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LETTER TO THE EDITOR

Is there an Ideal Model for Prenatal Screening of Aneuploidies?

Existuje ideální model prenatálního screeningu a diagnostiky aneuploidií?

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Over the last 20 years there has been a debate about the best model of screening for aneuploidies: to simplify, the alternatives are a combined test in the first trimester or an integrated test using biochemical parameters over the first and second trimesters. The inclusion of objective measurements of risks of pregnancy pathologies in the algorithm of first-trimester screening was immense progress, as well as an argument for the predominant use of this examination: this meant that detection of pregnancy risks and fetus morphology (premature delivery, preeclampsia, intrauterine growth retardation) as early as at the end of the first trimester came to the fore, so detection of aneuploidies was thus no longer the most significant outcome of this test. Now we are witnessing the dynamic onset of a new method, **N**on-**I**nvasive **P**renatal **T**esting (NIPT) or **S**creening (NIPS). This is based on detecting cell-free DNA in the peripheral blood of the mother, which can be performed as early as the completed 10th week of pregnancy. Arguably, NIPT can now determine the risk of Trisomy 21 with 99% sensitivity, while the sensitivities are similarly high for Trisomies 18 and 13; it can also determine the sex of the fetus with 99% sensitivity. The potential of this method may be even greater, but there are not yet sufficient reliable data for its clinical use, for instance, to detect micro-deletion syndromes. Nevertheless, the main issue I am addressing in this paper is whether, and how, NIPT should be incorporated in the current algorithm of prenatal screening, and for whom it is actually suitable. In the Czech Republic, as in most countries, NIPT is not covered by health insurance; therefore the economic aspect also plays an important role. On a strictly professional basis, a methodologically well-managed combined screening carried out in the first trimester (age, NT, PAPP-A, free beta subunit of hCG), or a well-performed integrated biochemical screening, with a declared detection rate of around 90%, may compete with NIPT for aneuploidies. However, those familiar with the issue know what the situation is in practice: only when the sonographists and biochemists are willing to undergo a rigorous audit may we talk about a quality performance of the first trimester screening for aneuploidies. On the other hand, information on the quality of NIPT is provided almost exclusively by the firms who carry out these tests, and not all of them have extended studies available to support their results. Furthermore, and most importantly, the majority of the studies so far have been carried out on high-risk populations. Perhaps we should first ask what the purpose of the prenatal diagnostic of aneuploidies is: do we want to avoid endangering the pregnancy on any account (implying the rejection of invasive examinations – an amniocentesis or chorion biopsy where the risk of miscarriage is 0.5% – 1%), or do we want to obtain as much information as possible on the chromosomal makeup of the fetus? If we reject invasive examinations on principle, then first trimester visualization (ultrasound) screening combined with biochemical screening (PAPP-A, free beta subunit of hCG) followed by NIPT may the only option. On the other hand, if the woman wishes to know as much as possible about the chromosomal makeup of the fetus and is willing to accept the 0.5% – 1% risk of losing the pregnancy, than amniocentesis with microarray is an ideal combination. G. DeVore mentioned (a personal statement), that NIPT detects only 61% of all chromosomal aberrations (numerical and structural, autosomal and gonosomal). Who, then, is today's NIPT suitable for? Or perhaps we should suggest instead who it is not suitable for: 1. All woman who do not mind the risk associated with amnio-

centesis. 2. Pregnant women for whom a morphological deviation of the fetus associated with a higher risk of aneuploidy was detected in the first-semester visualization screening (higher NT, omphalocele, significant heart defect, etc.) – for these pregnant women, it is better to offer a biopsy of chorion straight away. In all other cases, NIPT is a method of choice: 1. For pregnant women with normal results from the first trimester screening, if they wish to increase the reliability of determining the risk of Trisomy 21 to 99% (often these are pregnant women after IVF, where the cost of NIPT is only a fraction of the cost of IVF). 2. For pregnant women with a high risk of aneuploidy determined by the first-trimester screening, but with a normal morphology of the fetus (i.e. based on age or abnormal biochemical parameters).

NIPT works with maternal and fetal DNA, and the results of the test are not always fully predictable, as the initial genetic makeup of the pregnant women (and the fetus) does not have to fit in the simple scheme of "46,XY" or "46,XX" formula. For this reason, among others, pregnant women should consult the geneticist before undergoing the test, which is, by the way, stipulated by the Healthcare Services Act in the Czech Republic. Subsequent consultation about the results of the test is even more important, since even a normal NIPT result does not say anything about the baby being "healthy", and, by its nature, this test is not a substitute for amniocentesis. In a small percentage (approximately 3%, depending on the laboratory), the NIPT test may have to be repeated, with a new blood sample taken. The main problem is what is referred to as a low fetal fraction, where laboratories such as Ariosa (Harmony prenatal test) do not give the result if the fetal fraction is less than 4%, and recommend repeating the test to be on the safe side. A low fetal fraction is generally a problem for very obese patients. Some laboratories do not state the fetal fraction in the result, which is criticized by others, who challenge the reliability of the test where the fetal fraction is low. Another situation where the test cannot provide a valuable result is chromosomal mosaicism of the mother or the fetus.

To conclude, I dare say that amniocentesis and chorion biopsy are far from being "dead" examinations. Combined with microarray, amniocentesis presently provides the maximum information on the chromosomal makeup of the fetus. The examination, however, has to be indicated, and it should only be carried out by a highly experienced prenatal diagnostician who has had the opportunity to perform hundreds of these examinations each year. Moreover, although the current dynamic drop in the number of amniocenteses is welcome, the risk will grow of this examination being performed by professionals who are less experienced and trained than is ideal. NIPT has, and perhaps will continue to have, the sensitivity of a screening; it is no substitute for diagnostic amniocentesis. The basis of prenatal diagnostics will remain the first-trimester visualization screening, which permits the identification of pregnancy complications such as premature birth, preeclampsia and fetal growth retardation. NIPT is a sophisticated screening of the 21st century that is still developing and looking for its efficient clinical application.

Literature

1. Norton M, Brar H, Weiss J, Karimi A, et al. Non-Invasive Chromosomal Evaluation (NICE) Study: Results of a Multicenter, Prospective, Cohort Study for Detection of Fetal Trisomy 21 and Trisomy 18. Am J Obstet Gynecol. 2012 Aug;207(2):137.e1-8
2. Nicolaides KH, Syngelaki A, Ashoor G, et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol. 2012;207:374.e1-6
3. Ashoor G, Syngelaki A, Nicolaides KH, et al. Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method. Ultrasound Obstet Gynecol. 2013 Jan;41(1):21-5
4. Fairbrother G, Johnson S, Musci TJ, Song K. Clinical experience of noninvasive prenatal testing with cell-free DNA for fetal trisomies 21, 18, and 13, in a general screening population. Prenat Diagn. 2013 Jun;33(6): 580-3
5. Gil MD, Quezada MS, Bregnant B, Ferraro M, Nicolaides KH. Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. Ultrasound Obstet Gynecol. 2013 Jul;42(1):34-40
6. Verweij EJ, Jacobsson B, van Scheltema PA, et al. European Non-Invasive Trisomy Evaluation (EU-NITE) study: a multicenter prospective cohort study for noninvasive fetal trisomy 21 testing. Prenat Diagn. 2013 Jun;33(6):1-6
7. Wang E, Batey A, Struble C, et al. Gestational age and maternal weight effects on fetal cell-free DNA in maternal plasma. Prenat Diagn. 2013 Jul;33(7):662-6
8. Gil MD, Quezada MS, Bregant B, Syngelaki A, Nicolaides KH. Cell-free DNA analysis for trisomy risk assessment in first-trimester twin pregnancies. Fetal Diagn Ther. 2013 Nov 15 [Epub ahead of print]
9. Struble CA, Syngelaki A, Oliphant A, Song K, Nicolaides, KH. Fetal Fraction Estimate in Twin Pregnancies Using Directed Cell-Free DNA Analysis. Fetal Diagn Ther. 2013 Dec 7 [Epub ahead of print]

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