Current investigations in reproductive medicine – literature review

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Abstract

The last decades have witnessed the rise of reproductive medicine to the status of a significant branch of medicine. Its growing significance can be attributed to a significant increasing trend in the mean age for first-time pregnancies. In response to these challenges, a new series of investigations have been tested and approved, laying the foundation for a different approach to infertility. Genetic tests are the most innovative and relevant investigations in this field. This new diagnosis tool not only allows for the detection of genetic syndromes, but also for assessing the probability of inherited disease in the newborn. This article aims at reviewing the data from literature, highlighting the relevance of the recent investigations in reproductive medicine and conferring a framework for them.

Keywords: *reproductive medicine, infertility, endometrial biopsy, genetic tests, personalized treatment*

Rezumat

În ultimii ani am asistat la ascensiunea medicinei reproductive, care a devenit o ramură importantă a medicinei. Importanța medicinei reproductive poate fi atribuită creșterii vârstei medii la prima sarcină. Ca răspuns la aceste provocări, o nouă serie de investigații au fost testate și aprobate, punând bazele unei abordări diferite în ceea ce privește infertilitatea. În special testele genetice sunt cele mai inovatoare și relevante investigații în acest domeniu. Acest nou instrument de diagnosticare permite nu numai detectarea sindroamelor genetice, ci și evaluarea probabilității bolilor genetice la nou-născut. Scopul acestui articol este de a trece în revistă datele din literatura de specialitate, de a evidenția relevanța investigațiilor recente în medicina reproductivă și de a oferi un cadru de ansamblu despre acestea.

Cuvinte-cheie: *medicină reproductivă, infertilitate, biopsie endometrială, teste genetice, tratament personalizat*

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Introduction

Infertility represents an important public health problem, especially since its prevalence has increased over the last years. The latest estimation is that infertility affects one out of six people worldwide and up to 15% of couples who wish to conceive[1-3]. The World Health Organization (WHO) has ranked infertility in young couples as the fifth most serious global disability[4].

The evaluation of both couple members is needed, because infertility affects both women and men equally[1]. The age of the couple is the most important risk factor. Research has shown that, as the age of the partners increases at the time of conception, the incidence of infertility also increases[4,5]. According to the studies of Elussein et al., Masoumi et al., and Farhi and Ben-Haroush, tubal disorder has an incidence of 15-20%, being the second most common cause of female infertility[4,6-8]. Another significant cause of female infertility is represented by endocrine abnormalities, especially hypothyroidism, which are estimated to have a prevalence of 23.9% in infertile women[4,9].

Male infertility has a reported incidence between 30% and 45% in couples unable to conceive[4,6-8]. In specialty studies, abnormal semen parameters are seen in 7% of men[4,10]. It is relevant to mention that unexplained infertility, which is an exclusion diagnosis, is reported to have an incidence of around 30%[4,11].

As a consequence of the large variety of causes of infertility, reproductive medicine has developed new methods for assessing couple infertility, in addition to the classical battery of tests. Due to the vast causes of infertility, reproductive medicine has improved new methods of evaluation of couple infertility (hysterosalpingography, cervical samples, blood samples etc.). Currently, biochemical and instrumental analyses represent the most frequently used tests for infertility diagnosis, which establish the diagnosis in 65% of cases[1]. Genetic tests are used for the remaining 35% of cases[1]. In addition, genetic tests are also used in reproductive medicine to identify transmissible genetic diseases, offering the opportunity for personalized medical management[1]. DNA analysis has an indispensable role in determining the fertility potential of individuals and also in the development or disorders of *in vitro* embryos[12-17].

This article aims to illustrate the importance of the newly developed investigations in reproductive medicine and to provide significant information for understanding the importance.

Materials and method

Data were extracted from Google Scholar and PubMed databases, from primary articles, reviews and guidelines. The following terms were searched: "reproductive medicine", "infertility", "genetic tests", and "investigations in infertility". Published articles from 2018 that had been written in the English language were included. In the reference section, there are found all the publications from which the information was extracted.

Endometrial biopsy

Endometrium represents the implantation site, but infertile women present an alteration of it[18]. Endometrial biopsy with the histopathological exam can establish the diagnosis of luteal phase deficiency, although it has limitations regarding accuracy and precision[18]. It also can provide information about endometrial pathologies[18]. In developing countries, endometrial biopsy is a useful analysis for infertility, since complex immunological and hormonal assay procedures are unavailable for most people due to their costs[18].

Currently, endometrial biopsy is used to evaluate endometrial receptivity. An endometrial receptivity array can predict the receptivity status of endometrial biopsy samples[19]. Based on microarray technology coupled with a computational predictor, this analysis is more objective and accurate. In women with recurrent implantation failure, this investigation uses transcriptomic biomarkers to assess endometrial receptivity[19]. Therefore, tests for endometrial receptivity approach three main objectives: identifying problems in dating as synchrony between embryo and endometrium, determining endometrium malfunction, or identifying inflammatory factors which may cause malfunction of the endometrium[20].

Genetic tests

Infertility can be caused by various factors, including environment, age, anatomical issues or trauma. However, it is estimated that 50% of infertility cases are determinate by genetic disorders, and every healthy patient carries 5-8 genetic alterations associated with recessive genetic disorders[1,21,22]. Genetic tests offer a more specific diagnosis of infertility and of the risk of transmission to the offspring, but they do not consider the patient's personal or family history, because they use a standard algorithm for investigating infertility genes[1]. Therefore, a careful medical exam based especially on personal and familial medical history can lead to specific genetic tests[1,23].

Genetic tests for male infertility

The first indication for genetic tests in men is represented by an abnormal spermiogram, primarily severe oligospermia[1,24]. Male infertility caused by genetic disorders includes whole chromosomal aberrations, partial chromosomal aberrations, and monogenic diseases[1]. Currently, the main genetic tests used are the karyotype, the study of chromosome Y microdeletions, and the analysis of the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene[1]. However, several other mutations have been recently reported, and this is the reason why approximately 40% of causes of male infertility are undiagnosed[1,25,26]. Regarding chromosomal alterations, their prevalence is reported to be between 1.05% and 17%[1]. The most common type of sex chromosome aneuploidy in infertile men is Klinefelter syndrome, followed by Double Y syndrome[1,27-30]. Regarding partial chromosomal aberrations, the most frequent molecular genetic cause of male infertility is represented by microdeletions in the long arm of the Y chromosome (Yq), known as the AZF (Azoospermia Factor) region[1,30,31]. The prevalence of this mutation has been reported to be between 8% and 12% in men diagnosed with azoospermia and 3-7% in men diagnosed with oligozoospermia[1,30,31]. In these cases, genetic tests are even more significant, because a male offspring will have the same Yq microdeletion as the father, or a worse one[1,32]. Exams for single gene mutations are used to determine a single gene disorder[1]. The limitation of these tests is that in male infertility there are involved thousands of genes, but the current tests explore just a handful of genetic diseases[1,33,34].

Genetic tests for female infertility

Compared to men's infertility, there is not much data about genetic reasons for female infertility; therefore, fewer specific tests are currently used to investigate this pathology in female patients[1]. The main cause of female infertility is represented by syndromic diseases, while isolated infertility caused by genetic disorders is rare[1]. Thus, genetic tests are recommended, especially for patients with primary ovarian insufficiency (POI), limited to chromosomal aberrations and Fragile X Mental Retardation 1 (FMR1) pre-mutations[1]. Karyotype analysis is available and should be used since chromosomal disorders may carry a high risk of miscarriage and infertility[1,35]. In women, the most important structural disorders are represented by reciprocal or Robertsonian translocations, since they block meiosis and induce structural alterations of the X chromosome[1]. The balanced rearrangements do not represent a health issue for the carriers, but they can alter gametes, leading to infertility or miscarriages[1]. Oocytes with chromosomal abnormalities can appear in women with normal karyotypes, and the best-known risk factor is increased maternal age[1,36-38]. These errors occur during crossing-over and/or meiotic nondisjunction, and there are three main classes of abnormalities: 45X, trisomy, and polyploidy[1,36-38]. Since POI and FMR1 are the most frequent causes of infertility in women, patients with clinical manifestations should benefit from genetic tests, because, nowadays, there are various options in reproductive medicine. Moreover, these patients can benefit from personalized management[1].

Genome tests in reproductive medicine

Clinical applications of millions of individual genomic sequences have been used to create a more accurate therapeutic strategy and patient care, which nowadays is

defined as "precision medicine"[39,40]. According to reproductive medicine, genomic testing allows the couple to have a chance to conceive by using preconception carrier screening, preimplantation genetic testing, or conventional prenatal testing during pregnancy[39]. The most important advantage in this field is represented by patients with a known severe genetic disorder who could not access a molecular test for diagnosis and reproductive therapy[1]. Preconception genetic testing and subsequently informed family planning had an impressive result, translated into a decrease between 47% and 90% in the incidence of monogenic severe conditions[39,41]. Preconception genomic medicine is relevant to genome-wide sequencing applications (GS). The diagnosis of infertility can be established by using GS preconception. Also, this technique can determine the risk of diseases and predisposition for both partners or the future newborn. In conclusion, GS preconception can lead to personalized reproductive treatment[39].

Discussion

Reproductive medicine represents a vast field as it interferes with various medical specialties. Couple infertility is the main reason why patients apply to reproductive medicine, considering the need to obtain a causal factor. Therefore, many investigations have been performed during the last decades, and the new technologies have brought new perspectives. Besides these, it is necessary not to reduce the importance of the patient's medical and familial history, physical examination, clinical, paraclinical and laboratory tests. These are needed to establish possible risk factors or underlying pathology before performing other investigations[1].

Endometrial biopsy was considered for a long time the gold standard for the identification of luteal phase deficiency as a cause of female infertility. But in approximately 35% of cases the endometrial biopsy cannot establish the cause of infertility, and its use remains limited[18]. Currently, endometrial biopsy is used less often, but it still has an important role, especially for women with repeated implantation failure, because it can determine endometrial receptivity, so personalized embryo transfer can be applied[19].

Genetic tests for infertility – especially for men – represent a significant evaluation for couples who want to conceive. Although genetic tests have been developed, it is reported that a genetic diagnosis is established in only approximately 4% of infertile men. Also, approximately 20% of infertile couples are undiagnosed[1]. These reports are discouraging, especially compared to the fact that an accurate clinical examination and identification of the personal or familial history of infertility can be more accurate, by leading to specific genetic tests[1,23]. However, new extended genetic tests are developing. The European Society of Human Genetics (ESHG) and the European Society of Human Reproduction and Embryology have published a recommendation for the development and introduction of extended carrier screening[1,42].

Genomic medicine in reproductive medicine is a significant step in understanding the genetic and molecular base of reproductive processes and in having a certain diagnosis of infertility. Also, it is mandatory to have a specific infertility treatment. In addition, genome-wide sequencing is a major discovery that provides clear evidence of the genetic foundation of heterogeneity of the disease and its causes[39].

Conclusions

The newest technologies have gained significant importance in the diagnosis of certain infertility. Being an important health issue, the necessity of determining an accurate and personalized treatment for infertility is mandatory. Despite the new genetic tests, the importance of medical exams – including physical examination, patient history and blood tests – should not be neglected, because these can bring a presumptive diagnosis that can be useful for a specific genetic test. ■

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