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The Impact of Immune Checkpoint Inhibitors on Fertility Preservation and Pregnancy Outcomes

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Abstract

Immune checkpoint inhibitors have revolutionized cancer treatment by enhancing anti-tumor immune responses. However, their impact on fertility is an emerging concern, particularly among young patients, including children. This review aims to assess the effects of immune checkpoint inhibitors on reproductive health and fertility preservation strategies. Immune checkpoint inhibitors may cause endocrine-related adverse effects, such as hypophysitis, thyroid dysfunction, and adrenal insufficiency, which can disrupt gonadal function. In women, these therapies may reduce ovarian reserve, impair ovulation, and cause menstrual irregularities. In men, they may contribute to testosterone deficiency and reduced sperm production. Given that immune checkpoint inhibitors are used even in pediatric oncology, early fertility counseling and preservation strategies, such as oocyte and sperm cryopreservation, should be discussed before treatment. Additionally, recent evidence suggests that physical activity may have a protective effect on reproductive health in patients receiving these therapies by regulating hormonal balance and reducing inflammation. Immune checkpoint inhibitor therapy may contribute to pregnancy-related disorders, with reported adverse effects including miscarriage and preterm birth, however some studies document successful pregnancies in women exposed to this treatment. As immune checkpoint inhibitors continue to be widely used, further research is needed to clarify their long-term effects on reproductive health and optimize fertility preservation strategies for affected patients.

Key words: Fertility, immune checkpoint inhibitors, ICIs

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, significantly improving survival rates in various malignancies.[1–3] However, emerging evidence suggests that these therapies may have unintended effects on reproductive health, raising concerns among young cancer patients and survivors.[4] Research on the endocrine and reproductive consequences of ICIs remains limited. While previous studies have documented immune-related adverse events, their specific impact on ovarian and testicular function is not well understood.[5] Additionally, given the increasing use of ICIs in pediatric oncology, fertility preservation strategies are of growing importance.[6,7] This review aims to evaluate the effects of ICIs on reproductive health by analyzing current literature on gonadal function, hormonal changes, and fertility preservation methods. Understanding these effects is crucial for optimizing clinical care and ensuring informed decision-making for patients undergoing immunotherapy.[5]

Materials and Methods

This review aims to assess the impact of immune checkpoint inhibitors (ICIs) on the fertility of patients undergoing therapy with these drugs. A comprehensive literature search was conducted using the PubMed database with the following search terms: (Fertility) AND ("Immune checkpoint inhibitors" OR ICIs). The search included full-text studies published in English within the last 10 years, focusing on reproductive outcomes such as ovarian reserve, hormonal changes, spermatogenesis and pregnancy complications. Animal studies were included. Titles and abstracts were manually reviewed to assess the relevance of the studies and their alignment with the review’s objectives. The selected studies were then qualitatively analyzed and summarized to provide an overview of the findings. As this review was not designed as a meta-analysis, no statistical methods were applied.

1. Immune checkpoint inhibitors

1.1. Mechanism of action

Immune checkpoint inhibitors are key components of cancer therapy that modulate the immune response, allowing T lymphocytes to more effectively eliminate cancer cells. The primary targets of these inhibitors are the CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) receptor, the PD-1 (programmed death-1) receptor, and its ligand PD-L1 (programmed death-ligand 1).[8] Clinical trials are currently underway to evaluate the use of a LAG-3 inhibitor (lymphocyte-activation gene 3).[9]

CTLA-4 is an inhibitory receptor that competes with the costimulatory receptor CD28 for binding to B7 molecules (CD80 and CD86) on antigen-presenting cells.[10] Blocking CTLA-4 with monoclonal antibodies such as ipilimumab enhances T cell activation and proliferation, leading to a stronger antitumor response.[11] Ipilimumab has demonstrated efficacy in the treatment of advanced melanoma.[12]

The PD-1 receptor, present on the surface of activated T lymphocytes, binds to its ligands PD-L1 and PD-L2 on cancer cells and antigen-presenting cells, leading to inhibition of T cell effector functions.[13,14] Monoclonal antibodies such as nivolumab and pembrolizumab block PD-1, while atezolizumab and durvalumab target PD-L1, restoring T cell activity and promoting cancer cell elimination.[13] These inhibitors have proven effective in treating various cancers, including non-small cell lung carcinoma and urothelial cancer.[8,15]

LAG-3 is another inhibitory receptor found on T lymphocytes.[16] Blocking LAG-3 in combination with PD-1 inhibitors such as nivolumab produces a synergistic antitumor effect, as confirmed in clinical trials for advanced melanoma.[17]

1.2. Adverse Effects of ICIs

Although checkpoint inhibitors provide therapeutic benefits, they can also cause immune-related adverse effects due to excessive immune activation, including colitis, hepatitis, pneumonitis, and endocrine disorders.[18] There are reports suggesting that they may impact reproductive function, leading to fertility issues in both men and women.[19] Monitoring and

appropriate management of these adverse effects are crucial to ensuring patient safety.[18]

1.3. Treatment of children with ICIs

With the growing use of ICIs in pediatric oncology, strategies for preserving fertility are becoming increasingly important.[6,7] Immune checkpoint inhibitors (ICIs) are an effective treatment for various cancers, including some pediatric cases. Currently, most clinical trials involving children focus on those aged 12 and older. However, an exception is atezolizumab (an anti-PD-L1 therapy), which is being tested in children as young as 2 years old. However, the growing use of ICIs in clinical practice also presents new challenges, as more patients, including children, may experience long-term remission and will need to manage the lasting side effects of their treatment.[6,19]

2. Female fertility after ICIs treatment

Available data suggest a potential association between immune checkpoint inhibitor therapy and a reduction in ovarian reserve, as well as decreased oocyte production. This phenomenon is likely driven by increased immune cell infiltration within the ovary and elevated expression of tumor necrosis factor-alpha (TNF-α).[20] In studies conducted on mice, PD-1 checkpoint inhibition was found to reduce ovarian reserve, likely through an inflammatory response triggered by CD3+ T cell infiltration.[21] A noteworthy study utilizing positron emission tomography (PET) to examine the biodistribution of pembrolizumab labeled with the radionuclide 89Zr revealed significant tracer uptake and increased estimated radiation absorption in the ovaries of adult humans.[22] Moreover, evidence indicates that ICI treatment may contribute to deficiencies in sex hormones and gonadotropins.[19,23,24]

Findings from the ECOG-ACRIN E1609 trial demonstrated a significant decrease in anti-Müllerian hormone (AMH), estradiol, and luteinizing hormone levels in women aged 20–35 following adjuvant ipilimumab treatment. Similar results were observed in a case-control study involving 14 patients with stage III or IV melanoma treated with checkpoint inhibitors, further supporting the potential impact of ICI therapy on gonadal function.[23]

According to Silvestris et al. (2024)[25] ipilimumab interacts with ovarian tissue but does not cause significant morphological alterations. Atezolizumab may disrupt the menstrual cycle

and ovulation. Pembrolizumab enhances CD3+ lymphocyte infiltration in the ovary, potentially triggering inflammation and reducing ovarian reserve.

On the other hand De La Cruz et al. (2024)[26] using a syngeneic triple-negative breast cancer mouse model demonstrated that immunotherapies targeting PD-1 at therapeutically relevant doses did not alter ovarian follicle quality or quantity, estrous cycle patterns, or hormonal balance. Likewise, in tumor-free mice, PD-1 blockade had no impact on ovarian structure, follicle count, estrous cycle regularity, or ovulatory function.

Endocrine side effects affect about 15% of women treated with PD-1 inhibitor monotherapy and approximately 30% of those receiving a combination of PD-1 and CTLA-4 inhibitors. These adverse effects are considerably more prevalent in premenopausal women than in postmenopausal women or men. The resulting hormonal imbalances are generally permanent.[27] Conditions such as hypophysitis, thyroid dysfunction, adrenal insufficiency, and diabetes mellitus may lead to hormonal imbalances that disrupt the reproductive system.[24,27] Hypophysitis, for example, can impair the hypothalamic-pituitary-gonadal axis, potentially causing premature menopause and decreased libido.[19,23,27] Thyroid dysfunction and diabetes can further complicate conception.[27] Hypophysitis is relatively rare with PD-1 inhibitors but significantly more common in combination treatments, while hPDypothyroidism frequently occurs with PD-1 inhibitors. Adrenal insufficiency, often caused by adrenalitis, is more prevalent in patients receiving combination therapy, whereas type 1 diabetes remains a rare but serious complication mainly linked to PD-1 inhibitors.[23]

3. Female fertility preservation

Healthcare professionals should be well-prepared to discuss reproductive health risks while considering patients' ethical, religious, educational, and sociocultural perspectives. Topics such as fertility preservation, congenital anomalies, and stillbirths should be addressed while respecting individual values and preferences.[23] Options for fertility preservation in patients are presented in Table 1.

Initial patient asessment[23]	• Review the patient's oncology and reproductive history. • Discuss how cancer treatments may affect ovarian function and pregnancy. • Consider fertility preservation before starting treatment.
Fertility preservation timing[23,28]	**Before Treatment:** • Should be completed before initiating therapy. • Assess ovarian reserve through tests such as anti-Mullerian hormone, antral follicle count, luteinizing hormone, and estradiol levels. **During Treatment:** • Limited options exist, and they may carry risks like delaying treatment or reducing the chances of success
Fertility preservation options[4,5,23–25,28]	Discuss the advantages and disadvantages of available methods: • **Embryo Cryopreservation:** A well-established and widely accepted approach. • **Oocyte Cryopreservation:** Suitable for individuals who may consider donor sperm in the future. • **Ovarian Tissue Cryopreservation:** Still in the experimental stage and mainly intended for prepubertal patients. • **Ovarian stem cells:** An experimental approach that involves extracting ovarian progenitor cells and guiding their differentiation into mature oocytes. Using GnRH agonists for ovarian suppression is not recommended as a fertility preservation method during ICI therapy and is only applicable for patients undergoing chemotherapy.
Pregnancy planning[5,19,23]	• Preventing pregnancy during ICI therapy by using two forms of contraception. • Waiting at least 5–12 months after treatment before attempting conception, based on an individualized risk-benefit assessment. • Garutti et al. (2021) recommend minimum waiting time before conception after completing therapy: • 3 months for ipilimumab and durvalumab • 4 months for pembrolizumab • 5 months for nivolumab and atezolizumab

Table 1. Options for fertility preservation in women undergoing ICIs therapy[4,5,19,23–25,28]

Fertility preservation methods for women come with various challenges and risks. Oocyte

cryopreservation and in vitro fertilization require hormonal stimulation, which can take up to two weeks.[28] This delay may be problematic for patients with aggressive cancers that require immediate treatment. Additionally, the use of estrogen-based stimulation poses potential risks for those with hormone-sensitive tumors. Another option, ovarian cortex transplantation, carries the risk of reintroducing malignant cells, particularly in patients with hematologic cancers like leukemia. Even when performed successfully, its pregnancy success rate remains relatively low, often not exceeding 40%.[25,28]

An alternative approach involves retrieving immature oocytes followed by in vitro maturation. However, this method heavily depends on the skill of the operator, which can affect the viability of the collected oocytes. Moreover, individual variations in response to the procedure make its effectiveness unpredictable for oncology patients. Despite the availability of these techniques, each presents distinct limitations, requiring careful consideration of the patient's medical condition, cancer type, and future reproductive goals. A tailored approach is essential to selecting the most suitable fertility preservation strategy while minimizing risks.[25]

4. Male fertility – primary hypogonadism and endocrine dysfunction

The gonadotoxic effects of ICIs remain unclear, but potential mechanisms include direct disruption of testosterone production (primary hypogonadism) and indirect effects via endocrine dysfunction (secondary hypogonadism)[6]. Autoimmune orchitis and endocrine-related adverse events, such as hypophysitis and thyroiditis, have been reported and may contribute to decreased testosterone levels and impaired spermatogenesis[6,19,24]. Some studies describe cases of infertility, including azoospermia, associated with ICI therapy, though confounding factors complicate these findings[29].

Retrospective analyses suggest that ICIs may cause testicular dysfunction, including impaired spermatogenesis and Sertoli cell-only syndrome, although most patients retain normal sexual function and semen quality. Endocrine irAEs, particularly hypophysitis, are more frequently observed in males and can result in persistent testosterone deficiency. Additionally, combined therapy using anti-CTLA-4 and anti-PD-1/PD-L1 agents is linked to an increased risk of endocrine dysfunction.[6]

There is no available data on ICIs' effects on prepubertal testes. However, prepubertal testes may be more vulnerable to conventional cancer therapies due to continuous germ cell turnover. Some studies suggest the presence of PD-1 and PD-L1 proteins in mouse testes, but their functions remain unclear. Additionally, the incomplete blood-testis barrier before puberty may expose testicular cells to potential disruptions in spermatogenesis from ICI treatments. From puberty onward, ICIs could impact hormonal regulation and testosterone production, similar to adult patients.[5]

5. Male fertility preservation

Although limited data exist on the effects of ICIs on spermatogenesis and testicular function, leading oncology societies recommend fertility counseling for all patients. The American Society of Clinical Oncology further advises sperm cryopreservation before treatment, highlighting the cautious approach regarding ICIs' potential impact on fertility. Comprehensive discussions on reproductive health during cancer treatment, considering individual patient circumstances, are essential.[5,24,29]

While sperm collection and cryopreservation have been successful in boys as young as 12, testicular tissue banking remains the only fertility preservation option for younger patients. Given the long timeframe needed to assess reproductive toxicity in pediatric cancer patients, preclinical studies using animal models and human testicular biopsies are crucial to understanding ICIs' long-term reproductive effects and the need for fertility preservation before treatment.[5]

According to Cosci et al. (2022) patients with stage III or IV melanoma undergoing immunotherapy face an increased risk of testosterone deficiency during treatment. Therefore, regular monitoring of endocrine function is essential for the first three months of therapy, followed by continued observation for up to 12 months after treatment completion.[29]

6. Pregnancy and ICIs treatment

6.1.1. The mechanism of ICIs' impact on pregnancy

Successful pregnancy requires maternal immune tolerance toward the genetically distinct fetus. This tolerance is regulated by molecular mechanisms, including PD-L1 and CTLA-4, which are expressed at the fetomaternal interface to prevent an immune response against the fetus. Inhibiting these pathways may disrupt immune balance, potentially leading to fetal toxicity[19,30]. Unlike traditional chemotherapy, which is most teratogenic in the first trimester, ICIs may pose the greatest risk later in pregnancy. This may be due to changes in placental immunoglobulin (IgG) transport, which increases significantly in the third trimester, potentially enhancing fetal exposure. The degree of placental transfer varies among ICIs—atezolizumab (a PD-L1 inhibitor of the IgG1 subtype) has high placental permeability, whereas tremelimumab (a CTLA-4 inhibitor of the IgG2 subtype) is less readily transferred.[5] Blocking the PD-1/PD-L1 pathway with ICIs may create a pro-inflammatory uteroplacental environment by reducing regulatory T-cells (Treg) and altering the Treg-to-effector T-cell ratio. This disruption may increase the risk of implantation failure, miscarriage, and neonatal complications.[19]

6.1.2. Endocrine impact to pregnancy

Proper management of endocrine immune-related adverse events (irAEs) is crucial, particularly in the context of pregnancy, as they can pose life-threatening risks to both mother and fetus. Pregnancy is not recommended during the acute phases of thyroid dysfunction or hypophysitis due to increased maternal and fetal risks. Many chronic endocrine irAEs persist for months after stopping ICI therapy, with a significant proportion of patients requiring hormone replacement or systemic steroid treatment. However, prolonged steroid use can contribute to secondary hypogonadotropic hypogonadism and increase the likelihood of adverse pregnancy outcomes, including gestational diabetes and fetal developmental complications. While hormone replacement therapy may help address some fertility-related issues, adrenal insufficiency is often irreversible, necessitating lifelong management.[23]

6.2. Current state of knowledge

Overactivation of the maternal immune response may also contribute to pregnancy-related disorders such as pre-eclampsia, gestational diabetes, and antiphospholipid syndrome.[23] According to data from the World Health Organization's (WHO) adverse event reporting

system indicated that 56 patients experienced pregnancy-related side effects, with the most frequently reported symptoms including diarrhea, nausea, fatigue, abdominal pain, itching, and chest pain. The most commonly documented fetal complications were spontaneous miscarriages and preterm births.[22] There has been also a reported case of enteritis in a 4-month-old infant following in utero exposure to pembrolizumab.[31]

Despite these theoretical concerns, clinical reports have documented successful pregnancies in women exposed to ICIs, including combination therapies administered at different stages of gestation.[19,23] Further research is needed to fully understand the long-term effects of ICIs on pregnancy outcomes.[23]

Yang et al. (2025)[32] presented four cases of patients with Lynch Syndrome-associated Endometrial Cancer (LS-EC) who underwent ICI therapy and achieved complete remission. The findings suggest that ICIs could be a viable therapeutic option for LS-EC patients seeking to maintain reproductive potential.

6.3. Animal studies

Animal studies provide additional insight into potential risks. In monkeys, anti-CTLA-4 treatment led to reduced maternal weight, increased rates of abortion, stillbirth, and preterm delivery, with the most pronounced effects observed in the third trimester.[5,19] Studies in mice have shown that blocking PD-L1 increases miscarriage risk fivefold, but only in allogeneic pregnancies (where the fetus has genetically distinct paternal antigens), not in syngeneic pregnancies (where both parents are genetically identical). The degree of genetic disparity between the mother and fetus influences the necessity of immune tolerance mechanisms.[5,19] According to Helgadottir et al. (2024)[27] offspring of animals exposed to ipilimumab showed developmental abnormalities, whereas no notable defects were found in those exposed to nivolumab.

6.4. Expert recommendations on pregnancy planning during ICI therapy

Given these concerns, leading oncology organizations, including the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO), advise against pregnancy during ICI treatment. Current guidelines recommend the use of at least two forms of contraception

throughout treatment and for a minimum of five months after the last dose.[23]

7. Breastfeeding

NCCN guidelines advise against breastfeeding during and for at least five months after completing ICI therapy. Although there is no definitive evidence of harm to infants from breastfeeding during ICI treatment, a case report has shown a gradual accumulation of ipilimumab in breast milk. While the drug concentration in breast milk was significantly lower than in the bloodstream, traces of the active drug were detectable up to three weeks after the final dose.[23]

8. The impact of physical activity on fertility preservation after ICIs treatment.

Jamrasi et al. (2024)[24] described the beneficial effects of physical activity on fertility preservation in patients undergoing ICIs therapy. The detailed impact of ICIs on reproductive toxicity and the protective effects of exercise on its various aspects are presented in Table 2.

Aspect	Effect of ICIs	Potential Benefits of Exercise
Endocrine system disruption	Hypophysitis, leading to hormonal imbalances and hypogonadism.	Helps regulate the hypothalamic-pituitary-gonadal (HPG) axis, improving hormonal balance.
Ovarian function	Reduced ovarian reserve, impaired ovulation, and potential risk of premature ovarian failure.	Improved ovarian blood flow and hormonal regulation may protect ovarian function.
Spermatogenesis	Possible reduction in testosterone levels and impaired sperm production.	Increased testicular perfusion and enhanced testosterone production via metabolic regulation.
Fertility preservation	Cryopreservation of gametes is recommended before ICIs initiation due to gonadotoxicity risk.	Help maintain gonadal function, potentially improving fertility outcomes post-treatment.
Pregnancy-related risks	Increased miscarriage risk, potential impact on fetal development, and altered placental immune tolerance.	Reduces systemic inflammation, which may lower pregnancy-related risks in cancer survivors.
Inflammation and oxidative stress	ICIs induce pro-inflammatory responses and oxidative stress, which may contribute to reproductive dysfunction.	Modulates immune function and enhances antioxidant defenses, mitigating damage.
Long-term reproductive health	Potential long-term effects on sexual health, libido, and overall reproductive function due to hormonal imbalances.	Regular physical activity supports overall reproductive well-being and sexual health.

Table 2. The impact of immune checkpoint inhibitors on reproductive function and the potential protective role of exercise[24]

Conclusions

Immune checkpoint inhibitors have significantly improved cancer treatment outcomes, yet their impact on fertility remains a growing concern. This review analyzed available evidence on how these therapies affect reproductive function in both men and women. ICIs can lead to endocrine disorders such as hypophysitis and thyroid dysfunction, which may disrupt hormonal balance and impair gonadal function. In women, they have been associated with

diminished ovarian reserve and ovulation disorders, while in men, they may contribute to testosterone deficiency and spermatogenesis impairment. Given that ICIs are now used in younger patients, including children, early fertility counseling and preservation strategies should be considered. Options such as oocyte and sperm cryopreservation may help mitigate long-term reproductive risks. Additionally, emerging research suggests that physical activity may positively influence fertility by improving hormonal regulation and reducing inflammation. Although cases of normal pregnancies in patients treated with immune checkpoint inhibitors have been described, effective contraception is recommended for 5-12 months after treatment with these drugs. In addition, experts advise against breastfeeding for the first 5 months after ICIs therapy is discontinuated. Despite these findings, many aspects of the reproductive effects of ICIs remain unclear. Future research should focus on long-term fertility outcomes, the impact of different treatment regimens, and the development of targeted fertility-preserving strategies for patients undergoing immunotherapy.

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