# INVASIVE VERSUS NON-INVASIVE PRENATAL DIAGNOSIS: CONTROVERSY AND ETHICAL DILEMMAS

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***Abstract***

*Chromosomal diseases are a major public health problem due to their frequency, morbidity, increased mortality and chronic disability. The chromosomal disease prevention involves screening and prenatal diagnosis. The traditional prenatal diagnosis implies the use of invasive methods for biological material sampling, methods that bear certain risks for the mother as well as for the fetus (the most severe being the risk of miscarriage). Nowadays, we can talk about the prerequisites for developing non-invasive methods that do not generate any risks for the mother, or for the fetus; however, these methods are still characterized by numerous technical difficulties. The prenatal diagnosis, particularly the invasive one, is characterized by a series of ethical dilemmas, of which we mention: benefit versus harm, maternal autonomy versus fetal autonomy. Some of these dilemmas could be solved by non-invasive tests, but the social consequences of the use of such tests require the change of best practice guidelines and the elaboration of new methods of screening and prenatal diagnosis.*

***Key-words:*** *chromosome abnormalities, prenatal diagnosis, informed consent, informed decision, autonomy*

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***Life is a flame that is always burning itself out, but it catches fire again every time a child is born. (G.B. Shaw)***

**The importance of chromosomal diseases in pathology**

**THE CHROMOSOMAL DISEASES** are caused by unbalanced chromosome abnormalities (complete or partial monosomies/trisomies) visible under the light microscope through conventional techniques or methods of molecular cytogenetics, whose dimensions exceeds 4 megabases [1].

The frequency of chromosomal abnormalities is different at various stages of ontogenetic development, and their importance varies in different clinical situations. Thus, a quarter of female gametes and 10% of the male gametes have a chromosomal abnormality [1,2]. On the other hand, 5% of clinically recognized pregnancies present fetuses that have aneuploidy (trisomy/monosomy) [3,4]. The share of chromosomal abnormalities decreases as the pregnancy progresses, due to the presence of natural selection against fetuses with unbalanced anomalies. Thus, 40-60% of the products of spontaneous abortion in the first quarter present chromosomal abnormalities, while their percentage in dead neonates is 10 and just 1% in the case of live neonates [2]. The most important effects of the chromosome abnormalities are: spontaneous abortion (10% of all pregnancies) and the occurrence of multiple congenital anomalies (20% of them are caused by chromosomal aberrations and / or gene mutations) [5].

The chromosome abnormalities (in number and structure) are unbalanced gene dosage abnormalities (complete or partial monosomies/trisomies) which produce various phenotypic changes through genetic imbalance that are generally severe: multiple congenital abnormalities, impaired growth and development (mental retardation), abnormal sexualisation or gonadal dysgenesis, with major effects on a wide range of medical specialties (pediatrics, psychiatry, endocrinology, obstetrics and gynecology, etc.) [1, 2, 6].

**Prenatal diagnosis of chromosomal diseases**

The chromosome abnormalities can be considered a major public health problem, due to the phenotypic changes they produce - high morbidity and mortality, chronic disability that they induce and the absence of specific therapies. In this given context, the management of chromosomal diseases necessarily includes genetic counseling and prophylaxis through screening and prenatal diagnosis.

The prenatal diagnosis is a complex medical measure that provides information about the health of the fetus, which allows the parents to make a fully informed reproductive decision.

The strategies used nowadays for the detection of chromosome abnormalities in the fetus have two stages: the first consists in identifying pregnancies with high risk of the most common trisomies (21, 13 and 18); the second stage is based on the use of a diagnostic test in the cases that have been identified as presenting a high risk of having a child with the mentioned trisomies. The traditional methods of prenatal diagnosis that

have been introduced approximately 50 years ago involve chromosome analysis of fetal cells and represent the standard method for prenatal diagnosis. The methods of obtaining fetal biological material for prenatal diagnosis are: chorionic villus sampling, amniocentesis and cordocentesis [7, 8].

The main advantage of the karyotype test is accuracy, this technique allowing the detection of chromosome abnormalities visible under the microscope light (numerical or structural abnormalities - chromosomal deletion and duplication, de novo or familial unbalanced or balanced translocations, mosaic supernumerary chromosomes, triploidies). The primary disadvantage is the long period of time (10-14 days) required for cell culture. Usually, the prenatal diagnosis test is performed in the cases of high risk pregnancies, and the major detected abnormalities are autosomal trisomies (21, 18, 13), monosomy X and gonosomal trisomies (X, XXY sau XYY). Since trisomy 21, which causes Down syndrome, is the most common chromosomal abnormality in human species and is invariably expressed phenotypically through mental retardation, associated comorbidities and impossibility of self-care, the prenatal diagnosis is mainly concerned with detecting this abnormality. However, various other abnormalities are often fortuitously detected, some of them having already been described above, whose phenotypical expression is severe and others that are correlated with minor phenotypical changes or whose clinical manifestations have not been previously described. In the latter case posttest counseling must ensure a balance between positive and negative impact information and to identify, as far as possible, other testing methods that would increase the accuracy of the diagnosis [7, 8].

In order to detect, as rapidly as possible, the main chromosome abnormalities, several methods of rapid diagnosis of aneuploidy have been developed (Rapid Aneuploidy Detection), methods that present two versions: the “narrow” RAD allows the detection of chromosomes 21, 18 and 13, and the “broad” RAD which analyses the X and Y chromosomes as well [9].

**The particularities of parental couple counseling – invasive versus non-invasive prenatal diagnosis**

The use of a rapid method for prenatal diagnosis of aneuploidies implies different approaches of pretesting counseling. Thus, genetic counseling and informed consent only include adequate information on trisomy 21, lethal trisomies (13 and 18) and gonosomal abnormalities, data on fortuitous chromosomal abnormalities not being provided – they cannot possibly be detected through this method. However, the mother / the parental couple should be advised regarding the advantages and disadvantages of the traditional karyotype test in comparison to RAD, so that they could choose the prenatal diagnosis procedure in full knowledge [9].

Whatever the reasons for which the prenatal diagnosis test has been done (high risk pregnancy or at the request of the mother / parental couple) it can provide a positive or negative result. Whatever the nature of the result, it should be communicated to the couple complying with certain principles set out in the guidelines of good practice.

Thus, the American Down Syndrome Association recommends that doctors present the disability from the perspective of a disabled person, provide information about patient organizations and families, social assistance programs, possible adoption and inform the parental couple about the legislation protecting the rights of the persons with disabilities [10].

The options concerning pregnancy management should also be communicated in a nondirective, neutral and free of guilt manner to both of the couple members, considering that chromosomal nondisjunction responsible for 92% of the Down syndrome cases is a meiotic accident most frequent in the female gametogenesis (90% of all cases). Similarly, trisomy 21 through inherited Robertsonian translocation is the result of the malsegregation of derivative chromosomes, a phenomenon that is independent from the will of the balanced chromosome abnormality carrier or from environmental factors. As well, the mosaic trisomy 21 cannot be avoided through primary prophylaxis measures, given that the segregation error occurs after zygote formation [2].

In case of a positive prenatal diagnosis, the reproductive alternatives should be presented according to the principle of couple autonomy. The couple should be able to choose to continue the pregnancy, give birth to and raise a disabled child or to decide in favor of the termination of pregnancy, if the legal conditions for therapeutic abortion are complied with [11]. The final choice is to be made by the mother / parental couple; however, it should be an informed decision made only after the genetic information adapted to the cultural and emotional status of the mother / parental couple have been provided [1,11]. Furthermore, the decision of the mother / couple should be voluntary; it should not be in any way influenced by external factors – social, political or related to health insurance.

The patient's acceptance of the invasive prenatal diagnosis depends on social, religious and on cultural status [7, 12, 13]. The results of the prenatal diagnosis test determines the parents to analyze this problem from a medical point of view (statistical data and probable results, procedure risks and detection ratio), from a fundamentalist point of view (in terms of belonging to a certain religion) and from a lifestyle point of view (the impact of raising a disabled child) [7].

Considering the advantages, and especially the disadvantages of the invasive prenatal diagnosis, several attempts of elaborating non-invasive prenatal diagnosis techniques have been made (Non-Invasive Prenatal Diagnosis – NIPD), these methods being rapid, cheap, reliable and with minimal impact on the mother and the fetus. They are based either on the identification of fetal cells in the maternal bloodstream, or on the analysis of the placenta-derived cell-free fetal RNA/DNA present in the maternal bloodstream [14, 15]. The advantages of NIPD are: the reduction to zero of the risks concerning both the mother and the fetus, the precocity of the diagnosis (cell-free fetal DNA appears as early as the 5th week of intrauterine life) so that the final results are obtained at a gestational age at which medical termination of pregnancy is allowed by law [16].

An informed decision is most important taking into account the following reasons: it promotes the best

interests, protects the mother from being misled or forced to make a decision in conflict with her personal moral or religious precepts, it respects the autonomy of the mother / couple and it also protects the doctor from litigations [16].

The precocious performing of a non-invasive test and the short time necessary for obtaining the final results present one great advantage: the time the mother gains for reflection, deliberation and accumulation of new information that will facilitate the acceptance of a potential positive outcome [17].

On the other hand, if the mother chooses to terminate the pregnancy, this intervention will be performed at an optimal time in relation to the moral status of the embryo or fetus [18,19]. The immediate or mediated (delayed) ensoulment thesis was philosophically and religiously analyzed by Crîşmăreanu (2010), from the point of view of the potential abortion in cases of Down syndrome fetuses [20]. The supporters of the gradualist theory consider that selective abortion before the 8th week of gestation raises fewer moral objections regarding embryo status [18, 21]. The arguments are related to the moral status of the embryo which is relatively compared to that of the human person [22].The cell-free fetal RNA/DNA can be obtained as early as the 5th week of amenorrhea and brain development begins in week 8 of gestation (40 days) [18, 21].

The right not to know the test results must be respected, although controversies arising from this fact interferes with the feelings of the mother / the couple, resulting in another dimension of the benefit versus harm dilemma [23].

On the other hand, making the decision of pregnancy termination, considering only the results of uncertain tests, could generate feelings of guilt, confusion and anxiety to the mother / couple during pregnancy and later [23].

The implementation of routine non-invasive diagnostic tests, despite its increased efficiency and improved accessibility, creates ethical controversy concerning the negative impact of decision making after only a single testing phase, the mother not having the time to deliberate and acquire information [16,18].

Another issue raised by the use of NIPD is that of inequality concerning testing accessibility, given the fact that this type of prenatal diagnosis is performed through expensive techniques that are only partially covered by health insurance [24]. Based on these considerations, certain authors consider that the non-invasive prenatal diagnosis is equal to a contemporary form of eugenics, some privileged groups having the possibility of determining the genetic characteristics of their children. This approach is however contradicted by the fact that the state does not coercively involve in human reproduction, the reproductive autonomy being a high-level human right, and that the dysgenic effects of the prenatal diagnosis are low and temporary [1]. Remennick considers that the “good mother” concept includes "genetic responsibility" for the direct descendants and relatives, consistent with the notion of "medicalization of kinship" introduced by Finkler [25].

Newson (2008) examines the three alternative models of NIPD proposed by Annas: medical, commercial and

legal. In the case of the medical model, the doctor should recommend the performing of the test, as stated in various good practice guidelines, while in the case of the commercial model, the mother / the parental couple decides whether to take the test, based on personal knowledge, potentially being influenced by commercials, with or without the informed opinion of a doctor. The legal model partially involves the state in human reproduction; however it is not a case of eugenics, since the final decision belongs to the parental couple. Certainly, the mandatory prenatal diagnosis tests would raise awareness of pregnant women with regard to fetuses with abnormalities, possibly increasing the number of abortions (even though the state does not coercively intervene), determining a concomitant decrease in the number of children with disabilities, which can lead to changes in public attitudes towards disabled people and their families [26, 27].

Another controversial aspect of the secondary prophylaxis of chromosomal diseases consists in the fact that, in case of prenatal screening, the mother is often offered little information about the significance of a potential positive result and is rarely informed that the screening should be followed by a diagnosis test, so that pregnancy termination, as a reproductive option, should be taken into consideration only in case the chromosomal diagnosis confirms the presence of an abnormality. On the other hand, this problem could be easily solved through widely introducing the NIPD that will essentially change the genetic counseling in the case of chromosomal diseases due to the early pregnancy stage it can be performed in.

Considering the possible introduction of routine NIPD tests, five possible scenarios concerning the evolution of chromosome abnormalities identification have been elaborated: NIPD will constitute an additional test used in order to improve the evaluation of global risk; NIPD will be an intermediate phase between risk screening and invasive prenatal diagnosis in the case of high risk pregnancies; NIPD will replace the present prenatal tests; NIPD will be used instead of invasive prenatal diagnosis tests or it will become the only method of prenatal diagnosis, the latter scenario being the most probable in the opinion of most authors [18].

**The particularities of parental couple counseling in the case of chromosomal diseases associated with serious congenital abnormalities**

Another problem that doctor should bring to the attention of the mother / parental couple consists in the fact that the prognosis cannot be determined through prenatal diagnosis, the evolution varying between statistically established boundaries. Although each abnormality presents certain clinical characteristics, the common features of unbalanced chromosome abnormalities consists in the presence of multiple major congenital abnormalities (MCA) and in the marked delay in uterine growth. Among the MCA, one of the most important are the congenital heart malformations (CHM) present in approximately 30% of patients with chromosomal abnormalities, their incidence varying between values close to those of the general population and up to nearly 100% in trisomy 18 [28]. Moreover, the CHM together

with the central nervous system abnormalities are responsible for the high mortality specific to trisomies 13 and 18. The congenital heart malformations are also frequently present in trisomy 21, case in which the patient survival time is measured in years compared to days or weeks as in the case of trisomy 13 and 18 [29]. However, despite the severity of major congenital abnormalities, there are cases of patients suffering from trisomies 13 and 18 that have survived a long period of time after the surgical correction of the congenital heart malformation, which makes it impossible to determine an accurate prognosis. Although several decades ago patients with trisomy 13 and 18 could benefit only of "palliative" care, due to the "unfavorable" prognosis, subsequent studies have shown that birth in a specialized center, surgical correction and supervision in the intensive care services increases hope of survival [30].

Unfortunately, neither prenatal screening methods, nor fetal ultrasound and serological tests (double, triple), nor the invasive prenatal diagnosis followed by a chromosomal analysis can establish a certain prognosis, even if they establish the diagnosis. Thus, there are data showing that, in the presence of the same chromosomal abnormality, the pregnancy outcomes may be miscarriage, stillbirth of a baby with multiple malformations, giving birth to a baby with multiple malformations who dies shortly after birth or who can survive for a long period of time, without knowing the factors that modulate this development [31]. In this given context, the therapeutic abortion may be interpreted as a suffering limiting procedure as well as a method that eliminates the chance to live. The best example in this regard is the positive prenatal diagnosis of trisomy 21; there are cases of patients suffering from Down syndrome who die young, especially if they have a severe congenital heart malformation. However, there are persons with the same diagnosis that can live over 50 years, if they undergo a precocious surgical intervention. Nevertheless, in the light of cardiovascular surgery evolution, the chances of the latter category significantly increase [32].

The same dilemma – "A life of suffering" or "A chance to a different happiness" – occurs in the case of 22q11.2 microdeletion syndrome, given that this disease has a wide clinical variability even within the same family; some patients die because of severe conotruncal CHM. However, some patients have been known to have a favorable evolution after the surgical correction of these malformations. [33, 34]. Another controversial aspect concerning this chromosomal microdeletion consists in the fact that there is no phenotypic correlation between the size of the absent chromosomal fragment and the patient's phenotype [35]. Thus, prenatal detection of 22q11.2 microdeletions in the context of an existent CHM generates the existential dilemma of giving birth in a specialized center, followed by surgical correction of the heart malformation versus "therapeutic" abortion [28].

**Conclusions**

In conclusion, we ask this question: is the mother capable to decide the fate of her child if we have not yet elucidated all the data of the puzzle? We can also question how far we can

act through "artificial" selection, given that spontaneous abortions and stillbirths already represent a form of "natural selection".

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