



ISFP – Newsletter

Newsletter 2023 – January

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Checkpoint inhibitor immunotherapy diminishes oocyte number and quality in mice

Winship et al., Nat Cancer, 2022 Aug;3(8):1-13.

Background

Checkpoint inhibitor immune therapies are increasingly used in cancer such as melanoma, lymphoma, breast cancer etc. The therapies, using monoclonal antibodies, target key regulators of the immune system, the immune checkpoint regulators. Some cancer types dampen the immune response by stimulating these checkpoints. Inhibiting these checkpoints restores the immune system which allows T cells to promote an anti-tumor response.

Activation of the immune system leads to inflammation and immune-related adverse events in several organs, including endocrine organs such as the thyroid, pituitary and adrenal glands.

The impact on gonads and other fertility associated organs has only poorly been analysed.

Summary of the paper

Winship et al. evaluated the effect of the clinically approved immune checkpoint inhibitors (ICI) *Programmed cell death protein ligand 1* (PD-L1) and *Cytotoxic T lymphocyte-associated antigen 4* (CTLA-4) on the ovary using tumor-bearing and tumor-free mouse models.

Mice were treated with PD-L1 and CTLA-4 antibodies vs. IgG antibody controls and were sacrificed and analysed 1-100 days after checkpoint inhibitor treatment.

It was found in PD-L1 treated tumor-bearing mice:

- an intra-ovarian changed T cell spectrum, indicating increased T cell-mediated immune cell activation and a lower number of secondary follicles and luteal bodies, indicating an impact on folliculogenesis.

It was further found in PD-L1 and CTLA-4 treated tumor-free mice:

- a reduction of primordial follicles by around 50%, indicating a quantitative impact on primordial follicle pool,
- an increase of fragmented and dead oocytes after gonadotropin stimulation, indicating a qualitative impact on primordial follicles,
- a reduction of secondary follicles, indicating an impact on folliculogenesis,
- an immediate inflammatory intra-ovarian response, including TNF- α , likely contributing to the follicle loss,
- a TNF- α induced primordial follicle loss due to induction of apoptosis.

Winship et al. concluded that “that immune checkpoint inhibitors have the potential to impair both immediate and future fertility, and studies in women should be prioritized. Additionally, fertility preservation should be strongly considered for women receiving these immunotherapies....”.

Critical evaluation of the paper

Winship et al performed an excellent study evaluating the quantitative and qualitative effect of specific and clinically used checkpoint inhibitors on ovarian function in mice. They revealed for the first time what kind of impact immune therapies such as checkpoint inhibitors can have on the ovaries.



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However, more studies are required to draw clinical conclusions from this study for the following reasons:

- First, we do not know if these findings in mice can be transferred to the human system and if yes, to which extent.
- Second, we do not know if the impact on oocyte quality is long-lasting and therefore impacts long term fertility.
- Third, we do not know if the uterus and therefore placenta function are also affected.
- Fourth, we do not know how long pregnancies should be avoided after the end of the checkpoint inhibitor therapy.

Pregnancies after checkpoint inhibitor therapy have only sporadically been described so far. You et al., 2020 and Polnaszek, 2021 described each one pregnancy after checkpoint inhibitor therapy for gestational trophoblastic tumors. Both pregnancies were normal and children were healthy. Examination of the placenta did not reveal any abnormalities.

Due to the limited data, recommendations regarding the time needed to wait after checkpoint therapies to get pregnant are very weak (Salman et al., 2022, Kim et al. 2022). Kim et al. recommend to wait 6 months after the end of the ICI treatment before trying to conceive.

Conclusion

Immune checkpoint therapies do have an impact not only on fertility related endocrine glands but also on the ovaries. However, data are far too limited in humans to draw clinical conclusions regarding short term fertility, long term fertility and pregnancies.

Accordingly, Winship et al. are absolutely right stating that check point therapies have the potential to impair fertility and that studies in women should be prioritized.

However, their statement that fertility preservation should be strongly considered for women receiving these immunotherapies should be taken with caution as this statement is based on insufficient evidence.

Further studies are needed to give guidance on pregnancy outcomes and the need for fertility preservation in patients using these therapies.

References:

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*Please note: The newsletter reflects the opinion of the author and not of the ISFP.