

Abstract Details

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★ Abstract title:

LH gonadoprotection against ovarian damage induced by alkylating drugs in adult mouse ovaries

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Study question:

To evaluate if LH administration protects the follicular pool against gonadotoxic effects of oncologic treatment with alkylating drugs in adult mouse ovaries.

Summary answer:

LH treatment prevents follicular depletion induced by Busulfan and Cyclophosphamide in adult mouse ovaries by preserving higher number of follicles, especially primordial and primary populations.

What is known already:

Oncologic treatment with high-dose chemotherapy may impose deleterious effects on the ovary. Clinically, impact ranges through partial damage to a complete destruction of the follicular pool. The highest risk is associated to alkylating drugs, while platinum-based compounds like cisplatin associated a medium risk. Several methods are available to preserve fertility in cancer patients but further research is needed to develop new alternatives. Previous studies suggested that luteinizing hormone (LH) prevents the cisplatin-induced apoptosis in oocytes and preserves fertility in prepubertal mouse. We aim to validate the protective effects of LH on the mouse adult ovary against chemotherapy with alkylating agents.

Study design, size, duration:

Experimental study, with eleven 6 week-old CD-1 female mice allocated to the following groups: Control (n=3), Chemotherapy (ChT, n=4) and ChT+LH (n=4). Mice in the ChT groups received a dose of alkylating drugs to induce severe ovarian damage on day 0, at the same time with their own treatment (saline or LH, respectively). Animals were maintained during 12 days and then sacrifice to recover ovarian samples for further analysis.

Participants/materials, setting, methods:

A single intraperitoneal injection with 12 mg/Kg busulfan and 120 mg/Kg Cyclophosphamide was administered to mice of the ChT treated groups while controls received saline. Simultaneously, animals of the ChT and Ch+LH group also received 100ul of saline or equal volume with 1IU of LH, respectively. A week after, ovarian hyperstimulation was induced, animals mated with fertile males and sacrificed. The ovarian size, follicular growth and populations, ovulation and early embryo development were then evaluated.

Main results and the role of chance:

ChT administration reduced the ovarian weight after hyperstimulation (C:45.7±2.0mg, ChT:14.9±0.9mg and ChT-LH:14.6±3.2mg; p=0.001) and LH administration was not able to recover control values.

When the total amount of follicles was analyzed, a 10-fold decrease was observed after chemotherapy administration (C:1260±168, ChT:182±31; p=0.03). Nevertheless, LH administration reduced the severity of the follicular depletion (ChT-LH: 264±59; p=0.04). This improvement was mainly due to a better preservation of the primordial (ChT-LH:42±14 vs. ChT:7±5fol., p=0.032) and the primary populations (ChT-LH:132±8 vs. ChT:68±12, p=0.034). However, LH was not able to preserve the late preantral, antral and pre-

ovulatory populations already impaired by ChT.

The percentage of quiescent follicles decreased in the ChT group due to the burnout of dormant follicles induced by alkylating agents but LH treatment was able to minimize this effect ($p=0.034$) and to maintain values similar to controls (C: $15.7\pm 3.6\%$, ChT: $4.2\pm 3.4\%$ and ChT-LH: $15.8\pm 4.6\%$).

The amount of ovulated MII-oocytes and 2-cell embryos were seriously impaired in both ChT (MII: 8 ± 5 ; Embryos: 7 ± 5) and ChT-LH treated mice (MII: 10 ± 9 ; Embryos: 7 ± 10), when compared to controls (MII: 17 ± 2 ; E: 10 ± 2). However, LH administration increased the viability of the obtained MII-oocytes (ChT: $64.3\pm 27.5\%$ vs. ChT-LH: $90.4\pm 11\%$) and embryos (ChT: $63.9\pm 29.3\%$ vs. ChT-LH: $95.2\pm 8.2\%$) although no statistically significant.

Limitations, reasons for caution:

This is a preliminary study with a reduced sample size and therefore data should be confirmed in a larger population. Furthermore, LH effects on follicular development potential should be carefully assessed.

Wider implications of the findings:

We found that LH administration protects primordial and primary follicles in adult ovaries against the depletion and over activation induced by alkylant agents. However, LH was not able to preserve the already growing populations but allows the surviving follicles to produce oocytes and embryos with increased developmental potential.

Trial registration number:

Not applicable

Keywords:

luteinizing hormone (LH)
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