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Fertility counseling in women with hereditary cancer syndromes

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ABSTRACT

Hereditary cancer syndromes are a heterogeneous group of genetic conditions that are associated with an increased risk of developing cancer during lifespan. In affected women, parenthood may be accompanied by concerns for the offspring, considering the common autosomal dominant inheritance. Moreover, fertility preservation to prevent the detrimental effects of cancer treatments differs compared to other clinical contexts. The necessity to preserve gametes is indeed predictable and expected to be common. For these reasons, we advocate a personalized and early fertility counseling. Carriers should be aware of the risk of transmission. The possibility to perform elective oocytes cryopreservation, either before (previvors) or after (survivors) cancer diagnosis should be discussed. Finally, they should be informed about the options of preimplantation genetic test (PGT) and oocytes donation. In conclusion, physicians engaged in oncofertility should personalize the counseling for women with hereditary cancer syndromes, being aware of their peculiar needs.

1. Introduction

Hereditary cancer syndromes (HCS), also known as inherited cancer susceptibility syndromes or familial cancer susceptibility syndromes, are a heterogeneous group of genetic disorders that are associated with an increased risk of developing cancer during lifespan (Table 1). It is estimated that 5–10 % of all cancers are attributable to HCS, and this rate is markedly higher in younger subjects (Van Cott, 2020). More than 50 different syndromes have been identified and this number will increase in the next future (Brown et al., 2020). Most are autosomal dominant, but penetrance is typically variable. The clinical spectrum is also very variable and there is a consistent overlap among HCS for the type of associated cancers. For instance, the risk of breast cancer is enhanced in at least 16 different HCS (Van Cott, 2020). These syndromes should be suspected when cancers are diagnosed at an unusually young age, when multiple independent cancers occur in the same subject, when cancer developed bilaterally in paired organsor when two or more first-degree relatives are diagnosed with the same cancer (Brown et al., 2020).

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Table 1
Main characteristics of the most common hereditary cancer syndromes (HCS).

Syndrome	Gene Mutations	Genetics	Prevalence	Main type of cancers
Hereditary breast and ovarian cancer	BRCA-1 and BRCA-2	Dominant	1 in 300−500	Breast, ovary, pancreas, prostate.
Lynch syndrome (Hereditary non polyposis colorectal cancer)	MMR	Dominant	1 in 400−500	Colorectal, endometrial, gastric, ovarian, hepatobiliary tract, small bowel, ureter, bladder, gliobastoma, prostate, breast, pancreas,sebaceous neoplasms.
Neurofibromatosis type 1	NF1	Dominant	1 in 3,000	Peripheral nerves, optic nerve, pheochromocytoma, nephroblastoma (Wilms tumour), neuroblastoma, leukemia.
FAMM (Familial atypical multiple mole melanoma syndrome)	CDKN2A and others	Dominant	1 in 3,000−7,000	Melanoma, pancreas.
Tuberous sclerosis complex	TSC1 and TSC2	Dominant	1 in 6,000	Brain, renal.
Neuroblastoma	ALK and PHOX2B	Dominant	1 in 7,000−10,000	Neuroblastoma, adrenal.
FAP (Familial Adenomatosis Polyposis)	APC	Dominant	1 in 6,000−13,000	Colorectal, gastric, small intestine, thyroid, pancreas, brain, hepatobiliary tract.
Li-Fraumeni syndrome	p53	Dominant	1 in 5,000−20,000	Breast, soft tissue sarcoma, brain, osteosarcoma, adrenocortical.
Hereditary retinoblastoma	RB1	Dominant	1 in 17,000	Retinoblastoma
MEN 1 (Multiple Endocrine Neoplasia type 1)	MEN1	Dominant	1 in 5,000−50,000	Parathyroid, pancreas, gastrinoma, anterior pituitary.
MEN 2 (Multiple Endocrine Neoplasia type 2)	RET	Dominant	1 in 30,000	Thyroid, parathyroid, pheochromocytoma.
Von-Hippel Lindau disease	VHL	Dominant	1 in 36,000	Central nervous system, retinal hemangioblastomas, endolymphatic sac tumours, pancreas, renal.

Adapted from Brown et al., 2020; Van Cott, 2020. Prevalence are approximations: precise incidences depend on racial or ethnic groups.

Universal screening for HCS is currently deemed premature because of the concerns regarding the variable penetrance (that may be lower and unpredictable in subjects without a personal or familiar history of cancer) and the lack of robust validation studies and cost-beneficial analyses in the general population (Evans et al., 2020; Kulkarni and Kilby, 2021). On the other hand, testing subjects deemed at risk is of utmost clinical relevance because it can allow implementation of individualized screening schedules and lifestyle changes. It can also permit identifying relatives at risk (cascade testing) (Evans et al., 2020). With advancement in next-generation sequencing, multigene testing panels are becoming available, and one should expect a higher number of subjects with cancer and their relatives being diagnosed with HSC (Van Cott, 2020). The combination of rare and common variants analysis will soon provide more powerful and comprehensive assessment of the individual risk for HSC with variable penetrance (Khera et al., 2018; Fahed et al., 2020). Testing, however, needs an in-depth preliminary genetic counseling, a valid and long-standing psychological support, and a multi-disciplinary clinical environment to face the complex necessities of these patients.

In subjects with HCS, parenting and fertility preservation may take on distinguishing connotations. Parenthood may be accompanied by concerns for the offspring, considering the common autosomal dominant inheritance with the affected subjects having a 50 % chance to transmit the pathogenic variant to their children. Fears regarding the possibility to grow the offspring up to adulthood because of potentially fatal recurrences may further complicate the scenario. Finally, fertility preservation to prevent the detrimental effects of cancer treatments differs compared to other clinical contexts. Elective rather than urgent oocytes cryopreservation may be an option. The necessity to preserve gametes is indeed predictable and expected to be common given the typical development of cancer at young age. This aspect assumes relevance for women because, contrary to men, the clinical burden of fertility preservation procedures at the time of cancer diagnosis is markedly higher, and the efficacy in a urgent setting may be lower. In this article, we will focus on fertility counseling in women with HCS.

2. Desire of parenthood in HCS carriers

The impact of cancer treatments on reproductive health is a major but still frequently neglected aspect (Anazodo et al., 2019). This is surprising considering the modern shift in oncologic aims from keeping the patient alive to optimizing their quality of life (Anderson et al., 2021). A diagnosis of HCS presents additional specific challenges, for both previvors (i.e., carriers who have not yet developed cancer) and survivors.

Data on possible barriers and concerns regarding parenthood in women with HCS is limited. Most of the available evidence focused on BRCA-1/2 carriers (Brunstrom et al., 2016; Haddad et al., 2021). However, most likely, the attitude regarding family planning decisions may vary among different HCS. In BRCA-1/2 carriers, for instance, the need for risk-reducing measures such as bilateral adnexectomy may stress carriers and can have more direct repercussions on family planning. On the other hand, prophylactic salpingo-oophorectomy remains fundamental. Despite some important improvements in latest years, the capacity to manage ovarian cancer and its recurrences is still insufficient, and justifies this preventive intervention (Baert et al., 2021; Lainé et al., 2021). Even if risk-reducing salpingo-oophorectomy negatively impacts quality of life (Manchanda et al., 2022), it improves overall mortality (Hazard Ratio-HR: 0.32, 95 %CI: 0.19−0.54) and cancer mortality (HR: 0.06, 95 %CI: 0.02−0.17) (Eleje et al., 2018). There is consistent evidence showing that previvors report urgency for romantic partnership and family planning (Brunstrom et al., 2016; Haddad et al., 2021). Interestingly, albeit preliminary, there is also evidence of greater urgency for motherhood in childhood and young adolescent cancer survivors, regardless of being or not diagnosed with an HCS (Filippi et al., 2021a).

Sharing the genetic predisposition to the partner may be challenging and burdensome (Rauscher end Dean, 2017; Haddad et al., 2021). Discussion of this aspect as well as the possible impact on family planning may be difficult because it involves personal and intimate areas. There is also the need of a compassionate and wise attitude of the partner. Not all male partners can effectively cope with this situation. To note, it has been suggested that carrying BRCA-1/2 mutation in the Jewish communities could expose to social stigma and discrimination, reducing marriage prospects (Cousens et al., 2017). The emotional burden and in some cases the feeling of guilt for the possible pathogenetic variant transmission to the offspring is another major concern emerging from studies on BRCA-1/2 carriers (Donnelly et al., 2013; Haddad et al., 2021), and this is likely to be common to all HCS with dominant inheritance.

3. Fertility preservation: available options

Fertility preservation techniques are typically considered at the time of cancer diagnosis. They aim at allowing affected women to achieve parenthood after the end of oncological treatments. To note, the recent advent of immunotherapy and targeted therapy for the treatment of some form of cancer is not markedly changing the scenario. Their mode of action differs from conventional oncological chemotherapy, but a detrimental effect on future motherhood cannot be excluded too (Higham et al., 2020; Nakamura et al., 2020). Concerns recently also emerged for Poly (ADP-ribose) polymerase (PARP) inhibitors (Winship et al., 2020; Nakamura et al., 2020). In addition, the necessity to postpone pregnancy seeking of several years to complete treatments and follow-up may be detrimental regardless of treatment, at least in women who are diagnosed with cancer in the late thirties (*iatrogenic aging*). The importance of fertility preservation has recently been reinforced with the growing evidence that, in survivors, pregnancy is unremarkable to cancer prognosis and obstetrics course is only rarely affected (Griffiths et al., 2020; Lambertini et al., 2021a).

Fertility counselling and possible use of preservation techniques at the time of cancer diagnosis are univocally recommended by the worldwide recognized guidelines of the American Society of Clinical Oncology (ASCO), American Society of Reproductive Medicine (ASRM), European Society for Human Reproduction and Embryology (ESHRE), and European Society for Medical Oncology (ESMO) (Oktay et al., 2018; Practice Committee of ASRM, 2019; ESHRE Guideline Group on Female Fertility Preservation, 2020; Lambertini et al., 2020). Validated options include oocytes cryopreservation, embryo cryopreservation, ovarian cortex preservation and chemo-protection with the use of gonadotrophin-releasing hormone (GnRHa) agonists. Even if poorly studied, ovarian transposition and gonadal shielding for pelvic radiotherapy should also be listed among clinically validated fertility preservation options (Oktay et al., 2018; Practice Committee of ASRM, 2019; ESHRE Guideline Group on Female Fertility Preservation, 2020; Lambertini et al., 2020).

Even if oocytes retrieval aimed at storing eggs or embryos can be done without preliminary treatments with gonadotropins, most cases receive ovarian hyperstimulation regimen (lasting about two weeks). This enhances the number of mature eggs that can be stored and thus the effectiveness of the procedure. More than one attempt can be done to further increase the number of oocytes, but this seldom occurs because of the limited available time prior to initiate oncological treatments. Even if both embryos or oocytes can be stored, the latter option is currently considered more ethical because it better ensure woman's autonomy (Rienzi and Ubaldi, 2015). Ovarian cortex biopsy is gaining consent worldwide and, since 2019, it is no more considered experimental (Practice Committee of ASRM, 2019). It is the unique option in premenarchal girls, but its use is growing also after menarche, at least in younger women. GnRH analogues were shown to reduce the damage to the ovarian reserve, at least in women with breast cancer with or without BRCA-1/2 mutations (Lambertini et al., 2018, 2021b). However, the magnitude of the benefit is modest, and its systematic prescription remains debated. The ASCO guidelines suggest limiting its use to the setting of young women with breast cancer and when the other proven fertility preservation methods are not feasible (Oktay et al., 2018). Finally, it is worth underlining that more than one fertility preservation option can be concomitantly considered.

4. International guidelines recommendations for fertility preservation in women with HCS

Fertility preservation for women with HCS is a neglected issue. There is scant clinical data and only few opinion papers, mostly focusing on BRCA-1/2 carriers (Peccatori et al., 2018; Buonomo et al., 2021; Filippi et al., 2021b). Specific recommendation on fertility preservation for women carrying HCS are included in only one of the four above-mentioned guidelines (Lambertini et al., 2020). The authors stated that women should be encouraged to complete childbearing before planned risk-reducing gynaecological surgery, and that affected women should receive the same standards of fertility preservation as non-carriers. In addition, they recommend informing carriers of the possibility to undergo prenatal diagnosis (in the case of natural conception) or preimplantation genetic testing (PGT) (in the case of IVF procedures). The ASRM guidelines do not dedicate a specific session but give some few recommendations for BRCA carriers. They advise embryo or oocyte cryopreservation prior to risk-reducing surgery, and underline that, in this setting, women are faced with time frames that may permit multiple oocyte retrievals. They also underline that these women may be candidates for PGT (Practice Committee of ASRM, 2019). The remaining two guidelines do not mention HCS.

5. Oocytes cryopreservation

Elective oocytes cryopreservation in previvor, i.e., before the possible onset of cancer, may deserve consideration in women with HCS. The procedure can be done in a non-urgent setting and could be more beneficial since done at a younger age when the quality of the oocytes is superior. Moreover, one may foresee more than one cycle of treatment given the absence of time pressure, thus allowing to cryopreserve a greater number of oocytes. This approach could enhance the future chances of pregnancy with the stored material, and allow the possibility to give birth to more than one child.

Women carrying BRCA-1/2 represent optimal candidates to this approach. By the age of 40, the reported cumulative risk of breast cancer is 24 % for BRCA-1 and 13 % for BRCA-2 carriers while the cumulative risk of ovarian cancer is 2% for BRCA-1 and 0% for BRCA-2 (Kuchenbaecker et al., 2017). In other words, up to one in four women with BRCA-1 and one in eight with BRCA-2 may benefit from elective egg freezing. An in-depth cost-beneficial analysis is needed to disentangle whether this strategy deserves attention. In this regard, it is important to underline that these estimates represent the upper limit of the proportion of women who can benefit from oocytes cryopreservation. Indeed, since the curve of incidence grow exponentially with age, most women are diagnosed with cancer in the late thirties and the majority may have already completed their reproductive wishes. In addition, some women may not be interested to childbearing for personal reasons or because of the concerns regarding transmission of the mutation. The proportion of women who can benefit may be further decreased by prophylactic risk-reducing mastectomy. On the other hand, the beneficial effects of elective oocytes cryopreservation at young age can be boosted by the decision to perform preimplantation genetic testing for monogenic disorders (PGT-M) (Vuković et al., 2021; Kulkarni and Kilby, 2021). If a young carrier foresees performing PGT-M in her future, storing oocytes at a younger age when the number and quality of the gametes are higher could be wise. This is particularly relevant for women opting also for PGT-M because, given the dominant inheritance, one must expect a halved chance of success.

Elective oocytes cryopreservation in previvors, however, can be foreseen in some but not all HCS. Patients having cancer during childhood could not benefit of the procedure because the cancer developed too early. One could speculate that in these cases, one could electively freeze ovarian cortex and even oocytes in minors in the absence of cancer diagnosis. This option, however, is unwise because of the significant clinical burden and the absence of an urgent situation. Performing unnecessary procedures in minors is also ethically debatable (Mertes, 2015).

Conversely, oocytes cryopreservation may be considered in childhood and adolescent cancer survivors, i.e., in young adults with a history of cancer (Lehmann et al., 2020; Parissone et al., 2020; Filippi et al., 2021a). Since ovarian reserve progressively reduces with age, collecting and freezing oocytes at 18–20 years could allow to have children later when, possibly, the ovarian reserve will be exhausted. This is

particularly relevant in Western societies where women generally attempt to conceived in the late thirties (Mills et al., 2011).

6. Preimplantation genetic testing for monogenic disorders (PGT-M)

In vitro fertilization procedures allow to identify embryos that do and do not carry HCS and to transfer only embryos without the mutations. The procedure is complex and expensive and can be efficient only in selected women who have a high number of good quality oocytes and a definite genetic diagnosis (De Rycke and Berckmoes, 2020). Moreover, the use of PGT-M remains ethically debated in several cultures, including in the Western world (Quinn et al., 2014). The destiny of non-transferred embryos may also be a matter of concern. Therefore, adhesion to PGT-M programs greatly varies worldwide and is rarely covered by the Public Health system. Carriers should be aware of this option, but extreme attention should be given to the mode of communication to avoid unrealistic expectations or the later onset of feeling of guilt if they ultimately decide to refuse the procedure because of economical constraints or cultural beliefs.

In this regard, the Ethics task force of the European Society of Reproduction and Embriology (ESHRE) took a clear decision on the argument in 2003 and decreed PGT-M acceptable for HSC (Shenfield et al., 2003). However, the procedure initially has been scantly employed for HSC. According the ESHRE consortium for PGT from 1997 to 2007, HCS represented a minority of cases, and only three of them were listed among the 17 most common indications to the procedure: neurofibromatosis (9 °), familial adenomatous polyposis (12 °) and Von Hippel Lindau syndrome (17 °) (Harper et al., 2012). The relative importance of HSC progressively increased over time (Moutou et al., 2014; ESHRE PGT-M Working Group, 2020; van Montfoort et al., 2021). The latest available report of the consortium, referring to the period 2016–2017 and including 3,098 analyses for monogenic disorders, lists BRCA-1/2 as the second most common indication (after Huntington disease) and neurofibromatosis as the fourth (van Montfoort et al., 2021).

Possible barriers explaining the suboptimal uptake (at least in the early years) of PGT-M for HCS include scant awareness among HCS carriers and physicians, costs of the procedure (that is out-of-pocket in most countries) and additional psychological distress (Hughes et al., 2021; Vuković et al., 2021). At least for some HSC such as BRCA-1/2 carriers, difficulty accepting PGT-M may also be due to the adult onset and to the concerns regarding the safety of ovarian hyperstimulation, the variable phenotype and the availability of therapeutic options (Hughes et al., 2021). PGT-M may be more acceptable in the case of HCS, such as NF1, which include severe non-oncological manifestations such as psychomotor retardation and other multi-organ symptoms. On the other hand, the very strong psychological barrier in these women, in relation to any invasive prenatal diagnosis and subsequent termination of pregnancy ("not giving birth to an individual as themselves"), is one of the main reasons for which PGT-M is required. For most affected women, it is perceived as ethically more acceptable to carry out a preimplantation selection rather than to decide for termination.

The recent advent of multigene panels for general population screening and the identification of genetic variants of moderate penetrance is complicating PGT-M for HCS and there is the urgent need for a scientifically strong, equitable and ethically shared approach (Kulkarni and Kilby., 2021). Although some genetic scientific societies have drawn recommendations, the intervention of central public health policies is needed.

7. Oocytes donation

In cancer survivors, oocytes donation is generally advocated when ovarian reserve is prematurely exhausted following gonadotoxic therapies and the use of stored ovarian cortex or oocytes, if available, did not allow to achieve parenthood. This is obviously valid also for women with HCS who survived cancer. However, in this group, oocytes donation may be more attractive and potentially used also in other situations, including previvors, because it can prevent transmission of the predisposition to cancer to the offspring. This may be particularly valid for young women with a strong personal and familial history of cancers but without a patent molecular diagnosis of HSC. In these cases, indeed, even PGT-M cannot be expected to prevent transmission to the offspring.

Table 2
Main points to discuss during reproductive counselling of women with HCS.

Points	Arguments
1.	Risk of HSC transmission to the offspring
2.	Penetrance of the mutation
3.	Elective oocytes cryopreservation in previvors
4.	Elective oocytes cryopreservation in survivors
5.	Preimplantation genetic diagnosis
6.	Oocytes donation

To our knowledge, there are no studies specifically investigating oocytes donation in women with HCS. It could be interesting to obtain data on the future intentions of parenthood of these women, once they are properly educated on this possibility. To note, the social acceptability of gametes donation is growing in recent years (Skoog Svanberg et al., 2020), with public health coverage assured in an increasing number of countries. It seems reasonable to hypothesize that egg donation may play a growing role in HCS in the next future. To note, this approach is more cost-effective than fertility preservation and PGT-M, and could also avoid the associated additional burdens. There are issues with cultural beliefs, however, that can be overcome in some, but not all women.

8. Conclusions

Parenthood in women carrying HCS is a multifaceted and intricate issue. However, physicians taking care of these women should face the challenge and its complexity. A multi-disciplinary approach including oncologists, geneticists, psychologists, and experts in reproductive medicine is inevitably needed but, most importantly, an open-minded and nondirective attitude is fundamental. Extreme differences may emerge according to the specific HCS and personal or familiar history of cancers, as well as cultural and ethical views. Firm indications cannot be drawn but we advocate discussing and possibly offering to these women all available options, including oocytes cryopreservation, PGT-M and oocytes donation (Table 2). Economical constraints should also be included in the discussion.

Finally, we underline the importance of a dynamic counseling because women's views may change over time, in particular if first counseled at a young age. In addition, the counseling should be adjourned at the time of actual initiation of pregnancy seeking to also test the partner for HSC and to involve him in the decision-making. Receiving a genetic diagnosis of HCS is a major event. Giving time to accept and understand its multifaceted implications, including reproductive issues, is fundamental, in particular at young age (Evans et al., 2020). Reproductive counseling in these women should thus be a dynamic and long-lasting process, it cannot be limited to a single visit around the time of the definite diagnosis of HSC.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

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