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Carrier screening and pregnancy

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ABSTRACT

Recessive genetic conditions impose a significant burden, often leading to severe childhood disorders, many of which remain untreatable. It is estimated that 1–2 % of couples are at risk of having an affected child in the general population, with the risk being significantly higher in consanguineous couples. Understanding the increased risk of having a child with a recessive disorder empowers prospective parents to make informed reproductive choices. With technological advancements, genetic screening has evolved beyond identifying only a few common conditions. Expanded carrier screening (ESC) now offers a single test that covers a comprehensive list of recessive disorders, addressing those that contribute most significantly to the burden of these conditions within specific populations.

ESC is recommended for all couples planning a pregnancy, with particular emphasis on consanguineous couples or those who are subfertile. To ensure responsible use of ESC, clinical service delivery should adopt a multidisciplinary approach, providing couples with the information they need to make voluntary, informed decisions. This includes access to high-quality genetic testing, genetic counseling, and psychosocial support.

National professional societies and governments play a crucial role in shaping guidelines, policies, oversight, and funding to guarantee equitable access to high-quality ESC services.

1. Introduction

Carrier screening is a reproductive health strategy involving genetic testing on healthy individuals or couples to determine if they carry a recessive gene that could be passed on to their offspring. If both partners carry a pathogenic variant in the same gene for an autosomal recessive disease, their risk of having an affected child is 25 %. For X-linked recessive conditions, a female carrier of a pathogenic variant has a 50 % risk of having an affected male child.

Carrier screening for a single gene or a few specific genes has been performed for several decades in populations at higher risk for genetic diseases due to their ancestry or geographic origin. These targeted approaches have primarily focused on conditions such as sickle cell disease, hemoglobinopathies, and Tay-Sachs disease, particularly in Mediterranean and Ashkenazi Jewish populations [1]. More recently, pan-ethnic screening for common conditions in the general population, such as autosomal recessive cystic fibrosis, spinal muscular atrophy, and X-linked recessive Fragile X syndrome, has gained support from professional organizations and has been introduced in some countries [1].

Epidemiological data suggest that approximately 0.3 % of couples are at an increased cumulative risk of having a child affected by one of three key disorders: cystic fibrosis, spinal muscular atrophy, or X-linked recessive Fragile X syndrome. However, more than

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3000 genes have been associated with autosomal and X-linked recessive disorders, as cataloged by OMIM (Online Mendelian Inheritance in Man). Most of these conditions severely impact the quality of life of affected children and their families and have significant societal implications. Although each gene associated with recessive predispositions contributes relatively little to overall risk, it is estimated that about 1–2 % of couples in the general population are joint carriers of pathogenic variants in the same gene for selected severe recessive disorders [2].

New genetic technologies, particularly next-generation sequencing (NGS) approaches, offer the ability to analyze hundreds of genes simultaneously, enabling the identification of monogenic disorders through a single genetic test [3] and facilitating carrier screening for a broad range of selected genes through expanded carrier screening (ECS). While the commercial offer of ECS is already available for about 15 years [4], the screening test is still not standardised in most health systems. The disparity between the technological availability, clinical utility, and patient benefits of ECS and its limited accessibility within health systems underscores the urgent need for professional consensus and decisive action in health policy.

2. Clinical perspectives

The choice to have a healthy child is a fundamental human right. However, translating novel technologies and practices into standard care is often challenging, as it requires robust evidence to support professional arguments and inform health policies, which are essential for improving the health system.

2.1. Clinical context of ECS

Currently, primary prevention of genetic disorders is offered to couples known to be at increased risk due to having a child already diagnosed with a genetic disorder or a positive family history. Screening programs for the early detection of genetic disorders in the general population primarily focus on aneuploidies and copy number variations (CNVs). These programs typically combine gynecological procedures, such as fetal ultrasound and biochemical tests, with genetic testing methods, including molecular or classical karyotyping after amniocentesis or chorionic villus sampling and noninvasive prenatal testing (NIPT).

Expanded carrier screening (ECS) is offered both preconceptionally and during pregnancy. Preconceptionally, ECS may be offered to consanguineous couples, couples seeking assistance through medically assisted reproduction (MAR), gamete donors, and the general population.

Consanguineous couples are at an increased risk of having a child with a recessive disorder, even in the absence of known genetic diseases in the family. Traditionally, genetic counseling has used an empirical risk estimate of about 2 % for first-degree cousin couples. However, recent studies suggest that the actual risk is significantly higher. Fridman et al. reported a 16.5-fold increase in risk for first-degree cousins compared to the general population [2], while Sallevelt et al. found that 28 % of consanguineous couples had a 25 % risk of having a child with a recessive disorder [5]. The uptake of ECS among consanguineous couples seems to be high [6].

ECS is currently most frequently used in the context of MAR. It is estimated that infertility affects approximately 9 % of the population, with 56 % of these couples seeking medical care [7]. A recent study of European MAR centers found that 42.5 % offer ECS, while the majority provide targeted screening tests for specific recessive disorders. In 87.9 % of cases, the cost of ECS is borne by the patients [8]. While offering ECS to infertile couples is a reasonable approach to reducing the risk of a pregnancy affected by a recessive genetic condition, it remains unclear to what extent autosomal and X-linked genetic predispositions contribute to fertility problems. In other words, it is uncertain whether the rate of at-risk couples for recessive disorders is higher in the MAR population compared to the general population. Studies have reported a slightly increased rate among MAR couples, ranging from 1.2 % to 9.8 % [9–12]. Moreover, there is growing evidence that recessive genetic disorders may contribute to reduced fertility or early embryonic death, potentially manifesting as subfertility [13].

ECS is offered to gamete donors in 62.4 % of European MAR centers. Reports indicate that 17.6 % of donors were rejected based on ECS results [14]. Additionally, ECS may identify potential health risks in approximately 2 % of donors [15].

ECS in the general population is not yet systematically offered within public health systems. Initial efforts have been reported from Israel, Australia and Netherlands [16–18]. However, individuals can access screening privately through commercial companies. In some countries, targeted carrier screening is recommended, but it is often not covered by government healthcare programs. [19]. Compared to the risk of aneuploidies and copy number variations (CNVs), which is approximately 0.43 % [20], the risk that a couple is at increased risk of having a child with a recessive disorder is higher, at 1–2 %. It has been reported that among 8 % of children in a large academic institution diagnosed with autosomal recessive or X-linked recessive condition, 61 % of these diagnoses could have been predicted in advance if parents had undergone ESC [21]. Awareness of ECS may still be quite limited among couples planning a pregnancy, resulting in modest interest in the test. However, interest in carrier screening is expected to grow as awareness increases [22–24].

In the United States, most carrier screening is performed during pregnancy [25]. Professional societies have recommended ECS for all pregnant individuals and those planning pregnancy [26,27]. However, from both providers' and consumers' perspectives, scientific evidence regarding the implementation of ECS during pregnancy is still lacking.

2.2. Clinical utility of ECS

The primary goal of ECS is to facilitate reproductive autonomy and enable informed reproductive decision-making [28]. When ECS is offered before pregnancy, couples have a wider range of reproductive options, including in vitro fertilization (IVF) followed by

preimplantation genetic testing (PGT) for monogenic disorders, prenatal diagnosis with the possibility of terminating the pregnancy, gamete donation, adoption, accepting the risk, or choosing not to have children. However, if ECS is offered during pregnancy, the available reproductive options are much more limited.

Evidence supports that couples at risk, where both partners carry a genetic predisposition for the same recessive disease, often alter their reproductive planning based on this information [29,30].

In the context of MAR, providers offer ECS to reduce the risk of a pregnancy affected by a detectable inheritable genetic condition, thereby preventing potential suffering and burden for future parents [8].

Additionally, ECS may facilitate early therapeutic interventions during the neonatal period or, in the future, even during pregnancy [31–33].

Furthermore, ECS may have significant implications for maternal healthcare during pregnancy. Approximately 1 in 40 female patients were identified as carriers of a condition that could have maternal manifestations during pregnancy [34]. Twelve genes with potential for carrier manifestations were identified, with associated conditions including cardiomyopathy, hemorrhage, gestational hypertensive disorders, intrahepatic cholestasis of pregnancy, acute fatty liver, hyperammonemic crisis, and maternal virilization.

2.3. Service delivery pathway

The provision of ECS involves a collaborative, multidisciplinary approach and varies depending on the clinical context. However, across different contexts, several professional guidelines agree that the primary goal of ECS is to facilitate reproductive autonomy. It is recommended that ECS be offered to all couples who are considering pregnancy or are currently pregnant. [26,28,35]. Preconceptional testing is preferred over prenatal testing, as it allows for a broader range of reproductive options. Obstetricians and primary care physicians play a crucial role as they are often the first to provide care to patients of reproductive age. ECS testing should be voluntary, and it is essential to provide sufficient information, genetic counseling, informed consent, and psychosocial support. Priority should be given to severe childhood disorders in the ESC panels.

Governments and public health authorities should take an active role in the responsible introduction and oversight of ECS services to ensure their quality and accessibility. Several barriers currently hinder the effective provision of ECS, including fragmentation and inconsistencies in care delivery, inadequate knowledge and perceived limited clinical utility among providers, costs, confidentiality, and privacy concerns, and the absence of national guidelines [8,36,37]. Addressing these challenges is essential for successfully integrating ECS into healthcare systems.

Current evidence supports the cost-effectiveness of ECS[38,39].

3. Technical perspectives

There is considerable variability in the genes included in screening panels among different providers. Among the 2205 unique genes tested cumulatively, the number of genes in these panels varied from 44 to 2,054, with only 15 genes (0.7 %) included in all panels [40]. Moreover, international guidelines differ in their recommendations regarding the number of genes to be included in screening panels. The European Society of Human Genetics (ESHG) and the National Society of Genetic Counselors (NSGC) guidelines do not specify particular genes to be tested. In contrast, the American College of Medical Genetics and Genomics (ACMG) recommends a tiered approach, focusing on 113 specific genes associated with conditions with a carrier frequency of 1 in 200 or greater. However, carrier frequency can vary among different populations and is a dynamic concept influenced by continuously improving international genetic databases [41]. These variations underscore the importance of tailoring screening panels to reflect population-specific risks and the most up-to-date genetic information.

Including genes with a very low carrier frequency in a population can conflict with the concept of proportionality, as it adds unnecessary complexity to the interpretation and reduces the accuracy of the screening approach. Additionally, some centers offer screening for adult-onset genetic disorders with dominant predispositions, which is not aligned with professional recommendations [8].

There is also considerable variability in the methodological approaches, reporting of variants, and how screening tests are offered to couples. A recent survey of European MAR centers revealed that some use a single panel (44.8 ECS %), others offer multiple panels (25.3 %), while 29.9 % employ whole exome sequencing with a large in silico panel [8].

In the reporting of genetic variants to tested couples, pathogenic variants were reported in 89.7 % of cases, likely pathogenic variants in 64.1 %, and variants of unknown significance (VUS) in 16.7 %. The reporting of VUS can compromise the analytical specificity of the test and may lead to decision-making challenges and increased psychological stress for the couples. Therefore, professional guidelines advise against reporting variants of unknown significance (VUS) in ECS [28].

Simultaneous screening for both partners, which is the preferred approach, was offered by 57 % of centers, while sequential testing was offered by 25.6 % of centers [8].

5. Conclusions

Recessive genetic disorders impose a significant burden of severe childhood conditions, making carrier screening an increasingly promising public health prevention program within health systems. While technological advancements and favorable cost-effectiveness estimates support the expansion of ECS, service delivery pathways still require development. Despite several international guidelines, national professional recommendations are essential to guide the responsible use of ECS, and government programs

Practice points

- ESC should be offered to all couples planning a pregnancy, particularly those at increased risk for recessive disorders, such as consanguineous and those who are subfertile.
- ESC is best offered before conception, accompanied by pre-and post-test genetic counseling, informed consent, and access to psychosocial support.
- The gene panel should be tailored to include genes based on the national burden of recessive disorders, ensuring actionability and utility; adult-onset genetic predispositions should not be reported in the context of ESC.
- Only pathogenic and likely pathogenic variants should be reported, while variants of unknown significance (VUS) should be excluded.
- ESC should ideally be offered simultaneously to both partners.

Research agenda

- Long-term follow-up and evaluation of ECS are necessary across different clinical contexts to assess its effectiveness and impact.
- Further research is needed to understand the contribution of recessive genetic disorders to subfertility and the consequent increased risk of having an affected child in couples seeking MAR.
- Identifying the factors that contribute to the practical utility of ECS and influence reproductive decision-making is crucial for optimizing its application.

are needed to ensure equitable access to these services. Enhancing the knowledge of healthcare professionals and the general public could further improve the availability and utilization of ECS within health systems.

CRediT authorship contribution statement

Borut Peterlin: Writing – review & editing, Writing – original draft, Conceptualization. **Ana Peterlin:** Writing – review & editing, Writing – original draft, Conceptualization.

4. Ethical considerations

Several issues associated with the provision of ECS can be discussed through the principles of autonomy, proportionality, and justice. In the context of MAR, there is an inherent tension between the reproductive physician's mission to prevent suffering for parents and safeguard the welfare of potential children and the principle of parental autonomy. It is widely agreed that genetic screening should be voluntary, non-coerced, and based on informed choice. However, in the context of MAR, it is also considered ethically justifiable to proceed with treatment only if the couple agrees to preventive measures [42].

Couples' autonomy also heavily depends on the quality of information provided about ECS. It is challenging to deliver adequate pre-and post-test counseling that equips couples with the necessary knowledge and understanding during the informed consent process. This process must cover detailed information about the numerous diseases included in the panel, the reproductive options available, and the potential implications for the couple's health and that of their family [28].

In addition to the issues already discussed regarding the composition of gene panels and their proportionality, ECS may also have broader societal implications, including the potential for unwanted medicalization and the discrimination of carriers [43].

Equitable access to ECS is closely tied to the concept of justice. Currently, ECS is more frequently offered to consanguineous couples and those who specifically request the test [8]. However, due to the high cost and the lack of a standardized professional approach, ECS is not equitably accessible to couples undergoing MAR or those in the general population [43,44]. Government policies and funding could be crucial in improving the equitable availability and organizational aspects of ECS programs [45].

In the future, single-gene noninvasive prenatal testing for autosomal recessive conditions may offer an alternative to traditional carrier screening during pregnancy [46,47]. The advantage of this approach is that it enables the identification of pregnancies at risk for autosomal recessive disorders without requiring partner testing, while also detecting autosomal dominant conditions. However, further clinical validation studies are necessary before the technology can be applied in low-risk populations [48].

Declaration of competing of interest

Authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2025.102601.

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