PREMATURE OVARIAN FAILURE

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PRIMARY ovarian failure results from disappearance of follicles from the ovary. The diagnosis can be established by demonstrating elevated gonadotropin levels. Among patients who undergo ovarian biopsy, about 50% have no follicles. In the other 50%, follicles are identified, but they are usually arrested before the antral phase of follicle development and resist gonadotropin stimulation. In a few patients, normal functional follicles are present in the ovaries despite the finding of elevated gonadotropin levels. We shall review the etiology of primary ovarian failure in the context of experience with 89 cases.

NORMAL OVARIAN DEVELOPMENT

Differentiation of the embryonic gonad into testes or ovaries depends on the sex chromosomes. Presence of a Y chromosome will cause development of testes. The determinants of ovarian development exist on both of the long and short arms of the X chromosome.

An undifferentiated gonad appears in the human embryo as a thickening on the urogenital ridge at about four weeks of gestation, and consists of an outer layer of celomic epithelium covering the inner medullary cord. Germ cells arise in the endodermic wall of the primitive gut and migrate along the mesentery to the genital ridge. Celomic epithelium eventually forms the ovarian cortex, source of the granulosa cells, and the mesenchyme forms the medulla of the ovary, the source of the interstitial and theca cells.

Germ cells can be identified by their strong alkaline-phosphatase activity. At five months of gestation, as a result of successive mitotic divisions, the number of primordial germ cells has increased to about 6,000,000 oocytes, but the number diminishes to 2,000,000 at birth, and before puberty there are only about 300,000 follicles in the ovary.[1] Only a few ovulate, and later in life the number decreases further at the rate of about 1,000 a month. There is evidence that in early fetal life germ cells disappear rapidly because

of inadequate arrangement of the granulosa and theca layers around the oocytes.[2]

Between eight and ten weeks of gestation the oogonia initiate meiotic division, which proceeds until the prophase of the first meiotic division, and is then arrested until later in life when further maturation of the follicle is initiated. What causes a primary follicle to mature is unknown. There is some evidence that the granulosa cells produce an inhibitory factor that arrests follicular development at the primary follicle stage. Follicular maturation prior to the antral stage does not depend on gonadotropin since FSH receptors appear only at a later stage of follicular development.

Normal Menopause

Women normally develop ovarian failure at menopause. Although the actual cause of menopause is still not clear, several theories have been proposed, including disappearance of primordial follicles from the ovary, decreased responsiveness of ovarian follicles to gonadotropin stimulation and decreased sensitivity of the hypothalamus to circulating estrogens, with a consequent elevation of gonadotropin levels.

As mentioned previously, the number of ovarian follicles decreases with age until it is markedly reduced at the menopause. Costoff[3] found morphologically normal oocytes in all postmenopausal ovaries he examined and oocytes that also appeared normal by electron microscopy. Procope[4] found developing follicles in postmenopausal women with amenorrhea of at least one year's duration, and in three patients he found a corpus luteum. Gonadotropin levels were increased in all these patients. Thus, lack of ovarian follicles is not the initial cause of menopause, but the follicles that remain probably are less sensitive to the high levels of circulating gonadotropins.

In view of these observations, it is of interest to note that in rats the menopausal period is characterized by constant estrus. An ovary from a menopausal rat implanted in a young rat will again start to ovulate.[5] The aging of the reproductive function, at least in this species, appears to be a result of the aging of the central nervous system.

In human beings the FSH levels increase with age. Significantly higher FSH concentrations are found in the 40-50-year age group than in the 20-29-year group while estrogen levels remain unchanged. Reyes,[6] for example, found no decrease in estrogen levels with age, while others[7] have found

normal to elevated estrogen levels associated with elevated gonadotropin levels among perimenopausal women.

Sherman[8] observed high gonadotropin levels in the follicular phase of older menstruating women, and noted that long duration of high gonadotropin concentrations did not necessarily indicate absence of follicles. During both follicular and luteal phases, estrogen levels were lower among perimenopausal women, but in the early follicular phase estrogen secretion was comparable in perimenopausal and younger patients. Thus, the main hormonal difference between older and younger women was the higher FSH levels in the perimenopausal patients. These observations point to a decrease in the sensitivity of the hypothalamic negative feedback mechanism to circulating estrogens.

Inhibin is a protein hormone assumed to be produced by granulosa cells. The hormone seems to inhibit FSH secretion to a greater degree than LH. Marder[9] and DeJong[10] demonstrated "inhibin" activity in the follicular fluid of graafian follicles. Decreased production of inhibin during the perimenopausal and menopausal period could explain higher FSH levels during the perimenopausal period, but our knowledge of inhibin production and activity is still limited.

Premature Ovarian Failure

Premature ovarian failure was defined by Sele and Starup[11] as amenorrhea associated with high gonadotropin and low estrogen levels before the age of 30 in women who had had a normal menarche and normal development of secondary sexual characteristics. Other authors include patients who became amenorrheic before the age of 40. Premature ovarian failure occurs in 5-8% of all patients developing secondary amenorrhea.

In most patients with premature ovarian failure, especially during the earlier stages, the ovaries contain follicles, but the follicles are arrested before the antral stage.[12] Development prior to this stage does not depend on gonadotropins because gonadotropin receptors are not present. Arrested development occurs at the stage when gonadotropin receptors are needed for further maturation.

Lack of receptor formation may explain the insensitivity of the follicle to gonadotropins. Estradiol increases FSH receptors, while FSH, in the presence of estradiol, increases receptors for both FSH and LH in the granulosa cells of the developing follicles. However, LH decreases receptors for FSH,

LH and estradiol (associated with luteinization).[13] Administration of LH or HCG is followed by prolonged loss of LH receptors that is time- and dose-dependent.[14] The loss of specific hormone receptor sites is associated with a desensitization of ovarian adenyl cyclase and a reduction in 17,20 desmolase, 3 β-dehydrogenase and 17-hydroxylase activities.

Alternatively, desensitization of gonadotropin receptors may cause premature ovarian failure in some cases, and explain decreased sensitivity of follicles in menopausal ovaries. *In vitro* incubation with HCG of ovarian tissue from women with premature menopause decreases steroid synthesis.[15] In three of our patients with ovarian failure and relatively high basal estrogen levels, administration of exogenous gonadotropins decreased estrogen levels, an effect reported by others.[16]

Resistant Ovary Syndrome

The resistant ovary syndrome was first described in 1969 by Jones,[17] who reported on three patients with primary amenorrhea, normally developed secondary sexual characteristics, apparently normal follicular apparatus and increased gonadotropin levels. One of the three patients ovulated after a very high dose of exogenous gonadotropins, but this response has not been obtained in similar patients by others. Campenhout[18] gave up to 6,150 IU of FSH and LH daily with no response.

The resistant ovary syndrome has been described in patients with secondary amenorrhea.[19] Criteria for the diagnosis are: high gonadotropin levels, presence of normal primordial follicles on ovarian biopsy and lack of response to exogenous gonadotropin administration.

The characteristic histological finding is abundant primary follicles arrested at the antral stage of development although in some specimens, particularly those from patients with secondary amenorrhea, the number of follicles is diminished. The ovarian biopsy must be interpreted very carefully, especially if it is obtained by laparoscope, because in many cases the biopsy is not representative of the ovary. For example, pregnancy has been diagnosed in patients with no follicles in ovarian biopsy.[20] The resistant ovary syndrome appears to be an early stage of ovarian failure in which maturation arrest of the follicles occurs. Ultimately, the follicles disappear.

In rare instances, a patient with ovarian failure may have episodes of ovulation, and pregnancy is occasionally possible. A few spontaneous pregnancies have been described in patients with the resistant ovary syndrome. The pregnancies usually occurred during or immediately after estrogen adminis-

TABLE I. ETIOLOGICAL CLASSIFICATION

1) Genetic
a) Gonadal dysgenesis
b) Metabolic disorders
c) Immunological deficiency
2) Autoimmune diseases
3) Infections
4) Environmental causes
5) Iatrogenic causes
6) Idiopathic or unknown

TABLE II. GENETIC CAUSES OF OVARIAN FAILURE

Gonadal dysgenesis
1) With X chromosome deletion (Turner's syndrome)
2) With normal XX or XY complement (pure gonadal dysgenesis)
3) Trisomy 13 (Edward's syndrome)
4) Trisomy 18 (Patau's syndrome)
Metabolic disorders
1) 17-hydroxylase deficiency
2) Galactosemia
3) Mytonic muscular dystrophy (Steinert's disease)
Immunological deficiency
1) Ataxia telangiectasia
2) DiGeorge syndrome
3) Mucocutaneous fungal infections

tration.[21] Two of our patients conceived after a diagnosis of ovarian failure was established, but neither had received estrogen replacement therapy.

Etiology of Ovarian Failure

In most patients with ovarian failure, the etiology cannot be established. Table I summarizes the known causes of ovarian failure. Among the known causes, genetic disorders are the most common. Chromosomal anomalies are found in patients with primary amenorrhea and ovarian dysgenesis, but a genetic factor is involved in many patients with ovarian failure and normal karyotypes. Included in the genetic disorders are metabolic and immunological deficiency diseases. Ovarian failure is associated with an autoimmune disorder in a relatively high proportion of patients. The other major known cause of ovarian failure is iatrogenic.

Genetic causes of ovarian failure. Table II summarizes genetic causes of ovarian failure. The major genetic cause is an embryonal defect in the ontogenesis of the ovary that results in ovarian dysgenesis. No normal ovarian tissue is found on biopsy.

X chromosome deletion (Turner's syndrome). The most common cause of ovarian dysgenesis is sex chromosome anomaly. Typically, such patients have streak ovaries. McDonough[22] studied 82 patients with ovarian failure and found sex chromosome anomalies in 52. The most frequent single-cell anomaly was 45X0 (Turner's syndrome). Interestingly, he found sex chromosome anomalies only in individuals less than 63 inches tall. Sauer[23] reported a case of ovarian dysgenesis with balanced translocation of the long arm of an X chromosome to the short arm of one of the number seven autosomes, without deficiency in chromosomal material. Simpson[24] summarized current knowledge about the location of the ovarian determinants and concluded that determinants exist on both of the long and the short arms of the X chromosome. Duplication of one arm fails to compensate for the loss of the other, but individuals with distal breaks do not show ovarian dysgenesis. Individuals who have a deletion of the short arm are always short, and the long arm may or may not carry stature determinants.

The mechanism of the ovarian development in X chromosome deletions is unclear. There is evidence that oocytes require only one X chromosome to differentiate.[25] Singh[2] and Carr[25] compared ovaries of fetuses and embryos with XO genotype with ovaries of normal fetuses and found that XO fetuses have the same number of primordial germ cells as normal fetuses during the first three months of gestation, but later connective tissue increases in XO gonads. Germ cell formation and migration in XO gonads appears to be normal. The defect is in follicle formation. Because of a deficiency in the cells, germ cells that enter the first meiotic prophase cannot organize a primordial follicle and as a result degenerate.

There are many reports of ovarian function in patients with X chromosome anomalies.[22,26] At least 10-12% of patients with gonadal dysgenesis have some ovarian function.[22] The incidence of menstrual function in mosaicism is considerably higher. Wray[26] studied patients with the 45XO karyotype or mosaicism who became pregnant and found a high frequency of congenital anomalies, mainly gonadal dysgenesis and trisomy 21, among the offspring. Only 15 out of 48 pregnancies resulted in a normal fetus.

Ovarian dysgenesis with normal XX or XY complement. Patients with gonadal dysgenesis and a normal chromosomal complement may have either 46XX or 46XY karyotypes. They usually reach normal stature. The diagnosis of streak ovaries can be made only by visualization of the ovaries. Thirty-six percent of the patients with primary ovarian failure that McDonough[22] described had normal chromosomes, and of these 40% have some menstrual function.

Simpson[24] found 61 cases of 46XX gonadal dysgenesis reported in the literature prior to 1971. Very few of them had Turner's stigmata; only eight were short in stature and a few had nerve deafness, but a significant number of the parents were consanguineous. There is also evidence of a familial aggregation of females with 46XX gonadal dysgenesis, suggesting that XX gonadal dysgenesis is an autosomal recessive disorder. A disorder of monozygotic twins was described[27] in which only one twin was affected. Thus, there may be two variants of the syndrome, one with a genetic cause and the other with an environmental component that affects the gonads and causes early destruction of the ovary.

Gonadal dysgenesis with a 46XY karyotype is less common. Absence of functional gonadal tissue results in development of a female with normal genitalia. Almost all patients are normal or tall in stature.[27] Fraisier[28] described a pair of affected monozygotic twins, and others[29] have reported the syndrome in siblings. It is probably an X-linked recessive disorder.

Autosomal anomalies. Ovarian dysgenesis has been described with autosomal anomalies,[30] mainly infants with trisomy 18 (Edward's syndrome) and trisomy 13 (Paton's syndrome). These anomalies have no clinical significance because they are incompatible with life, but their occurence indicates that ovarian determinants are present in the autosomes as well as the sex chromosomes.

Metabolic Disorders

A few patients with ovarian failure and 17-hydroxylase deficiency have been described.[31] This enzyme is necessary for the synthesis of estrogens and cortisol, but it is not required for the synthesis of the mineralocorticoids. Patients usually present with primary amenorrhea, failure to develop secondary sexual characteristics, increased gonadotropin levels and hypertension. The ovaries are usually enlarged and develop multiple cysts secondary to excessive stimulation by the elevated gonadotropin levels.

Galactosemia. Patients treated early in life with a galactose-free diet have a high frequency of ovarian failure.[32] Patients who are not treated develop mental retardation, but not ovarian failure. The ovarian failure may result from metabolic derangement in the ovary or change in the bioactivity of the gonadotropin molecule, which contains galactose and galactosamine. Several studies[33,34] have shown a direct effect of galactose or its metabolites on the parenchyma of the ovary, which may explain the ovarian failure. To prevent damage to fetal ovaries mothers at risk should follow a galactose-free diet during pregnancy.

TABLE III. AUTOIMMUNE DISEASES ASSOCIATED WITH PRIMARY OVARIAN FAILURE

Addison's disease	Diabetes mellitus
Hypothyroidism	Rheumatoid arthritis
Hypoparathyroidism	Vitiligo
Myasthenia gravis	Idiopathic thrombocytopenia
Pernicious anemia	Alopecia areata
Autoimmune hemolytic anemia	

Myotonic muscular dystrophy (Steinert's disease). Myotonic dystrophy is a myopathy mainly involving the distal musculature of the extremities and cranial muscles and associated with cataracts and osseous lesions. Inheritance is by a dominant trait with variable penetration. In its congenital forms, maternal intrauterine factors may be involved in the penetration of the abnormal gene.[35] Gonadal failure is common among affected males, and damage to the seminiferous tubules ranges from abnormal spermatogenesis to complete tubular fibrosis. Fifteen to 20% of affected females suffer from oligomenorrhea, and some have increased gonadotropin levels although hypothalamic-pituitary function is normal.[36]

Immunological Deficiency

Ovarian failure is associated with ataxia telangiectasia[37] and Di George's syndrome,[38] and has been described among patients with T-cell anomalies and mucocutaneous infection.[39] Patients with immunological deficiency diseases have a strong tendency to develop autoimmune disease, but the mechanism of the associated ovarian failure is unclear.

Ovarian Failure As An Autoimmune Disorder

Ovarian failure occurs in a relatively high proportion of women with autoimmune diseases (Table III). The most common association is with Addison's disease.[40] Irvine[41] described 168 patients with Addison's disease of whom 25% had ovarian failure. He also noted an association between primary amenorrhea and hypoparathyroidism. Hypothyroidism and pernicious anemia were also associated with gonadal and adrenal failure. Other autoimmune diseases associated with ovarian failure are Hashimoto's disease,[42] idiopathic thrombocytopenia, rheumatoid arthritis with vitiligo,[43] alopecia areata, Cushing's disease,[41] autoimmune hemolytic anemia and myasthenia gravis.[44,45]

Irvine could not demonstrate circulating antiovarian antibodies not associated with antiadrenal antibodies in patients with amenorrhea, but others[46] found antiovarian antibodies that did not react with adrenal tissue in two patients. Results of absorption studies indicate that the antigens are similar in the adrenal cortex, theca interna of the ovary, granulosa cells, interstitial cells and placental trophoblast.[40,41] The antigens are related to enzymes involved in the various pathways of steroid synthesis. Different antigens are involved in different patients. The possibility that antibodies to such antigens interfere with gonadotropin receptor sites has been raised. Coulam[47] found that the antigen comprises about 2-3% of the ovarian protein. It is unlikely that gonadotropin receptors will be found in such quantity.

McNatty[48] studied the effect of sera from patients with antiovarian antibodies on granulosa cells in culture and found a reduction of progesterone production by the sera-treated cells. The receptors are not needed at this stage, and the media contained no HCG. Austin[49] concluded from his study that no circulating antibodies interfere with HCG-LH receptors. However, Escobar[44] and Chiauzzi[45] described patients with myasthenia gravis and ovarian failure, and presented evidence to suggest that in those patients the antibodies are directed at the FSH receptors.

Infections

Mumps is the infection most frequently associated with ovarian failure. There is evidence that the ovary is most sensitive to damage by the mumps virus during the fetal and pubertal periods.[50] Mumps during puberty can cause ovarian failure even in cases of subclinical infection.

Ovarian destruction occurs in 3% of women with pelvic tuberculosis.[51] The incidence of elevated gonadotropin levels in such patients is unknown. The main causes of amenorrhea in women with pelvic tuberculosis is destruction of the endometrium and intrauterine adhesions.

Environmental Causes

Women who smoke cigarettes have an earlier menopause than nonsmokers.[52] Jick's[52] study indicated a dose-related effect of smoking and the age at menopause. The average age at spontaneous menopause was 49.6 among nonsmokers and 44.3 among smokers in the group studied. Polycyclic aromatic hydrocarbons can destroy oocytes in mice[53] and alter oocyte meiosis, a dose-related effect, but the hydrocarbons do not affect the response

TABLE IV. IATROGENIC CAUSES OF OVARIAN FAILURE

1) Radiation
2) Chemotherapy
   a) Cyclophosphamide
   b) Busulfan (Myleran)
   c) Drugs possibly involved
      Metotrexate
      6-mercoptopurine
      arabinosylaytosine
      actinomycin
      adriomycin
      dauomycin
      Thioguanine
      hydroxyurea
      L-asparaginase
      procarbiazin
3) Adnexal surgery

of the ovary to gonadotropin stimulation.[54] Cigarette smoke contains many polycyclic aromatic hydrocarbons that may cause oocyte destruction among humans in the same fashion.

Iatrogenic Causes of Ovarian Failure

A marked improvement in survival of patients with certain neoplastic diseases raises the problem of ovarian failure secondary to radiation and chemotherapy. Some iatrogenic causes of ovarian failure are listed in Table IV.

Radiation. Low-dose radiation in the range of 250-500 rads causes permanent ovarian failure in 60% of patients, and 800 rads usually suffices to cause artificial menopause.[55] Patients treated for Hodgkin's disease and lymphoma may receive radiation to the pelvic nodes in the range of 4,400-4,500 rads. Because of the high cure rate, efforts to preserve ovarian function are worthwhile. Oophoropexy and shielding of the ovaries during radiation will reduce the amount of radiation received by the ovaries to the range of 350-400 rads, and preserve ovarian function in 59% of such patients. No congenital anomalies have been reported in the offspring of treated patients.[56]

Chemotherapy. Treatment with busulfan is frequently associated with amenorrhea and ovarian failure, and cyclophosphamide is also commonly associated with development of ovarian failure. Treatment with a low dose for a short period of time, as used for non-neoplastic diseases, does not cause ovarian failure, but with high doses and longer duration of treatment, ovarian ablation is a frequent complication of cyclophosphamide therapy in women.[57]

The histological appearance of the ovaries after cyclophosphamide therapy reveals abundant primordial follicles with maturation arrest beyond the primary follicle stage. The same picture is seen in the resistant ovary syndrome.[58] Warne[57] described patients who developed ovarian failure during cyclophosphamide therapy. A few of them regained normal ovarian function after termination of therapy. Later the follicles gradually disappear. few authors[58,59] have described patients who developed ovarian failure after treatment for malignant diseases with various combinations of chemotherapeutic agents, and in such patients it is impossible to identify a single drug as responsible for the ovarian damage.

Surgery. Nine percent of our patients developed ovarian failure following pelvic surgery, mainly for endometriosis and other benign ovarian neoplasms. It has to be emphasized that every effort should be made during surgery to minimize damage to the ovary, preserve as much ovarian tissue as possible and prevent damage to the ovarian blood supply, especially in patients who desire children.

Increase of Gonadotropin Levels with Normal Ovaries

Increased gonadotropin levels can occur as a primary condition, as in cases of pituitary tumors secreting FSH. Other possible causes are abnormal, biologically inactive FSH and LH molecules, and presence of antigonadotropin antibodies.

Gonadotropin-secreting tumors. Gonadotropin-secreting pituitary tumors have been described in patients with primary ovarian failure, but pituitary enlargement is usually secondary to end organ failure, as hypothyroidism and hypoadrenalism.[60] There are a few reports of autonomous FSH-LH secreting pituitary adenomas in males.[61] Snyder[62] presented two cases of FSH-secreting tumors, one in a patient with normal functioning testes and the other in a patient with normal testosterone levels. Kovacs[61] noted that removal of the pituitary adenoma in one of his patients was followed by increased serum testosterone levels and return of sexual potency. In this case, it is likely that the high gonadotropin levels "down regulated" the LH receptors, and removal of the adenoma reversed the condition. The same author noticed a considerable structural difference between the adenoma cells and nontumorous FSH-secreting cells, and speculated that the tumor cells were undifferentiated precursors or committed stem cells which, despite their morphological immaturity, were capable of producing FSH. No such tumor has been described in a female.

Abnormal FSH and LH molecules. Silva DeSa[63] described abnormal

forms of gonadotropins in patients with premature ovarian failure, but the gonadotropins in his patients were not tested for bioactivity. Most evidence suggests that in most cases the LH and FSH molecules are active. Most of DeSa's patients had previously normal menses, thus demonstrating the ability to produce normal gonadotropins. Furthermore, they did not respond to exogenous gonadotropins. Koninck[64] determined the molecular weight of the gonadotropins in his patients and found them similar to the gonadotropins detected in postmenopausal women. Jones demonstrated that the gonadotropins from her patients were biologically active in rats.[17]

Antigonadotropin antibodies. Appearance of antigonadotropin antibodies is one possible explanation for ovarian failure. Rabinowitz[65] and Beers[66] described anti-FSH antibodies in patients with low FSH levels, and possibly similar antibodies play a role in some patients with ovarian failure and high gonadotropin levels.

Hypothyroidism

Most studies suggest decreased secretion of gonadotropins by hypothyroid women. However, juvenile hypothyroidism and some cases of adult-onset hypothyroidism[67] are associated with elevated levels of gonadotropins. The gonadotropin levels decline after treatment with thyroid preparations. Mechanisms that might cause elevated levels in hypothyroidism are: Alteration in ovarian steroidogenesis secondary to the hypothyroid state; elevated levels of common neurotransmitters such as norepinephrine that increase both TRH and LHRH; and a nonspecific action of TRH at a very high level on release of gonadotropins.

Clinical Studies

Over a five-year period 89 patients with premature ovarian failure were seen in our infertility unit. Criteria for the diagnosis were amenorrhea and elevated gonadotropin levels before the age of 35. The patients were classified according to the diagnoses in Table V. The diagnosis and management of representative cases is described below.

Ovarian dysgenesis. In 31 patients ovarian dysgenesis was confirmed by laparoscopy. All had primary amenorrhea, but six patients menstruated spontaneously a few times. Five had a 46XO karyotype, 1 had 46XX-q and the other patients were mosaics (45XO/46XX, 45XO/46/XY/46XY-q, 45XO/46XX). Nineteen patients had ovarian dysgenesis with a normal 46XX karyotype and 4 had a 46XY karyotype. *Case report.* A.L., age 25, was

TABLE V. 89 CASES OF PRIMARY OVARIAN FAILURE

Sex chromosome anomaly	8
Pure ovarian dysgenesis	23
Cancer therapy	13
Surgery (benign disease)	7
CNS lesions	3
Idiopathic	27
Total	89

seen because of primary infertility. Menarche occurred at age 12 and menses every 2-3 months since. Height was 56½ inches, and the patient had normal hair distribution, short and webbed neck, shield type chest and well-developed breasts. External genitalia, uterus and adnexa were normal but the vaginal mucosa was atrophic and the cervix was small with no mucus seen. The laboratory findings included: FSH-10.8 mIU/ml, LH-7.3 mIU/ml, urinary estrogens 15ug/24h and karyotype 46X X-q/45X-q. Because of the normal gonadotropin and spontaneous menses, induction of ovulation was attempted. Treatment with Pergonal, six ampules daily for 12 days, resulted in no response. Ovarian biopsy showed stroma containing fibro-hyaline nodules lined with coelomic epithelium. No ova or follicular structures were noted. In the following two years urinary estrogens decreased to undectable levels, while gonadotropin levels rose: FSH-44.1 mIU/ml, LH-12.4 mIU/ml, and the patient became amenorrheic. Despite ovarian dysgenesis, this patient demonstrated some menstrual function and estrogen production without ovulation.

Cancer therapy. Thirteen patients developed ovarian failure after therapy for various malignant diseases. Six patients were treated for Hodgkin's disease, three for leukemia, one for Ewing's sarcoma, one for chondrosarcoma, one for Wilm's tumor and one for malignant melanoma. Therapy was radiation alone in two patients, chemotherapy in four and radiation and chemotherapy in seven.

Case Report. Patient had menarche at age 13, followed by regular menses. At the age of 30 a diagnosis of Hodgkin's disease was established and the patient was given radiation therapy. Oophoropexy-transposition of the ovaries to the midline was done to reduce the quantity of radiation received by the ovaries, but the patient became amenorrheic. She was seen again at age 37 because of onset of vaginal bleeding. The possibility of reversal of the ovarian failure was raised, but gonadotropin levels were high: FSH-94

mIU/ml, LH-62 mIU/ml. Endometrial curretage was performed and endometrial carinoma was discovered.

Postpelvic surgery. Eight patients developed ovarian failure following adnexal surgery. Of these, four had surgery for endometriosis, one patient had a bilateral cystectomy and two had unilateral cystectomy and wedge resection of the contralateral ovary.

Autoimmunose disease. Seven patients had known autoimmune disease: four had hypothyroidism, two had lupus erythematosus and one had myasthenia gravis.

Central nervous sytem lesion. Three patients had a central nervous system lesion. One had temporal lobe epilepsy, one had multiple sclerosis and one had a nonprolactin-secreting pituitary ademona.

Idiopathic ovarian failure. Twenty-seven patients had ovarian failure with normal karyotypes and no other lesions. Twenty of the patients had evidence of episodic ovarian function. They menstruated spontaneously on occasion, and four of them had episodes of ovulation proven by biphasic temperature curves and endometrial biopsy. Two patients conceived spontaneously after the diagnosis of primary ovarian failure was made. One delivered at term and one miscarried. Ten patients had normal-appearing follicles on biopsy and were treated with human menopausal gonadotropins (HMG) but none responded. In three, basal estrogen levels decreased while on HMG therapy.

Case report. D.M., age 28, was seen in 1974 because of primary infertility. At that time the patient menstruated regularly. Ovulation was indicated by the biphasic B.B.T. and secretory endometrium on biopsy. She was seen again in 1978 complaining of irregular menses occurring and at two-six month intervals. The basal body temperature was monophasic. In October 1978 the patient complained of hot flushes. Gonadotropin levels were FSH-14 mIU/ml, LH-12.1 mIU/ml. In December 1978 the patient was given clomiphene 200 mg daily for 5 days. Blood estrogen levels rose to 335 pg/ml, but ovulation did not occur. The hot flushes persisted, and a repeat gonadotropin measurement showed FSH-33.9 mU/ml and LH-33.2 mIU/ml.

From February until May 1979 the patient had 3 menses with biphasic B.B.T. Ovulation was indicated by a progesterone level of 7.2 ng/ml and a finding of secretory endometrium on endometrial biopsy. Random gonadotropin levels were FSH 6.7 mIU/ml and LH-80 mIU/ml. The patient became amenorrheic again. In August 1979 a D&C showed inactive endometrium, and laparoscopy revealed small, inactive ovaries. At that time, gonadotropin levels were FSH - 59 mIU/ml, LH - 36.2 mIU/ml. This pa-

tient demonstrated early onset of ovarian failure with periods of amenorrhea and a gradual increase in gonadotropin levels.

Case report. L.G.J., age 34, G1 P1, was seen for secondary infertility of six years duration. The patient had a normal menarche at age 13, conceived at age 24 and had a normal delivery. At age 25 she had a subtotal thryoidectomy, and subsequently her menses became increasingly irregular, occurring every three-four months. In December 1978 she was given clomiphene 200 mg daily for five days and responded with ovulation. However, she did not respond to repeat clomid therapy or to Pergonal, up to 6 ampules daily for 10 days. Serum gonadotropin levels were FSH - 37 mIU/ml, LH - 34.4 mIU/ml. In March 1979 gonadotropin levels were FSH - 35.8 mIU/ml, LH - 21.9 mIU/ml and the patient became amenorrheic. A diagnosis of ovarian failure was made but six months later the patient conceived spontaneously.

Conclusions

Primary ovarian failure is a condition with multiple etiologies. Genetic causes are most prevalent in early onset of the condition and autoimmune disorders most prevalent in later onset of ovarian failure. The etiology in a large number of patients remains unknown.

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