Could AMH treatment have a role in fertility preservation?

For a long time, the role of anti-Mullerian hormone (AMH) was thought to be confined to development, and specifically the suppression of Mullerian tubes in male fetuses. It was an orphan hormone in females until it was found to be produced in ovarian follicles by granulosa cells, providing a useful indicator of ovarian reserve and is nearly extinct in serum after the menopause. Related to inhibin, it is another inhibitory hormone although it acts locally to suppress recruitment of primordial follicles into the growing pool. Thus, the hormone is promising for regulating and monitoring fertility, and a recent paper by Roness et al. finds evidence of an application for preserving fertility in cancer patients (*Journal of Assisted Reproduction & Genetics* 2019).

The authors address the problem of follicle destruction by chemotherapy, which reduces the ovarian reserve and tip cancer patients into a premature menopause. They used mice treated with the alkylating agent cyclophosphamide as a model to test the hypothesis that AMH protects the reserve by suppressing follicle recruitment to growing stages that are acutely sensitive to the toxin. They are originators of the hypothesis that the side-effects of chemotherapy on the ovary are not only caused by apoptosis but by super-recruitment of follicles to attenuate the reserve through a process they call 'burn-out', for which the intracellular mechanism is now becoming understood. It is not straightforward to weigh the relative responsibility of these two processes, but the basis of their claim has been confirmed independently, and, hence, they have turned attention to blocking follicle burn-out.

Young adult female mice were treated with a sub-sterilizing dose of cyclophosphamide and/ or AMH. Three weeks later, almost half of the primordial follicle stock had disappeared: whereas sole treatment with the hormone had no effect. But given in combination the hormone had a significant protective effect against the toxic effects of drug: follicle numbers were boosted by a third and the animals were correspondingly more fertile. The study provided evidence that the hormone acted directly on the ovaries.

If fertility could be spared in cancer patients by a procedure as elementary as the injection of a hormone it would be a wonderful advance. The prospect is even more theoretically attractive because the benefit may not be limited to a single chemotherapeutic regimen or type of cancer. This paper is only a first tentative step toward that goal and the logical next step is for experiments in vitro and using xenografts with human tissue. The mice were injected four times a day to offset rapid disappearance from the circulation, so it is probably going to be necessary to develop a long-acting synthetic analogue to be fully effective. The authors have provided preliminary evidence that AMH does not interfere with cancer therapy, since the cytotoxic impact of cyclophosphamide on breast cancer cells in vitro was not blunted by AMH. This paper opens a new path in AMH research in fertility preservation.

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FERTILITY PRESERVATION

Pharmacological administration of recombinant human AMH rescues ovarian reserve and preserves fertility in a mouse model of chemotherapy, without interfering with anti-tumoural effects

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Abstract

Purpose To determine whether pharmacological administration of recombinant human anti-Mullerian hormone (rAMH) protects the ovarian reserve and preserves fertility without interfering with anti-tumoural cytotoxic action of chemotherapy.

Methods Intraperitoneal delivery of rAMH and ovarian post-receptor activity were assessed with immunohistochemistry and western blot. Differential follicle counts and reproductive outcomes were assessed after cyclophosphamide (Cy) administration, with/without concurrent administration of rAMH. Interference of rAMH with Cy chemotoxicity was assessed on a human breast cancer cell line and an in vivo mouse model of human leukaemia.

Results rAMH reached the ovary after intraperitoneal injection and demonstrated post-receptor bioactivity. Cy administration in mice caused primordial follicle activation, as shown by a decrease in primordial follicle population accompanied by an increase in early growing follicles and granulosa cell proliferation. Co-administration of rAMH reduced follicle activation, thereby protecting the primordial follicle reserve, and improving long-term fertility and reproductive outcomes. rAMH co-administration did not interfere with the cytotoxic actions of Cy in vitro on breast cancer cell line or in vivo in a model of human leukaemia.

Conclusion This study demonstrates that rAMH is bioactive in the ovary for a limited time, and that pharmacological administration of rAMH during chemotherapy treatment reduces follicle activation and primordial follicle loss and significantly improves reproductive outcomes in a mouse model, and does not interfere with the therapeutic actions of the treatment. Further investigation is necessary to determine whether it has similar protective effects in the human ovary.

Keywords Fertility preservation · Chemotherapy · Anti-Mullerian hormone · Follicle activation

Introduction

The cause of premature ovarian insufficiency (POI) in cancer survivors is chemotherapy-induced loss of the primordial follicle (PMF) reserve [1]. While there are several methods currently available to help preserve fertility in cancer patients (including embryo, oocyte, and ovarian tissue cryopreservation [2–4], these methods are all invasive procedures and are limited by patient age and status or limited by the timeframe necessary before treatment. As such, there has been a focus on developing preventative pharmacological methods for fertility preservation, which will be suitable for all patients, and enable them to retain their natural fertility by preventing the loss of ovarian follicle reserve during chemotherapy [5, 6].

Chemotherapy-induced loss of the ovarian follicle reserve occurs via multiple routes, both extrinsic to the dormant follicle such as stromal fibrosis [7, 8] and intrinsic to the dormant follicle population. We previously demonstrated that alkylating agent cyclophosphamide (Cy) induces PMF loss in mice via dormant follicle activation and 'burn-out' [9]. Other studies have since corroborated this 'burn-out' effect, both with Cy ([10]—in mice; [11]—in human ovarian tissue) and with another ovotoxic chemotherapy drug, cisplatin [12, 13]. This accelerated follicle activation appears to be caused by dysregulation in pathways that control follicle dormancy

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