

# Can Pregnancies Be Achieved in Premature Ovarian Insufficiency?

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## Keywords

Premature Ovarian Insufficiency, genes, ovulation, ovarian scratch, ovarian activation

Premature ovarian insufficiency (POI) occurs in 1% of women under age 40 years and in 0.1% under age 30 years. The definition typically involves secondary amenorrhea and sometimes is extended to include primary amenorrhea. Once evident, no treatment has been efficacious, and indeed no management can be recommended. Nonetheless, a portion of affected women still retain some dormant primordial follicles and a few will experience occasional ovulation or menstruation after long periods of amenorrhea. This clinical observation is, in fact, the rationale used in the appellation POI rather than premature ovarian failure, which implies futility of treatment.

Clinicians are well aware that women receiving chemotherapeutic agents, exposed to toxicants, or having undergone certain surgical procedures can manifest POI. However, the etiology of POI is otherwise usually unclear. Cytogenetic studies reveal 10% to 13% of POI cases show chromosomal abnormalities, usually 45, X/46, XX, or structural autosomal rearrangements.<sup>1</sup> Single gene perturbations have shown proven causality in functional studies. Fragile X premutation (55-100 nucleotides GTT repeats) approximates 5% of cases in European populations, but seemingly less in Chinese and Japanese.<sup>1</sup> In the past decade, it has become clear that single-gene mutations explain a significant number of POI cases. A surprise has been that the putative genes involve not only those expected on the basis of their roles in oogenesis but others whose roles lie in DNA repair. Women with POI have been shown to have autosomal perturbation in FSHR, NOBOX, FIGLA, GDF9, NRSA1, NANOS3, STAG3, SYCE1, MEM8/9, and HFM. On the X chromosome, perturbations include BMP15, PGRMC1, and FMRI. See Qin et al<sup>1</sup> for detailed discussion.

The prevalence of a given single-gene mutation in a woman with POI approximates 1% to 2% in a given ethnic group in a given study, exceptions being FSHR in Finland and Fragile X premutation in European women. No large-scale whole genome or exome studies have been reported. Extant publications have relied on candidate gene studies. The only whole genome, agonistic study was a genome-wide association study with 800 Chinese in the discovery group. The most significant association was a presumptive regulatory region in a noncoding regulatory (8q22.3).<sup>2</sup> Overall, perhaps 25% of POI cases show a monogenic explanation.

Lack of a clear biological basis for most cases of POI means that therapy has usually been offered on an empiric basis. It is not surprising these approaches have yielded disappointing results. The highly productive group from Shandong University (Jinan, China) led by Professors Chen, Qin, Zhao, and colleagues has made many genetic discoveries in the etiology of POI. In this issue, they address therapy, recruiting POI women  $\leq 38$  years, follicle stimulating hormone (FSH)  $>40$  IU/L, and secondary amenorrhea  $\geq 6$  months.<sup>3</sup> Alternative explanations for POI were excluded (chemotherapy, prior ovarian surgery, chromosomal abnormalities, thyroid dysfunction).

The hypothesis tested is that ovarian biopsy and “scratching” enhance ovarian activity and, hence, improve reproductive outcomes. Eighty (80) women were recruited. Surgical procedures involved removal of small pieces of the left ovary, plus 3 “superficial” scratches without hemostasis in the right ovary. After surgery, hormone replacement therapy was administered for 6 months. Primary outcome was decreased FSH, increased E2, and demonstrable follicle development by ultrasound. Eleven patients met these criteria and were offered ovulation stimulation followed by in vitro fertilization/embryo transfer (ET). Eight of the 11 underwent ovarian stimulation with human menopausal gonadotropins, whereas 3 others underwent a “natural” protocol. Oocytes were inseminated and good-quality embryos transferred. Overall, there were 3 metaphase II oocytes, from which 2 embryos developed. One additional oocyte lacked zona pellucida; 6 oocytes were “empty.” Two embryos reached day 3. Transfer of one yielded a single healthy baby; the other embryo was transferred to another patient but did not result in a pregnancy.

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A similar approach was pursued by Suzuki et al<sup>4</sup> from Stanford University, who removed strips of ovarian tissue, auto-transplanted and initiated ovulation stimulation regimes. Of 37 women with POI, 9 showed follicle growth; 2 pregnancies occurred. This approach was more invasive than that of Zhang et al.<sup>3</sup> Thus, if the approach of Zhang et al is validated, it will offer a simpler more cost-effective option than the prior two-step regimen. In addition, Lunding et al<sup>5</sup> just described another laproscopic autotransplantation approach for fragmented ovarian cortical tissue.

The rationale for success with any of these approaches is inactivation of a dormant pathway (in vitro activation). One potential explanation for success is interference with the HIPPO signaling pathway, which is pivotal for regulation of cell proliferation and determining organ size and is highly conserved.<sup>6</sup> In turn, recent reports describe stimulation of the phosphatidylinositol-3-kinase-AKT-forkhead box O3 pathway to activate dormant primordial follicles.<sup>7</sup>

The current study seeks to determine if follicular growth can be achieved mechanically, with only a simple surgical intervention, certainly less than previously achieved with ovarian wedge resection procedures. Alternatively, a second step might involve removal of ovarian tissue, activating AKT with exposure to phosphatase and tensin homolog inhibitors and phosphatidylinositol-3-kinase activators. These factors are obligatory for follicle activation.

If effective, how many women with POI have dormant remaining follicles to benefit? Does a plausible, less invasive pathway exist? Indeed, “continuous” clomiphene has been administered with concomitant ultrasound to detect evolving follicles. Follicles observed are aspirated and fertilized with resulting ET. Pregnancies have been achieved.

At present, the authors are not espousing imminent applicability. Naturally, the call is made for additional observational studies, and randomized clinical trials are desired. Like many innovations in reproductive medicine, application will attract naysayers. Nevertheless, we should recall the hackneyed but

still wise aphorism: Perfection is the enemy of good. Given daunting odds for achieving pregnancy in women with POI, ovarian biopsy scratching seems not an unreasonable hypothesis.

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