Chapter 6

Chromosomal Abnormalities and Menstrual Cycle Disorders

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Additional information is available at the end of the chapter

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Abstract

Chromosomal abnormalities have long been recognized as a cause of menstrual cycle disorders, premature ovarian insufficiency, and recurrent pregnancy loss. In women with X chromosome abnormalities, premature ovarian insufficiency is mainly a consequence of ovarian follicle depletion, due to insufficient initial follicle number and/or spontaneous accelerated follicle loss. The level of X chromosome mosaicism and its reproductive significance is still under debate. In our study, we evaluated the contribution of X chromosome abnormalities in women with sporadic idiopathic premature ovarian insufficiency (POI) and in women with a history of recurrent pregnancy loss. The results show that X aneuploidy and low-level mosaicism have reproductive significance in the phenotypically normal women with recurrent pregnancy loss and/or fertility problems. These results have practical implications for genetic counseling and fertility treatment.

Keywords: X chromosome, X chromosome mosaicism, amenorrhea, premature ovarian insufficiency, recurrent pregnancy loss

1. Introduction

Chromosomal abnormalities have long been recognized as a cause of abnormal sexual development, recurrent pregnancy loss, infertility, menstrual cycle disorders, and premature ovarian insufficiency (POI). Regarding the genetic causes of menstrual cycle disorders and POI, they can either be chromosomal or caused by single genes, involving the X chromosome or autosomes. The X chromosome abnormalities represent 13% of the cases, followed by the FMR1 gene premutation that represents 6% of the cases [1].

In November 2010, the International Federation of Gynaecology and Obstetrics formally accepted a new classification system for causes of abnormal uterine bleeding and menstrual cycle disorders in the reproductive years. It was developed in response to concerns about the design and interpretation of basic science and clinical investigation that relates to the problem of abnormal uterine bleeding and is based on the acronym PALM-COEIN (polyps, adenomyosis, leiomyoma, malignancy and hyperplasia–coagulopathy, ovulatory disorders, endometrial causes, iatrogenic, not classified) [2]. Chromosomal abnormalities are usually involved in ovulatory disorders, which lead to POI and infertility.

2. Menstrual cycle disorders

Menstruation is the regular discharge of blood and mucosal tissue from the inner lining of the uterus through the vagina as a result of periodic hormonal changes. Bleeding that can be defined as a "period" is described according to the four parameters [2]:

- regularity of onset,
- frequency of onset,
- duration of menstrual flow, and
- heaviness (or volume) of menstrual flow (**Table 1**).

Clinical dimensions of menstruation and menstrual cycle	Descriptive term	Normal limits (5–95th percentiles)
Frequency of menses	Frequent	<24 days
	Normal	24–38 days
	Infrequent	>38 days
	Absent	No bleeding
Regularity of menses	Regular	Variation ± 2–20 days
Cycle-to-cycle variation over 12 months	Irregular	Variation > 20 days
Duration of flow	Prolonged	>8 days
	Normal	4,5–8 days
	Shortened	<4,5 days
Volume of monthly blood loss	Heavy	>80 mL
	Normal	5–80 mL
	Light	<5 mL

Adapted from Munro et al. [2].

Table 1. Normal/acceptable limit values for menstrual parameters.

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Regular menstrual cycles are usually the outward manifestation of cyclical ovarian activity and ovulation. The establishment of regular ovulatory cycles at puberty depends on a complex series of interactions involving the hypothalamus, anterior pituitary, and the ovaries. With these series of complex interrelated events, it is hardly surprising that disorders of ovulation are relatively common causes of menstrual cycle disorders and POI.

Ovarian function in an ovulatory patients can be divided into three main groups [3]:

- hypergonadotrophic hypogonadism,
- hypogonadotrophic hypogonadism, and
- normogonadotrophic anovulation.

As per the World Health Organization, menstrual cycle disorders can also be classified either as a primary disorder of the ovaries or as a result of secondary causes:

- in primary ovarian insufficiency, the ovary fails to function normally in response to appropriate gonadotropin stimulation provided by the hypothalamus and pituitary (hypergonadotrophic hypogonadism),
- in secondary ovarian insufficiency, the hypothalamus and pituitary fail to provide appropriate gonadotropin stimulation (hypogonadotrophic hypogonadism) (**Figure 1**).

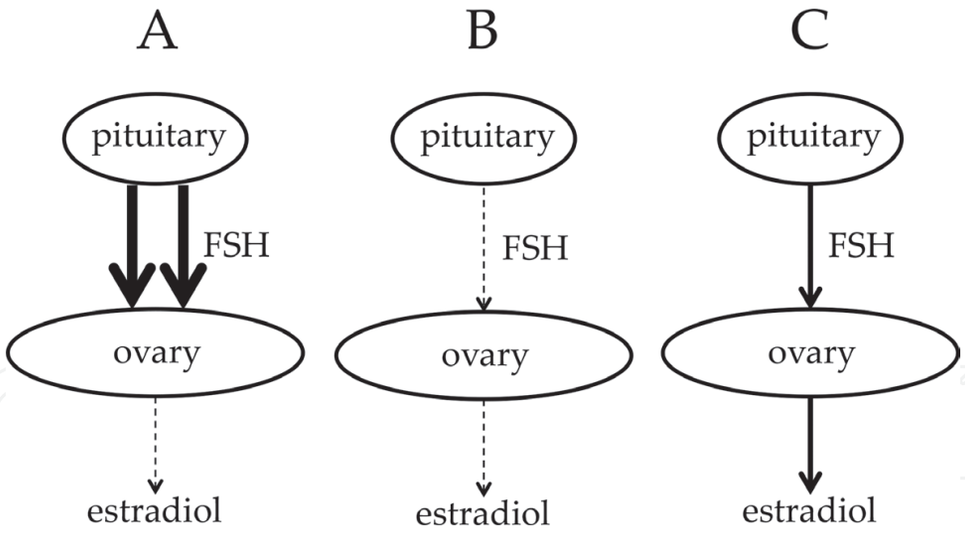

Figure 1. Gonadotrophic stimulation of the ovaries. A—hypergonadotrophic hypogonadism, B—hypogonadotrophic hypogonadism, C—normogonadotropic eugonadism. Adapted from Gersak [4].

3. Premature ovarian insufficiency

Premature ovarian insufficiency (POI) is a condition characterized by:

- amenorrhea (for at least 4 months),

- hypoestrogenism, and
- elevated serum gonadotropin levels two recordings of serum concentrations of follicle-stimulating hormone (FSH) of more than 40 IU/L at least 1 month apart in women younger than 40 years (>2 SD under the mean menopausal age).

Our current understanding of human ovarian reserve presumes that the ovary establishes several million nongrowing (primordial, intermediate and primary) follicles at around 5 months of gestational age. A steady decline of that number then follows, reaching the approximate value of 1000 at menopause, at the average age of 50–51 years [5–7]. With approximately 450 monthly ovulatory cycles that occur in the reproductive lifespan of a healthy human female, this progressive decline in nongrowing follicle count is chiefly attributed to follicle death by apoptosis. The peak of primordial follicle population, established at around 20-week postconception, determines the individual's age at menopause. Therefore, it is estimated that early or late menopause is related to low or high (respectively) peak follicle population at 18–22 weeks postconception. Women with around 295,000 nongrowing follicles per ovary at birth will reach menopause at the average age. In contrast, the ovaries of women, who are destined to have an earlier menopause, include around 35,000 nongrowing follicles at birth each, while those of women reaching a late menopause have over 2.5-million nongrowing follicles at birth each (**Figure 2**) [7].

Premature ovarian insufficiency can be caused by:

- ovarian follicle dysfunction,
- ovarian follicle depletion, or by
- mutations in genes associated with primary ovarian insufficiency.

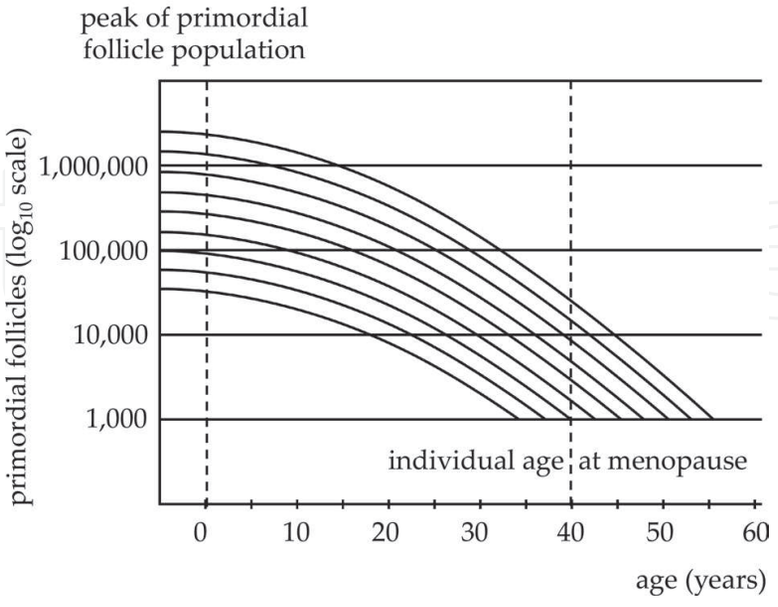

Figure 2. The correlation between ovarian reserve and age at menopause. This figure describes the hypothesis that the peak nongrowing follicle population established at around 20 weeks post-conception determines an individual's age at menopause. Adapted from Wallace and Kelsey [7].

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They all result in a premature depletion of the primordial follicle pool [3, 5].

Acquired ovarian insufficiency can also occur because of a range of conditions that result in the destruction or loss of ovarian tissue (e.g., endometriosis, ovarian surgery, chemotherapy or radiotherapy).

4. Chromosomal abnormalities and premature ovarian insufficiency

Chromosome abnormalities have long been recognized as a main genetic cause of POI (**Figure 3**).

In women with numerical and structural abnormalities of the X chromosome, premature ovarian insufficiency is mainly a consequence of ovarian follicle depletion, due to an insufficient initial follicle number and/or spontaneous accelerated follicle loss.

Once they develop amenorrhea and are found to have elevated gonadotropin levels, ovarian failure is permanent except in a few extremely rare reported cases. These patients should not be given false hope; the term "primary ovarian insufficiency" instead of premature ovarian failure, premature menopause, or early menopause might be misleading for them unless its use is accompanied by honest, thorough, and compassionate counseling [8].

4.1. Monosomy X

Turner syndrome (monosomy X) occurs with an incidence of 1 in 2500 female births, which makes it the most common X chromosome abnormality leading to POI [9]. One fifth to one-third of affected girls is diagnosed as newborns because of puffy hands and feet or redundant nuchal skin. The second third of girls with 45,X are diagnosed in mid-childhood upon investigation of short stature. The rest are given their diagnosis at puberty due to primary or secondary amenorrhea.

Until the 18th week of gestation, the number of nongrowing follicles in the 45,X-fetus is normal. The presence of normal gonadotropin levels in the first 3–6 months of life suggests that residual ovarian function exists but does not ensure that the initiation and progression of puberty will be normal [9, 10].

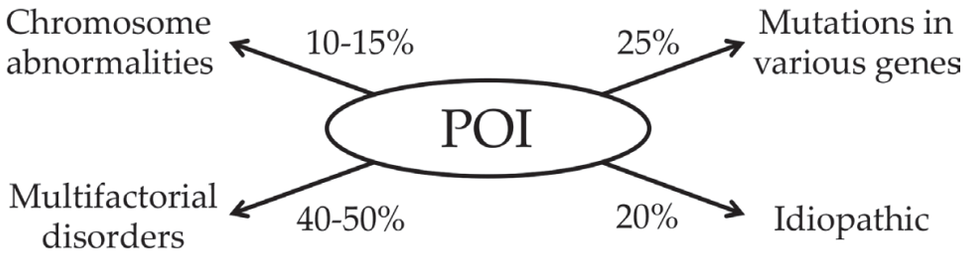

Figure 3. Causes of premature ovarian insufficiency (POI).

In many girls, pubic and axillary hair will develop spontaneously, because 45,X does not change the adrenarche. Some girls even possess enough residual ovarian function for breast budding and vaginal spotting to occur. Still, secondary amenorrhea will develop.

Although one X chromosome is sufficient to allow for ovarian differentiation, oocytes require two active X chromosomes. Therefore, haploinsufficiency of many genes located on the X chromosome in individuals with Turner's syndrome results in oocyte apoptosis and oocyte depletion within the first 10 years of life. The definite cause of the accelerated apoptosis is unknown. Two genes on the X chromosome are clearly implicated in premature ovarian insufficiency: bone morphogenetic protein 15 (BMP15) and fragile X mental retardation 1 (FMR1) [5, 11, 12]. Additional genes on the X chromosome have been implicated, however, but not proven, to have a role in ovarian failure specifically in females with 45,X.

The BMP15 gene is located on the short arm of the X chromosome (Xp11.2), within one of the "POF critical regions" (locus POF4; MIM number 300510) [12, 13]. Castronovo et al. performed a high-resolution comparative genome hybridization (CGH)-array analysis in a cohort of 45,X patients with or without spontaneous menarche [14]. They identified a tandem duplication of a single BMP15 gene in an 11-year-old patient with 45,X karyotype, who caught the pediatrician's attention because of a short stature but experienced a spontaneous menarche followed by regular menses for more than 4 years. Consistent with haploinsufficiency of the short stature homeobox gene (SHOX), this patient was short (145 cm at 34 years) despite growth hormone treatment. BMP15 duplication on the conserved X chromosome might have preserved a sufficient gene dosage in the developing ovary during the first meiotic phases, when a double dose of X-linked genes is required [12, 14]. BMP15 duplication led to the conservation of a certain amount of functional follicles at pubertal age and the ability to compensate, at least partially, for the loss of one copy of the other X-linked genes. BMP15 gene contributes to the ovarian phenotype of 45,X patients, supporting the hypothesis that BMP15 represents the first ovary-determining gene to have been identified on the X chromosome, which lends additional support to the idea that inactivating mutations in this gene can predispose to POI [12, 13].

4.2. Trisomy and polysomy X

Trisomy X or 47,XXX occurs in about 1 in 1000 newborn girls [15]. They generally have an unremarkable physical development, although there is a tendency toward tallness, usually presenting with an accelerated growth until puberty. Most of them have normal sexual development and are able to conceive children, but the occurrence of premature ovarian insufficiency probably exceeds the one in the general population. Recently, Stagi et al. reported that young 47,XXX girls show a premature activation of the GnRH pulse generator, which can occur even without puberty signs. In their study, basal and peak FSH levels in 47,XXX individuals were higher than in the control group, while E2 and inhibin levels, along with ovarian volume, were reduced, leading to a reduced gonadal function [16].

Trisomy X is associated with a very small amount of phenotypic abnormalities compared with autosomal trisomy states. The important factor is dosage compensation. Only one X

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chromosome in each cell needs to be fully active, whereas the other one is genetically inactivated. The inactivation occurs early in blastogenesis. The process originates at an X inactivation center within Xq13 and spreads in both directions. Certain parts of the X chromosome however are not subject to inactivation. The pseudoautosomal regions (PAR1 and PAR2) remain genetically active and function disomically [17]. Approximately 5–10% of additional genes outside the PAR regions on the X chromosome also escape X-inactivation.

In trisomy X, two of the three X chromosomes are inactivated. However, genes residing in the PAR regions along with other genes that escape X-inactivation are expressed from all three X chromosomes. The inactivation process is almost successful, resulting in an apparently normal in utero survival of 47,XXX fetuses. The fact that PARs are not subject to inactivation and may function in a trisomic or even polysomic state, it is hypothesized that the phenotypic abnormalities associated with trisomy X result from overexpression of these genes [18]. One exception is the SHOX gene, which escapes X-inactivation and is associated with the tall stature in polysomy X conditions.

Deficiency or overexpression of specific gene products on the X chromosome also influences oocyte quality.

Theoretically, it could be expected that three X chromosomes display 2:1 segregation during meiosis, with the production of an equal number of X and XX oocytes. However, no discernible increased risk for chromosomally abnormal offspring of 47,XXX women has been demonstrated [19]. This suggests that a "meiotic quality control" mechanism may exist to eliminate the errors. The spindle assembly checkpoint (SAC) monitors attachment to microtubules and tension on chromosomes. Usually, until all chromosomes are properly assembled at the spindle equator (chromosome congression) and under tension from spindle fibers, a complex between the anaphase promoting factor/cylosome (APC/C), its accessory protein Cdc20, and proteins of the SAC keep the APC/C in an inactive state [20].

4.3. X chromosome mosaicism

Mosaicism describes the presence of two or more populations of cells with different genotypes in one individual. If it occurs at the first cell division after conception, only two cell lines are possible. If nondisjunction occurs at a later cell division, two or more cell lines can persist [19].

When an abnormal number of sex chromosomes are seen in a low percentage of cells, the result could be interpreted either as a technical artifact, a genuine mosaicism, or being age related. The last option—loss of one X chromosome to give an occasional 45,X cell—is a normal characteristic of aging in 46,XX females. The rate of X chromosome loss in prepubertal females is around 1.5–2.5%, rising to 4.5–5% in women older than 75 years [21]. In contrast to sex chromosomes, the frequency of autosomal chromosome loss does not change during the course of aging.

The level of X chromosome mosaicism and its reproductive significance is still under debate. For clinical changes to occur, a minimum of 6% of X chromosome aneuploidy is

required [22, 23]. "True" mosaicism represents the presence of more than 10% of aneuploid cells, whereas "low-level" mosaicism is defined as 6–10% of aneuploid cells. The frequency of X chromosome mosaicism in women with sporadic form of POI has been estimated to be between 3 and 21% [23]. Upon comparison between patients with X-chromosome mosaicism and those with a balanced structural autosomal rearrangement, patients with X-chromosome mosaicism have a significantly higher incidence of diminished ovarian reserve [24].

Additionally, X-chromosome mosaicism may be a manifestation of impaired genetic control of chromosome nondisjunction.

The diminished ovarian reserve and impaired genetic control of chromosome nondisjunction are probably also involved in the higher abortion rate and recurrent miscarriages in women with X-chromosome mosaicism.

4.4. X chromosome rearrangements

A variable degree of gonadal dysgenesis occurs in patients with X chromosome rearrangements. The majority of patients have oligomenorrhea, followed by secondary amenorrhea or POI [25].

Cytogenetically visible rearrangements occur in specific Xq regions. Two main critical regions have been located on the long arm of X chromosome, at Xq13-q21 and at Xq26-q27 [25, 26]. A few deletions in distal Xq have also been reported. Marozzi et al. described three POI cases with Xq chromosome deletions: two terminal, with breakpoints at Xq26.2 and Xq21.2, and one interstitial, with breakpoints at Xq23 and Xq28 [27]. In all three cases, the Xq deletion size and position did not correlate with age at POI occurrence. The smallest deleted region associated with POI was Xq26.2-q28. Rossetti et al. reported a distal interstitial deletion of the X chromosome in a fertile mother and her two affected daughters [28]. Also, Eggermann et al. presented a familial case of POI women with a small deletion from Xq27.2/Xq27.3 to Xqter [29]. In a population of 90 POI patients, Portnoi et al. identified three women bearing a large terminal Xq deletion involving Xq21-qter [30].

Mechanisms proposed for the explanation of the ovarian defect include the following: direct disruption of relevant loci and a position effect, caused by rearrangements on contiguous genes [1]. Position effect is a mechanism that involves the deletion or translocation of regulatory domains to a different position on the genome, which might be the cause of changes in gene transcription [12, 31].

The reason why women with similar X-chromosome rearrangements show a relatively great variability in the degree of ovarian failure is unclear. It may be related to natural cell selection, leading to X inactivation in germ cell precursors. In females with X-chromosome abnormalities, a nonrandom X inactivation is normally seen, resulting in a pattern that reflects the predominance of cells with the most functional gene imbalance.

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Duplication located at the telomeric Xq region may alter pairing of X chromosomes during meiosis and therefore induce oocyte depletion [12].

5. Subjects and methods

Our study included 319 women with menstrual cycle disorders (sporadic idiopathic POI or secondary amenorrhea) referred to our Department of Obstetrics and Gynaecology in the period between 2000 and 2014. The diagnosis of POI was based on the criteria of either at least 6 months of amenorrhea or the age of menopause less than 40 years, combined with two consecutive values of serum follicle stimulating hormone (FSH) higher than 40 IU/l. Women with primary amenorrhea or gonadal dysgenesis, FRAXA permutation, mutations in the *FOXL2* or inhibin *INHα* genes were excluded.

During the same period, 424 women with a history of recurrent pregnancy loss and regular menstrual cycles were identified. A history of recurrent pregnancy loss was defined as two or more consecutive pregnancy losses before 22 weeks of gestation.

All women gave their informed consent.

Cytogenetic studies were carried out on peripheral blood samples, cultured for approximately 72 h. For each routine chromosomal analysis, 20–30 Giemsa-banded cells were analyzed, with three of those cells karyotyped. If the initial cytogenetic analysis revealed any cells with sex-chromosome hypoploidy or hyperploidy, 100 cells were counted and analyzed. The presence of more than 10% of aneuploid cells was characterized as true mosaicism, whereas low-level mosaicism was defined as 6–10% of aneuploid cells.

6. Results

Chromosome abnormalities were found in 62 (19.4%) women with POI. Twenty-six patients (26/319, 8.1%) had true X chromosome mosaicism; 28 patients (28/319, 8.7%) had low-level X mosaicism. Different types of sex-chromosome mosaicism present in our subject group (and their frequency) are shown in **Table 2**, while other abnormal karyotypes (8/319, 2.5%) are shown in **Table 3**.

Prevalence of chromosome abnormalities in patients with a history of recurrent pregnancy loss is represented in **Table 4**. Out of 424 women, X chromosome mosaicism was observed in 39 of them. Twenty-two (22/424, 5.2%) had true sex chromosome mosaicism; 17 had low-level X mosaicism.

Among those 39, 6 women had aneuploid offspring (**Table 5**). Moreover, one of those six, a woman with low-level X mosaicism, gave birth to a girl with true X mosaicism.

Number of patients	Type of sex chromosome mosaicism
18	45,X/46,XX
8	45,X/47,XXX
5	47,XXX/46,XX
19	45,X/47,XXX/46,XX
1	45,X/46,X,i(Xq10)
1	47,XXX/48,XXXX/46,XX
1	45,X/47,XXX/48,XXXX/49,XXXXX/46,XX
1	45,X/47,XXX/49,XXXX/47,XXY/46,XY/46,XX

Table 2. Sex chromosome mosaicism in women with POI (n = 54).

Patient	Age at karyotyping	Chromosome abnormalities [number of metaphases]
1	23	46,XX;t(X;16)dn [20]
2	36	46,XX;t(8;10)dn [20]
3	19	46,XX,t(4;12)(q21.1;p11.2)dn [20]
4	31	46,XX[30]/46,XX fra(2)(q13)[20]
5	32	46,X,del(X)(q21)dn [20]
6	25	46,X,i(X)(q10)dn [20]
7	35	45,X[44]/46,X,i(X)(q10)[2]/47,X,i(X)(q10),i,(X)(q10)[1]/46,XX[2]
8	33	46,X,del(X)(p11.2)[32]/45,X[27]/47,X,del(X)(p11.2,del(X)(p11.3)[3]

Table 3. Chromosome abnormalities (without X chromosome mosaicism) in women with POI (n = 8).

Number of pregnancy loss	Number of patients (n = 424)	Number of patients with X chromosome mosaicism (n = 39)	Number of patients with other chromosome abnormalities (n = 64)
2	134	16	21
3	201	19	34
4	33	3	6
≥5	13	1	3

Table 4. Prevalence of chromosome abnormalities in patients with a history of recurrent pregnancy loss.

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Offspring with aneuploidy	Chromosome abnormalities (number of aneuploid cells, %)	Mother's chromosome abnormalities (number of aneuploid cells, %)
1	46,XX,+14,der(13;14)(q10;q10) dn; stillbirth	45,X/46,XX (>10%)
2	45,X/46/XX (>10%); live born	45,X/47,XXX/46,XX (<10%)
3	47,XXX/46,XX (<10%); live born	45,X/47,XXX/46,XX (>10%)
4	47,XY,+21; live born	45,X/47,XXX/46,XX (>10%)*
5	47,XXY/46,XX (>10%); live born	47,XXX/48,XXXX/46,XX (>10%)
6	46,X,i(Xq); live born	45,X/46,X,i(Xq) (100%)

* Patient No. 32 has also a brother with Down syndrome (47,XY,+21).

Table 5. Offspring with aneuploidy born to women with X chromosome abnormalities and recurrent pregnancy loss.

In 7 out of the aforementioned 39 patients (19%), pregnancies occurred with the assistance of ovulation induction.

7. Discussion

Our study has established an important role of X chromosome abnormalities in women with sporadic idiopathic POI or history of recurrent pregnancy loss. With routine G-banding, at least 50 cells have to be analyzed in order to exclude the presence of 6% mosaicism with a 0.95 level of confidence [32]. With an evaluation of 20 metaphases, only a mosaicism greater than 14% can be found with the same confidence.

If true and low-level mosaicisms are regarded as identical abnormal results, this study found mosaicism in 16.8% of patients. In our previous study, X chromosome mosaicism was found in 21.9% of patients [23].

Wu et al. [33]. reported 5 out of 61 (8.2%) POI cases with X chromosome mosaicism. In a Hong Kong group of 312 women with secondary amenorrhea, 11 cases with karyotype 45,X/46,XX and 3 cases with mosaic triple/poly X were found [34]. Lakhal et al. detected 34 (5.9%) patients with homogeneous or mosaic X-chromosome aneuploidy out of 568 with secondary amenorrhea. In contrast, Portnoi et al. identified no 45,X/46,XX or 46,XX/47,XXX chromosome mosaicisms in any of their POI patients or controls [30].

In our present study, true X chromosome mosaicism was found in 8.1% of women with sporadic idiopathic POI, whereas low-level mosaicism was found in 8.7%. Based on our present and previous results [23], we presume that at least two different subgroups of patients with X chromosome mosaicism exist. The mean age of women with true X mosaicism and low-level X mosaicism was significantly different in both studies; in our recent study, the values were

26.0 ± 5.65 years and 35.92 ± 3.87 years, respectively. Although peripheral blood does not reflect the situation in other tissues well, that is, in ovarian tissue, the onset of POI occurred earlier in women with true X mosaicism. In all patients, karyotyping was performed within a 12-month period after the last menses.

In couples with recurrent spontaneous abortion, X chromosome mosaicism was identified in 3–16% [33, 35–39]. In 50 cells counted, Düzcan et al. showed mosaicism of either structural rearrangements or aneuploidies of sex chromosomes in 7 cases out of 354 with reproductive failure [38]. In our present study, a significant number (≥6%) of X chromosome aneuploidy in lymphocyte cultures was found in 9.2% of women with history of reproductive failure. Five liveborn children and one stillborn with aneupoidy were identified. Unfortunately, we have no data about chromosomal aneuploidy in embryonic/fetal tissue recovered from the abortuses of the same women before they visited our department. Kaneko et al. reviewed 117 pregnancy outcomes in 49 cases of 45,X/46,XX, 45,X/47,XXX, 45,X/46,XX/47,XXX and 45,X/46,XX/47,XXX/48,XXXX mosaicism [40]. For cases with information available, miscarriage rate was 30%, stillbirth rate was 7%; 43% of babies were normal, and 20% were abnormal. Sex chromosome abnormalities were observed in 7% of the children of 45,X/46,XX women and in 23% of the children of 45,X/46,XX/47,XXX women; not one 45,X/47,XXX woman had a child with X aneuplody [19]. Kuo and Guo reported a 68.6% miscarriage rate in patients with X chromosome mosaicism and diminished ovarian reserve (FSH level of >11.0 mUI/ml), and as high as 44.1% for cases without diminished ovarian reserve [24].

Despite the lack of data about fetal karyotypes, an increased risk to have a child with aneuploidy may apply to our patients. Supporting this assumption, both the child and the brother of one of the previously mentioned 39 women with X chromosome mosaicism (**Table 5**) had Down syndrome (**Table 5**). This finding may reflect a genetic tendency toward mitotic and meiotic nondisjunction or errors in the "meiotic quality control" mechanism [20]. The fact that the meiotic segregation error of one chromosome may affect the segregation of other chromosomes was demonstrated also in XO female mice [41].

Information on meiotic and mitotic errors has become available with the advent of preimplatation genetic diagnosis—sequential testing of the first and second polar bodies [42]. In contrast to the traditional concept that aneuploidies mainly originate from female meiosis I, direct testing in patients of advanced reproductive age (average age 38.5 years) showed that chromosome abnormalities originate from both meiosis I and meiosis II in comparable proportions and are predominantly of chromatid origin. Although isolated errors in either meiosis I or meiosis II were observed, approximately one half of oocytes with meiosis I errors also had sequential meiosis II errors. The result of such sequential errors shows that ideally, almost one-third of these zygotes should be "euploid."

Balanced zygotes may represent a phenomenon of aneuploidy rescue in female meiosis [42]. The inherent predisposition for genomic instability in meiosis divisions can probably explain the nature of recurrent spontaneous abortions in women with X mosaicism [20, 40].

In a mosaic ovary, aberrant X chromosome pairing and impaired genetic control of chromosomal nondisjunction may cause premature germ cell death, thus decreasing the number of

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germ cells and accelerate follicle atresia [19, 24]. One obvious explanation could also lie in the haploinsufficiency of loci on the X chromosome [12, 14].

8. Conclusion

POI is a clinical syndrome defined by loss of ovarian activity before the age of 40 years. Although the prevalence is only 1%, POI is associated with numerous health problems preceded by menstrual cycle abnormalities and subfertility. The proper diagnostic criteria for POI are still lacking. In 2016, the ESHRE Guideline Group on POI published a less restrictive definition such as oligo/amenorrhea for at least 4 months and an elevated FSH level up to 25 IU/l on two occasions more than 4 weeks apart.

According to the results from several studies mentioned in this chapter, as well as ESHRE guidelines, cytogenetic analyses should be considered for all women with unexplained sporadic noniatrogenic POI. X chromosome abnormalities cause up to 20% of the cases, of which the contribution of "true" and "low-level" X chromosome mosaicism represents a significant proportion.

X aneuploidy and low-level mosaicism are reproductively significant also in phenotypically normal women with recurrent pregnancy loss.

In recent years, array-comparative genomic hybridization and next-generation sequencing are becoming important genetic tests in everyday practice, increasing the etiologic diagnosis rate up to 30%. However, they fail to detect chromosomal rearrangements if breakpoints are either located in introns or not associated with a gain or loss of genetic material [43]. On the other hand, FISH may be the most appropriate method for confirming a suspected numerical mosaicism. According to the ISCN, numerical and structural abnormalities still have to be excluded at a classical banding level.

We share the opinion that women with X mosaicism may be at increased risk of producing chromosomally abnormal offspring and should be offered prenatal diagnosis. These results have practical implications for genetic counseling and fertility treatment.

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References

[1] Cordts EB, Christofolini DM, Dos Santos AA, Bianco B, Barbosa CP. Genetic aspects of premature ovarian failure: a literature review. Arch Gynecol Obstet. 2011;**283**:635-43. doi:10.1007/s00404-010-1815-4

[2] Munro MG, Critchley HO, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol. 2012;**207**:259-65. doi:10.1016/j.ajog.2012.01.046

[3] ESHRE Capri Workshop Group. Health and fertility in World Health Organization group 2 anovulatory women. Hum Reprod Update. 2012;**18**:586-99. doi:10.1093/humupd/dms019

[4] Gersak K. Genetika zenske neplodnosti/Genetica dell'infertilità femminile. In: Peterlin B, (editor). Genetika v ginekologiji/La genetica in ginecologia. 1st ed. Ljubljana: Design studio; 2014. pp. 108-21. ISBN: 978-961-230-464-5

[5] De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010;**376**:911-21. doi:10.1016/S0140-6736(10)60355-8

[6] Coulam C, Adamson S, Annegers J. Incidence of premature ovarian failure. Obstet Gynecol. 1986;**67**:604-06.

[7] Wallace WH, Kelsey TW. Human ovarian reserve from conception to the menopause. PLoS One. 2010;**5**:e8772. doi:10.1371/journal.pone.0008772

[8] Reindollar RH. Turner syndrome: contemporary thoughts and reproductive issues. Semin Reprod Med. 2011;**29**:342-52. doi:10.1055/s-0031-1280919

[9] Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;**351**:1227-38.

[10] Heinrichs C, Bourdoux P, Saussez C, Vis HL, Bourguignon JP. Blood spot follicle-stimulating hormone during early postnatal life in normal girls and Turner's syndrome. J Clin Endocrinol Metab. 1994;**78**:978-81.

[11] Trolle C, Hjerrild B, Cleemann L, Mortensen KH, Gravholt CH. Sex hormone replacement in Turner syndrome. Endocrine. 2012;**41**:200-19. doi:10.1007/s12020-011-9569-8

[12] Persani L, Rossetti R, Di Pasquale E, Cacciatore C, Fabre S. The fundamental role of bone morphogenetic protein 15 in ovarian function and its involvement in female fertility disorders. Hum Reprod Update. 2014;**20**:869-83. doi:10.1093/humupd/dmu036

[13] Layman LC. Editorial: BMP15—the first true ovarian determinant gene on the X-chromosome?. J Clin Endocrinol Metab. 2006;**91**:1673-6.

[14] Castronovo C, Rossetti R, Rusconi D, Recalcati MP, Cacciatore C, Beccaria E, et al. Gene dosage as a relevant mechanism contributing to the determination of ovarian function in Turner syndrome. Hum Reprod. 2014;**29**:368-79. doi:10.1093/humrep/det436

[15] Otter M, Schrander-Stumpel CT, Curfs LM. Triple X syndrome: a review of the literature. Eur J Hum Genet. 2010;**18**:265-71. doi:10.1038/ejhg.2009.109

[16] Stagi S, di Tommaso M, Scalini P, Lapi E, Losi S, Bencini E, Masoni F, Dosa L, Becciani S, de Martino M. Triple X syndrome and puberty: focus on the hypothalamus-hypophysis-gonad axis. Fertil Steril. 2016;**105**:1547-53. doi:10.1016/j.fertnstert.2016.02.019

[17] Mangs HA, Morris BJ. The human pseudoautosomal region (PAR): origin, function and future. Curr Genomics. 2007;**8**:129-36.

[18] Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L. Triple X syndrome with rare phenotypic presentation. Indian J Pediatr. 2008 Jun;**75**:629-31. doi:10.1007/s12098-008-0120-8

[19] Gardner RJM, Sutherland GR. Chromosome Abnormalities and Genetic Counseling. 2nd ed. New York: Oxford University Press; 1996. p. 478. ISBN 0-19-510615-6

[20] Vogt E, Kirsch-Volders M, Parry J, Eichenlaub-Ritter U. Spindle formation, chromosome segregation and the spindle checkpoint in mammalian oocytes and susceptibility to meiotic error. Mutat Res. 2008 Mar 12;**651**:14-29.

[21] Guttenbach M, Koschorz B, Bernthaler U, Grimm T, Schmid M. Sex chromosome loss and aging: in situ hybridization studies on human interphase nuclei. Am J Hum Genet. 1995;**57**:1143-50.

[22] Homer L, Le Martelot MT, Morel F, Amice V, Kerlan V, Collet M, De Braekeleer M. 45,X/46,XX mosaicism below 30% of aneuploidy: clinical implications in adult women from a reproductive medicine unit. Eur J Endocrinol. 2010;**162**:617-23. doi:10.1530/EJE-09-0750

[23] Gersak K, Veble A. Low-level X chromosome mosaicism in women with sporadic premature ovarian failure. Reprod Biomed Online. 2011;**22**:399-403. doi:10.1016/j.rbmo.2011.01.002

[24] Kuo PL, Guo HR. Mechanism of recurrent spontaneous abortions in women with mosaicism of X-chromosome aneuploidies. Fertil Steril. 2004;**82**:1594-601.

[25] Gersak K, Writzl K, Veble A, Liehr T. Primary amenorrhoea in a patient with mosaicism for monosomy X and a derivative X-chromosome. Genet Couns. 2010;**21**:335-42.

[26] Vásquez-Velásquez AI, Torres-Flores J, Leal CA, Rivera H. Apparent neotelomere in a 46,X,del(X)(qter→p11.2:)/46,X,rea(X)(qter→p11.2::q21.2→qter) novel mosaicism: review of 34 females with a recombinant-like dup(Xq) chromosome. Genet Test Mol Biomarkers. 2011;**15**:727-31. doi:10.1089/gtmb.2011.0017

[27] Marozzi A, Manfredini E, Tibiletti MG, Furlan D, Villa N, Vegetti W, et al. Molecular definition of Xq common-deleted region in patients affected by premature ovarian failure. Hum Genet. 2000;**107**:304-11.

[28] Rossetti F, Rizzolio F, Pramparo T, Sala C, Bione S, Bernardi F, et al. A susceptibility gene for premature ovarian failure (POF) maps to proximal Xq28. Eur J Hum Genet. 2004;**12**:829-34.

[29] Eggermann T, Meschede D, Schüler H, Palm S, Gläser D, Horsthemke B, et al. Premature ovarian failure associated with a small terminal Xq deletion: narrowing the POF1 region down to Xq27.2/Xq27.3-qter. Clin Genet. 2005;**67**:434-7.

[30] Portnoi MF, Aboura A, Tachdjian G, Bouchard P, Dewailly D, Bourcigaux N, et al. Molecular cytogenetic studies of Xq critical regions in premature ovarian failure patients. Hum Reprod. 2006;**21**:2329-34.

[31] Tachdjian G, Aboura A, Portnoï MF, Pasquier M, Bourcigaux N, Simon T, et al. Cryptic Xp duplication including the SHOX gene in a woman with 46,X, del(X)(q21.31) and premature ovarian failure. Hum Reprod. 2008;**23**:222-6.

[32] Hook EB. Exclusion of chromosomal mosaicism: tables of 90%, 95% and 99% confidence limits and comments on use. Am J Hum Genet. 1977;**29**:94-7.

[33] Wu RC, Kuo PL, Lin SJ, Liu CH, Tzeng CC. X chromosome mosaicism in patients with recurrent abortion or premature ovarian failure. J Formos Med Assoc. 1993;**92**:953-6.

[34] Wong MS, Lam ST. Cytogenetic analysis of patients with primary and secondary amenorrhea in HongKong: retrospective study. Hong Kong Med J. 2005;**11**:267-72.

[35] Horsman DE, Dill FJ, McGillivray BC, Kalousek DK. X chromosome aneuploidy in lymphocyte cultures from women with recurrent spontaneous abortion. Am J Med Genet. 1987;**28**:981-7.

[36] Radojcic Badovinac A, Buretic-Tomljanovic A, Starcevic N, Kapovic M, Vlastelic I, Randic L. Chromosome studies in patients with defective reproductive success. Am J Reprod Immunol. 2000;**44**:279-83.

[37] Morel F, Gallon F, Amice V, Le Bris MJ, Le Martelot MT, Roche S, et al. Sex chromosome mosaicism in couples undergoing intracytoplasmic sperm injection. Hum Reprod. 2002;**17**:2552-5.

[38] Duzcan F, Atmaca M, Cetin GO, Bagci H. Cytogenetic studies in patients with reproductive failure. Acta Obstet Gynecol Scand. 2003;**82**:53-6.

[39] Gonçalves RO, Santos WV, Sarno M, Cerqueira BA, Gonçalves MS, Costa OL. Chromosomal abnormalities in couples with recurrent first trimester abortions. Rev Bras Ginecol Obstet. 2014;**36**:113-7. doi:10.1590/S0100-72032014000300004

[40] Kaneko N, Kawagoe S, Hiroi M. Turner's syndrome-review of the literature with reference to a successful pregnancy outcome. Gynecol Obstet Invest. 1990;**29**:81-7.

[41] Hunt P, LeMaire R, Embury P, Sheean L, Mroz K. Analysis of chromosome behavior in intact mammalian oocytes: monitoring the segregation of a univalent chromosome during female meiosis. Hum Mol Genet. 1995;**4**:2007-12.

[42] Kuliev A, Verlinsky Y. Meiotic and mitotic nondisjunction: lessons from preimplantation genetic diagnosis. Hum Reprod Update. 2004;**10**:401-7.

[43] Pasquier L, Fradin M, Cherot E, Martin-Coignard D, Colin E, Journel H, et al. Karyotype is not dead (yet)! Eur J Med Genet. 2016;**59**:11-5.

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