Is a naturally reduced antimüllerian hormone at a young age linked to an increased risk of cancer development?

Despite intense research, the pathophysiological mechanisms of premature ovarian aging, leading to reduced ovarian reserve and possibly infertility in young women, are still poorly understood. Well-established risks for reduced ovarian reserve are aggressive ovarian surgery, endometriosis and cytotoxic therapy; however, gene mutations such as the Fragile X syndrome can also cause premature follicle loss and a reduced ovarian reserve.

Hence, in addition to the fact that a reduced ovarian function causing infertility already imposes a heavy psychological burden on the affected patients, data point toward a possible link between gene mutations, impaired DNA repair mechanism, and also an increased risk for the development of cancer. The possible impact of infertility on long-term health and life expectancy is demonstrated by a recently published paper, which describes a 10% increased risk of death in infertile women, with a 47% increased risk of cancer death (1).

The paper by Oktay et al. (2), published in the current issue of *Fertility & Sterility,* evaluated the precytotoxic ovarian reserve as well as the recovery postcytotoxic treatment in patients with BRCA mutation. The authors clearly demonstrated, that patients affected by BRCA gene mutation endured a pronounced decline of antimüllerian hormone (AMH) levels as well as a reduced recovery after chemotherapy, compared to nonaffected women. The findings described herein and previously published research of the same group support the hypothesis that DNA repair deficiency is a shared mechanism among ovarian aging, infertility, and cancer, as both BRCA genes belong to the family of DNA double-strand break (DSB) repair genes, playing a critical role in the protection of DNA integrity.

DNA damage can occur as a result of endogenous or exogenous events and might arise in different varieties. The DSBs, in which the phosphate backbones of the two complementary DNA strands break simultaneously, represent the most cytotoxic forms of lesion. As the genome integrity is of utmost importance for cell survival, and as damage to the genome may lead to mutagenesis and cancer, cells have evolved specialized repair pathways to deal with DNA lesions, the so-called "DNA damage response" (DDR). Functioning DDR is crucial to health, and individuals affected by mutations in the DDR genes can display a variety of disorders of the nervous, immune, and reproductive systems as well as being susceptible to premature aging and cancer development (3).

The DDR also plays a crucial role in the generation of gametes, inasmuch as during meiosis, the exchange of genetic material between homologous chromosomes is required. This exchange involves the formation of DSBs and their subsequent repair by homologous recombination. Defects in the repair system of the DSBs during meiosis might result in infertility.

The influence of mutations in the DDR becomes obvious in patients affected by Fanconi-anemia (FA). FA is an autosomal-recessive disorder characterized by progressive bone marrow failure and an extremely high predisposition to cancers and reduced fertility, among other congenital abnormalities. Most of the FA patients have a greatly reduced number of gametes, and in female FA patients, reduced fertility can manifest as primary ovarian insufficiency (POI). It is known that FA proteins participate in the DSB repair model of genetic recombination at meiotic prophase; however, the precise link between their role in DNA repair and fertility has not been extensively described in humans (4).

DNA repair capacity varies among individuals, and correlation between reduced DNA repair capacity and a susceptibility to a variety of hematological cancers has been described previously. Similar to patients with BRCA 1 mutation, in whom a reduced ovarian reserve was shown, girls and young women affected by leukemia and lymphoma (Hodgkin and non-Hodgkin) also have reduced AMH levels as a marker of the ovarian reserve, even prior to initiation of cytotoxic therapy (5).

These reduced AMH levels could theoretically be caused by impaired granulosa cell function due to an impaired DNA repair mechanism. Hence, in the light of the findings of Oktay et al. (2), impairment of the DNA repair capacity might be a common root for both, not only posing an increase in the risk for developing cancer, but also causing early ovarian aging and low ovarian reserve. Further research into the link between an impaired DNA repair system cancer risk and low ovarian reserve is warranted and of the utmost importance. Moreover, as AMH levels are a common tool in the investigative process of infertility, special focus should be placed on young patients with a natural low ovarian reserve, as they might be prone to a higher cancer risk in the case of an impaired DDR system. Further on, young cancer patients are not only prone to a reduced ovarian reserve as a consequence of the cytotoxic treatment, but also to a reduced number of gametes, possibly due to an impaired DNA repair system. As they are subjected to a pronounced decline of AMH levels and a reduced recovery after chemotherapy, the implementation of fertility preservation techniques in their treatment regimen should be mandatory.

If this theory is confirmed in future studies, patients with a naturally reduced ovarian reserve at a young age should be advised more often to undergo preventive cancer screening, leading to early intervention for long-term health outcomes.

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