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CONTRIBUTION OF MEDICAL GENETICS ADVANCES TO BETTER HUMAN PROCREATIVE OUTCOME

DOPRINOS NAPRETKA MEDICINSKE GENETIKE BOLJEM ISHODU HUMANE PROKREACIJE

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Abstract

Recent advances in medical genetics contributed to better understanding of the role that genome plays in health and disease. New genetic technologies have quickly brought an increasing amount of information about the fetus. Despite a remarkable medical achievement, a 3-5% of couples from general population have some difficulties in procreation, manifesting as a broad spectrum of adverse pregnancy outcome, with a strong genomic impact. Assessment of genetic risks to procreative difficulties should be evaluated from at least three perspectives: prior to conception, prenatal and postnatal. The needs and indications for prenatal genetic diagnosis constantly increase and many efforts have been made towards the development of early, rapid and non-invasive prenatal diagnostic tests. Several methods (FISH, QF-PCR, aCHG, NGS) have been introduced recently, aiming to perform early and rapid prenatal or preimplantation diagnosis, and also non-invasive prenatal diagnosis from maternal blood (NIPD). The increasing ability to evaluate fetal genome comes with significant responsibility for clinicians. The importance to maintain the high-standards of clinical practice in medical genetics was Europe-wide recognized. The EuroGentest Expert Group, ESHG Quality committee and Councel of Europe provided recommendations and guidelines for genetic diagnosis and services, which should be applicable to both, invasive and non-invasive testing, with mandatory informative, non-directive pre-test and post-test genetic counseling. A high awareness should be driven on the principles of procreative liberty and potential misuse of genetic prenatal diagnostics for non-medical purposes. A particular sensitivity should always be applied when we are involved in the „creation" of embryo and when we are in the position to make, or to influence to the decision: who is, and who is not worth to contribute to „genetic pool" of mankind.

INTRODUCTION

The ability to bring into existence a new life, through capability of reproduction, commonly is defined as procreation. Successful procreation could be defined as a process, starting before conception and closing with bringing a healthy offspring into the world. Vast majority of procreative processes occurs spontaneously and result in healthy newborn. However, there are also a considerable number of couples with broad spectrum of difficulties in procreation, starting from infertility, through various adverse pregnancy outcomes to delivering a child with severe disease. In such cases more than couple, decided to have a child, should be involved in „creation" of successful reproduction. Recent medical advances and technologies have brought the ability to intervene in various biological processes regarding human reproduction, but also have changed the perception of human life and death and brought numerous ethical challenges [1].

The definition of successful procreation could be differently interpreted from various medical and ethical prospective. For parents procreation should lead to a "perfect" child with desirable gender. For reproductive specialist and obstetrician, it is a successful conception, pregnancy and normal delivery resulting with a newborn in good condition. For clinical geneticist and pediatrician the result of successful procreation should be an offspring without any perinatal accident and with no untreatable disorder which severely influences a quality of life of child and his/her family. On the

other hand, considered collectively, from population and social prospective, successful procreation should create a new generation, a newborn-population with small rate of fetal/neonatal deaths, congenital anomalies and hereditary diseases, and with perfect gender balance. In the situation when we need to support procreation, we have to be aware that our choices determine who will come into being, but also how the next generations will look like [2, 3].

Influence of genomic burden to successful procreation

There is a broad spectrum of factors that are held responsible for unsuccessful procreation, manifesting as infertility, recurrent pregnancy loss, presence of fetal congenital anomalies, intrauterine growth restriction, unexplained fetal death or delivery of a child with severe disorder. The etiology of all those adverse outcomes still remains unclear in at least half of such events, although a strong genomic impact is increasingly recognized [4]. It is expected that 3-5% of couples from general population will have fertility or pregnancy problems related to genetic factors, and/or will have a child affected with a genetic disorder [5]. Recent advances in medicine and medical genetics contributed to better understanding of the role that genome plays in health and disease [6]. Despite the mission of the Human Genome Project, whose „true payoff will be the ability to better diagnose, treat, and prevent disease"(Frensis Collins, the director of HGP), vast majority of genetic disorders are not yet treatable, and the McKusic's negative eugenic approach remains the best available management of genetic disorders [7, 8].

Assessment of genetic risks to procreative difficulties should be evaluated from at least three perspectives:

1. prior to conception, focusing on couples with infertility and recurrent pregnancy loss;

2. prenatal, focusing on pregnancies with risk for chromosomal abnormalities, congenital anomalies, rare single gene disorders, intrauterine growth restriction and unexplained sudden fetal death;

3. postnatal, focused on a child with severe genetic disease

The most common group of genetic disorders is chromosomal aberrations, and they are the main cause of severe developmental abnormalities during pregnancy and infancy. This group of genetic disorders is present in 0,5% of newborns, and majority of them can be diagnosed by cytogenetic analyses. Couples and pregnancies in high risk for fetal chromosomal abnormalities are well recognized, due to development of new technologies in the fields of medical genetics, biochemistry and sonoembriology. Advanced maternal age, familial balanced chromosomal rearrangement carrier state and increased risk detected by screening tests for risk of fetal chromosomal abnormalities are the most common indications for prenatal diagnostics of these conditions [9, 10].

There are more than 10000 single gene diseases, with genetic diagnostic merely available for less than half of them, and even in those cases, there are numerous difficulties on the road to final and reliable genetic diagnosis . Dominant single gene diseases are evident in one of parents, or they appear as „de novo"genetic conditions, with no increased risk for further offspring. On the other hand, recessive single gene diseases can be present in carrier state and could be passed down quietly through many generations. Every human individual carries 14 - 18 recessive single gene mutation, which can cause a severe genetic disorder in homozygous state [11, 12].

Given the fact that recessive gene's carriers predominantly do not have family history or symptoms of the disease, the only way to identify increased risk for recessive single gene diseases is carrier screening, but only for the disorders which appear with high frequency in certain population. Additionally, mutation detection rate varies, from ≤50% to ≤10%, and depends on number of mutation within gene candidate, and this fact is the most challenging issue in the field of genetic testing, especially in the process of preparing the design for genetic testing and genetic interpretation, and pretesting and post-testing counseling, about nature of disease, recurrent risk and possibilities for prevention. The selection for screening of carriers for recessive genes should be elected from a specific geographical and population area based on following criteria: carrier rate, detection rate, ethnic groups, body systems affected, physical damage, cognitive disturbance, quality of life, reduction in life expectancy and treatment availability [13].

There is also a wide spectrum of complex, polygenic diseases, which are predominantly responsible for isolated, non-syndrome congenital anomalies and with very limited possibilities for specific genetic analyses. The etiology of such epilog of dysmprphogenesis appears to be multifactorial, with strong genomic impact, but around 60% of those cases remain unexplained, despite constant research focus on the topic [14]. Genome-wide association analyses have showed a limited contribution of individually important genomic markers, with further necessity for identification of specific gene yield in complex diseases [15].

Invasive prenatal diagnosis of genetic diseases

Prenatal diagnosis of genetic diseases is performed using invasive procedures for more than 40 years, but with about 1% associated risk of fetal loss [16]. The most frequently offered and performed invasive prenatal diagnostic is cytogenetic testing in pregnancies with high risk for chromosomal abnormalities (advance maternal age, positive results of biochemical screening tests, detected fetal ultrasound abnormality or familial chromosomal rearrangement). Few years ago, long-term cell culture, chromosome banding and cytogenetic analyses (karyotyping) were the leading methods for evaluation of chromosomal abnormalities risks. Despite the fact that karyotyping is broadly used for the identification of chromosome aberration, this method remains time-consuming, invasive and limited to relatively large genomic changes of 7-10 million base pairs or larger.

The needs and indications for prenatal diagnosis constantly increase and many efforts have been made towards the development of early, rapid and non-invasive prenatal diagnostic tests, and recently in combination with some single gene testing or whole genome analyses [17]. The majority of genetic disorders could be detected by usual type of

prenatal diagnosis (i.e. karyotyping), accomplished on multiple cells chromosomal analyses, obtained during pregnancy following chorionic villus sampling (CVS), amniocentesis (AC) or fetal umbilical blood sampling by cordocentesis (FUBS).

Following advanced reproductive technologies (ART), such as in-vitro fertilization (IVF), preimplantation genetic diagnosis (PGD) is developed for early and rapid, prior to implantation, detection of chromosomal and some single gene diseases (usually autosomal recessive) by using molecular analysis techniques on single cells removed from the embryo. PGD on single cells is considered medically indicated only for diagnose of specific, detectable single gene mutations, when parents are known carriers of mutation and in embryos for whom the PGD will eliminate the need for subsequent invasive prenatal diagnosis by CVS or AC. Detection of fetal chromosomal abnormalities, performing PGD technologies is currently not as reliable as cytogenetic analysis performed prenataly, following CVS or amniocentesis. This method is not medically indicated for preimplantation genetic screening (PGS), such as screening embryos for chromosomal abnormalities in the absence of specific inherited genetic conditions identified in either parent, with exception if one of the parents has a documented balanced translocation [18, 19].

Several methods (FISH, QF-PCR, CHG) have been introduced recently, aiming to perform early and rapid prenatal diagnosis or PGD. The most prominent advantage of these new technologies is faster turn-around time and earlier available results, providing the information, necessary for the further genetic counseling and pregnancy management for fetus with chromosomal abnormalities or single gene disorders. However, most of them currently are not reliable as cytogenetic analysis of full karyotipe, performed from long-term cultivated, prenataly taken fetal cell samples (AC, CVS).

FISH

Fluorescent in-situ hybridization (FISH) for the chromosomes 13, 14, 15, 16, 18, 21, 22, X and Y, in advanced maternal age is used for rapid prenatal and PGD chromosomal aneuploidies screening. This relatively low-cost method, with no cell cultivation enables results within 48 hours after sampling [20]. Using this method up to 95 % of chromosomal aberrations could be detected, instead of almost 100 % (99,8%) detection with full cytogenetic analysis of karyotype. Error rate in FISH is etimated between 5 and 10%, and also elevated mosaicism rate and 40% of mosaicism turn-out to euploid state after 5th day of embryos, were reported as main disadvantages of this method [20, 21].

QF-PCR and MLPA

Quantitative fluorescent polymerase chain reaction (QF-PCR) and multiplex ligation-dependent probe amplification (MLPA) are tailored for detection of specific chromosome aberrations, based on a specific probe usage. This method of prenatal diagnosis allows results within 1 – 2 days, but this diagnostics limited to the most frequent autosomal [13, 18, 21] and gonosomal (X and Y) aneuploidies, accompanied by the risk for fetus/placenta discrepancy in 1-2% of cases, with majority of chromosomal abnormalities being of placental origin, while fetal abnormal karyotype is a rare occurrence [22]. Recently improved QF-PCR, allows simultaneous detection of chromosome aneuploidies and mutations for common monogenetic diseases like: cystic fibrosis, congenital adrenal hyperplasia and spinal muscular atrophy.

Micro-array technology

More recently, micro-array technology has been introduced into prenatal diagnostic and screening. There are two types of arrays that are in use for prenatal genetic testing: comparative genomic hybridization array (aCGH) and single nucleotide polymorphism (SNP)-based arrays, both designed to determine the number of chromosomes [19, 21].

Routine aCGH analysis provides detection of chromosome abnormalities otherwise imperceptible by cytogenetic analysis and also identifies abnormalities like chromosomal microdeletions and duplications. Array-CGH or Chromosomal Microarray Analysis (CMA) is increasingly used in prenatal diagnosis, including PGD genetic testing, following IVF procedures, using the single cell for genetic analyses (polar body, blastomere). The main applications of array are preimplantation genetic screening, preimplantation genetic diagnostic of fetal aneuploidies and complex chromosomal rearrangements and translocations, but recently also for single gene fetal disorder[23]. The primary advantage of microarray technologies is proper detection of micro-aberrations and small pathogenic chromosomal variants, with estimated rate of 1,3 to 17% of detected chromosomal abnormalities, compared with normal findings according to the conventional cytogenetic analyses [24].This method also does has a several constraints in chromosome aberration detections, such as weakness in detection of triploidies, balanced chromosomal rearrangements and low level mosaicisms [25].

NGS

Next generation sequencing (NGS) is the latest promoted method for DNA analyses, which brought a lew light into genomic diseases assesment. This method integrated almoust all advantages of previosly developed DNA techniques, enabling examination of all 23 chromosomes, detection of abnormalities of all chromosomes with high resolution, including deletions, duplications and unbalanced chromosomal regions. NGS also enable detection of single gene and complex genetic disorders, and this is the most reliable method for selecting embryos with the highest implantation potential. The results of NGS can be obtained within 12-24 hours (26). Cost-effectiveness of these procedures is not sufficiently assessed and some negative consequences should be considered, particularly in the field of ethics, such as: ethical issue of detecting Mendelian and quantitative traits, the criteria to be used for embryo selection, the control mechanisms to be used for embryo selection?

Non-invasive prenatal diagnosis of genetic diseases

The idea of analyzing fetal cells segregated from maternal blood, with no risk to the fetal development, started several decades ago. Much research has to be done to the development of reliable and consistent diagnostic protocols. Cell

free fetal DNA (cffDNA) in maternal blood is recently used for non-invasive prenatal diagnosis (NIPD). The major clinical use of cffDNA genotyping has been for the NIPD of fetal RHD status and fetal sex in the pregnancies at risk of hemophilia or other X-linked disorders. This valuable source of fetal material is recently used as a screening for fetal chromosomal and/or some single gene fetal disorders.

Most promising NIPD tests are: massively parallel sequencing (MPS) highly multiplexed targeted single-nucleotide polymorphism (SNP) amplification and sequencing and methylated DNA Immunoprecipitation (MeDIP). These techniques are predominantly focused on common fetal aneuploidies, such as trisomy 13, 18, 21 and X and Y aneuploidies [27]. A patient with a positive result, attained by NIPD, should be referred for genetic counseling and offered invasive prenatal diagnosis of entire karyotype or one of rapid PD. Some of these techniques also detect parental origin of fetal chromosomes and uniparental disomy, and will allow detection of triploidy, microdeletions/microduplications, and haplotype reconstruction. NIPD should be considered as a first line test for aneuploidy screening in general pregnant population and could help lessen the unnecessary invasive PD and maternal anxiety, but it does not replace the accuracy of invasive prenatal diagnosis with CVS or AC, which remain the ultimate option for confirmation/exclusion of positive NIPD tests [28]. Despite all technological efforts, NIPD screening for fetal aneuploidies, using cffDNA has proven to be difficult, and it is commercially limited for 21, 18 and 13 chromosome aneuploidies. Before introduction of NIPD tests into routine diagnostic, more evidence is needed from broad perspective of issues, such as diagnostic accuracy, cost-effectiveness, and ethical issues.

Integration of knowledge and ethical demands - Quality of genetic services

Last several decades have brought a tremendous improvement in the field of medical genetics. New genetic technologies have quickly brought an increasing amount of information about the fetus, into pregnancy care providing, with mandatory pre- and post-testing non-directive genetic counseling [29].

Clinical guidelines are increasingly recommending the incorporation of new discoveries in genomic medicine into routine care, especially the transfer of genetic knowledge from research laboratories into clinical practice. Data derived from gene testing, genetic consultations, and genetic counseling in particular, represents a set of information apart from the rest of the patient's clinical record, and this data is regarded as „especially protected personal information" (i.e. genetic pedigree and results of genetic testing).

The importance of building a strong and coherent background for genetic counseling professionals was recognized in last decades and minimum education standards and competence are needed to ensure patient safety. Particularly in the light of rapid development of molecular genetics, the shortage of health professionals in the field of genetics was recognized. Europe-wide recognition is of tremendous importance to maintain the high-standards of clinical practice in human and medical genetics areas, as well as cross-border mobility and collaboration [30]. The assessment of existing quality frameworks for genetic counseling in Europe, provided by ESHG Genetic Services Quality Committee, has shown great variation ranged from no service (the situation in most countries) to well-organized genetic counseling on a national level (small number of countries). Furthermore, the majority of general health professionals have inappropriate knowledge and skills in medical genetics and many are unaware of the technical, ethical, legal and psychosocial implications of genetic testing and importance of genetic counseling. Furthermore, the public is largely unaware about genetic risks and the possibilities of their prevention.

Despite a long history of prenatal testing, there are still no overall guidelines to ensure minimum standards of care for women and the incoming children. With increasing use NIPD there is a concern that prenatal testing will become too "routine" and additionally misused for non-medical purposes. Multidisciplinary team of medical professionals should have an integrated approach to assure the best interest for family, future child and society.

The increasing ability to evaluate fetal genome comes with significant responsibility for clinicians. Pre-test and post-test counseling is mandatory and should be informative, non-directive and should prepare patients for the reproductive decisions they have to make. The EuroGentest Expert Group and ESHG Quality committee [31, 32] provided guidelines for prenatal diagnosis which should be applicable to both, invasive and non-invasive testing. The objective of prenatal diagnostic counseling is to enable families to make informed choices consistent with their needs and support them in dealing with the outcome. General principles include the need for appropriately trained genetic counselor, ensuring informed decision making and the availability of pre-test and post-test counseling [29, 33]. This type of service requires effective communication between clinical geneticist and family, sensitive counseling with interpreters if needed, and consideration of wider family implications. Counseling topics should include psychosocial and ethical issues as well as information about the condition, the available diagnostics and available options.

In accordance with GenDg and ESHG Quality committee protocols genetic diagnostics has to be performed in accordance with following recommendations:

1. Responsible doctor has to be qualified for human genetic counseling
2. Performed results have to be reported to responsible doctor, not directly to the patient
3. In Europe, NIPD for fetal aneuploidies is only available for trisomias 21, 13, and 18, which is in accordance with the IVD directive of the EU [34].

According to Council of Europe recommendation, professional genetic counseling prior to genetic testing is mandatory. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, recommends „development and strengthening of genetic services to maximize the benefits of genetic application in health care for all patients ... and provide adequate genetic counseling in an equitable manner" [35].

Specific attention should be driven on the principles of procreative liberty and potential misuse of genetic prenatal diagnostics for non-medical purposes, such as prefertilization, preimplantation or prenatal gender selection. Working in the field of assisted reproduction and prenatal diagnostics, professionals are actively involved in the „creation" of the embryo, and are considered to be co-responsible for the outcome of the procedure and the welfare of the potential children, but also for the future generations and society.

CONCLUSION

Recent scientific development in the field of medical genetics demands the necessity of integration of all medical and clinical genetic knowledge and skills, with a mission to provide optimal quality of medical genetic service, in accordance with the recommendations of Council of Europe, GenDg protocols, EuroGentest and IVD directive of the EU. Developing and following the national guidelines could be a proper way assure quality of genetic service and ethical control at the national levels. Using all recent advances in medical genetic, we should be aware of medical and ethical challenges. We should use the advances wisely, carefully taking into consideration who is authorized to make a decision: potential parents, affected individual, doctor, society?

… And, we should permanently assess do we, medical professionals have appropriate education, enough awareness and will to combat towards misuse of genetic tests? A particular sensitivity should always be applied when we are in the position to make or to influence to the decision who is, and who is not worth to contribute to "genetic pool" of mankind.

Sažetak

Savremena dostignuća u medicinskoj genetici doprinijela su boljem razumijevanju uloge humanog genoma u zdravlju i nastanku bolesti. Nove genetičke tehnologije ubrzano nam donose veliki broj informacija o fetusu. I pored značajnih medicinskih dostignuća , 3-5% parova iz opšte populacije imaju određene probleme u prokreaciji, koji se manifestuju širokim spektrom nepovoljnih ishoda trudnoća, sa prepoznatim snažnim genomskim doprinosom. Procjena genetičkih rizika na uspješnost prokreacije trebala bi se razmatrati kroz majmanje tri perspective: prekoncepciji, prenatalno i postnatalno. Indikacije i potrebe za prenatalnom genetičkom dijagnostikom konstantno su u porastu I uloženo je puno truda u pravcu razvoja rane, brze i neinvazivne prenatalne genetičke dijagnostike. U skorije vrijeme uvedeno je nekoliko metoda (FISH, QF-PCR, aCHG, NGS), sa ciljem da se obezbijedi rana i brza prenatalna i preimplantacijska dijagnostika, ali i neinvazivna prenatalna dijagnostika nasljednih bolesti iz krvi majke (NIPD). Sve učestalija mogućnost evaluacije fetalnog genoma praćena je značajnom odgovornošću kliničara. Potreba uspostavljanja visokih standarda kliničke prakse u medicinskoj genetici prepoznata je širom Evrope. EuroGentest ekpertska grupa, ESHG komitet za kvalitet i Savjet Evrope obezbijedili su preporuke i vodiče za genetičku dijagnostiku i genetičke službe, koje bi trebalo primjenjivati i na invazivno i na neinvazivno prenatalno genetičko testiranje, sa obaveznim informativnim i nedirektnim genetičkim savjetovanjem prije i nakon sprovedenog testiranja. Visoku svjesnost trebalo bi usmjeriti na principe prokreativnih sloboda i potencijalnih zloupotreba prenatalne genetičke dijagnostike u nemedicinske svrhe. Sa posebnim senzibilitetom uvijek treba postupati kada smo uključeni u „kreaciju" embriona i kada smo u poziciji da donosimo, ili da utičemo na donošenje odluke: ko je, a ko nije vrijedan da doprinese „genskom bazenu" čovječanstva.

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