Case Report

Spontaneous conception in 40-year-old infertile woman with polycystic ovaries after complete reversal of endometrial intraepithelial neoplasia: A case report with review of literature

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ABSTRACT

We report a case of polycystic ovary syndrome and prolonged infertility in which endometrial intraepithelial neoplasia was reversed with high dose progesterone therapy. Spontaneous conception after failure of assisted reproductive techniques highlights the role of endometrial receptivity.

KEY WORDS: Endometrial intraepithelial neoplasia, fertility preservation, polycystic ovary syndrome

INTRODUCTION

In women with anovulatory polycystic ovary syndrome (PCOS), continuous exposure of uterine endometrium to higher levels of estrogens in the absence of antiproliferative effect of progesterone can cause hyperplasia and atypical changes.[1] This situation also predisposes these women to a higher risk of developing endometrial carcinoma.[2,3]

Early detection and appropriate treatment of atypical hyperplasia can prevent frank invasion, reverse intraepithelial neoplasia, and preserve fertility.[4]

CASE REPORT

A 28-year-old woman first presented in 2002 with 7 years history of primary infertility. She had oligomenorrhea since menarche. Her body mass index was 28. There was no hirsutism. Pelvic ultrasonography depicted normal looking uterus with 9.6 mm thick endometrium and bilateral polycystic ovaries. Her hormonal and biochemical parameters were normal. The endometrial histology revealed proliferative endometrium without hyperplasia or atypia. There was no associated tubal or male factor for infertility.

She was clomiphene-resistant and had previously received three unsuccessful cycles of controlled ovarian stimulation (COS) with intrauterine insemination (IUI). She was planned for in vitro fertilization (IVF), for which her ovaries were stimulated in a gonadotropin-releasing hormone agonist downregulated cycle. Six oocytes were retrieved from which two Grade 1 embryos were obtained and transferred. The result for pregnancy remained negative.

After about 10 years at 38 year age, she revisited with the complaints of hypo-oligomenorrheic cycles. She had stopped taking cyclic progestins therapy. Ultrasonographic examination showed normal uterus with 14.8 mm thick endometrium. A mixed echogenic cystic lesion measuring 3.8 cm × 4.6 cm was identified in the right ovary. Left ovary appeared polycystic. Anti-mullerian hormone level was 2.8 ng/ml.

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Right ovarian cystectomy for benign ovarian dermoid was done. Hysteroscopic examination showed multiple patches of irregular, polypoidal endometrium. Selective endometrial sampling from these polypoidal structures followed by curettage was done. Endometrial histology showed an excessive glandular pattern which was more than stroma. There were foci of adenomatous changes in the form of glandular crowding and budding besides few glands exhibiting obstruction of lumina. The histological findings were consistent with endometrial intraepithelial neoplasia (EIN) according to the International Endometrial Collaborative Group.\(^{[5]}\)

She was given a choice between hysterectomy and conservative hormonal therapy.\(^{[6]}\) She opted for conservative hormonal therapy. Written informed consent was obtained after extensive counseling. Considering her age IVF was undertaken first, and all 14 Grade 1 embryos obtained, were cryofrozen.

She was started on medroxyprogesterone acetate 200 mg daily in three divided doses for 6 months. Endometrial biopsy at 3 months showed secretory glands embedded in a decidual stroma. It also showed fragments of stratum basalis with proliferative glands with excessive progesterone exposure. Second 3-month follow-up histology revealed proliferative endometrium with excessive progesterone exposure. Follow-up histology 3 months after stopping progesterone showed normal proliferative endometrium.

Three good quality frozen and thawed embryos were transferred after endometrial preparation with oral estradiol valerate tablets 6 mg daily in divided doses. The result of embryo transfer was negative. Endometrial histology did not show any evidence of atypia or hyperplasia even after repeated exposure to estradiol. Two more futile attempts of embryo transfer were done after the endometrium was prepared with oral and transdermal estradiol.

Thereafter, she was advised cyclical progesterone for withdrawal bleeding.

She revisited the center after 2 years with complaints of 5 months of amenorrhea. The ultrasonography showed a viable 10 weeks pregnancy. Thereafter, her pregnancy was uneventful, and she delivered a full-term female baby by cesarean section. She has been now advised to undergo hysterectomy or levonorgestrel-releasing intrauterine system for long-term prevention of recurrence.

**DISCUSSION**

The oncologic and reproductive outcomes are two important aspects that need to be considered in EIN with polycystic ovarian syndrome patients. Reversal of pathology, prevention of recurrence, and progression are the primary end points of conservative management. The primary aim of conservative management is fertility preservation. There are no well-defined clinical or histological guidelines to assess the response to hormonal therapy. Most successful and acceptable results have been shown with high dose progestins.\(^{[7,8]}\) Progestins have antiproliferative actions related to antiandrogenic and antiestrogenic effect. Progestins target hormonal receptors expressed in lesions to initiate tumor cell death and induce apoptosis in neoplastic endometrial glands. This also causes stromal decidualization and thinning of endometrial lining.\(^{[9]}\)

In a systematic review and meta-analysis of 370 patients from 24 studies, the authors supported 12- and 24-month remission probabilities of 78.0% and 81.4%, and recurrence probabilities of 9.6% and 29.2%, respectively. In multivariate analysis, there was higher remission probability which did not show any association with higher recurrence probability with previous pregnancy (odds ratio [OR] = 2.70, 95% confidence interval [CI] =1.23–5.89), infertility (OR = 2.26, 95% CI = 1.05–4.87), and treatment with megestrol acetate (OR = 2.70, 95% CI = 1.20–6.02). Among the 263 patients, the progression rate was 39 (14.8%) with myometrial invasion on the hysterectomy specimen. Pregnancy rate as reported was 31.5% (111 out of 351 patients); 60 (54.1%) were ART conceptions, and 26.1% (29 cases) pregnancies were spontaneous.\(^{[10]}\)

The present case report discusses a 40-year-old woman who conceived naturally after almost 3 years of complete remission of precancerous endometrial changes with progestin therapy. There was a resumption of ovulation in an otherwise anovulatory PCOS woman followed by successful natural implantation. The case emphasizes the importance of unreceptive endometrium that may because of failure of multiple embryo transfer attempts even after complete reversal of EIN. Thus, there is a possibility that time taken by endometrium to become receptive for implantation is longer than as an apparent return to a normal histology.

Noncompliance by patients regarding cancer preventive cyclical progesterone therapy is very common. In this patient, normal histological pattern was documented nearly 10 years before the development of EIN. This underlies the need for better patient education program and counseling for maintenance of long-term health of PCOS women.

**CONCLUSION**

We recommend histologic evaluation of endometrium at regular intervals in PCOS cases. In early intraepithelial
lesions, conservative medical therapy can preserve and restore fertility; although the return of fertility may take longer time than histological reversal.

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Conflicts of interest
There are no conflicts of interest.

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