal of Ultrasound in Medicine*, 21, 1387–1394.
- Canick, J. A., & Messerlian, G. (2005). *Patient information: Prenatal detection of Down syndrome*. Retrieved May 24, 2005, from <http://patients.uptodate.com/topic.asp?file=antenatl/16784>
- Cicero, S., Curcio, P., Papageorgiou, A., Sonek, J., & Nicolaides, K. (2001). Absence of nasal bone in fetuses with Trisomy 21 at 11–14 weeks' gestation: An observational study. *Lancet*, 358, 1665–1667.
- Copel, J. A., & Bahado-Singh, R. O. (1999). Prenatal screening for Down's syndrome—A search for the family's values. *The New England Journal of Medicine*, 341, 521–522.
- Crane, J. P., & Gray, D. L. (1991). Sonographically measured nuchal skinfold thickness as a screening tool for Down syndrome: Results of a prospective clinical trial. *Obstetrics & Gynecology*, 78, 318–319.
- Cuckle, H. S., Wald, N. J., & Thompson, S. G. (1987). Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and alpha-fetoprotein level. *British Journal of Obstetrics and Gynaecology*, 94, 387–402.
- DiMaio, M. S., Baumgarten, A., Greenstein, R. M., Saal, H. M., & Mahoney, M. J. (1987). Screening for fetal Down's syndrome in pregnancy by measuring maternal serum alpha-fetoprotein levels. *New England Journal of Medicine*, 317, 342–346.
- Graves, J. C., Miller, K. E., & Sellers, A. D. (2002). Maternal serum triple analyte screening in pregnancy. *American Family Physician*, 65, 915–920, 922.
- Killingsworth, L. M. (2001). *Prenatal risk assessment by use of the quad screen with dimeric inhibin A*. Retrieved June 8, 2005, from <http://www.shmc.org/var/documents/lab/Quad%20Screen%20Update.pdf>
- Kuller, J. A., & Laifer, S. A. (1995). Contemporary approaches to prenatal diagnosis. *American Family Physician*, 52, 2277–2283, 2285–2286.
- Luthy, D. (1999). Maternal markers and complications of pregnancy. *The New England Journal of Medicine*, 341, 2085–2086.
- Mennuti, M. T., & Driscoll, D. A. (2003). Screening for Down's syndrome—Too many choices? *The New England Journal of Medicine*, 349, 1471–1473.
- National Institute of Child Health and Human Development [NICHD]. (2005). *Facts about Down syndrome*. Retrieved June 3, 2005, from <http://www.nichd.nih.gov/publications/pubs/downsyndrome/down.htm>
- Newberger, D. S. (2000). Down syndrome: Prenatal risk assessment and diagnosis. *American Family Physician*, 62, 825–836.
- Nyberg, D. A., & Souter, V. L. (2001). Sonographic markers of fetal trisomies. *Journal of Ultrasound in Medicine*, 20, 655–674.
- Nyberg, D. A., Souter, V. L., El-Bastawissi, A., Young, S., Luthardt, F., & Luthy, D. A. (2001). Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. *Journal of Ultrasound in Medicine*, 20, 1053–1063.
- Rowley, P. T. (1984). Genetic screening: Marvel or menace? *Science*, 225, 138–144.
- Saller, D. N., & Canick, J. A. (1996). Maternal serum screening for Down syndrome: Clinical aspects. *Clinical Obstetrics & Gynecology*, 39, 783–792.
- Souter, V. L., Nyberg, D. A., Benn, P. A., Zebelman, A., Luthardt, F., & Luthy, A. (2004). Correlation of second-trimester sonographic and biochemical markers. *Journal of Ultrasound in Medicine*, 23, 505–511.
- Stempfle, N., Hutten, Y., Fredouille, C., Brisse, H., & Nessmann, C. (1999). Skeletal abnormalities in fetuses with Down's syndrome: A radiographic post-mortem study. *Pediatric Radiology*, 29, 682–688.
- The Columbia Encyclopedia (6th ed.). (2001–2005). *Down syndrome*. New York: Columbia University Press. Also, retrieved December 3, 2005, from www.bartleby.com/65/do/Downsyn.html
- Thompson, M., McInnes, R., & Willard, H. (1991). *Thompson and Thompson genetics in medicine* (5th ed.). Philadelphia: Saunders.
- Wald, N. J., Huttly, W. J., & Hackshaw, A. K. (2003). Antenatal screening for Down's syndrome with the quadruple test. *The Lancet*, 361, 794–795.

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