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Ultrasound Obstet. Gynecol. 4 (1994) 353–354

Editorial

Screening for fetal chromosomal abnormalities: need to change the rules

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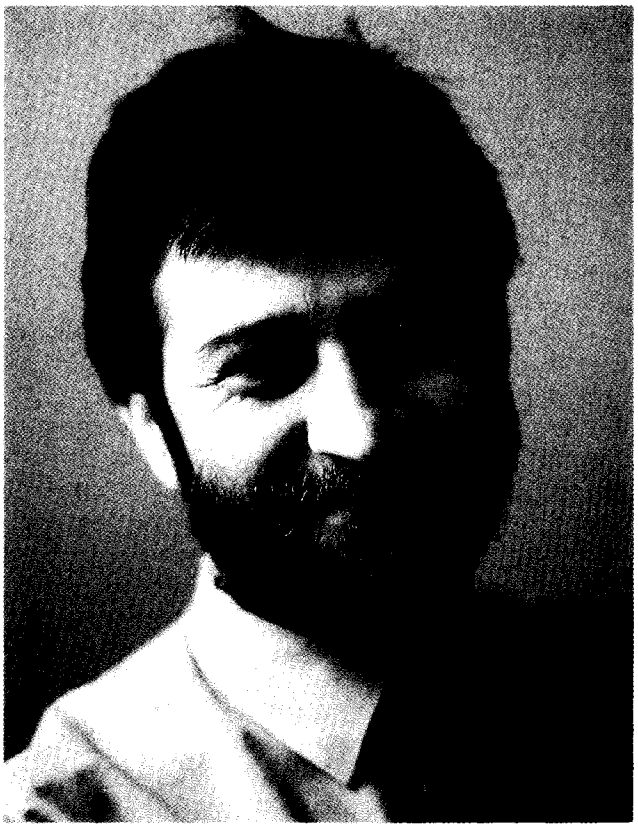
> . . . more than half of the Mongolian imbeciles in institutions are the last-born children mostly of long families and in a considerable proportion, from one-half to one-third, the mothers were at the time of gestation approaching the climacteric period and, in consequence, the reproductive powers were at a low ebb. Which of the two factors, the advanced age of the mother or her exhaustion by a long series of previous pregnancies, is the most potent factor is open to doubt. Both act concurrently in most cases.
>
> *Shuttleworth*, 1909

Chromosomal abnormalities are important causes of perinatal death and childhood handicap. It is, therefore, not surprising that a high risk of a cytogenetic disorder is and has been the commonest indication for invasive prenatal diagnosis.

The first method of selecting pregnancies for invasive testing was based on the observation, originally made by Shuttleworth, that the incidence of fetal chromosomal abnormalities is associated with maternal age. In the early 1970s, when amniocentesis for fetal karyotyping was introduced, the risk of the procedure was uncertain and it was, therefore, offered only to women with a minimum age of 40 years. Gradually, as the application of amniocentesis became more widespread and because it appeared to be quite safe, the 'high-risk' group was redefined to include women with a minimum age of 35 years; this 'high-risk' group constituted approximately 5% of the pregnant population. At that time, the available statistics on maternal age-related risks for chromosomal abnormalities were those for trisomy 21 in live births and it was thought that, for a 35-year-old, this risk was about one in 250. Conveniently, this was apparently similar to the estimated procedure-related risk of miscarriage from amniocentesis. Thus was created the concept that invasive testing is offered to 5% of pregnant women and/or when the risk of an affected pregnancy is equal to or more than the risk of miscarriage from the test.

Twenty years later, we now know that the risk of delivering a baby with trisomy 21 for a 35-year-old is about one in 385 and the risk of miscarriage from amniocentesis performed by an experienced operator is about one in 100. In addition, the proportion of pregnant women with a minimum age of 35 years is now approximately 8%, rather than 5%, and this group contributes only 20–30% of the chromosomally abnormal babies. Therefore, there is a need to redefine the rules for offering fetal karyotyping. Furthermore, it should be clear by now



that medically imposed decisions based on arbitrary equations of the burdens of miscarriage against those of the birth of a chromosomally abnormal baby are contrary to the basic principle of informed consent.

We now have two additional techniques for invasive testing, chorion villus sampling (CVS) and cordocentesis, and two additional methods for non-invasive assessment of risk for a chromosomal abnormality. These new methods take into account not only maternal age but also the concentration of various fetoplacental products in the maternal circulation (maternal serum biochemistry) or fetal morphometry (ultrasonography).

CVS for first-trimester diagnosis was introduced in the early 1980s and it has survived rigorous investigations as to its safety during the last decade. It is now clear that, provided CVS is carried out by experienced operators at a minimum gestation of 11 weeks, it is equally as safe as amniocentesis at 16 weeks but with the advantage of providing early results. Early amniocentesis has also been tested but recent evidence suggests that this is more risky than CVS. In patients presenting beyond 20 weeks,

karyotyping can be performed by CVS or cordocentesis; the latter has the advantage of providing additional information on the fetal condition and not just the karyotype.

At 16 weeks' gestation, the median maternal serum concentrations of human chorionic gonadotropin (hCG) (total, free-α and free-β), estriol and α-fetoprotein in trisomy 21 pregnancies are sufficiently different from normal to allow the use of various combinations of all or some of these substances to select the 'high-risk' group. This method of screening is proving to be more effective than maternal age alone and, for the same rate of invasive testing (about 5%), it can identify 2–3 times as many of the trisomy 21 fetuses. Recent evidence suggests that it would be at least as effective to screen in this way by using pregnancy-associated plasma protein A and free-β hCG in the first trimester of pregnancy. Biochemical screening has unfortunately complied with all the rules of the previous decades that invasive testing should be offered only to the 'screen positive', 'high-risk' group, defined by the arbitrary cut-off level of one in 250–300 (the over-estimated risk of a 35-year-old delivering a baby with trisomy 21 and the under-estimated risk of miscarriage from amniocentesis).

The other method of assessing risks for chromosomal abnormalities is ultrasound. During the last 20 years, several studies have described the ultrasonographically detectable phenotypic expression of most major chromosomal abnormalities. In the first trimester, a common feature is increased nuchal translucency thickness and studies to date suggest a possible detection rate for all major fetal trisomies of about 80%, for an invasive procedure rate of 5%. In later pregnancy, each chromosomal abnormality has its own syndromal pattern of defects. Trisomy 21 is associated with a tendency for brachycephaly with shortening of the frontothalamic distance, flattening of the face, nuchal edema, atrioventricular septal defects, duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the limbs, sandal gap and clinodactyly of the 5th finger. Trisomy 18 is associated with strawberry-shaped head, choroid plexus cysts, absent corpus callosum, enlarged cisterna magna, facial cleft, micrognathia, nuchal edema, heart defects, diaphragmatic hernia, esophageal atresia, exomphalos, renal defects, growth retardation and shortening of the limbs, overlapping fingers and talipes. In trisomy 13, common defects include holoprosencephaly, facial cleft, cardiac and renal defects and polydactyly. The lethal type of Turner syndrome presents with large nuchal cystic hygromata, generalized edema and cardiac defects, and in triploidy there is either a molar placenta or severe early-onset asymmetrical growth retardation, ventriculomegaly, micrognathia, cardiac defects and syndactyly.

Ultrasonographic studies have also established that chromosomal abnormalities are more common among fetuses with multi-system malformations than in those with isolated defects. Indeed, there is considerable controversy surrounding the possible significance of apparently isolated defects or subtle deviations from normality in anatomy and measurements. These 'chromosomal markers' are initially described in referral centers investigating high-risk pregnancies and often no data are provided on the background risk for chromosomal abnormalities in the population examined or even on the presence of other fetal defects or 'markers'. However, a common conclusion is that 'parents should be offered invasive testing because, in the presence of this marker, the risk is similar or even higher than the one in 250–300 for a 35-year-old'.

There is a rapidly increasing list of these 'chromosomal markers' and, since each is found in 1–5% of normal pregnancies, we will soon be confronted with the reality that the majority of fetuses may have at least one such marker. Inadequate evaluation of the true significance of these markers constitutes the real risk of ultrasound scanning. The adverse implications in terms of iatrogenic anxiety for the parents and fetal death from invasive testing will overshadow the fears that ultrasound may cause dyslexia, left-handedness or even growth retardation.

With CVS, amniocentesis and cordocentesis, we now have a series of techniques for prenatal diagnosis from 11 weeks' gestation, and we now know that, in the hands of experienced operators, these procedures carry a risk of miscarriage of about one in 100. We also know that all women carry a risk of having a chromosomally abnormal fetus. This risk increases with maternal age and decreases with gestational age (the relative rate of miscarriage of chromosomally abnormal fetuses is higher in early pregnancies). We now need to define how this background risk is modified by the results of a series of potentially complementary ultrasonographic and biochemical parameters at different gestations.

Our responsibility is to provide parents with accurate assessment of risks. The perception of the risk of miscarrying a wanted pregnancy, or the birth of a chromosomally abnormal baby is dependent upon the individual expectations of the parents. We must let them decide in favor or against invasive testing rather than create arbitrary definitions of high and low risk.

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