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Impact of Cancer Therapy on the Ovarian Reserve: The Role of Inflammatory Signaling*

The connection between inflammation and fertility is not completely understood. Inflammation is essential for normal ovarian function (1), but there is evidence suggesting that inflammation can negatively impact fertility. Clinical observations have long suggested that inflammation adversely affects female fertility, particularly in the context of chronic disease. Several conditions that induce systemic inflammation (e.g., inflammatory bowel disease, systemic lupus erythematosus, and autoimmune diseases like rheumatoid arthritis or plaque psoriasis) are diagnosed in hundreds of thousands of women annually, and many of these women are in their reproductive years. Unfortunately, there is limited data on the correlation between systemic inflammatory conditions, ovarian reserve, and infertility. Considering the broad and varied distribution of diseases with a chronic inflammatory component, as well as the diversity of medical treatments available and under development for modulating inflammatory signaling, a deeper investigation of the mechanistic contribution of inflammation to reproductive health and pathologies is warranted.

In recent years, various high-resolution -omics analyses of the ovary in the context of health, disease, and aging have shed light on the links between inflammation and ovarian function. Single-cell transcriptomic analysis of the primate ovary has provided a comprehensive assessment of cell-type-specific mechanisms that underlie ovarian aging, highlighting a correlation between reduced function and inflammation (2). However, there is limited clinical data directly linking inflammation with decreased ovarian reserve and/or function. Chronic pelvic inflammation has been suggested to diminish ovarian reserve, as evidenced by a correlation between bilateral tubal occlusion and lower serum levels of anti-Müllerian hormone (AMH) (3). Additionally, obesity, which is known to increase systemic levels of inflammatory signaling, has been associated with anovulation, infertility, miscarriage, and pregnancy complications. While the mechanisms that account for reproductive dysfunction in these patients are likely multifaceted, emerging evidence suggests links between obesity-induced low-grade chronic inflammation and impaired folliculogenesis, reduced implantation, increased risk of anovulation and infertility, and delayed time to conception (4).

To complement clinical observations, genetic studies in mice have enabled rigorous assessment of discrete inflammatory modulators in the context of fertility. In a mouse model of TNF-α knockout, there is a two-fold larger reserve of follicles at birth and a longer reproductive lifespan compared to wild-type (WT) mice (5). Furthermore, TNF-α knockout ovaries had lower levels of Caspase 3 in oocytes and a significantly lower expression of Bad and Bax compared to WT ovaries. These results suggest that TNF-α may serve as an important intraovarian mediator of the primordial follicle pool, potentially by driving the growth arrest and/or attrition of primordial follicles during the period of fetal germ cell expansion. Physiologically, TNF-α is a pivotal component of the normal immune response, serving to promote activation. Nevertheless, excessive activation of TNF-α signaling is associated with chronic inflammation and can eventually lead to the development of pathological conditions and disease.

Our own research, in line with findings from TNF-α-knockout studies, has indicated that systemic chemotherapy, specifically cyclophosphamide, triggers an acute inflammatory response in WT mice ovaries. Additionally, direct systemic administration of TNF-α to mice resulted in decreased ovarian reserve, comparable to the effects seen with cyclophosphamide exposure. Maladaptive TNF-α signaling has provided the basis for developing effective therapeutic tools, such as TNF-α inhibitors, with several compounds approved for clinical use. One example is Adalimumab (Humira®), a fully human IgG1 monoclonal antibody designed to specifically block the binding of human TNF-α to its receptors (6). Building on our observations, we conducted a pilot study to evaluate whether anti-TNF-α treatment could reduce ovarian damage when used in combination with alkylating chemotherapy (cyclophosphamide). Surprisingly, we found not only no protective effect but also a deleterious effect of treatment, even compared to chemotherapy alone, which increased with higher dosing. These preliminary observations underscore the challenge of defining the normal versus pathological influences of inflammatory signaling during folliculogenesis.

Given the broad range of pharmacologic treatments for autoimmune inflammatory diseases that have already been approved for clinical use, we have also tested the protective effect of some of these compounds. We administered a panel of anti-inflammatory compounds in advance of cyclophosphamide, and found that Ruxolitinib (Ruxo), a Janus kinase (JAK) inhibitor used to treat myelofibrosis and graft versus host disease, shows promise as a therapeutic intervention. Specifically, Ruxo pretreatment reduces the loss of primordial follicles and transcriptomic analysis of pretreated ovaries shows a reversal of the hyperinflammatory phenotype elicited by cyclophosphamide. Building on these preliminary findings, we are conducting systematic dose titration and timing to define optimal treatments for broader testing.

Summary

Overall, inflammation plays a significant role in reproduction. The impact of inflammatory cytokines and cellular targets which they influence is complex and can have opposing effects. It is crucial to maintain balanced signaling to prevent tissue damage, and further research is needed to gain a clear understanding of the mechanisms involved. This understanding is vital to distinguishing between the normal physiological functions of inflammation and the harmful inflammatory processes that can lead to tissue damage. Considering the finite nature of the ovarian reserve, the impact of chronic inflammation on fertility in reproductive-aged women should be highlighted in doctor-patient consultations. Minimizing the negative bystander effect of inflammatory signaling in these patients may increase the likelihood of maintaining normal ovarian function and fertility.

References

1. Espey LL. Ovulation as an Inflammatory Reaction-A Hypothesis. Biol Reprod. 1980;22:73–106.
2. Wang S, Zheng Y, Li J, Yu Y, Zhang W, Song M, Liu Z, Min Z, Hu H, Jing Y, He X, Sun L, Ma L, Esteban CR, Chan P, Qiao J, Zhou Q, Izpisua Belmonte JC, Qu J, Tang F, Liu GH. Single-Cell Transcriptomic Atlas of Primate Ovarian Aging. Cell. 2020 Feb 6;180(3):585-600.e19.
3. Cui L, Sheng Y, Sun M, Hu J, Qin Y, Chen ZJ. Chronic Pelvic Inflammation Diminished Ovarian Reserve as Indicated by Serum Anti Mülerrian Hormone. PLoS One. 2016 Jun 6;11(6).
4. Robker RL, Wu LL, Yang X. Inflammatory pathways linking obesity and ovarian dysfunction. J Reprod Immunol. 2011;88:142–148.
5. Lan-lan Cui, Guiwen Yang, Jie Pan, Cong Zhang. Tumor necrosis factor α knockout increases fertility of mice. Theriogenology, Volume 75, Issue 5, 2011, pages 867-876.
6. Mease, P.J. Adalimumab in the treatment of arthritis. Ther. Clin. Risk Manag. 2007, 3, 133–148.

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