Title: Hypoxia leads to diminished ovarian reserve in an age dependent manner

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Abstract

In a previous study(1) we have shown that perinatal hypoxia causes premature activation and growth initiation of dormant follicles leading to diminished ovarian reserve. We now investigated whether hypoxic ovarian damage is due to increased growth and "burnout" of follicles or due to increased apoptosis, and whether this damage it is age dependent. Animal studies were carried out using adult 6-week-old (n=8) and one-day-old newborn (n=20) ICR female mice. Animals were sacrificed, ovaries were harvested and immediately cultured for 3 hours at 37◦C to hypoxia (1% O_2 and 99% N_2) or normoxia (21% O_2 and 5% CO_2). Afterwards, sections were prepared and stained with H&E for follicular counts. For immunohistochemistry, sections were stained with Ki-67 (proliferation marker), anti-Caspase 3 and anti-FOXO3A (apoptosis markers). Exposure to hypoxia resulted in a significant reduction in the proportion of primordial follicles out of the total follicular pool as compared to normoxia in both adult dams and newborn pups (3.17±2.75% vs. 17.89±4.4%; p=0.004 and 40.59±14.88% vs. 81.92±31.56%, p=0.001, respectively). This decrease was concomitant with an increase in the proportion of growing- primary and secondary follicles. Notably, the impact was strikingly more pronounced in adult dams than in newborn pups (6-fold vs. 2-fold, respectively). Ki67 staining revealed higher scores of cell proliferation in follicular granulosa cells after exposure to hypoxia than normoxia. However, Caspase 3 and Foxo3A staining did not show any differences in these markers of apoptosis in oocytes, granulosa cells, theca cells, or stromal cells when exposed to hypoxia versus normoxia. Our study demonstrates that direct tissue hypoxia leads to the premature activation and initiation of growth in dormant follicles leading to diminished ovarian reserve.

This effect is associated with increased granulosa cell proliferation without concomitant changes in apoptosis. Hypoxic damage is age dependent, with adult ovaries exhibiting a more pronounced susceptibility than newborn ovaries. Collectively, these findings support the possibility of follicular "burn out" as a potential mechanism responsible for hypoxia-induced loss of ovarian reserve.

Biography (upto 150 words)

Ofer Fainaru, MD, PhD; Director of IVF Unit and Sperm Bank, Rambam Medical Center; Head of the Laboratory of Reproductive Sciences at Clinical Research Institute Rambam (CRIR); Assistant Professor at Technion – Israel Institute of Technology; Completed his MD Degree Summa Cum Laude (1998) at Tel Aviv University and his PhD at the Department of Molecular Genetics (2005), Weizmann Institute of Science. Certified in Obstetrics and Gynecology Summa Cum Laude (2006), Tel Aviv Souraski Medical Center. Dr. Fainaru completed his Postdoctorate Fellowship (2008) at The Vascular Biology Program, Harvard Medical School, and a Clinical Fellowship in Reproductive Endocrinology and Infertility (2009), University of Toronto. Honors and awards: European Molecular Biology Organization (EMBO) (2007), Fulbright (2006) and Rothschild (2006) fellowships; Legacy research grant from the Israel Science Foundation (ISF) (2009); Meyer Foundation (2011); Sima Leor Foundation grant (2012); Israeli Ministry of Health, Chief Scientist grant (2014) Crown Family Foundation grant (2016). Dr. Fainaru authored more than 60 scientific publications in peer reviewed journals, book chapters, and responsible for several international patents.

Recent publication:

1. Gutzeit O, Iluz R, Ginsberg Y, Nebenzahl K, Beloosesky R, Weiner Z, **Fainaru O**. Perinatal hypoxia leads to primordial follicle activation and premature depletion of ovarian reserve. J Matern Fetal Neonatal Med. 2021 Jun 13;1-5.

2. Gutzeit O, Segal L, Hertz R, Burke Y, Paz G, Hantisteanu S, Ginsberg Y, Hallak M, Pencovich N, Beloosesky R, Weiner Z, and **Fainaru O**. Progesterone treatment enhances the expansion of placental immature myeloid cells in a mouse model of premature labor. J Reprod Immunol. 2019 Feb;131:7-12.

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