REVIEW ARTICLE

Eastern Journal of Medicine

East J Med 23(2): 135-140, 2018
DOI: 10.5505/ejm.2018.14622

Genetics of premature ovarian failure

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ABSTRACT

Premature ovarian failure was defined as the cut-off of menstrual period for at least 4-6 months before 40 years of age, and FSH values measured over a month were over 40 IU/L. Although etiology is not fully understood, it is thought that genetic, immunological and environmental factors can play a role. Nowadays, translational and deletion in the critical regions (Xq13-26) on the X chromosome are defined in the developmental light in the genetic area. New approaches have been developed in clinical follow-up and treatment in recent years. It has been reported that caution should be taken in the follow-up, especially in terms of osteoporosis. In this article, recent literature on premature ovarian failure attempted to reveal current genetic etiology of premature ovarian failure.

Key Words: Premature ovarian failure, genetic reasons, ovarian aging

Definition

Premature Ovarian Failure (POF), was defined by Fuller Albright in 1942, is existence of hypergonadotropic hypogonadism and menstruel cycles disorders among women aged below 40 (1,2). This syndrome characterized with symptoms related with lack of sex steroids, metabolic effects and decreasing of fertility, is also named as gonadal disgenesis, premature/early menopause, hypergonadotropic hypogonadism/amenorrhoea, ovarian disgenesis in literature (2). Ovarian functions can be continued for a while unlike natural menopause in these women. Intermittent follicle development in about half of women with POF, occasionally ovulation in quarter of them and spontaneously pregnancy and parity in 5-10% have been reported (3-6). Therefore 'menopause' word should not be used when advice given. Recently there are some opinions about use of primer ovarian failure (1,6-8) or premature ovarian disfunction (9,10) instead of premature ovarian failure because of long clinical process, thought that using these terms is more comprehensible and less traumatic for patients cause of variable and reversible process of POF.

Epidemiology

POF incidence increases with age; <20 age 0.01%, <30 age 0.1% and <40 age 1% (11). 10-28% prevalence in women with primer amenorrhoea and 4-18% prevalence in women with seconder amenorrhoea have been reported (10,11). Incidence shows alterations with ethnical origin; 1.4% in Afro-Americans and Hispanics, 1% in Caucasians, 0.5% in Chineses and 0.1% in Japaneses (12). Smoking increases POF risk, late menarche, irregular menstruation and lactation decrease the risk (13).

Etiology

The underlying mechanisms for POF are small number of follicles at beginning, rapid atresia/apoptosis of follicles, follicles that are unresponsive to gonadotropins, inadequate follicle maturation or destructions of follicles with autoimmunity, chemo-radiotheraphy, environmental toxins and infections. The etiology is unknown in 90% of cases as well as genetic factors have an essential part in known factors. It has been reported that there is a familial story in 4-30% of POF cases (14). Possibility of having POF is higher in other family members who have familial POF story than sporadic cases. Knowledge of which one is familial or sporadic has an importance for advising and planning of pregnancy times for other family members are likely to be affected (14). The other POF reasons can be summarized as autoimmunity, environmental factors (viral infections, toxins) and iatrogenic (Chemotherapy, RT, surgical approaches). (Chart-1)

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Received: 26.04.2017, **Accepted:** 30.05.2017

Genetical reasons

Disorders associated with X chromosome: One X chromosome in female mammals become inactivated to equilibrate number of X chromosome between male and female mammals, but some genes escape from being inactivated. While one X chromosome is enough for ovarian differentiation, functional two X chromosomes are needed for normal oogenesis and ovarian functions (8,14,15). Numeral and structural defects of X chromosomes like monosomy-trisomy, deletion and translocation make the biggest group among POF reasons.

Syndrome of Turner; total monosomy/ mosaism of X chromosome; is characterized with ovarian failure, short height and typical phenotypes, endocrine and autoimmune disorders. Rapid follicular atresia in intrauterine life at the second half of pregnancy has been thought as the underlying mechanism of ovarian failure occurred in Turner. The most common caryotypes are 45,X/46,XY; 45,X/46,XX; 45,X/47,XXX in mosaic individuals; the most common structural anomaly is isochromosome of long arm of X chromosome (i(Xq)). Phenotypes can change from person to person and contrary to popular belief it does not depend on dosage in other words does not depend on being mosaic or pure 45X. Persons who have pure 45,X cell series can not show whole phenotypical features, may menstruate and become pregnant. 10-15% of women with Turner have pubertal modifications, 5% have normal menstrual cycles and 1-2% are able to become pregnant spontaneously. Nevertheless amenorrhea occurs before age 30 in these women, it has not been known that when will follicles run out; there are some cases reporting patients menstruate at thirties. Diagnosing at infantile period or early childhood provides early hormone replacement treatment and telarche/pubertal development start without delay. Despite of efficacies have not been proved yet, it has been thought that with early diagnose, oocyte cryopreservation before oocytes run out is a hopeful option for fertility for these patients (16).

Fragile X Syndrome is the most common reason of familial mental retardation and autism; is seen about 1/4000 in men, 1/4000-8000 in women (17). Molecular basis of this syndrome is increasing CGG repetition on 5' point (5' UTR) of FMR1 (Fragile X Mental Retardation 1) gene part [is on long arm of X Chromosome (Xq27)] that is not exposed to translocation. And according to repetition number this syndrome is classified to 4 group as normal, grey zone, premutation and total mutation (18-20). CGG repetition on 5' UTR is below 45 in normal or untagged persons. And average is known as 29-30, 45-54 is defined as grey zone. If repetition number of these nucleotide series is>200, it is defined total mutation; it precipitates that FMR1 gene transcription stop with hypermethylation, lack of FMRP protein and Fragile X Syndrome characterized mental retardation. Expression of total mutation is total in men and patients show whole characteristics of syndrome. Phenotypic features are variable in women due to inactivation of X chromosome. 55-200 repetition number is named premutation. And premutation is related with POF substantially, after Syndrome of Turner, it is the most common congenital cause of POF (17-20). Premutation is also related with tremor ataxia syndrome (FXTAS) is a progressive neurodegenerative disaese that is associated with Fragile X (17).

Prevalence of FMR 1 gene premutations have been reported as 1/86 among women who have mental retardation story at their family, 1/257 among women who have no risk factor (21). POF risk increases 20-fold in persons who have premutations; POF prevalence has been reported as 13-26% in these women (17). In a study, it has been reported that paternal premutations is more related with POF risk than maternal ones (3.7% against 28%) (22), however it has not been supported with following studies (17,23). POF risk seems to be related with premutations repetition number; it has been reported that risk increases to 80-100 repetition, decreases above 80-100 (24,25).

CGG repetitions have been thought to be related with ovarian reserve directly at the number of repetitions below premutation intervals which means grey zone or normal recently (26). In studies, it has been indicated that normal level of CGG repetitions is 26-34 (avg. 30) among normal ovarian reserved women and while CGG repetitions increase, at the 35-55 interval, AMH, FSH, gathered oocytes number with ovarian stimulation and measured ovarian reserve deteriorate among women under 38 age. According to these verifies, CGG repetitions number has been thought to reflect 'premature ovarian aging' or 'occult premature ovarian failure' (these are defined as mild forms of POF) and has been thought to be part of the process leading to POF (26).

Maternal premutations are not stable and can change to total mutation while transferring to next generation. Minimum repetitions that change to

total mutation are 59; possibility of changing from premutation to total mutation increases with increased repetitions (17).

Trisomy X is the most common anueploidy and is seen as 1/1000 in women. It has been reported that trisomy X has no negative effect on fertility but in these women POF incidence is likely to be higher than normal population (27). Nevertheless exact prevalence is unknown, in a series including 52 women, it has been reported that 3.8% of them have POF and likely to be related with autoimmune thyroid disease (28).

Deletion and translocation of X chromosome can also be resulted with POF. Notwithstanding X chromosome deletions are on short arm, POF is mostly related with Xq13-25 regions (14).

Translocations between Xq13-27 where is accepted as critical zone for ovarian functions is a cause of POF and two locus have been defined, POF1 (Xq26-qter) and POF2 (Xq13.3-Xq21.1)(14,15). POF1 translocations cause POF between 24-39 age and POF 2 translocations cause POF between 16-21 (14).

Table 1. POF (Premature Ovarian Failure) Etiology

Genetic *Associated with X Chromosome*
• Syndrome of Turner • Fragile X Syndrome • Deletions • Translocations • Trisomy X • Mutations in BMP-15 and GDF-9 genes
Associated with Autosomal Chromosomes (Related with Syndromes)
• Galactosemia (Mutation at GALT gene) • Blefarophymosis-ptosis-epicantus inversus syndrome (Mutation at FOXL2 gene) • Pseudohypoparathyroidism 1a (Mutation at GNAS1 gene)
Associated with Autosomal Chromosomes (Isolated)
• Inactivated mutations at FSH and LH receptors genes • Ataxia-Telangiectasia • BRCA1 mutation • Mutation in Inhibin A gene • EIF2B, 4 and 5 mutations • PGRMC1 mutation
Autoimmune Diseases • With adrenal autoimmunity • With extra-adrenal autoimmune diseases
Infections • Parotitis oophoritis • Tuberculosis • Malaria • Shigella • Varicella • Cytomegalovirus • Herpes Simplex
Toxins • Inorganic composites- Cd, Pb, Cr IV • Synthetic organic composites- Solvents, pesticides, chemical industrial composites • Polyaromatic hydrocarbons- dimetilbensantrasen, benso-a-piren
Iatrogenic • Pelvic surgery • RT/CT

Bone morphogenetic protein 15 (BMP-15) and growth differentiation factor 9 (GDF-9) are expressed from ovarian follicles and are member of TGF-beta family. BMP-15 takes part for follicle maturation, regulation of follicles sensitivity to FSH, prevention of granulosa cell apoptosis and ovulation regulation. Gene of BMP-15 is in Xp11.3 locus and its mutations have been indicated to be related with POF and infertility, prevalence is 1.5-12% in women with POF (15). GDF-9 is BMP-15 homolog; takes part in folliculogenesis and has synergistic effect on granulosa cells functions similarly. It has been reported that prevalence of these gene variations is 1.4% in women with POF (15).

Disorders associated with autosomal chromosomes: Galactosemia is a hereditary, autosomal recessive galactose metabolism disorder which depends on lack of glucose-6P urydiltransferase. It is characterized with liver, kidney, heart and complications. Gene of this enzyme is on short arm of 9. chromosome (9p13) and over 220 mutations have been defined. In spite the fact that POF was reported in 67% of women with galactosemia previously, almost every women who have homozygous mutation on GALT gene have POF sooner or later. Mechanisms that have been thought to cause POF, are apoptosis and damage on ovarian tissue on account of increased galactose and its metabolites/ decreased UDP-galactose levels, acceleration of follicular atresia because of abnormal glycosilation of glycoproteins like FSH and/or FSH receptors and epigenetically alterations (like alteration because of toxicity on ARH1 (Aplaziras homolog1) that is tumor suppressor gene take part on folliculogenesis, down regulation on GDP-9 gene). Severity of clinical table shows varieties between patients even they have same phenotype. Even though high FSH levels are observed at early ages (4 months-4 ages), can appear sooner. POF clinical process indicates fluctuations in these women. Response to exogenous gonadotropins stimulation an even spontaneously pregnancies have been reported (15,29). Blefarophymosis-pytosis-epicantus inversus syndrome is an autosomal dominant disorder characterized with typical eye lid symptoms cause of mutation on FOXL2 (Forkheadbox L2). Type 1 (one of two type f this syndrome) is related with POF. FOXL2 gene is on long arm of 3. chromosome (3q23) and takes essential part on folliculogenesis, follicular development and continuation, ovarian differentiation. Over hundreds mutations are defined. Ovarian phenotype is variable substantially; clinical spectrum indicates alterations in the way that menstrual disorders, infertility and ovarian failure. Extra-syndromic mutations of FOXL2 causes POF rarely (14,30).

Pseudohypoparathyroidism type 1a originates from GNAS1 gene (20q13) mutations cause inactivations of G-proteins alpha unites (Gs-alpha) that takes part on excitation of peptide structured receptors with activated situation. Lack of Gs alpha activation is resulted with end organ resistance to a lot of peptide structured hormones like PTH at kidneys, TSH at thyroid, GNRH at pituitary (31). Reproductive disorders like delayed puberty, incomplete sexual maturation, amenorrhoea, oligoamenorrhoea, POF and infertility are frequent causes of partial resistance of theca and granulosa cell to gonadotropins in these patients and clinical table shows alteration (32).

Inactivated mutations on FSH and LH receptors genes are more rare causes for POF (33,34). Clinical table varies according to mutation types on FSH receptor genes, being homozygous/heterozygous and being partial/total resistance to FSH. Not having pubertal development can conclude with primary amenorrhea, secondary amenorrhea and POF (33). LH receptors mutations conclude with oligoamenorrhea, secondary amonerrhea or infertility mostly. LH levels are higher, FSH levels are normal/slightly higher and estradiol levels are compatible with midfollicular phase, there are antral follicles in overs but there is no ovulation (34).

BRCA1 mutations have been indicated to be related with infertility and poor response to ovarian stimulation recently. Due to BRCA mutations have been indicated to conclude with DNA repair disorders and apoptosis in cells except reproductive cells, it has been thought that oocytes can run out with same mechanisms and can be resulted with POF in patients have these, Ataxia mutations (35). Ataksia-telangiectasia, mutations in inhibin A, EIF2B, 4 and 5 (eucaryotic translation initiation factor), PGRMC1 (Progesterone receptor membrane component 1) are other genetical causes conclude with POF (14).

In a study made in Turkey, several genetic abnormalities have been found in 52% of 75 women with POF. X chromosome deletions, translocations and numeral disorders detected in 16 of them (21.3%); Syndrome of Swyer in 2 of them, Fragile X premutations in ‘ of them and galactosemia in 1 patient (36).

Expectations of treatments in near term

Few cases of premature ovarian failure can conceive without fertility treatment. Therefore, other alternatives for these cases are in vitro fertilization, oocyte donation and adoption. Studies are being planned to investigate the applicability of glucocorticoid therapy in these cases. Another alternative in terms of fertility is oocyte attachment, oocyte freezing and embryo freezing. Heterologous overt tissue transplantation is a separate treatment alternative and further work is needed on this issue.

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