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Invasive Prenatal Diagnostic Procedures 2005

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Amniocentesis and Chorionic Villus Sampling have been the two most common prenatal diagnostic procedures for decades. There are wide variations in utilization, operator skills, quoted procedure risks, actual observed risks, and patient choices that come from highly variable counseling as to those risks. The compilation of published data suggests procedure risks of amniocentesis to be about 1/200 and in very skilled hands to be slightly lower. The risks of CVS in very experienced hands may also be about 1/200. Most studies comparing CVS to amniocentesis in skilled hands have found equivalency of risks. No well controlled studies support claims of amniocentesis risk at 1/1000 or lower. There is no increased risks of limb reduction defects followng CVS at 10 weeks or greater, but there is an increase in Talipes from "Early Amniocentesis." In the first trimester CVS is the safer procedure.

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Since the first documented attempts at invasive prenatal diagnosis in the 1960s,[1,2] there have been continued evaluations of the risks and benefits of such procedures.[3,4] Patients considering prenatal diagnosis struggle between having a baby with a serious genetic disorder and losing an otherwise normal pregnancy in an attempt to obtain reassurance of a normal outcome.[5] From a public health standpoint, a balance is required between cost and offering preventive genetic services to as many patients as possible. Based on the importance of these issues, it is surprising that relatively few well-controlled, randomized studies have been performed. Space limitations of this article limit extensive discussion of the available data. The interested reader is referred to several compilations.[4-6]

The major concern of invasive prenatal diagnostic testing is the frequency of procedure-induced pregnancy loss. The literature and, even more importantly, patient counseling have been extremely variable in their estimation of this rate. Some reports and clinicians quote risks as low as 1/650 or less.[7] On the other extreme is the only randomized trial of second-trimester amniocentesis, performed by Tabor and coworkers, that suggests an additional risk of fetal loss of almost 1%.[8] The largest compilation of controlled studies has been performed by Seeds, who reviewed 68,119 mid-trimester amniocenteses and found an excess pregnancy loss of 0.6% among controlled studies. When added to the background rate of loss seen in unsampled patients of 1.08%, the total loss rate to 28 weeks gestation is approximately 1.7%.[9]

Historical Perspective

Amniocentesis for genetic diagnosis began in the late 1960s and early 1970s as a tertiary procedure reserved for the highest risk patients.[1,2] Ultrasound as a clinical tool was still on the horizon, and the procedure was performed essentially blindly. By waiting until 16 to 17 weeks, adequate fluid surrounded the fetus and the chance of successful retrieval of fluid while avoiding the fetus was felt to be reasonable.[3,4] Early reports suggested complications rates of about 2%, which, although nontrivial, were felt to be reasonable in high-risk situations, such as those at risk for Mendelian disorders (eg, Tay-Sachs Disease), previous aneuploidy, or previous neural tube defects.

As both laboratory and imaging technology advanced, so did the use of invasive testing. The spread of amniocenteses and later chorionic villus sampling (CVS) followed the traditional paradigm of technology development, ie, going through phases of "development" followed by "diffusion."[10,11] Amniocentesis and later CVS started as "quaternary" technologies with patients traveling to a few major

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centers to find experienced physicians to perform the procedures.[3] By the late 1970s for amniocentesis and the late 1980s for CVS, the procedures had become tertiary ones, ie, with one or more centers located in large cities having experienced physicians. With improving ultrasound guidance, an increasing number of physicians began to perform procedures. As the phase of diffusion occurred, utilization increased with little attention paid to the potential impact on complication rates as more physicians were performing fewer procedures per practitioner.

The diffusion phase for CVS began in the early 1990s when the United States Food and Drug Administration and the American Medical Association removed the restrictions on CVS, moving it from an experimental procedure to a routine one.[3] Utilization in cities was rising rapidly as experienced operators were becoming common. There was a general anticipation of a shift of prenatal diagnosis to the first trimester.[12] Then, in March 1991, Firth and coworkers published a letter to the editor of the Lancet in which they described their experience in Oxford, England of their new program.[13] Five of their first 289 procedures, performed transabdominally at 7 to 8 weeks, resulted in babies with severe limb reduction defects. Four of these had oromandibular limb hypogenesis syndrome, which is rare (1:150,000 births in unsampled pregnancies). While reporting these cases, the author appropriately asked the readership if anyone had comparable experience.

Most major centers in the US and Europe could not confirm these concerns, most likely because the majority of physicians were performing CVS transcervically at 10 weeks or more. An exception to this came from Taiwan where a similar cluster of severe limb defects following CVS was reported.[14] As with the experience from Oxford, most of the procedures were performed before 63 days gestation. In October 1991, Burton and coworkers reported results from the program at Michael Reece Hospital in Chicago. Four of their first 500 cases had relatively minor distal transverse limb reduction defects. These varied from the Oxford and Taiwan experience in both the severity of the defects and the timing of the procedure. Despite this difference and the lack of supporting data from other US centers, they recommended that the procedure be abandoned for routine prenatal diagnosis. This led to widespread attention in the lay press and considerable patient "panic" as utilization of CVS in the US rapidly fell. When the paper was published in May 1992, the data showed a number of inconsistencies with the generally accepted outcomes reported by other centers. Most importantly, their center had a pregnancy loss rate 4 times the published average (8% versus 2%), and when 2 instrument insertions were required, the loss rate was 20%.[15] The conclusion of most experts in the field was that this report reflected a unique set of circumstances, perhaps related to operator inexperience or technique, and not a systematic problem with CVS.

Presently, it has been confirmed that the risk of limb reduction defect following CVS performed by an experienced practitioner after 10 weeks gestation is identical to the background unsampled population.[16,17] However, if CVS is performed at an extremely early gestational age (eg, 6-8 weeks), the risk of severe limb reduction defects is elevated. This risk of over 1% is demonstrated in series from both Brambati and coworkers and Wapner and Evans,[18,19] which describe "early CVS" performed at approximately 7 weeks gestation. Most of these procedures were performed to accommodate patients' religious convictions. For example, in Orthodox Judaism, pregnancy terminations are considered acceptable only up to 40 days postconception. Therefore, for a couple with a 25% risk of a Mendelian disorder, the increased risk of pregnancy loss and a limb reduction defect from an earlier procedure may be an acceptable choice after appropriate informed consent.

Table 1 Frequency of Talipes Equinovarus following "Early" Amniocentesis by Gestation Age at Sampling

Procedure Weeks	CVS (%)	Early Amniocentesis (%)	
11-12	0	1.25	
13	0.16	0.76	
14	0.20	0.20	
Totals	0.16	0.66	$P = 0.02$

A similar "window of vulnerability" associated with earlier sampling has been described for amniocentesis. In the mid to late 1990s, programs began offering "early amniocentesis" between 10 and 14 weeks as an alternative to CVS.[20] Subsequent data from prospective randomized trials revealed that amniocentesis performed less than 14 weeks 0 days had approximately a 1% higher pregnancy loss rate than CVS.[21] Unexpectedly, there also was a dramatic increase in the frequency of Talipes equinovarus. Club feet occurs in 1 to 3/1000 live births in the general population, but was seen in 1.5% of pregnancies exposed to early amniocentesis.[21-23] Although the mechanism remains unproven, studies from Europe and North America independently found that about 15% of patients undergoing early amniocentesis had amniotic fluid leakage, compared with less than 1% following mid-trimester amniocentesis or CVS. Pregnancies leaking fluid after "early amniocentesis" had approximately a 15% risk of Talipes.[21] The risk of fluid leakage and subsequent deformation diminish when procedures are performed after the amnion and chorion fuse at 14 weeks (Table 1).[23] The present consensus is that, for patients desiring invasive prenatal diagnosis before 13 completed weeks, CVS is the considerably safer choice. At 14 weeks, the data are not definitive in either direction.

Current Data

With the expansion of first-trimester screening seen already worldwide and anticipated to occur in the US, there will be an increasing number of patients confronting elevated risks of aneuploidy before 13 weeks of gestation. As a result, they will have to choose among three distinct options: await amniocentesis at 16 weeks, have an immediate CVS, or have no procedure. How they are counseled as to the risks and ben-