# Pregnancies in patients with premature ovarian failure

**F. Gücer[1], W. Urdl[2], D. Pieber[1], M. G. Arikan[1], A. Giuliani[2], H. Auner[2]**

*[1]Department of Obstetrics and Gynecology, University of Graz (Austria);*
*[2]Department of Obstetrics and Gynecology, Subunit for Gynecologic Endocrinology and Reproductive Medicine, University of Graz (Austria)*

**Summary**

We present 5 women with premature ovarian failure (POF) who were treated with different regimes and conceived. Three patients conceived spontaneously while on cyclic estrogen/progestagen replacement therapy. One patient conceived after high-dose gonadotrophin treatment. Embryo transfer with oocytes donated from a third party donor was performed in one patient abroad. Due to legal reasons the heterogenous oocyte donation for patients with POF cannot be performed in some countries such as Austria. Therefore, many patients who desire pregnancy cannot receive optimal treatment for their condition.

*Key words:* Premature ovarian failure; Pregnancy; Oocyte donation.

## Introduction

Premature ovarian failure (POF) or premature menopause is defined as hypergonadotropic amenorrhea and estrogen deficiency in women younger than 35 years of age [1]. The incidence is estimated at 1% [2] and 10% of women with secondary amenorrhea have premature ovarian failure [3]. Most women with ovarian failure are amenorrhoic but may occasionally menstruate and ovulate sporadically [4]. The etiology of POF is diverse and usually unknown. Current treatment regimes for women who desire to conceive are most often unsuccessful.

We describe 5 women with premature ovarian failure who were treated with diverse methods and then conceived. The literature on the management of this disease is also discussed.

## Case reports

*Patient 1*

A 27-year-old nullipara, nulligravida was referred because of secondary amenorrhea, flush and a desire for pregnancy. The serum levels of follicule stimulating hormone (FSH) and luteinizing hormone (LH) were high (FSH 50 mlU/ml, LH 42 mlU/ml; normal range for women in the reproductive phase: FSH 2.4 - 21 mlU/ml, LH 2.2 - 24.8 mlU/ml). Leukocyte karyotyping was 46, XX. No specific antibodies were detected in the serum. Biopsy of the ovaries showed atretic and primordial follicles. The patient was started on cyclic estrogen-progestagen replacement therapy (Cyclacur®, Schering, Estradiol valerate at mg 2 daily, from day 1 to day 21, Norgestrel 0.5 mg daily, from day 11 to day 21). Twenty-two months after starting the replacement therapy, she became pregnant. The baby was delivered by primary caesarean section. Postpartum the flush symptoms recurred again, and cyclic estrogen progestagen replacement therapy was restarted two months postpartum. Again she became pregnant after two months of treatment. The second baby was also delivered by caesarean section. Since the second delivery the patient has cyclic estrogen-progestagen replacement therapy.

*Patient 2*

A 28-year-old nullipara, nulligravida developed POF after chemotherapy and irradiation for Hodgkin's disease (grade IV). She presented with flushes and hypergonadotropic, secondary amenorrhea (FSH 42 mlU/ml and LH 27 mlU/ml). Cyclic estrogen progestagen replacement therapy (Cyclacur®, Schering) was started and she became pregnant two months later. One month postpartum she again reported hot flushes. Serum levels of gonadotropins were elevated (FSH 36.6 mlU/ml, LH 19.4 mlU/ml) and estradiol serum concentration was low (16.6 pg/ml). Cyclic replacement therapy was restarted.

*Patient 3*

A 29-year-old uni para was referred because of secondary sterility and amenorrhea 8 years after the delivery of her first child. Serum gonadotropin levels were elevated (FSH 77 - mlU/ml, LH 76 mlU/ml). Leukocyte karyotyping showed a Turner mosaic (45, XO/46, XX) and immunologic studies showed no abnormal findings.

Laparoscopic biopsy revealed streak ovaries without follicles. She was started on cyclic estrogen-progestagen replacement therapy (Trisequens®, Novo Nordisk, estradiol 2 mg daily from day 1 to day 12, norethisterone acetate 1 mg daily and estradiol 2 mg from day 12 to day 22 and estradiol 1 mg from day 22 to day 28). Fifty-three months after starting hormone replacement therapy she conceived spontaneously and delivered a healthy baby.

*Patient 4*

A 27-year-old nulligravida presented with hypergonadotropic amenorrhea (FSH 94 mlU/ml and LH 53 mlU/ml): Leukocyte karyotyping was 46, XX and immunologic investigations revealed no abnormal findings. An ovarian biopsy contained a single primordial follicle. After 12 months of unsuccessful cyclic estrogen-progestagen replacement therapy (Trisequens®, Novo Nordisk) high-dose gonadotrophin therapy (Humegon®, Organon, 300-450 IU FSH and 300-450 IU LH daily) was initiated.

Ovulation was induced with human chorionic gonadotrophin (Pregnyl®, Organon, 5000 IU) when sonography showed a follicular diameter of 18 mm. After the third cycle the woman became pregnant and delivered a healthy baby.

Received May 2, 1997
revised manuscript accepted for publication June 5, 1997

*Patient 5*

A 32-year-old nulligravida presented with primary sterility. Right salpingo-oophoorectomy had been performed six years previously because of endometriosis. Two months previously an endometriotic cyst was removed from the left ovary. Hypergonadotropic amenorrhea and menopausal symptoms followed this operation and were treated with a combination of estradiol and progestagen (Trisequens®, Novo Nordisk) for two years. Because oocyte donation is illegal in Austria [26], oocyte donation and in vitro fertilization were performed at a clinic in Italy. This treatment lead to pregnancy and the delivery of a healthy baby.

## Discussion

POF is a collective term for diverse disorders of different etiology including patients with "follicular depletion" and "gonadotropin-resistant ovary syndrome" (Table 1). The prognosis for fertility is usually poor. Between 1986 and 1996, 47 women with POF were seen at our department. Eleven had no desire for pregnancy. Only 5 of the 36 remaining women (14%) were able to become pregnant.

These five patients were treated by different methods. Three patients conceived spontaneously while on cyclic estrogen-progestagen replacement therapy. Other authors have reported patients with premature ovarian failure who have conceived spontaneously or while on estrogen-progestagen replacement or oral contraceptives [4-9]. Elevated FSH levels down-regulate FSH receptors on the granulosa cells. Exogenous estrogens may promote new FSH receptor formation. Estradiol has no affinity to granulosa cell FSH binding sites. However, in vivo estrogens increase synergistically with FSH the number of FSH receptors. Thus exogenous estrogens could sensitize the granulosa cells to FSH. Ylostalo *et al.* [7] reported five patients with POF who showed decreased gonadotropin levels and an increased serum estradiol level when treated with an estrogen/progestagen combination. Three of these 5 women became pregnant after treatment.

During estrogen-progestagen therapy endometrial response can be followed sonographically. This response is correlated with histology and the hormones [10]. Nevertheless, standard hormone replacement therapy in POF restores endometrial blood flow to normal [11].

POF can also be treated by high-dose gonadotropins for ovarian stimulation [12, 13]. There are some reports of successful human menopausal gonadotropin (HMG) treatment, but overall success rates remain low [14, 15].

Table 1. — *Etiology of premature ovarian failure*

| |
|---|
| A) Premature Follicular Depletion |
| I - Autoimmune disease |
| II - Chromosomal disorders |
| III - Iatrogenic |
| IV - Viral infections |
| V - Enzymatic defects |
| VI - Idiopathic |
| B) Gonadotropin Resistant Ovary Syndrome |

Check *et al.* [15] reported an ovulation rate of 19% in a prospective trial with 361 cycles of HMG treatment. The pregnancy rate in this study was 5.2% (19/361) per cycle.

To suppress elevated gonadotropin levels, Surrey and Cedars [14] administered a gonadotropin releasing hormone agonist (GnRH-a) subcutaneously followed by concomitant HMG stimulation in six patients. Ovulation was induced in only one of these patients. Van Kasteren *et al.* [16] conducted a placebo-controlled, randomized, double-blind trial (n=15 in each group) of intranasal GnRH-a with concomitant HMG stimulation. Three of 15 cycles were ovulatory in the group that received additional GnRH-a versus none in the placebo group. However, 7 patients in the study group showed one or more autoantibodies. In 3 of them ovulation was induced by treatment. However, the small numbers of patients in each group precludes a definitive conclusion about the efficacy of infertility treatment with GnRH-a in POF.

The return of menstrual function after administration of glucocorticoids in patients with autoimmune ovarian failure has been reported [17]. However, the demonstration of circulating antiovarian antibodies can be misleading depending on the variation in sensitivity and specifity of tests used. A high-dose, short-term administration of glucocorticoids in some women with autoimmune ovarian failure leads to pregnancy [18]. Corenblum *et al.* [19] reported that a high-dose short-term administration of glucocorticoids normalizes the serum gonadotropin levels. Serum $E_2$ concentration increased and 2 of 11 patients with POF conceived. Both successfully treated women suffered from a concomitant autoimmune disease (Hashimoto's thyreoditis).

The development of assisted reproductive techniques has enabled women with ovarian failure to conceive after oocyte donation and hormone replacement therapy. Oocyte donation abroad was successful in one of the patients in our series. Several studies report the successful use of donor oocytes for in vitro fertilisation and embryo transfer in patients with POF [20-24]. Remohi *et al.* [24] observed higher pregnancy rates after oocyte donation in women without POF, but with a lower response to gonadotrophins compared to women with POF (64% v. 37%). Other authors found no differences between success rates of donor oocyte IVF-ET in patients with or without POF [25]. Other types of assisted reproduction such as the gamete intrafallopian transfer or tubal embryo transfer using donated oocytes have also been successfully employed in patients with POF. Gamete intrafallopian transfer with donated oocytes achieves an average pregnancy rate of between 36% and 54% per treatment cycles in women with POF [20]. In one series the pregnancy rate after tubal embryo transfer with donated oocytes in patients with POF was 82% per transfer [23].

In conclusion, oocyte donation seems to be the ideal way to treat patients with POF who want to have a baby. However, solely due to legal reasons the heterogeneous oocyte donation for patients with POF cannot be performed in some countries such as Austria [26]. Therefore, many patients who desire pregnancy cannot receive optimal treatment for this condition.

## References


[1] Tulandi T., Kinch R. A.: "Premature ovarian failure". *Obstet. Gynecol. Surv.*, 1981, *36*, 521.

[2] Coulam C. B., Adamson S. C., Annegers J. F.: "Incidence of premature ovarian failure". *Obstet Gynecol.*, 1986, *67*, 604.

[3] Bachmann G. A., Kemmann E.: "Prevalence of oligomenorrhea and amenorrhea in a college population". *Am. J. Obstet. Gynecol.*, 1982, *144*, 98.

[4] Wright C. S. W., Jacobs H. S.: "Spontaneous pregnancy in a patient with hypergonadotrophic ovarian failure". *Br. J. Obstet. Gynaecol.*, 1979, *86*, 389.

[5] Shapiro A. G., Rubin A.: "Spontaneous pregnancy in association with hypergonadotropic ovarian failure". *Fertil. Steril.*, 1977, *28*, 500.

[6] Shangold M. M., Turksoy N. R., Bashford R. A. *et al.*: "Pregnancy following the 'insensitive ovary syndrome'". *Fertil. Steril.*, 1977, *28*, 1179.

[7] Ylostola P., Huhtaniemi I., Reinila M.: "Induction of ovulation with low-dose-estrogen-progestin therapy in amenorrhoic patients". *Int. J. Fertil.*, 1982, *27*, 153.

[8] Aiman J. and Smentek C.: "Premature ovarian failure". *Obstet. Gynecol.*, 1985, *66*, 9.

[9] Alper M. M., Jolly E. E., Garner P. R.: "Pregnancies after premature ovarian failure". *Obstet. Gynecol.*, 1986, *67*, 59S.

[10] Dockery T. C. L., Ramsewak S. S., Klentzeris L. *et al.*: "The variation of endometrial response to standard hormone replacement therapy in woman with premature ovarian failure. An ultrasonographic and histological study". *Br. J. Obstet. Gynecol.*, 1991, *98*, 656.

[11] Achiron R., Levran D., Sivan E. *et al.*: "Endometrial blood flow response to hormone replacement therapy in women with premature ovarian failure: a transvaginal Doppler study". *Fertil. Steril.*, 1995, *63*, 550.

[12] Johnson T. R., Peterson E. P.: "Gonadotropin-induced pregnancy following 'premature ovarian failure'". *Fertil. Steril.*, 1979, *31*, 351.

[13] Check J. H., Jeffrey J. S.: "Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy". *Fertil. Steril.*, 1984, *42*, 919.

[14] Surrey E., Cedars M. I.: "The effect of gonadotropin suppression on the induction of ovulation in premature ovarian failure patients". *Fertil. Steril.*, 1989, *52*, 36.

[15] Check J. H., Nowroozi K., Chase J. S. *et al.*: "Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea". *Fertil. Steril.*, 1990, *53*, 811.

[16] Van Kasteren Y. M., Hoek A., Schoemaker J.: "Ovulation induction in premature ovarian failure: a placebo-controlled randomized trial combining pituitary suppression with gonadotropin stimulation". *Fertil. Steril.*, 1995, *64*, 273.

[17] Rabinowe S. L., Berger M. J., Welch C., Rand *et al.*: "Lymphocyte dysfunction in autoimmune oophoritis". *Am. J. Med.*, 1986, *81*, 347.

[18] Cowchock F. S. , McGabe J. L., Bruce N. *et al.*: "Pregnancy after corticosteroid administration in premature ovarian failure polyglandular endocrinopathy syndrome". *Am. J. Obstet. Gynecol.*, 1988, *158*, 118.

[19] Corenblum B., Rowe T., Taylor P. J.: "High-dose short-term glucocorticoids for the treatment of infertility resulting from premature ovarian failure". *Fertil. Steril.*, 1993, *59*, 988.

[20] Lutjen P., Trounson A., Leeton J. *et al.*: "The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure". *Nature*, 1984, *307*, 174.

[21] Asch R. H., Balmaceda J. P., Ord T. *et al.*: "Oocyte donation and gameta intra fallopian transfer in premature ovarian failure". *Fertil. Steril.*, 1988, *49*, 263.

[22] Serhal P. F., Craft I. L.: "Oocytes donation in 61 patients". *Lancet*, 1989, *I*, 1185.

[23] Rotsztejn D. A., Remohi J., Weckstein L. *et al.*: "Results of tubal embryo transfer in premature ovarian failure". *Fertil. Steril.*, 1990, *54*, 348.

[24] Remohi J., Vidal A., Pellicer A.: "Oocyte donation in low responders to conventional ovarian stimulation for in vitro fertilization". *Fertil. Steril.*, 1993, *59*, 1208.

[25] Lydic L. M., Liu J. H., Rebar R. W. et al.: "Success of donor oocyte in vitro fertilization-embryo transfer in recipients with and without premature ovarian failure". *Fertil. Steril.*, 1996, *65*, 98.

[26] Bernat E.: "Between rationality and metaphysics: the legal regulation of assisted reproduction in Germany, Austria and Switzerland - a comparative analysis". *Med. Law*, 1993, *12*, 493.



Address reprint requests to:

WOLFGANG URDL, MD, Prof
Department of Obstetrics and Gynecology,
Subunit for Gynecologic Endocrinology
and Reproductive Medicine
University of Graz.
Auenbruggerplatz 14
A- 8036 Graz (Austria)