MANAGEMENT OF INFERTILITY IN PREMATURE OVARIAN FAILURE: A CASE REPORT AND LITERATURE REVIEW

(Received 31 August, 1992)

A.Türker, M.D. / O. Djahanbakhch, M.D. , MPhil. FRCOG M.D.*****
T.Çamlıbel, M.D., FACOG*

* *Associate Professor, Department of Obstetrics and Gynecology, International Hospital, İstanbul, Türkiye.*
** *Specialist, Department of Obstetrics and Gynecology, Okmeydanı Social Security Hospital, İstanbul, Türkiye.*
*** *Consultant, Royal London Hospital, London University, London, England.*

SUMMARY

We herein present a case of pregnancy in a 39-year-old woman with secondary amenorrhea, hypergonadotropinemia, and hypoestrogenemia achieved after the use of hormone replacement therapy for two months. This has made us review the literature to search for the pregnancies reported on patients with premature ovarian failure. Surprisingly, we have found 43 pregnancies in 37 cases. It was also interesting to see that hormone replacement therapy had been included in the treatment protocol in about 55 % of the pregnancies and 23 % had occurred spontaneously. The treatment modalities and their mechanism of action are discussed.

Key words: Premature ovarian failure, premature menopause, menopause, infertility.

INTRODUCTION

Premature ovarian failure (POF) or premature menopause is the appearance of primary or secondary amenorrhea, hypergonadotropinemia and hypoestrogenemia in women before the age of 40 (1-3). It represents a condition in which the ovaries have undergone differentiation and have functioned but function failed before the usual time of menopause because of an acceleration of the naturally occurring process of atresia of oocytes (4). The condition is benign, but has a marked emotional impact, especially in women who are desirous of getting pregnant.

We have recently achieved a pregnancy in a patient with POF by using hormone replacement therapy (HRT) and reviewed the literature to find out the pregnancies reported on women with this condition, with special attention to the therapies administered and the underlying causes.

CASE REPORT

A 39-year-old lady was referred by her general practitioner with secondary amenorrhea of 15 months' duration and secondary infertility. She had conceived previously twice, 4 and 3 years prior to her referral. The first pregnancy was spontaneous and the second followed an induction of ovulation with clomiphene citrate. Both pregnancies had ended in intrauterine deaths at 22 and 23 weeks gestations. All investigations after the pregnancies including fetal histopathology, thyroid function tests and chromosomal analysis of both partners showed no abnormality except that smooth muscle and reticulin antibodies were positive. Before her attendance at our clinic she had been investigated at another hospital where gonadotropins were noted to be elevated on two occasions.

The patient had her menarche at the age of 13. Her menstrual periods were regular, occurring every 26 to 30 days with 3 to 6 days of bleeding. During two years prior to the last menses she had become oligomenorrheic. The patient had nothing relevant to her condition in the past medical and family history.

On examination she appeared quite well. General physical and pelvic examinations revealed no abnormalities .LH and FSH levels measured 3 times two weeks apart were found to be in the menopausal range (FSH 40IU/l,LH 40IU/l), estradiol was low (less than 30 pg/ml) and prolactin level was normal.

After a full discussion of her condition, two options were offered to the patient: 1. Ovulation induction with HMG following the use of GnRH analogs or estrogens. 2. Consideration of GIFT or IVF-ET with donor oocyte. She was put on HRT and started having cyclical bleeding. In the third cycle she missed her menses and found to be pregnant.

She had an uncomplicated pregnancy and delivered a healthy baby at term. After the delivery she has had no menses and commenced HRT.

THE LITERATURE REVIEW

We have been able to find 43 pregnancies in 37 patients clinically diagnosed as POF and published so far in the literature (Table I) (5-26).

Table I. Documentation of pregnancies in the literature, occurred in patients with premature ovarian failure

Observers (year)	Number of pregnancies (patients)	Diagnosis*	Therapy (duration in months)	Outcome of pregnancy
Polansky et al (1976)	1 (1)	POF**	HRT** (1) - PT**	Ongoing
Shapiro et al (1977)	1 (1)	POF	HRT (3)	ND**
Shangold et al (1977)	1 (1)	POF	HRT (4)	CS**
Starup et al (1978)	3 (2)	TS**, 45x0	HRT (180) - PT	IUD**
		TS, 45x0	HRT (3) - PT	CS
		(AOD)**	HRT, cortisone (36)	CS
Szlachter et al (1979)	3 (3)	POF	HRT (27)	Ongoing
		POF	HRT (12)	TOP**
		POF	HRT (4)	ND
Wright et al (1979)	1 (1)	POF	SP**	ND
Johnson et al (1979)	1 (1)	POF	HMG** (1)	?
O'Herlihy et al (1980)	8 (6)	POF***	SP	ND
		POF***	SP	ND
		POF***	SP	ND
		POF***	SP	Ongoing
		POF***	SP	Ongoing
		POF***	HMG (?)	ND
		POF***	HMG (?)	ND
		POF***	CC** (?)	ND
Ataya et al (1983)	1 (1)	POF	SP	SA**
Voight (1984)	1 (1)	POF	HRT (12)	BO**
Check and Chase (1984)	2 (2)	POF	HRT + HMG (2)	Ongoing
		POF	HRT + HMG (5)	Ongoing
Ohsawa et al (1985)	1 (1)	POF	HRT (18)	ND
Amos (1985)	3 (1)	POF	HMG (1)	BO
		POF	HRT (1)	BO
		POF	HRT (16)	ND
Finer et al (1985)	1 (1)	(AOD)	Hydrocortisone, fludrocortisone, L - thyroxine (2)	ND
Alper et al (1986)	6 (6)	POF	HRT (10)	EP**
		POF	OC (7) - PT	TOP
		POF	HRT (12) - PT	ND
		POF	HRT (1)	ND
		POF	SP	ND
		TS	HRT (60), OC (24)	CS
Chan et al (1987)	1 (1)	POF	HRT (12)	CS
Cowchock et al (1988)	1 (1)	(AOD)	Prednisone, Fludrocortisone (3), HRT (120)	ND
Taylor et al (1989)	2 (1)	(AOD)	HRT, cortisone, fludrocortisone (120)	IUD
		(AOD)	SP	ND
Check et al (1989)	1 (1)	(AOD)	OC (1) - PT	?
Check et al (1989)	1 (1)	POF	HRT + HMG (7)	CS
Jequier (1990)	2 (2)	POF	HRT (7)	ND
		ROS	HRT (1)	Ongoing
Letterie (1990)	1 (1)	POF	SP	ND

* Patients with neither ovarian biopsy nor antiovarian antibody report have been classified as POF. But for some patients the most likely diagnosis based on available data is given in brackets.

** POF indicates premature ovarian failure : ROS, resistant ovary syndrome; aod, autoimmune ovarian disease; HRT, hormone replacament therapy; HMG, human menopausal gonadotropins; OC, oral contraceptives; CC, clomiphene citrate; Sp, spontaneous pregnancy; ND, normal delivery; CS, cesarean section; TOP, termination of pregnancy; PT, posttreatment; IUD, intrauterine death; Ts, Turner's syndrome; SA, spontaneous abortion; BO, blighted ovum and EP, ectopic pregnancy.

*** The patients do not properly fit the description of POF.

Classification of the cases according to the etiology and treatment schedule is as follows (Table II): In 26 cases (70 percent) the etiology was not known because either it was not properly investigated (some cases had been labelled as resistant ovary syndrome without an ovarian biopsy) or the investigations were inconclusive. All these patients have been classified under idiopathic cases. In this group 14 pregnancies occurred with HRT, 4 with HMG, 3 with HRT+HMG, 1 with CC while 8 pregnancies developed spontaneously.

In 2 patients, a genetic disorder appeared to be responsible for the condition. One of them who had Turner's syndrome used HRT twice and became pregnant shortly after the discontinuation of the therapy each time. In the other patient a mosaicism of 45, X0 was detected and she fell pregnant while receiving oral contraceptives (OC).

The autoimmune ovarian disease group consisted of 5 patients who were diagnosed when there was an evidence of antiovarian antibodies or an ovarian histopathology suggesting an autoimmune etiology or a strong suspicion of the disease in view of the concurrent occurence of other autoimmune diseases. In this group one spontaneous pregnancy occurred; in one patient pregnancy followed the cessation of 1 month course of OC therapy for an ovarian cyst and 4 other pregnancies developed while the patients were taking cortisone either alone (1 case) or in combination with HRT (3 cases).

2 pregnancies occurred in 2 patients with POF, apparently due to chemotherapy, one spontaneously and the other following 7 month course of OC use. One patient whose ovarian function failed after radiotherapy conceived with HRT.

There has been only one patient with histologic evidence of resistant ovary syndrome, who achieved pregnancy with HRT.

Table III shows outcome of the pregnancies. Of these

Table II. Pregnancies achieved by various treatment schedules in POF.

	CC	HMG	HRT	HRT + HMG	OC	HRT + Cortisone	Cortisone	Spont. Pregn.	Total pregn. (Patients)
Idiopathic cases	1	4	14	3				8	30 (26)
Genetic etiology			2		1				3 (2)
Autoimmune disease					1	3	1	1	6 (5)
Chemotherapy induced - POF					1			1	2 (2)
Radiotherapy induced - POF			1						1 (1)
Resistant ovary syndrome			1						1 (1)
Total number	1	4	18	3	3	3	1	10	43 (37)

Table III. Outcome of the pregnancies in women with POF (n)

Normal deliveries	(25)
Ectopic pregnancy	(1)
Blighted ovum	(3)
Spontaneous abortion	(1)
Second trimester intrauterine death	(2)
Terminations	(2)
In progress (uncomplicated)	(7)
Unreported	(2)
Total	(43)

43 pregnancies, 25 resulted in delivery of a healthy baby. 1 ectopic pregnancy occurred. 3 pregnancies were associated with blighted ovum (2 in the same patient). One resulted in spontaneous abortion in the first trimester while two others ended in the second trimester death of the fetuses, one of those was macerated and hydrocephalic. 2 pregnancies were terminated with the patients' wishes. In 7 patients the pregnancies were going on at the time of preparation of the papers, and the fates of two other pregnancies were not reported.

DISCUSSION

POF was accepted to be an irreversible disease until the middle of 1970 s. Women with this disease used to be given a grave prognosis for future fertility and usually referred for adoption as the one and only chance of having a baby once it was diagnosed. As it has recently been found that POF might be reversible in certain situations it is important to find out the underlying etiology in women who desire to become pregnant.

Genetic disorders are the most common among the known causes of POF and karyotyping should be done in every patient to exclude this possibility. Autoimmunity - caused POF usually occurs in association with other autoimmune disorders, especially of thyroid and adrenal glands. In these cases circulating antibodies to the ovarian tissue and histologic finding of lymphocytic and plasma cell infiltrates in proximity to the follicles have been demonstrated. Radiotherapy, chemotherapy and surgical removal of the ovaries may cause POF iatrogenically. The chance of causing POF is dose - related in radiotherapy whereas it seems to be age related in chemotherapy. Mumps virus infection is a well known cause of ovarian damage and failure during the fetal and pubertal periods. Ovarian destruction is reported to occur in up to 3 percent of women with pelvic tuberculosis (27). Galactosemia and deficiency of 17-hydroxilase enzyme are associated with POF. The diagnosis of idiopathic POF should be made by exclusion.

The resistant ovary syndrome is a condition with unknown etiology and has the clinical and endocrinologic characteristics of POF. Ovarian biopsy is necessary to make the diagnosis and generally shows many primordial follicles arrested before the antral stage of development. Therefore ovarian biopsy may help to uncover the underlying pathology (Table IV).

The current observations suggest changes in the management of patients with POF who desire to conceive. Elevated serum FSH levels on at least two separate occasions are necessary for a diagnosis of POF but this does not rule out the possibility of future conception. Spontaneous ovulation and pregnancy can rarely occur without treatment and expectant management is an option (10,12,13,19,22,26),

Ovarian sampling is a more active approach. Laparotomy is the preferred route for this purpose because specimens taken by laparoscopy may not contain enough tissue to be representative of the entire organ (7,9,10,12,28). But there is a controversy in regard to the necessity of performing an ovarian biopsy, (19). Its advantage is that it allows determination as to whether viable follicles remain in the ovary or whether many primordial follicles are present (resistant ovary syndrome). Also it may confirm an autoimmune oophoritis when a lymphocytic infiltrate is seen. However there are disadvantages in performing a biopsy. The absence of follicles may simply reflect an inadequate sample. The absence of follicles does not necessarily assure a response to therapy. And the risks of general anesthesia and major surgery as well as the possibility of postoperative adhesion formation are concerns.

Another option is to obtain a frozen section of the ovarian biopsy at laparoscopy and, if no follicles are seen, proceed with laparotomy (19). Overall, the disadvantages of ovarian biopsy must be weighed against the time, expense and inconvenience of medical therapy.

As an alternative to ovarian sampling, the degree of gonadotropin suppression in response to exogenous estrogen administration (FSH levels of less than 30IU/l for at least two days following IM injection of 1 mg estradiol benzoate) has been suggested to predict ovarian follicular activity (13).

If an ovarian biopsy is performed and reveals primordial follicles it sems to be wise to use HRT first (5-9, 14-17, 19-25). In addition to its higher success rate obtained early in the therapy, it costs less as compared with high dose gonadotropine therapy. And the best regimen appears to be conjugated estrogens for three weeks combined with a progestin in the third week followed by a drug free period of one week for 6-8 months since about 50 percent of the pregnancies were achieved in this period of time. Ovulation may occur during or shortly after the therapy and the couples should actively attempt conception. Its exact mechanism of action is not clear but some mechanisms have been proposed. It has been shown that estrogens promote differentiation of granulosa cells and increased responsiveness to FSH as well as enhancement of the appearance of LH receptors induced by FSH. Endogenous gonadotropin levels are decreased by administration of exogenous estrogens. It is thought that a reduction in gonadotropin levels might bring about a change in gonadotropin sensitivity of the ovary and renew ovarian responsiveness to the gonadotropins. And the rebound surge of the gonadotropins after the cessation of the therapy may also trigger follicular maturation and ovulation (29).

It is generally thought that gonadotropins are less effective than estrogens for induction of ovulation in patients with POF, as the addition of exogenous

gonadotropins to already elevated endogenous gonadotropins does little to stimulate follicular maturation (8). Patients who fail to respond may benefit from a combination of high dose exogenous estrogens and high dose gonadotropins. It has been reported that in 60 percent of the patients ovulation was induced with this treatment (15,23). The explanation for achieving pregnancy with this regimen is that chronically elevated FSH levels down - regulate FSH receptors on the granulosa cells, decrease FSH responsiveness and desensitize any remaining follicles. Suppressing FSH with estrogen allows the restoration and formation of FSH receptors, and enables some follicles to respond to exogenous FSH. In this respect GnRH analogs (e.g. leuprolid acetate) may also be used.

Table IV. Histological findings in POF

Resistant ovary syndrome	Primordial follicles arrested at or before antral stage
Autoimmune ovarian disease	Lymphocytic +plasma cell infiltrates in proximity of follicles
Other	No follicles

Patients with autoimmune ovarian failure treated for coexisting immune disease with corticosteroids and/or plasmapheresis may have a concomitant remission in the ovarian failure (30,31). It has been suggested that these patients may benefit from estrogen or oral contraceptive therapy (8,21-23). It is thought that decreased gonadotropin stimulation to the granulosa -theca cells reduces granulosa-theca cell activity and thereby reduces the expression of trigger antigens that are present only on maturing follicles. Reduction of the antigenic burden leads to a quieting of the autoimmune response and allows remission to occur (32). Here again GnRH analogs may be used for this purpose.

Finally, it can be seen from the figures in the literature that the rates of spontaneous abortion and congenital anomaly were not higher than those in general population. This observation rules out the possibility of only defective oocytes being left in the ovaries of POF sufferers.

When brought together these reports in the literature give a general idea for the management of infertility in patients with POF, but an extensive randomized study with different types of therapies is yet to be done in order to make a more certain conclusion.

REFERENCES

1. *de Moraes-Ruehsen M, Jones GS. Premature ovarian failure. Fertil Steril 1967;18:440-461*
2. *Jacobs HS. The premature menopause. In The Management of Menopause and The Post-Menopausal Years. Baltimore: University Park Press, 1976:359*
3. *Starup J, Sele V. Premature ovarian failure. Acta Obstet Gynecol Scand 1973;52:259-268*
4. *Cohen I, Speroff L. Premature ovarian failure: Update. Obstet Gynecol Survey 1991;46:156-162*
5. *Polansky S, De Papp EW. Pregnancy associated with hypergonadotropic hypogonadism. Obstet Gynecol 1976;47:47S-51S*
6. *Shapiro A, Rubin A. Spontaneous pregnancy in association with hypergonadotropic ovarian failure. Fertil Steril 1977;28:500-501*
7. *Shangold MM, Türksoy RN, Bashford RA, Hammond CB. Pregnancy following the "insensitive ovary syndrome". Fertil Steril 1977;28:1179-1181*
8. *Starup J, Philip J, Sele V. Estrogen treatment and subsequent pregnancy in two patients with severe hypergonadotropic ovarian failure. Acta Endocrinol 1978;89:149-157*
9. *Szlachter BN, Nachtigall LE, Epstein J, Young BK, Weiss G. Premature menopause: A reversible entity. Obstet Gynecol 1979;54:396-398*
10. *Wright CSW, Jacobs HS. Spontaneous pregnancy in a patient with hypergonadotropic ovarian failure. Br J Obstet Gynecol 1979;86:389-392*
11. *Johnson TR, Peterson EP. Gonadotropin-induced pregnancy following "premature ovarian failure". Fertil Steril 1979;31:351-352*
12. *O'Herlihy C, Pepperell RJ, Evans JH. The significance of FSH elevation in young women with disorders of ovulation. Br Med J 1980;281:1447-1450*
13. *Ataya KM, Mudawwar F, Allam C, Karam K. Hypergonadotropism with pregnancy. Am J Obstet Gynecol 1983;146:341-343*
14. *Voigt S. Pregnancy in a young woman with hypergonadotropic ovarian failure. Acta Obstet Gynecol Scand 1984;63:733-734*
15. *Check JH, Chase JS. Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy. Fertil Steril 1984;42:919-922*
16. *Ohsawa M, Wu M, Masahashi T, Asai M, Narita O. Cyclic therapy resulted in pregnancy in premature ovarian failure. Obstet Gynecol 1985;66:64S-67S*
17. *Amos WL. Pregnancy in a patient with gonadotropin-resistant ovary syndrome. Am J Obstet Gynecol 1985;153:154-155*

18. Finer N, Fogelman I, Bottazzo G. Pregnancy in a woman with premature ovarian failure. Postgrad Med J 1985;61:1079-1080
19. Alper MM, Jolly EE, Garner PR. Pregnancies after premature ovarian failure. Obstet Gynecol 1986;67:59S-62S
20. Chan CLK, et al. Oocyte donation and in vitro fertilization or hypergonadotropic hypogonadism: Clinical state of the art. Obstet Gynecol Survey 1987;42:350-362
21. Cowchock FS, McCabe JL, Montgomery BB. Pregnancy after corticosteroid administration in premature ovarian failure (polyglandular endocrinopathy syndrome). Am J Obstet Gynecol 1988;158:118-119
22. Taylor R, Smith NM, Angus B, Horne CHW, Dunlop W. Return of fertility after twelve years of autoimmune ovarian failure. Clin Endocrinol 1989;31:305
23. Check JH, Chase JS, Wu CH, Adelson HG. Ovulation induction and pregnancy with an estrogen-gonadotropin stimulation technique in a menopausal woman with marked hypoplastic ovaries. Am J Obstet Gynecol 1989; 160:405-406
24. Check JH, Chase JS, Spence M. Pregnancy in premature ovarian failure after therapy with oral contraceptives despite resistance to previous human menopausal gonadotropin therapy. Am J Obstet Gynecol 1989;160:114-115
25. Jequier AM, Conception in the resistant ovary syndrome occurring during hormone replacement therapy: A report of 2 cases. Aust NZ J Obstet Gynecol 1990;30:176-178
26. Letterie GS, Bork MD, Miyazawa K. Intermittent ovarian failure. J Reprod Med 1990;35:731-733
27. Nogales-Ortiz F, Tarancon I, Nogales FF. The pathology of female genital tuberculosis. Obstet Gynecol 1979;53:422-428
28. Sutton C. The limitations of laparoscopic ovarian biopsy. Journal of Obstetrics and Gynecology of the Bristish Commonwealth 1974;81:317-320
29. Rebar RW, Erickson GF, Yen SSC. Idiopathic premature ovarian failure: Clinical and endocrine characteristics. Fertil Steril 1982;37:35-41
30. Coulam CB, Kempers RD Randel RV. Premature ovarian failure: Evidence for the autoimmune mechanism. Fertil Steril 1981;36:238-240
31. Meldrum DR, Frumar AM, Shamonki IM et al. Ovarian and adrenal steroid-genesis in a virilized patient with gonadotropin-resistant ovaries and hilus cell hyperplasia. Obstet Gynecol 1980;56:216-221
32. Nelson LM, Merriam GR. Premature ovarian failure (Letter). Am J Obstet Gynecol 1990;162:874-876

MARMARA MEDICAL JOURNAL
INSTRUCTIONS TO AUTHORS

1. Manuscripts, letters and editorial correspondence should be sent to "Editor, Marmara Medical Journal, Marmara University, Faculty of Medicine, Istanbul-Turkey" by first class mail (airmail for overseas).
2. Submissions considered for publication are received with the understanding that no part of the submission has previously appeared elsewhere in any but abstract form.
3. Manuscripts should be typed double-spaced on standard-size typewriter paper with margins of at least 2.5 cm. This includes references, tables and figure-legends. The original typescript and two high-quality copies of the manuscripts should be submitted.
4. Number pages consecutively in order and place author (s) name, highest degree, institutional affiliations and address below the title.
5. Marmara Medical Journal invites papers on original research, case reports, reviews, short communications for practical applications, letters, editorials, book reviews and announcements. The number of typewritten pages should not exceed 10 for original articles, 12 for reviews, 4 for case reports and 1 for letters.
6. Original articles and research papers should normally be divided into following sections: A. (1) An informative summary for not more than 200 words must be included and should appear at the beginning of the paper. (2) Key words. (3) Introduction. (4) Materials and Methods. (5) Results. (6) Discussion,and (7) References.

   B. References must be typed in double spacing and numbered consecutively as they are cited. The style of references is that of the Index Medicus. List all authors when there are six or fewer, when there are seven or more, list the first three, then "et al". Sample references follow:

   1. Steward JH, Castaldi PA. Uremic bleeding: a reversible platelet defect corrected by dialysis. QJ Med. 1967; 36 : 409 - 23.

   2. Bearn AG. Wilson's Disease In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. The metabolic basic of inherited disease. New York : McGraw - Hill, 1972: 103-50.
7. Tables should be as few as possible and should include only essential data. Tables should be typed in double spacing on separate sheets and have a legend for each. Diagrams or illustrations should be drawn with black Indian ink on white paper and should be given Roman numerals. Each illustration should be accompanied by a legend clearly describing it : all legends should be grouped and typewritten (double spaced) on a separate sheet of paper. Photographs and photomicrographs should be unmounted high-contrast glossy black-on-white prints and should not be retouched. Each photograph or illustration should be marked on the back with the name (s) of the author (s), should bear on indication of sequence number and the top should be marked with an arrow. All measurements should be given in metric units.
8. Manuscripts are examined by the editorial board usually sent to out-side referees. The editor reserves the right to reject or to return the manuscript to the author(s) for additional changes if all the guidelines and requirements are not uniformly completed. Only two copies of the rejected papers are returned to the author (s).
9. Proofs will be submitted to the author responsible for proof correction and should be returned to the editor within 5 days. Major alterations from the text cannot be accented.
10. Correspondence and communications regarding manuscripts and editorial material subscriptions and payments should be sent to:

    The Editor
    Marmara Medical Journal
    Marmara University, Faculty of Medicine
    Haydarpaşa - Istanbul.