FEATURE ARTICLE

Screening for Aneuploidy: A Complex Ethical Issue

By Fr. John F. Tuohey, PhD, Director, Providence Center for Health Care Ethics, Providence St. Vincent Medical Center, Portland, OR

Background

In January 2007, the American College of Obstetricians and Gynecologists (ACOG) issued a set of clinical recommendations for screening for aneuploidy,[1] a change in the number of chromosomes. The recommendations made particular mention of the relatively common trisomy 18 (1 in 3,000), the less common trisomy 13 (1 in 5,000),[2] and the most common and generally well known trisomy 21 (Down syndrome, 1 in 800-1,000). There are two recommendations that are of particular interest from an ethical perspective. The first states that both nuchal translucency (NT) measurement and biochemical markers screening should be offered during the first trimester (0-12 weeks). If this screening is positive for aneuploidy, meaning there is significant chance of a child having Down syndrome for example, the woman should be offered genetic counseling and the option of having the diagnostic tests chorionic villus sampling (CVS—done between weeks 11-12) or amniocentesis (done between weeks 16-20). The recommendation is based on the "good and consistent scientific evidence"[3] that when CVS or amniocentesis is performed on a population of women screened with these procedures in the first trimester, "there is a higher chance of identifying an affected fetus than there would be if the diagnostic test was preformed in an unscreened population."[4] The first-trimester screening, which *per se* poses no clinical risk to the fetus, also allows a woman to make a more informed decision whether to undergo the diagnostic tests that do pose a relatively significant clinical risk to the fetus. This recommendation is in-line with most practice standards.[5]

The second, and the one on which I will focus here, is based on "limited or inconsistent scientific evidence."[6] It states that both first-trimester screening and mid/second trimester CVS or amniocentesis should be available to all women who present for prenatal care before 20 weeks of gestation "regardless of maternal age."[7] This recommendation is a departure from the current practice of screening those women who, because of advanced maternal age of 35 years and older,[8] are more likely to have a child with an aneuploidy, particularly Down syndrome.

Of the recommendations from ACOG, this one is most likely to challenge the Catholic health care ministry. Health providers that offer genetic screening will have to decide if they will now perform the first-trimester screening for all pregnant women regardless of age. Genetic counselors and health practitioners will need to decide if they should encourage all pregnant women regardless of age to have this first-trimester screening performed, or restrict their encouragement to the traditional population. Health insurance plans will need to decide for whom they will now cover this screening. The purpose of the following is to identify those insights from within our tradition to help inform these decisions.

The importance of 'risk' in ethical analysis

People often use the terms 'risk' and 'chance' interchangeably. We might hear before cardiac surgery, "There is a risk/chance of stroke with this procedure." Greater care is found in research; an institutional review board (IRB) will generally look askance at language in a consent form suggesting there is a 'chance' of some effect. An IRB will insist that a consent form clearly state the 'risks' involved in the protocol. There is good reason for this, and that same clarity is important in genetic screening/diagnostic testing.

Risk, in the context of ethics especially, is directly associated with *harm. Chance* may or may not be associated with harm. In the example above, the context associates the term chance with harm. One might also say 'if I purchase a lottery ticket there is *a chance* I could be a millionaire.' We generally do not say we are *at risk* for being a millionaire. In ethics, risk is a technical term that relates to harm, and corresponds to the ethical principle of nonmaleficence. Nonmaleficence is the ethical principle having to do with whether some risk and harm is proportionate to some benefit to be achieved, or whether there is an ethical obligation to protect someone from some harm. A common example of this is the elderly person at risk for therapeutic harm because she forgets to take her medications. Without a clear understanding of the degree of risk and harm in this case, we cannot come to clarity as to what our ethical obligation of nonmaleficence, if any, towards someone might be.

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This discussion of 'risk' and 'chance' is relevant because in the ACOG recommendations there is confusion in the way risk is discussed. At page 219, the text speaks of "women whose fetuses are at increased risk." For the most part, however, it talks about "women at risk for having a child with an aneuploidy," such as on page 221. Without clarity as to what 'risk' is, what the relevant risks and harms are in a particular case, and who is at risk for what harms, it is impossible to come to clarity with regard to our ethical obligations, and hence impossible to come to clarity as to how to respond to these recommendations in our ministry. This needs to be sorted out.

To speak of the woman being 'at risk' for a Down syndrome is not technically accurate. Clinically, it is the fetus that is *at risk* for an aneuploidy, because the *aneuploidy harms the fetus.* The woman, given her maternal age, has a greater or lesser *chance of having a child* with an aneuploidy. The woman's maternal age puts the fetus at risk for an aneuploidy, as well as increases the chances she will have a child with an aneuploidy. The aneuploidy *per se* does not harm the woman, and hence the woman is not, in an ethical sense, 'at risk' for some harm. If the woman is not at risk for harm, it is difficult to identify the nonmaleficence obligation to protect her by providing this screening.

This distinction between risk and chance is subtle in common speech, but in ethics the distinction is critical. The ethical obligation of nonmaleficence is primarily related to degree of risk and harm. If there is no risk or harm, but instead a chance of some undesired outcome, the ethical obligations under nonmaleficence will be different. There is generally a greater ethical obligation to protect people from *risk of harm* than from a *chance of harm*. We probably would not hire a home health nurse in order to protect an elderly man because there is *a chance* he will forget his medications. We might do so, however, if there is a significant *risk* he will forget, and that the harm of forgetting is of consequence. Decisions to encourage, offer, provide, or cover these screening and diagnostic procedures need to be based on actual risk of a definable harm for which there is some ethical obligation to offer protection. The fact that there is a chance something might happen, even something untoward, is not generally a sufficient ethical argument to act. This is especially important in light of studies suggesting that the perception of risk is more influential on decisions in this context than the reality of risk.[9]

Ethical obligations to pregnant women in this context

Do we have an ethical obligation to protect women in general from the risk of having a child with an aneuploidy? As stated above, it is not clinically correct to say the woman is 'at risk' because the aneuploidy put the fetus at risk for harm, not the woman. Hence, there would seem to be no absolute obligation to offer these procedures based on a risk assessment.

I don't want to suggest that virtually no harm may result to a woman having a Down syndrome child. That harm, however, is contingent on factors that are related to, but not caused by, the aneuploidy. A woman may experience great emotional distress at learning of a positive screening or diagnosis for Down syndrome, and we certainly do not want to discount that. But, the degree of emotional distress and its impact is contingent on other factors. The woman's emotional well-being, family support systems, and religious beliefs, independent of her child's health, are critical factors in whether or not harm will be experienced by her because of the birth of a baby with an aneuploidy.[10] If there is an ethical obligation to protect the woman from harm, it would seem to be to protect her from the harm related to *these* factors. The obligation to help reduce the chances of having a Down syndrome child, and an obligation to minimize the risk/harm related to having a Down syndrome child, are distinct ethical obligations. Before responding to the ACOG recommendations, we need to take a careful look at exactly what the potential harms are, their causes, and our ethical obligations, if any, to protect the woman from them.

On the other hand, this is not to say there are no nonmaleficence obligations toward the woman. We can still ask if there is some obligation to reduce the chances of a woman having a child with an aneuploidy. If a woman can be identified as having a greater chance of having such a child, it is appropriate for Catholic health care to identify and quantify the chances so that reproductive decisions can be made, as well as to assist in preparing for the birth of a child with an aneuploidy if that should come to pass. Genetic testing and counseling in this context are permissible.[11] It is for this reason that Catholic health care has traditionally offered screening, diagnostic testing, and counseling for women 35 years of age and over. The tradition allows and encourages couples to make procreation decisions as fully informed as possible of the chances of an aneuploidy,[12] and most would agree that the better informed parents are of what is happening during a pregnancy, the better they will be able to make decisions for the well-being of the child.

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Ethical obligations to the child in this context

If it is the fetus that is at risk for being harmed by an aneuploidy, then from an ethical perspective there may be some ethical obligations of nonmaleficence to protect the fetus. These obligations will be limited by some clinical realities, first among which is because Down syndrome is related to maternal age, there are no preventative therapies available to protect the fetus once conceived from having this aneuploidy. Obligations to protect from harm will be limited to the risk of screening for and confirming the presence of the aneuploidy. The first trimester screenings recommended by ACOG are of extremely minimal risk to the fetus *per se,*[13] unlike with the more invasive diagnostic tests to confirm the findings of the screen. If there is a nonmaleficence obligation to protect the fetus, it would seem to be to protect the fetus from these diagnostics.

One writer suggests that only 15 percent of all pregnancies are at sufficient 'genetic risk' to justify the risks to the fetus of invasive diagnostics.[14] For CVS, those risks may include a procedure-related fetal loss rate of 1-2 percent.[15] Risk associated with amniocentesis may include a procedure-related fetal loss rate before 24 weeks of 1.12 percent and 24-28 week premature birth rate of 0.40 percent, rates reported to be "significantly higher" than among woman who do not have these diagnostic tests.[16] These risks, like all risks inherent in clinical procedures, need to be ethically justified by the benefit they provide.

Because there are no therapeutic interventions to treat Down syndrome, the risks to the fetus of these diagnostics cannot be justified by a direct benefit to the fetus. However, the risk to the fetus posed by these diagnostics might be able to be justified by a proportionate 'need to know' on the part of the parents. Standard practice seems to agree that a woman 35 years of age or older has a sufficient chance of having a child with this condition to demonstrate a proportionate 'need to know' that can justify the risks.[17] A serious discussion is needed to discern if the minimal chances of a woman 35 years of age or less having a child with an aneuploidy constitutes a similar 'need to know' that is proportionate to the risks posed to the fetus.

In fairness, the ACOG report does argue that if first-trimester NT and biochemical markers screening is done, "fewer women would go on to second-trimester screening."[18] If this turns out to be the case in practice, the recommended first-trimester screening may reduce the risks to the fetus by reducing the call for these invasive tests. However, if these screenings are available to all women regardless of age, some fetuses will be put at risk for these invasive tests because of the false-positive results that will occur. Even if the false-positive rate is low as a percentage of those screened, increasing the number of women screened will have the effect of increasing the total number of false-positive results, and thus increase the total number of diagnostics performed. If we take a false-positive rate of 5 percent,[19] as many as five screens in 100 will be a false-positive and lead to mid/second trimester diagnostics. If 1,000 screens are done, the rate remains low at 5 percent, but the number of false-positives becomes as many as 50 for a tenfold increase. Extending the screening to all women regardless of age may create a risk of unnecessary invasive diagnostics for some fetuses not otherwise at this risk, except for the fact that a woman with a small chance of having a child with an aneuploidy was amongst that false-positive group.

As a general ethical principle, risks should be minimized, not multiplied. The risk of the total number of false-positives and the risk to the fetus of diagnostics that result from those false-positives can be minimized by limiting the screening to those instances when there is a likelihood that there will be something for the screen to detect (an aneuploidy) and that risks to the fetus of diagnostics can be justified; that is, by restricting the screens to the smaller 'need to know/high chance' population of women 35 years of age and older.

At least one other fetal risk concern that will need to be addressed is that 90-93 percent of pregnancies with a diagnosis of Down syndrome in the United States result in elective termination, according to the literature.[20] An important question here is whether the fetus diagnosed with Down syndrome is at a greater *risk* for termination, or if there is a greater *chance* of termination? This may seem at first to be about semantics, but it is an important distinction that needs to be sorted out within the Catholic ethical tradition. Because of the ethical relationship of risk to harm, if the fetus is *at risk* for abortion, then *any* involvement in screening or diagnostics might be said to constitute immediate material cooperation. Immediate material cooperation in abortion is prohibited.[21] If this is the case, the ministry may need to revisit the question of whether any screening and diagnostics for Down syndrome is permissible regardless of maternal age. On the other hand, if the actual decision to

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abort a Down syndrome fetus is contingent on other factors, as may be the case,[22] then it might be said that the screening and diagnostics increase the 'chances' rather than 'risks' of termination. If this is the case, then any cooperation involved would be mediate. The ethical relevance of any relationship between screening and diagnostics and decisions to terminate need to be sorted out before decisions can be made as to whether or how to implement this recommendation into the ministry.

Justice obligations to the common good

One of the goals of Catholic health care ministry is to keep health care affordable. For the ministry, this is not simply a business strategy—it is a moral imperative. Hence, it would seem that across the continuum of care the justice principles of equity and stewardship will be key to making decisions about the ACOG recommendation. There is evidence that the recommendation to provide first-trimester screening to all women may run counter to a goal of maintaining affordability.[23] This is in stark contrast to examples in which screening can be very cost effective, such as combining MRI with genetic screening for breast caner.[24] The ACOG recommendation that all women be screened regardless of age may lead to a similar result as was experienced with the use of computer enhanced mammography: higher screening costs and increased numbers of unnecessary diagnostic tests based on false-positive results.

Increasing the costs of health care through screenings and diagnostic tests that are not cost effective does not generally serve the common good. Rather than working toward making health care affordable, it could make it even less so. The result could be a greater number of under and uninsured people in society. A 2006 survey reported by Reuters of 163 mostly Fortune 500 companies found that 95 percent planned to reduce health benefits to retirees in the next five years, and 16 percent expected to eliminate those benefits due to increases in costs. We need to carefully consider if implementing this recommendation is good stewardship.

In making decisions about stewardship, of course, we do need to be mindful of the justice principle of equity—treating all people equally. Do we have a justice obligation to treat all pregnant women in the same way, providing the same health care regardless of age? At this juncture, I agree with the conclusion regarding equity found in the 1983 President's Commission Report, "Screening and Counseling for Genetic Conditions" is fully consistent with our Catholic moral tradition:

Equity is best served when a decision whether to promote screening for a particular population reflects a balancing of benefits and harms, given the incidence of the disease in the population, rather than an aim to give equal access to screening to all groups, regardless of the population-based incidence.[25]

Conclusion

The ACOG recommendation to provide first trimester screening for aneuploidy such as Down syndrome to all women regardless of age poses a significant ethical challenge for the Catholic health care ministry. I do not think there are any easy answers to the questions about what we as a ministry should do with these recommendations, especially since the evidence for these recommendations is uncertain at best. I have not sought to provide answers here. I have attempted to identify those aspects of the recommendations that pose the greatest ethical concerns for us, and hopefully offered some helpful insights to inform our discernment.

NOTES

1. ACOG Practice Bulletin, "Fetal Chromosomal Abnormalities: Clinical Considerations and Recommendations," *Obstetrics and Gynecology* 109 (2007): 219.
2. SA Rasmussen, LY Wong, Q Yang, KM May, and JM Friedman, "Population-based analyses of mortality in trisomy 13 and trisomy 18," *Pediatrics* 111 (2003): 777-84. Mortality for these trisomies may be as high as 93 percent. See CJ Moran, JB Tay, and JJ Morrison, "Ultrasound detection and perinatal outcome of fetal trisomies 21, 18, and 13 in the absence of a routine fetal anomaly scan or biochemical screening," *Ultrasound in Obstetrics and Gynecology* 20 (2002): 482-485.
3. ACOG, 224.
4. ACOG, 219.
5. See Hayes, "First-Trimester Prenatal Screening Using Nuchal Translucency Combined with Maternal PAPP-A and Free Beta-hCG Levels," www.hayesinc.com, December 12, 2005.
6. ACOG, 224.
7. ACOG, 224.
8. See Hayes.
9. TM Marteau, J Kidd, R Cook, S Michie, J Slack, and RW Shaw, "Perceived risk not actual risk predicts uptake of amniocentesis," *International British Journal of Obstetrics and Gynaecology* 98 (1991): 282-286.
10. There are also studies to suggest that decisions to continue or terminate a pregnancy are related to a variety of issues when there is evidence of Down syndrome, and that only gestational age at the time of diagnosis is a significant independent predictor of pregnancy termination. See RL Kramer, RK Jarve, Y Yaron, MP Johnson, J Lampinen, SB Kasperski, and MI Evans, "Determinants of parental decisions after the prenatal diagnosis of Down syndrome," *American Journal of Medical Genetics* 79 (1998): 172-174.
11. USCCB, *Ethical and Religious Directives for Catholic Health Care Services* (ERDs) Washington, DC, Fourth Edition (2001): nos. 50 and 54.
12. Pius XII "Address to the Italian Midwives" (1951).

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13. Some may argue that the fetus is at risk for being aborted as a result of these tests. That will be addressed later in this essay.
14. See RJ Wapner, "Chronic Villus Sampling," in ed. JT Queenan, JC Hobbins, and CY Spong, *Protocols for High-Risk Pregnancies* (Blackwell Publishing, 2005), at pages 119 and 122.
15. AB Caughey, LM Hopkins, and ME Norton, "Chorionic Villus Sampling Compared with Amniocentesis and the Difference in the Rate of Pregnancy Loss," *Obstetrics & Gynecology* 108 (2006): 614. I am grateful to Mark Repenshek, PhD, for this reference and for his insights into this issue.
16. F Muller, D Thibaud, F Poloce, MC Gelineau, M Bernard, C Brochet, C Millet, JY Real, and M Dommergues, "Risk of amniocentesis in women screened positive for Down syndrome with second trimester maternal serum markers," *Prenatal Diagnosis* 22 (2002): 1036-1039.
17. I have been unable to find in the literature any rigorous ethical analysis of this practice, however.
18. ACOG, 222.
19. K Spencer, V Souter, N Tul, R Snijders, and KH Nicolaides, "A screening program for trisomy 21 at 10-14 weeks using fetal nuchal translucency, maternal serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A," *Ultrasound in Obstetrics and Gynecology* 13 (2002): 231-237; F Orlandi, G Damiani, TW Hallahan, DA Krantz, and JN Macri, "First-trimester screening for fetal aneuploidy: biochemistry and nuchal translucency," *Ultrasound in Obstetrics and Gynecology* 6 (1997):381-386; TEJ Ind and NM Fisk, "Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy," *British Journal of Obstetrics and Gynaecology* 102 (1995): 758-759.
20. C Mansfield, S Hopfer, and TM Marteau, "Termination rates after prenatal diagnosis of Down syndrome, spina bifida, anencephaly, and Turner and Klinefelter syndromes: a systematic literature review," *Prenatal Diagnosis* 19 (1999): 808-812. This is similar to 90 percent results found by DW Britt, ST Risinger, V Miller, MK Mans, EL Krivchenia, and MI Evans, "Determinants of parental decisions after the prenatal diagnosis of Down syndrome: Bringing in context," *American Journal of Medical Genetics* 93 (1999): 410 - 416.
21. ERD, no. 70.
22. See Kramer et al. above. Even if the cooperation is mediate material, it may still not be permissible. If the percentage of elective terminations is accurate, the sheer volume may make the distinction between mediate and immediate merely academic.
23. See, AH Harris, "The cost effectiveness of prenatal ultrasound screening for trisomy 21," *International Journal of Technology Assessment in Health Care* 20 (2004): 464-468; M Shohat, H Frimer, V Shohat-Levy, H Esmailzadeh, Z Appelman, Z Ben-Neriah, H Dar, A Orr-Urtreger, A Amiel, R Gershoni, E Manor, G Barkai, S Shalev, Z Gelman-Kohen, O Reish, D Lev, B Davidov, B Goldman, "Prenatal diagnosis of Down syndrome: Ten year experience in the Israeli population," *American Journal of Genetic Medicine,* Part A 122A (2003): 215-222.
24. See SK Plevritis, AW Kurian, BM Sigal, BL Daniel, DM Ikeda, E Stockdale E, and AM Garber, "Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging" *Journal of the American Medical Association* 295 (2006): 2374-84.
25. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Screening and Counseling for Genetic Conditions,* Washington, DC, US Government Printing Office (1983), p. 84.

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