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REVIEW ARTICLE

Ultrasound-Guided Invasive Procedures in Genetic Prenatal Diagnostics

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ABSTRACT

There is a wide range of noninvasive screening methods that aim to identify the subgroup of fetuses that are in a high risk of chromosomal defects. Invasive procedures should be offered to women in the high-risk group identified with the highest possible detection rate and the lowest false-positive rate.

The method of choice at 11 + 0 - 13 + 6 weeks is chorionic villus sampling. An early amniocentesis is much more dangerous and should be abandoned. CVS should be performed not earlier than at 11 + 0 weeks of pregnancy. Amniocentesis should be performed no earlier that at 15 + 0 weeks. Earlier procedure is associated with significantly higher rate of talipes equinovarius, amniotic fluid leakage and miscarriage. The umbilical cord insertion is a preferable site for fetal blood sampling. Care must be taken to distinguish between the vein and the artery, and the vein must be sampled, not the artery.

The operator's experience is very important issue. It has been postulated that to achieve a reasonable experience one should perform a minimum of 100 chorionic villus samplings, and a reasonable number of invasive procedures should be performed yearly.

Keywords: Invasive procedure, Karyotyping, Chorionic villus sampling, Amniocentesis, Fetal blood sampling.

INTRODUCTION

Every invasive procedure for fetal karyotyping is unenviably associated with the risk of miscarriage, otherwise it could be offered to every pregnant woman. Over many years, a wide range of noninvasive screening methods that aim to identify the subgroup of fetuses that are in a high risk of chromosomal defects has been developed. This approach allows decreasing the overall rate of miscarriage and increasing the number of affected fetuses detected. Invasive procedures should be offered to women in high-risk group identified with the highest possible detection rate (DR) and the lowest false-positive rate (FPR). FPR equals to the number of invasive procedures.

Historically, karyotyping was offered to women who were 35 years old or more. Maternal age as a method of screening allowed to identify only approximately 30% of trisomy 21 cases for 5% FPR. Later, triple test has been developed as a method of screening. Combination of AFP, hCG and E3 allowed to identify approximately 70% of triple 21 for the same FPR. Triple test is usually performed between 15 and 18 (20) weeks.[1] At that stage, in high-risk group, amniocentesis is performed for karyotyping. Depending on the quality and availability of cytogenetic service, it may take between 2 and 6 weeks to receive the result of the full karyotype. Quick tests like rapid FISH or QF-PCR might be a solution, but that again depends on the quality and availability of cytogenetic service. Furthermore, that approach increases overall cost and it is not always reimbursed by national health service or insurance company (depending on local or national solutions). Another problem associated with late karyotyping (fetal blood sampling after 20 weeks) is the legal limit for pregnancy termination that often is set at 23 to 24 weeks. Also, termination of pregnancy is safer at 14 weeks than at 23 weeks, both from medical and psychological point of view.

Considering above-mentioned reasons, there is a tendency to shift fetal karyotyping towards earlier gestational age. Fast development of sonographic and biochemical methods of screening for chromosomal defects at 11 + 0 to 13 + 6 weeks, provided a powerful tool to identify high-risk group. Combination of maternal age, nuchal translucency, fetal heart rate and pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) gives a detection rate of 90% for a 5% false-positive rate.[2]

The method of choice at that stage of pregnancy is chorionic villus sampling (CVS) (Fig. 1). An early amniocentesis is much more dangerous and should be abandoned altogether or reserved for very special situations. CVS should be performed not earlier than at 11 + 0 weeks of pregnancy. CVS before 11 weeks is associated with higher risk of complications including malformations of extremities (including amputations), micrognathia and microglossia. The aim of the procedure is to collect, under ultrasound guidance, tissue (chorionic villi) for karyotyping. Except for rare cases of confined placental mosaicism, the karyotype of the fetus and the chorion (placenta) is same. From technical point of view, there are two possible approaches—transcervical and transabdominal. In Europe,

transabdominal approach seems to be much more popular. Transcervical approach is associated with higher risk of complications. CVS should be performed under continuous ultrasound guidance, using 16 to 18G needles.

During all invasive procedures, the uterine wall should be punctured at right angle or as close to 90° as possible. The uterine wall should be punctured in one go otherwise if the tip of the needle gets stuck in the muscle and a contraction occurs that immobilizes the needle what can compromise the whole procedure. After puncture of maternal skin, subcutaneous tissue and uterine wall and introduction of the tip of the needle and its distal part couple centimeters into the soft chorionic tissue, a sterile syringe connected to the needle applies the negative pressure. Subsequently, the needle moves under continuous ultrasound supervision, forward and backward in the chorion and the villi are sucked into the needle. The needle is moving along the long axis of the chorion ensuring possible long distance of penetration. When the needle is removed, the operator has to remember to apply the negative pressure as long as the needle is inside the body and during its removal. When the needle is removed the tissue sample "jumps" from the needle into the syringe.

The total pregnancy loss of transabdominal CVS is comparable to that of second-trimester amniocentesis (OR 0.90, 95% CI, 0.66-1.23). Transcervical CVS is associated with a significantly higher risk of miscarriage (OR 1.40, 95% CI, 1.09-1.81).[3]

In a randomized trial, the procedure-related fetal loss of amniocentesis was estimated to be 1.0% (95% confidence interval (CI), 0.3-1.5%).[4] Amniocentesis should be performed no earlier than at 15 + 0 weeks. Earlier procedure is associated with significantly higher rate of talipes equinovarius, amniotic fluid leakage and miscarriage.[5] There is also some evidence that it might be beneficial to delay the amniocentesis until 16+0 weeks.[6] In amniocentesis, the needle movement should be sharp and steady that helps immediate puncture of the amnion and helps to avoid tenting of the amnion.The sample of 15 to 20 mL of amniotic fluid is taken. When rapid test for major aneuploidies is planned, more fluid should be collected (Figs 2 to 4).

The umbilical cord insertion is a preferable site for fetal blood sampling, a free loop being the second choice (Fig. 5). Care must be taken to distinguish between the vein and the artery, and the vein must be sampled, not the artery. High anterior is the best location of the placenta but even low posterior should not be a problem for an experienced operator. In the later instance, the operator has to puncture a free loop of the placenta or intra-abdominal part of umbilical vein (Fig. 6). Care

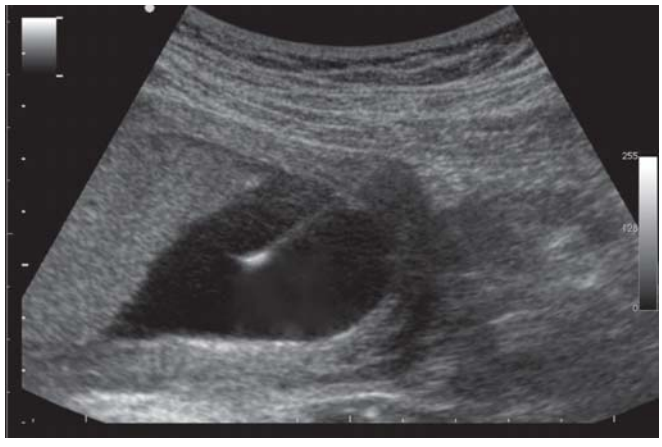

Fig. 2: Amniocentesis

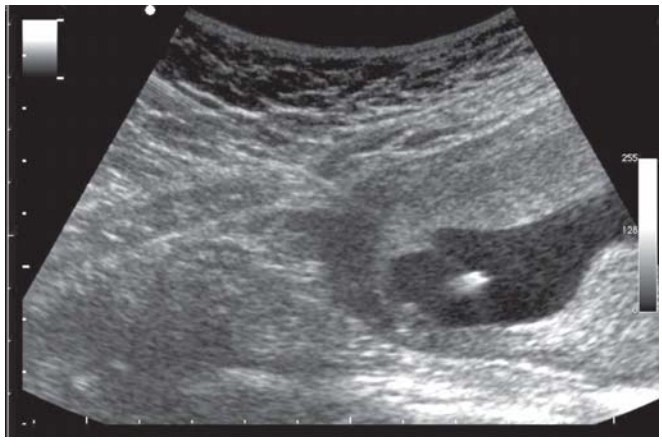

Fig. 3: Amniocentesis: Placenta cannot be avoided

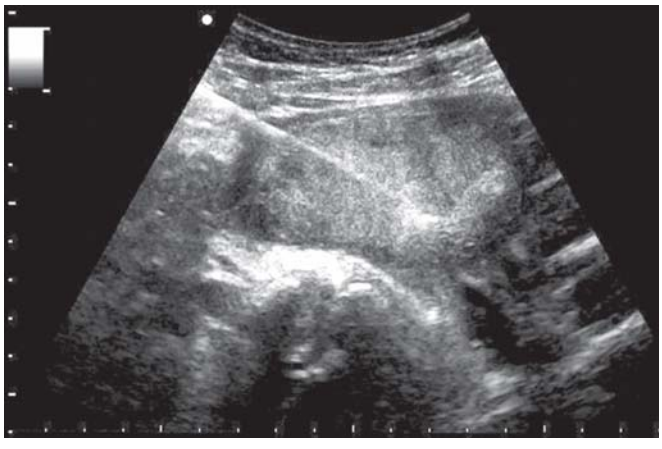

Fig. 1: Chorionic villus sampling: The placenta in high anterior

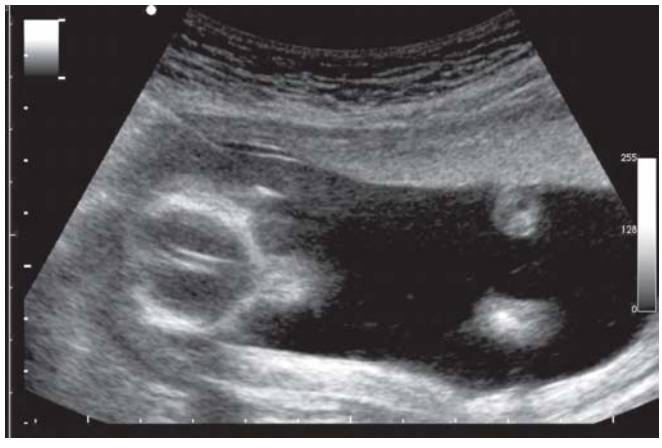

Fig. 4: Amniocentesis: The needle is too close to the fetal face

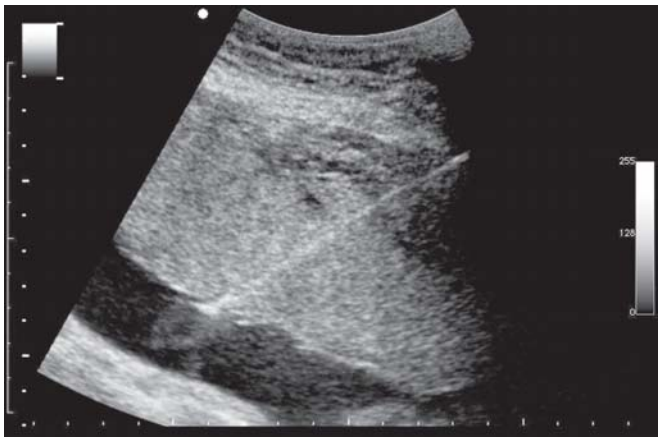

Fig. 5: Fetal blood sampling: Umbilical vein at the cord insertion

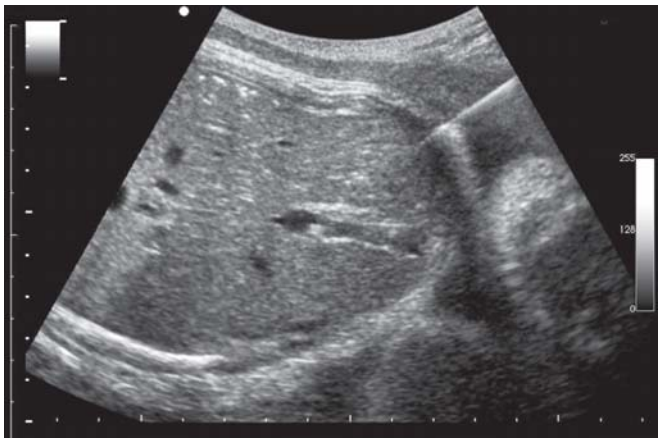

Fig. 6: Fetal blood sampling: Intra-abdominal part of the umbilical vein

must be taken to ensure a right angle between the needle and the wall of the umbilical vein for the free loop approach. One sharp movement allows for the puncture of the umbilical vein's wall. A minor deviation of the direction of the needle might result in the tip of the needle moving sideways and ending in the Wharton's jelly. After sampling of 1 to 2 mL of fetal blood the needle is removed. Usually a short bleeding from the puncture site occurs that may look particularly impressive on high-resolution ultrasound machine's screen and frighten an inexperienced operator or even the patient if she is watching the screen. It is advised not to look for signs of bleeding, as it is inevitable. Fetal heart rate check should be performed couple of minutes later. The procedure-related loss rate is estimated to be approximately 0.8 to 2.5%.[7]

In most cases, fetal blood lymphocyte culture allows to receive full karyotype results earlier than amniocyte culture. It is a huge advantage, especially in cases when karyotyping for suspected chromosomal defect is performed late in pregnancy, close to legal limit of termination.

Important issue is the operator's experience. It has been postulated that to achieve a reasonable experience one should perform a minimum of 100 CVS, and a reasonable number of invasive procedures should be performed yearly.[8-10] Due to increased efficacy of non-invasive screening, there is a tendency to increase detection rate and also to decrease FPR. As a result, the overall number of invasive procedures for fetal karyotyping has fallen. Undoubtedly, this is beneficial for patients as it leads to reduction in miscarriage rate but creates a new problem in training and maintaining skills.[11] It is, therefore, important that experienced operators perform invasive procedures in centers with sufficient number of procedures performed yearly.

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