Best Practice & Research Clinical Obstetrics and Gynaecology 42 (2017) 2–10

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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Preconception and prenatal genetic counselling

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Keywords:
preconception care
prenatal care
genetic counselling
genetic testing
mass screening
folic acid

Identifying individuals at risk of having children affected by genetic conditions or congenital anomalies allows counselling that aims to inform reproductive decisions. This process takes place either at the preconception or early prenatal stage, although more options are available if risks are identified before the pregnancy. Preconception counselling covers issues that can affect the health of the mother and baby including folic acid supplementation. Carrier screening for autosomal recessive diseases, such as beta thalassaemia, has resulted in a significantly reduced incidence in many countries. National organisations, however, advocate more in-depth research before such screening recommendations apply to the general population. Recently, advances in genomic technologies have made it possible to greatly expand the scope of genetic screening, with the aim of providing more comprehensive information to prospective parents. This is a complex field, and research should focus on how the technology can be put to best use in the future.

Introduction

Genetic counselling is the process through which individuals who are either affected by, or may be at risk of developing, a condition that may have a genetic basis, or are at risk of having children affected by such a condition, receive information and advice about its natural history and management, its transmission and the available reproductive options. It constitutes an important component of preconception and prenatal care [1].

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http://dx.doi.org/10.1016/j.bpobgyn.2017.04.003
1521-6934/

Preconception care encompasses a series of measures that aim to improve the health of both mother and baby in a future pregnancy. It covers a wide range of issues including diet, lifestyle, maternal health and associated treatment, working conditions, environmental exposures, and genetic diseases and diseases with a genetic contribution [2]. A number of issues that are covered at the preconception stage may surface, and will be relevant, at the prenatal stage, although the optimal time to address many of these concepts will be before the pregnancy, and the emphasis will be on that stage. This review will primarily explore counselling as it relates to genetic conditions or complex multifactorial conditions that have a genetic basis.

The assessment of prospective parents for possible genetic risks and the issue of relevant genetic testing/screening will be discussed, in addition to counselling in relation to occurrence/recurrence risks for genetic conditions and congenital anomalies. The impact of the rapid evolution in recent years of genomic medicine and genomic technologies on the options available at the preconception and prenatal stage will be explored, with emphasis on expanded carrier screening. The associated pitfalls and challenges will be discussed, as will the ways in which genetic counselling can evolve to support prospective parents in navigating an increasingly complex landscape.

Preconception care

In recent years, increasing emphasis has been placed on behalf of governments and relevant professional organisations on the design of a comprehensive approach to the provision of advice and care to prospective parents and individuals of reproductive age [2–4]. This has been, to a large extent, driven by the persistent incidence of adverse pregnancy outcomes, congenital anomalies and genetic conditions that are associated with significant morbidity and mortality and place high demands on already strained healthcare systems. The organisation of preconception care inevitably varies around the world, but it has certain common core components. At the heart of this process lies the preconception interview during which healthcare professionals such as general practitioners, family physicians, obstetricians or specially trained nurses or midwives meet with prospective parents, give generic health promotion advice, assess the potential for risk, provide information and counselling, and set in motion referrals to other specialists as appropriate. Assessment of risk involves the taking of a detailed medical, social and family history.

Counselling and congenital malformations

The need for a healthy, balanced diet is discussed with women at this stage, and the specific issue of folic acid supplementation, with a daily dose of 0.4 mg starting at least 4 weeks before conception and continuing throughout the first trimester of pregnancy, should be emphasised [5]. In a seminal Medical Research Council study in 1991, folic acid was shown to significantly reduce the rate of recurrence of neural tube defects [6]. In the case of women with a previously affected child, the recommended daily dose is 4-5 mg. Neural tube defects provide an important paradigm of a congenital malformation with multifactorial aetiology, combining both environmental and genetic contributions [7]. Empirical data from the pre-folic acid era demonstrate a significant recurrence risk, which correlates with the number of affected siblings, pointing towards a genetic contribution [8]. Multiple studies have shown a significant reduction in the incidence of neural tube defects with folic acid supplementation [9,10]. There is, however, a residual risk as not all cases can be prevented [11], and there has been significant work aiming to develop strategies to deal with these folic acid-resistant cases. The vitamin-like substance inositol has received significant attention in that respect, and work in mice and preliminary human studies have identified the need for large-scale trials [12,13].

A number of studies have also suggested that in addition to its effect on neural tube defects, periconceptional folic acid supplementation reduces the risk of specific types of congenital heart disease such as conotruncal defects [14]. A recent meta-analysis of epidemiological observational studies has also provided evidence that folic acid supplementation reduces the risk of congenital heart disease [15]. This is a potentially significant additional protective effect, and more research is needed to explore its basis.

Despite the weight of evidence, many pregnant women either miss out on folic acid supplementation or start taking the supplements only after the pregnancy has been confirmed, which is often after the critical period of development of the neural tube in the embryo. The reasons are multiple and include an unplanned pregnancy or the absence of counselling or advice in the preconception period. Conversely, a planned pregnancy, a preconception visit to a medical professional and preconception counselling positively correlated with the use of folic acid before the pregnancy [16–18]. Other factors that were associated with higher levels of preconception supplementation were higher maternal age and higher level of education [16,17]. In view of the significant percentage of unplanned pregnancies, it can be argued that folic acid supplementation should be used by all women of child-bearing age [17,18]. Moreover, the provision of preconception counselling needs to be enhanced and needs to reach those women that are more likely to miss out on this very important intervention. In the case of women who are at higher risk of having children with congenital malformations because of a previously affected family member, preconception counselling should encompass recurrence risks and folic acid supplementation, with genetic professionals potentially playing a role in this process. A study on counselling in relation to recurrence of congenital heart disease showed that women with higher educational level were more likely to have received relevant counselling [19].

The preconception stage also provides the best opportunity to advise prospective parents in relation to other factors that can be linked to congenital anomalies such as foetal exposure to alcohol. This can lead to a spectrum of anomalies including central nervous system abnormalities, growth deficiency and dysmorphic features [20]. Genetic factors that modulate the teratogenic effect of alcohol, such as those that influence alcohol metabolism, are being unravelled and will enhance our understanding of this important health issue in the future [21].

Genetic aspects of preconception counselling

A well-taken history during the initial preconception interview is central to the identification of potential genetic risks to both mother and baby in a subsequent pregnancy. A carefully constructed genogram can be used to record family relationships and diagnostic details. A number of electronic versions exist, but in my opinion, a hand written version using standard symbols is both efficient and effective [22]. There are a number of circumstances that raise concerns including the previous birth of an affected child, a complicated obstetric history featuring recurrent pregnancy losses, a confirmed or possible genetic (or other) diagnosis in either of the prospective parents, and a family history of known (or suspected) genetic disorders or of children born with congenital anomalies. Moreover, the ethnic background of the prospective parents and the possibility of consanguinity need to be explored.

It is, of course, likely that in some of the scenarios outlined above, the individuals involved will already be under the care of other specialists, including clinical geneticists, and that issues such as recurrence risk will have been specifically addressed and the options available to the parents outlined in detail. Furthermore, if the prospective mother is herself affected by a genetic condition, there may be specific obstetric issues to be assessed and managed by obstetricians familiar with these conditions. These issues are beyond the scope of this review. However, it will suffice to say that if pointers to genetic risk that require referral to other specialists and healthcare professionals are identified, the referrals will follow the primary preconception consultation as appropriate. At the same time, it may be appropriate to consider offering genetic testing/ screening according to local guidelines and recommendations following careful counselling about the relative advantages and disadvantages. The following sections explore the issues of genetic testing/screening.

Relevance of family history

Let us consider the example of Fragile X syndrome, which is the most common inherited cause of intellectual disability [23]. It is caused by an expansion in the CGG trinucleotide repeat in the FMR1 gene on the X chromosome. A full mutation, characterised by more than 200 CGG repeats, causes intellectual disability in males and milder intellectual disability in a proportion of affected females. Premutation carriers (55-200 repeats) are at risk of late-onset cerebellar ataxia (mainly males) and premature ovarian failure in females. Female premutation carriers can have children with full

mutations as a result of expansion of the CGG repeats. As female premutation carriers may have no relevant family history, it has been proposed that carrier screening should be offered to inform reproductive options. Currently, the American College of Medical Genetics and Genomics recommends carrier testing only for women with relevant family history of intellectual disability [24]. The guideline argues against population screening on the basis of the complex genetics of FMR1-related disorders, which is mainly associated with the variable phenotype in premutation carriers and female full mutation carriers and the relevant counselling challenges. A systematic review by Hill et al. has identified evidence that offering screening for Fragile X in either the preconception or prenatal settings would be acceptable by women but argued that targeted counselling by appropriately trained professionals should be developed to support individual choice [25]. More research is needed before Fragile X testing can be offered consistently to women without a relevant family history, and emphasis should be placed on developing appropriate counselling to address the complexities of the genetics of the condition and allow informed choice [26,27].

Genetic screening and relevance of ethnicity

Mutation screening is particularly relevant in autosomal recessive conditions [28–31]. In these conditions, the majority of mutated alleles are found in heterozygote carriers who are themselves unaffected by the condition and may be unaware of their carrier status. The genogram may not identify any specific clues, and a child with an autosomal recessive condition may be the only affected individual in the family. The carrier frequency for specific autosomal recessive disorders varies significantly between different populations and sub-populations and is linked to ethnic background.

On a global scale, cystic fibrosis, thalassaemia, sickle cell disease and Tay–Sachs disease represent common autosomal recessive conditions in terms of carrier frequency, with significant variation in different populations [29]. For example, the carrier frequency for mutations in the HBB gene (which codes for the beta globin chain of haemoglobin), which are associated with beta thalassaemia, is high in countries in the Mediterranean basin and estimated to be 1 in 7 in Cyprus [32]. Another haemoglobinopathy caused by a mutation in the HBB gene is sickle cell disease, and individuals of African origin have a high carrier frequency, depending on the specific population. Mutations in the HBA1 and HBA2 genes, which cause alpha thalassaemia, are frequent in Southeast Asian populations. The carrier frequency for mutations in the CFTR gene, which cause cystic fibrosis, is high in individuals from Northern European populations (1 in 25), and the carrier rate for Tay–Sachs disease, a metabolic condition caused by deficiency in Hexosaminidase A enzyme leading to progressive neurodegeneration, is 1 in 30 in individuals with Ashkenazi Jewish background.

The seriousness of the conditions and their relatively high prevalence in specific populations have led to the consideration of offering carrier screening to identify prospective parents who may be heterozygous for pathogenic mutations. Technically, such screening takes the form of either a genetic mutation test (such as in cystic fibrosis) or electrophoresis or high-performance liquid chromatography for haemoglobinopathies. If both prospective parents are identified as carriers of an autosomal recessive disorder, they will have a 1 in 4 chance of having an affected child in a subsequent pregnancy. Confirmation of carrier status at the preconception stage allows prospective parents to make informed decisions in relation to their reproductive options. If they are concerned about the probability of having an affected child, they may opt for preimplantation genetic diagnosis so that embryos produced with assisted reproductive techniques can be tested before being implanted back into the uterus [33]. There may also consider options such as the use of donor gametes, avoidance of having children or adoption. Clearly, these are options that would not have been available to the prospective parents if their carrier status is identified after conception. Alternatively, prospective parents may decide to proceed with a pregnancy and opt for early prenatal diagnosis and have the option of a termination of an affected pregnancy or planning for the birth of an affected child.

If carrier screening is offered, it should be comprehensively supported by genetic counselling by an appropriately trained healthcare professional and should be based on the principle of informed consent [34]. Counselling should encompass a description of the disorders for which testing is being offered and the currently available treatments, the nature of the test being offered and any limitations associated with it, including any residual risk following a negative result, and a detailed discussion of

the available reproductive options as outlined above. Moreover, the potential problems and pitfalls associated with genetic screening such as the potential psychological impact and increased stress levels and possible stigmatisation should be explored [35]. However, a number of studies have identified perceived advantages amongst prospective parents participating in genetic screening, mainly as a result of the individuals feeling empowered to make informed decisions [36,37].

Recommendations for genetic carrier screening either to the general population or to specific subpopulations and ethnic groups are determined at a national level. In the Unites States, various professional bodies such as the American College of Obstetricians and Gynaecologists, the American College of Medical Genetics and Genomics, and the National Society of Genetic Counsellors recommend screening all women of reproductive age regardless of ethnicity or ancestry for cystic fibrosis [38,39]. This panethnic screening approach is based on genetic screening for the most common mutations in the population. Particular emphasis was placed on including mutations that are known to be associated with classical cystic fibrosis and not with milder or variable phenotypic variants so as to avoid putting prospective parents in a difficult position [40]. The panel of mutations included in the screening is reviewed depending on the evidence of carrier detection rates, and a study conducted 8 years after the introduction of screening determined that no additional mutations are needed to be incorporated in the test [40,41]. In the Netherlands, a report on preconception care identified cystic fibrosis as a clear candidate for consideration of implementation of carrier screening but stopped short of recommending the introduction of such testing across the nation and suggested additional studies to be performed to assess potential benefits [2]. In the United Kingdom, a Cochrane review on genetic risk assessment for common autosomal recessive disorders identified evidence from observational studies of potential benefits of the introduction of preconception carrier screening but indicated the lack of relevant randomised controlled trials [29].

In the case of haemoglobinopathies, the United Kingdom has a national programme that offers screening to all pregnant women and, subsequently, to their partners if women are shown to be carriers [42]. A limitation of this approach is that it affords limited options to carrier parents as the pregnancy is already established. Moreover, there is evidence that the way screening is offered, as part of a wider array of prenatal tests, affects the quality of pre-screening education and counselling [43]. The screening recommendation by the American College of Obstetricians and Gynaecologists is based on ethnic background and uses a combination of assessment of haematological indices (mean cell volume and iron studies), haemoglobin electrophoresis and molecular genetic analysis of the HBA1, 2 genes [44]. In the Netherlands, as in the case of cystic fibrosis, the report by the National Health Council identifies the benefit of preconception screening for these conditions but states that more evidence is needed before deciding how it can be implemented on a national basis [2]. A systematic, preconception, nationwide screening programme for thalassaemia has been implemented in Cyprus for a number of years and has resulted in a very significant reduction in the incidence of beta thalassaemia [32,45].

Carrier screening for a number of autosomal recessive conditions is offered to individuals with Ashkenazi Jewish background in the United States [46]. The American College of Obstetricians and Gynaecologists in 2009 recommended offering screening for Tay–Sachs disease, cystic fibrosis, Canavan disease and familial dysautonomia. The American College of Medical Genetic and Genomics is making further recommendations in addition to the conditions described above [47]. In the case of Tay–Sachs disease, the screening programme has resulted in a dramatic reduction in the incidence of the disorder [48,49].

Consanguinity

Consanguineous marriages are common in many countries and are frequently encountered in certain migrant communities in the western world. Consanguineous marriages are associated with an increased probability of children being born with an autosomal recessive condition because the prospective parents are related to each other and are more likely to both transmit a common deleterious mutation to their offspring [50]. The genetic risk involved depends on the degree of relationship: first cousin partnerships are associated with a 3-5% risk of a congenital malformation, genetic disease or adverse pregnancy outcome such as stillbirth or neonatal death [50–52]. This should be compared

with a 2-3% risk for such adverse pregnancy outcomes in the general population. When counselling consanguineous couples, a detailed family history must be taken, and the identification of a genetic diagnosis will inform any appropriate referrals and the advice given to the prospective parents. In addition to counselling about the general risks associated with consanguinity, carrier screening can be offered for conditions that are relevant for the specific population/ethnic group according to existing national recommendations [50]. An issue that is relevant to preconception counselling is perceived challenges in inquiring about consanguinity in the first place, and a study of the practice of Australian midwives suggested that they were reluctant to inquire directly about this issue when taking a family history [53]. The authors suggested specific training into how to raise this issue as part of the routine family history so as to ensure that this type of important information is accurately recorded.

Expanded carrier screening

The past few years have witnessed impressive advances in genomic technologies. The introduction of next-generation sequencing techniques has provided a fast and efficient method for large-scale genetic testing and has made available novel diagnostic tools to genetic professionals [54]. The development of multigene panels and genome sequencing approaches has made it possible to design new strategies for genetic screening at the preconception and prenatal stages with the aim of enabling prospective parents to make better informed choices [55]. The argument has been that rather than rely on targeted screening based on ethnicity, an expanded carrier screening programme, largely for autosomal recessive diseases, could be established for the entire population. Such an approach would allow screening for multiple conditions and could detect mutations in individuals that would otherwise have been missed by an ethnicity-based approach as a consequence of increasingly mixed ethnic populations. A study of individuals undergoing expanded carrier screening in the United States used a theoretical modelled risk approach to compare the effectiveness of this new technique with that of established screening practices. Expanded screening was more effective in identifying hypothetical at-risk foetuses than current screening, and this was partly because the current targeted approach relies on the way individuals identify themselves as belonging to specific ethnic groups [56].

A central component of such an expanded population screening strategy is the selection of disorders to be tested for. Although there is no consensus, professional organisations and specialists in the field propose that conditions should be considered for inclusion in the panels if they affect cognitive function and quality of life or may require early intervention so that timely identification of carrier status in prospective parents would allow for appropriate reproductive choices and/or optimal pregnancy, perinatal and neonatal management [55]. Furthermore, caution should be exercised when considering conditions that have an adult onset and reduced penetrance [55,57]. Another key issue is to decide whether to screen for specific mutations or to use a gene sequencing approach. The former approach would rely on the knowledge of common mutations and the availability of reliable data that would allow an estimate of residual risk in the case of a negative result. The latter approach runs the risk of complicating the result with the potential identification of genetic variants, the phenotypic significance of which may be unknown. In this case, the laboratories would need to have clear guidance about only reporting variants with clear or likely pathogenicity [55].

In view of the complexities described above, the introduction of such a programme would need to be supported by well-structured pre- and post-test genetic counselling by appropriately trained professionals. The expanded list of genetic disorders would make it impractical to discuss all of these in detail, although information about the conditions should be made available either through information leaflets or appropriate electronic resources [57]. During pre-test counselling, the possibility that a result could have implications for the health of the individual being tested (such as in Fragile X) should be specifically flagged up. Post-test counselling would focus on specific findings and would expand on their significance and the options available, such as testing of a partner.

There is clearly some way to go before an expanded carrier screening programme can be offered on a population-wide basis. Future research will focus on the effectiveness and benefits of such a programme on the health of the population and will need to systematically explore the views of patients and health professionals [58–60].

Summary

The overall scope of preconception and prenatal care is to improve the health of both the mother and baby. Within the context of such care, counselling relating to genetic issues that can potentially affect a pregnancy is primarily aimed at providing high-quality information and advice to prospective parents and, in doing so, empowering them to make informed reproductive decisions. Emphasis will continue to be placed on measures that can further reduce the incidence of congenital malformations. In relation to genetic diseases, genetic carrier screening for autosomal recessive conditions in the preconception and prenatal stage informs genetic counselling. Currently, such screening focuses on a small number of conditions and is frequently offered depending on the ethnic background of prospective parents. Even for this small number of relatively prevalent autosomal recessive conditions, there is ongoing debate about the value of population-wide screening. In recent years, the evolution of genomic technologies has raised the prospect of expanded screening to be offered to all prospective parents. Ultimately, it is how this information is used that will determine its benefit.

Conflicts of interest

none.

Practice points

- Women should take 0.4 mg folic acid daily in the periconceptional period (starting at least 4 weeks before conception and continuing throughout the first trimester of pregnancy) to prevent the occurrence of neural tube defects
- Appropriate counselling in relation to genetic risk assessment should be made available to prospective parents according to national guidelines

Research agenda

- Prevention of neural tube defects by inositol
- The effect of preconception carrier screening on reproductive outcomes in common autosomal recessive disorders
- Comparison of expanded carrier screening with current screening practices

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