Hormones
https://doi.org/10.1007/s42000-019-00141-5

REVIEW ARTICLE

Premature ovarian insufficiency in adolescence: a chance for early diagnosis?

Lina Michala[1] · Katerina Stefanaki[2] · Dimitris Loutradis[1]

Received: 30 September 2019 / Accepted: 11 October 2019

Abstract

Premature ovarian insufficiency (POI) is typically diagnosed when amenorrhea is combined with high gonadotrophins and hypoestrogenemia in a woman under 40 years of age, although, more rarely, POI can develop in adolescence and present with delayed puberty or amenorrhea, depending on the timing of follicular depletion or insult to the ovary. In a proportion of girls, the diagnosis may be made at an early stage of POI, presenting with abnormal uterine bleeding, when some follicular function is still retained. The natural history of POI in this group of patients is not clear; however, they could represent a subgroup with a unique opportunity for early intervention and thus the provision of fertility preservation options. While the etiology of POI in a large number of girls remains unknown, a growing number will be identified as carriers of genetic mutations, offering clinicians a yet greater opportunity to provide genetic counseling to other female family members. The aim of this review is to provide information regarding the etiology, diagnosis, and treatment of POI in adolescents while detailing the new options for fertility preservation when POI is diagnosed at an early stage.

Keywords Premature ovarian insufficiency · POI · Abnormal uterine bleeding · AUB · Fertility preservation

Introduction

Premature ovarian insufficiency (POI), defined as follicular depletion in women under the age of 40 years, is a devastating condition, as it will lead to a series of short- and long-term complications relating to hypoestrogenism as well as to subfertility. Although more commonly diagnosed in women in the third or fourth decade of life, POI can be identified in adolescence at a rate of approximately one in 10,000 (1). POI is considered a spectrum which will eventually lead to the triad of amenorrhea, raised gonadotrophins, and hypoestrogenism (2). Transient or partial resumption of ovarian activity, however, has been documented in over 50% of women based upon hormonal measurements, pelvic ultrasonography, or spontaneous conceptions.

Though POI in adolescents is often related to chromosomic abnormalities, represented mostly by Turner syndrome, it is becoming clear that genetic abnormalities are perhaps the most important cause in this age group. While it is estimated that only 10–15% of women with POI have a recognized genetic basis for this disorder, this percentage will no doubt increase with time as more genetic mutations are identified as being linked with the condition (3). Furthermore, the number of iatrogenic POI in adolescents is rising, primarily due to improved childhood cancer survival rates, since better therapeutic modalities, however successful, take a toll on ovarian function. POI due to gonadotoxic agents, surgery, or radiation to pelvic organs is nowadays a recognized hindrance to quality of life in cancer survivors (4). Viral illnesses and environmental agents can interfere with follicular function and lead to insidious POI, which could further account for the large number of unexplained cases of POI, along with unknown genetic mutations (5).

In most cases, the mechanism of POI is one of follicular depletion (6). Follicle dysfunction, however, can also lead to a similar phenotype. Causes of follicle dysfunction may be autoimmune lymphocytic oophoritis (7) or, rarely, a mutation in the FSH receptor (8).

✉ Lina Michala
linamichala@med.uoa.gr

[1] 1st Department of Obstetrics and Gynaecology, Medical School, National and Kapodistrian University of Athens, Alexandra General Hospital, 80 Vassilissis Sofias Avenue, 115 28 Athens, Greece

[2] Department of Therapeutics, Medical School, National and Kapodistrian University of Athens, Alexandra General Hospital, Athens, Greece

Published online: 11 December 2019

Clinical presentation

Though the ovaries normally fail at the time of menopause when virtually no viable oocytes remain, ovarian failure can occur prematurely at any time from embryonic development onwards. If failure occurs early, no pubertal development will ensue and the girl will present with delayed puberty. At a later stage, there may be pubertal blockage or primary or secondary amenorrhea.

An early sign of ovarian failure may be anovulatory cycles leading to abnormal uterine bleeding (AUB). Although AUB is a common occurrence in adolescents due to an immature hypothalamic-pituitary-ovarian axis, it is important to identify those girls who could have a secondary cause of their irregular cycles. A hormonal profile, including FSH, LH, and estradiol measurements, should be performed in girls who have persistent AUB beyond 2 years after menarche or when menstrual irregularities deteriorate after an initial improvement.

Vasomotor symptoms are rare in adolescents and are unlikely to be a presenting complaint of POI in this age group (9). Vaginal atrophy and dryness are also unlikely to be presenting features unless the adolescent is sexually active. Even so, she might be reluctant to come forward with this vagina-related concern unless directly questioned.

Algorithm for diagnosis and investigations for POI

Several laboratory tests are indicated in women with amenorrhea or persisting abnormal uterine bleeding, including measurement of FSH, LH, androgens, prolactin, and TSH, and the same principles should be applied in adolescents (10). A pregnancy test, necessary for all girls and women with secondary amenorrhea, will not be required for girls with no pubertal development.

FSH levels are typically greater than 30 mIU/ml in women with ovarian failure (11). If the FSH level is greater than 15 mIU/ml on initial screening, usually in girls who still maintain a cycle and some degree of ovarian function, the measurement should be repeated, and serum estradiol should be measured at the same time, to document a relatively suppressed FSH as a result of elevated estradiol due to an unruptured follicle. In addition, the simultaneous measurement of basal LH levels is helpful to determine whether a high FSH level is secondary to an ovulatory surge, in which case LH will be significantly higher.

Estradiol concentrations above 50 pg/ml, irregular bleeding, and visualization of ovarian follicles on ultrasound all provide strong evidence of remaining ovarian function, despite developing POI. This information should be considered in order to offer fertility preservation options in this group of girls.

Once the diagnosis of POI has been established, a series of investigations should be performed to identify a possible cause of the condition. Additional tests should include karyotyping with a 30-cell count, testing for an FMR1 premutation, and testing for the presence of adrenal autoantibodies by either 21-hydroxylase (CYP21) immunoprecipitation or indirect immunofluorescence, and thyroid autoantibodies (12–15). It goes without saying that if Turner syndrome is identified, the diagnostic assessment should include screening for associated congenital conditions as well as autoimmune or metabolic related diseases (16).

Anti-Mullerian hormone

The role of anti-Mullerian hormone (AMH) in the evaluation of POI, especially in adolescents, remains controversial (9). Normal values in relation to age have been proposed; however, there is variability depending on stage of puberty, with some researchers suggesting that there is a plateau or even a decline in AMH during pubertal development (17). AMH, on the other hand, has the advantage of allowing diagnosis of POI among patients with only marginally increased gonadotropin levels (18). Furthermore, AMH can be tested at any time during the menstrual cycle, unlike gonadotrophins that should ideally be assessed in the early follicular phase (19). Results are also unaltered by use of hormone replacement therapy (HRT), which allows for testing without stopping any treatment that has already been instituted (20). In girls with Turner syndrome and continuing ovarian function, it has been suggested that AMH is a useful marker of ovarian decline which enables initiation of fertility preservation techniques prior to complete ovarian failure. According to a longitudinal study, the best cutoff value for AMH as a marker of POI was identified as 3 pmol/l. Both the sensitivity (probability of having POI when AMH < 3 pmol/l) and the specificity (probability of having ovarian function when AMH > 3 pmol/l) were 95% (21).

Another group of patients in whom AMH has been used as screening for ovarian failure is cancer survivors. According to the harmonized recommendations for POI surveillance, it may be reasonable to use AMH in conjunction with FSH and estradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy (22). AMH can be useful in the differential diagnosis of patients with raised gonadotrophins and hypoestrogenism, where primordial follicles are still present and possibly visible on ultrasound. Normal AMH in this setting maybe suggestive of FSH resistance due to a mutation in the FSH receptor or autoimmune destruction of the growing follicle which is due to steroid cell autoantibody presence (23).

Nevertheless, it is important to consider that AMH drops in women with centrally induced amenorrhea, either congenital

or functional, despite the fact that their ovarian follicular count is expected to be normal. In women with functional hypothalamic amenorrhea (FHA), AMH levels increase after administration of pulsatile GnRH, whereas a proportion of women with idiopathic hypogonadotropic hypogonadism (IHH) and Kallmann syndrome are shown to have low baseline levels of AMH, which, however, rise after ovulation induction with recombinant FSH. These examples suggest that AMH should only be used cautiously in identifying POI, particularly once FHA and IHH have been safely ruled out as causes of amenorrhea (24).

Causes of POI in adolescents

Chromosomal causes

Turner syndrome

Turner syndrome (TS) results from a sex chromosomal anomaly characterized by the presence of one normal X chromosome and a missing or structurally abnormal second sex chromosome. It affects 50 per 100,000 live born girls. The phenotype includes female gender, short stature (SHOX gene haploinsufficiency accounts for 50–75% of the height deficit), and primary ovarian failure. The abnormalities with the greatest impact on health are left-sided cardiac abnormalities (including coarctation, bicuspid aortic valve, and dilated aortic root), which occur in about 50% of patients, and renal anomalies, which are present in approximately one-third of the girls. Adolescence may be delayed if ovaries are streak and nonfunctional, but can also proceed normally in those with preserved ovarian function, as is usually the case with mosaicism.

Triple X syndrome

Triple X syndrome, *or* 47,XXX, is a recognized cause of POI. However, as the phenotype of affected women is often normal, with few or subtle distinguishing features, it is uncertain how often the condition is related to POI. A proportion of women will indeed be identified solely during investigation for recurrent miscarriages rather than for subfertility or amenorrhea (25).

Swyer syndrome

Swyer syndrome, or 46,XY gonadal dysgenesis, is a rare cause of delayed puberty and is due to sporadic mutations on the SRY gene or other testes-determining factors (TDFs) in an individual with a 46,XY karyotype. The condition is typically identified due to delayed puberty, although in some instances it may become evident due to the presence of a dysgerminoma in childhood, or if there is a non-concordant male karyotype at amniocentesis with a female genital phenotype antenatally or at birth.

If the diagnosis of Swyer syndrome is made, a laparoscopic gonadectomy should be planned, as dysgenetic gonads are at increased risk of developing a gonadoblastoma or dysgerminoma (26).

Additional rare causes of POI derived from X chromosomes are presented in Table 1.

Genetic causes

The search for POI genes has to date largely focused on coding variants, presuming plausible protein disruption. However, only 1.5% of the genome is protein-coding and a number of POI-associated variants in whole genome studies have been found within intronic or intergenic regions. The aim of genetic mapping and understanding of the pathophysiology of POI is to provide genetic counseling to other members of the family and to allow for fertility preservation prior to establishment of overt ovarian failure (27).

FMR-1 premutation

Fragile X syndrome (FXS) is caused by a full mutation on the *FMR1* gene and a subsequent lack of FMRP, the protein

Table 1 Causes of POI derived from X chromosomes

Mechanism	Specific mutations
Structural alterations, mutations in, or absence of an X chromosome	Mutations in POF1 (Xq26-q28)
Gonadal dysgenesis with stigmata of Turner syndrome (most 45,X)	Mutations in POF1 together with Fragile X (FMR1) premutations (Xq27.3)
Gonadal dysgenesis without stigmata of Turner syndrome	Mutations in POF2A or 2B (Xq22 or Xq21)
Pure gonadal dysgenesis (46,XX)	Mutations in POF4 together with mutations in bone morphogenetic protein 15 (Xp11.2)
Premature ovarian failure with mutations in the X chromosome	Mutations with a 46, XY karyotype (pure gonadal dysgenesis)
Trisomy X with or without mosaicism	Mutations in Xp22. 11-21.2 (Swyer syndrome)

product of *FMR1*. FXS arises from a full mutation repeat expansion (> 200 CGG repeats in the 5′ untranslated region) in the *FMR1* gene, located on the X chromosome. *FMR1* premutations consist of 55–200 CGG repeats. *FMR1* premutations have been associated with POI, as well as fragile X-associated tremor ataxia syndrome, psychiatric problems, hypertension, migraines, and autoimmunity (28).

The *FMR1* premutation is known to be the most common genetic cause of primary ovarian insufficiency. It has been estimated that about 3% of adolescents with FMR1 premutations will experience some form of menstrual cycle irregularity. Several studies concluded that 1.4% of premutation carriers experience a final menstrual period before the age of 18, whereas the incidence of cessation of menses for premutation carriers before age 40 is about 15–24%. The gravity of the syndrome depends on CGG repeats, with a peak risk of POI at 80–100 repeats (29).

FSH receptor (2p21-p16)

FSH/FSH receptor (FSHR) signaling plays a key role in normal gonadal function by regulating follicular growth, estrogen production, and oocyte maturation. In 1994, Aittomaki et al. found homozygous mutations (c.566C.T, p.A189V) in the extracellular portion of the FSHR G-protein in women of six Finnish families with hypergonadotrophic ovarian failure. FSHR mutations are primarily found in Finnish women with POI, but rarely in other geographic areas, where mutations appear to be mostly sporadic (30–32).

Galactosemia

POI is a common long-term complication reported for girls and women with profound GALT (galactose-1-phosphate uridyltransferase deficiency) (9p13) deficiency, with an estimated incidence of > 80%. Patients with trace levels of residual GALT activity demonstrate a milder phenotype. Serum AMH levels, used clinically as an indicator of follicular function and ovarian reserve, are low in galactosemic girls in comparison with age-matched controls, even in girls younger than 2 years. Elevated FSH levels have been observed in galactosemic girls as early as 10 months of age, suggesting early destruction of follicles (33).

Other genetic causes

Several other specific gene mutations can result in POI, along with other syndromic features, such as blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) type I; autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED) or central nervous system leykodystrophy and ovarian failure (34–38).

Many other genes have emerged as POI candidates, but in nonsyndromic POI, only a minority have been proven unequivocally as causative by functional validation.

The main mutations involving POI are summarized in Table 2.

Autoimmune primary ovarian insufficiency

POI of autoimmune origin is often associated with adrenal or other autoimmunity or is isolated. POI combined with adrenal autoimmunity and adrenal failure is the most frequent type, observed in 60–80% of patients. Autoimmune oophoritis is characterized by mononuclear inflammatory cell infiltrate in the theca cells of growing follicles, while early-stage follicles do not demonstrate lymphocytic infiltration (39, 40).

The combination of autoimmune oophoritis and Addison's disease is usually identified in the context of two types of autoimmune polyendocrine syndromes (APS): type I (APECED) and type II (a polygenic syndrome with autoimmune Addison's disease with adrenal insufficiency and other autoimmune illness without hypoparathyroidism) (40–43).

Table 2 Summary of mutations involving POI

Mutations of reproductive hormones	Mutations inactivating LH or FSH Mutations in inhibin A (INHA)
Mutations of hormonal receptors	NR5A1is a nuclear receptor which regulates follicular growth and development in the granulosa cells.
Other genetic mutations	FOXL2 (a forkhead transcription factor associated with the blepharophimosis/ptosis/epicanthus inverse syndrome
	ELF2B (a family of genes associated with CNS leukodystrophy and ovarian failure)
	Mutant or reduced levels of PGRMC1 PGRMC1 (Progesterone receptor membrane component1) (Xq22-q24).
	AIRE (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome)
	STAG3 (encoding a meiosis-specific subunit of cohesion) (7q21.3-22.2)
	BMP15 (bone morphogenetic factor 15, involved with folliculogenesis) BMP15 is located on chromosome Xp11.2 and is a member of the transforming growth factor (TGF) family.

POI can also be associated with localized or systemic non-adrenal autoimmune disorders, such as Hashimoto's thyroiditis, hypoparathyroidism, hypophysitis, type 1 diabetes mellitus, and non-endocrine autoimmune diseases, including systemic lupus erythematosum (SLE), Sjogren's syndrome, rheumatoid arthritis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, vitiligo, alopecia areata, celiac disease, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis multiple sclerosis, and myasthenia gravis (44–48).

Treatment of POI

Hormone replacement therapy

The aim of hormone replacement therapy (HRT) is to induce breast development, maturation of the uterus, onset of menses, increase in stature, and maintenance of skeletal health. Estradiol levels are introduced at the age of 12 when POI is due to a known condition, such as Turner syndrome or galactosemia (49, 50). Starting treatment at this age does not generally affect final height. However, most otherwise healthy girls with POI will present at age 13 or later, as this is the age of investigation of delayed puberty. The usual strategy is to administer estrogen alone, starting at a low dose and gradually increasing it until a withdrawal bleed is induced, at which stage a progestin is added to the regime. The best available evidence supports the use of 10 mg of oral medroxyprogesterone acetate per day for 12 days each month (51–53). This usually occurs at 18 months or later after initiation of treatment. A randomized controlled trial showed that optimal results are achieved with the administration of transdermal estradiol, starting at 0.0125 mg/day, with the dose doubled every 6 months to a maximum dose of 0.05 mg/day.

Once breast development is complete and progesterone is introduced, the preferred approach is a combination dose of 0.10 mg estradiol per day by transdermal patch along with 10 mg of medroxyprogesterone acetate by mouth per day from the first to the12th calendar day of each month.

For girls who will undergo gonadotoxic treatment or radiation to the pelvis, there is a growing interest in cell/tissue-based HRT. There are two case reports to support this hypothesis. The first girl was a 13-year-old who received a bone marrow transplant for sickle cell disease and, after having 3 out of 23 stored ovarian pieces transplanted, she entered puberty. The second girl developed POI when she was 9 years old due to treatment for Ewing sarcoma, and frozen ovarian cortical fragments were transplanted to the remaining ovary. In both girls, the graft failed after 2 years (54, 55), suggesting possibly that the graft has a limited lifespan after transplantation.

Fertility preservation

In the early stages of POI, primordial follicles exist in the ovary and, for this reason, it is crucial to identify POI early so as to offer timely options for fertility preservation. Although embryo cryopreservation is the most established method of fertility preservation, it is not a suitable therapeutic choice for most adolescents, given the need to use donor sperm. Oocyte cryopreservation shows advantages for these patients and is a method approved by the American Society for Reproductive Medicine. Nevertheless, there are no data to determine the expected pregnancy rate in the future for girls with any cause of POI who have cryopreserved oocytes.

In TS adolescents with ongoing but declining ovarian function, ovarian stimulation, aspiration, and vitrification of mature oocytes should be offered. This would by no means be an easy process for young, non-sexually active girls. Follicular tracking can be performed by transabdominal scanning; however, oocyte retrieval will require a transvaginal approach, and this might be unacceptable for some girls and their families. For those girls diagnosed with TS early in childhood, when it is uncertain how ovarian function will fare, cryopreservation of ovarian tissue could be an option. However, it is uncertain how ovarian tissue in TS women will perform when it is transplanted or whether in vitro maturation will be feasible.

In women with normal ovarian function in whom ovarian tissue is removed prior to gonadotoxic treatment and autotransplanted at a later stage, restoration of ovarian activity is reported by 4 months, with a live birth rate of about 25% (56). Most of these pregnancies have been described in adult women; however, a recent report described a live birth in a young woman where tissue had been removed at age 14 and cryopreserved, prior to a myeloablative conditioning for stem cell transplantation for sickle cell anemia (57). With these data in mind, some European countries have already integrated ovarian tissue cryopreservation (OTC) as an established procedure (58).

Conclusion

Ovarian insufficiency in adolescence presenting as delayed puberty, amenorrhea, or abnormal uterine bleeding has significant long-term consequences for the girl, including the effect on future fertility. Diagnosis at an early point in those girls who still retain some follicular activity may offer an invaluable chance to intervene early, institute appropriate hormonal replacement treatment, and offer fertility preservation options whenever possible.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bakhsh H, Dei M, Bucciantini S, Balzi D, Bruni V (2015) Premature ovarian insufficiency in young girls: repercussions on uterine volume and bone mineral density. Gynecol Endocrinol 31(1):65–69
2. Rebar RW (2009) Premature ovarian failure. Obstet Gynecol 113(6):1355–1363
3. Caburet S, Arboleda VA, Llano E, Overbeek PA, Barbero JL, Oka K et al (2014) Mutant cohesin in premature ovarian failure. N Engl J Med 370(10):943–949
4. Koyama H, Wada T, Nishizawa Y, Iwanaga T, Aoki Y (1977) Cyclophosphamide-induced ovarian failure and its therapeutic significance in patients with breast cancer. Cancer. 39(4):1403–1409
5. Insler V, Melmed H, Mashiah S, Monselise M, Lunenfeld B, Rabau E (1968) Functional classification of patients selected for gonadotropic therapy. Obstet Gynecol 32(5):620–626
6. Zhong Q, Layman LC (2012) Genetic considerations in the patient with Turner syndrome–45,X with or without mosaicism. Fertil Steril 98(4):775–779
7. Hagen CP, Aksglaede L, Sorensen K, Mouritsen A, Andersson AM, Petersen JH et al (2012) Individual serum levels of anti-Mullerian hormone in healthy girls persist through childhood and adolescence: a longitudinal cohort study. Hum Reprod 27(3):861–866
8. Bakalov VK, Gutin L, Cheng CM, Zhou J, Sheth P, Shah K et al (2012) Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. J Autoimmun 38(4):315–321
9. Gordon CM, Kanaoka T, Nelson LM (2015) Update on primary ovarian insufficiency in adolescents. Curr Opin Pediatr 27(4):511–519
10. Practice Committee of the American Society for Reproductive M (2004) Current evaluation of amenorrhea. Fertil Steril 82(1):266–272
11. Baker VL (2013) Primary ovarian insufficiency in the adolescent. Curr Opin Obstet Gynecol 25(5):375–381
12. Marozzi A, Vegetti W, Manfredini E, Tibiletti MG, Testa G, Crosignani PG et al (2000) Association between idiopathic premature ovarian failure and fragile X premutation. Hum Reprod 15(1): 197–202
13. Nelson LM (2009) Clinical practice. Primary ovarian insufficiency. N Engl J Med 360(6):606–614
14. Bakalov VK, Anasti JN, Calis KA, Vanderhoof VH, Premkumar A, Chen S et al (2005) Autoimmune oophoritis as a mechanism of follicular dysfunction in women with 46,XX spontaneous premature ovarian failure. Fertil Steril 84(4):958–965
15. Allen EG, Grus WE, Narayan S, Espinel W, Sherman SL (2014) Approaches to identify genetic variants that influence the risk for onset of fragile X-associated primary ovarian insufficiency (FXPOI): a preliminary study. Front Genet 5:260
16. Kallio S, Aittomaki K, Piltonen T, Veijola R, Liakka A, Vaskivuo TE et al (2012) Anti-Mullerian hormone as a predictor of follicular reserve in ovarian insufficiency: special emphasis on FSH-resistant ovaries. Hum Reprod 27(3):854–860
17. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH (2011) A validated model of serum anti-mullerian hormone from conception to menopause. PloS one. 6(7):e22024
18. Miyoshi Y, Ohta H, Namba N, Tachibana M, Miyamura T, Miyashita E et al (2013) Low serum concentrations of anti-Mullerian hormone are common in 53 female childhood cancer survivors. Horm Res Paediatr 79(1):17–21
19. Coccia ME, Rizzello F (2008) Ovarian reserve. Ann N Y Acad Sci 1127:27–30
20. Bath LE, Wallace WH, Shaw MP, Fitzpatrick C, Anderson RA (2003) Depletion of ovarian reserve in young women after treatment for cancer in childhood: detection by anti-Mullerian hormone, inhibin B and ovarian ultrasound. Hum Reprod 18(11):2368–2374
21. Lunding SA, Aksglaede L, Anderson RA, Main KM, Juul A, Hagen CP et al (2015) AMH as predictor of premature ovarian insufficiency: a longitudinal study of 120 Turner syndrome patients. J Clin Endocrinol Metab 100(7):E1030–E1038
22. van Dorp W, Mulder RL, Kremer LC, Hudson MM, van den Heuvel-Eibrink MM, van den Berg MH et al (2016) Recommendations for premature ovarian insufficiency surveillance for female survivors of childhood, adolescent, and young adult cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. J Clin Oncol 34(28):3440–3450
23. De Bellis A, Bellastella G, Falorni A, Aitella E, Barrasso M, Maiorino MI et al (2017) Natural history of autoimmune primary ovarian insufficiency in patients with Addison's disease: from normal ovarian function to overt ovarian dysfunction. Eur J Endocrinol 177(4):329–337
24. Bry-Gauillard H, Larrat-Ledoux F, Levaillant JM, Massin N, Maione L, Beau I et al (2017) Anti-Mullerian hormone and ovarian morphology in women with isolated hypogonadotropic hypogonadism/Kallmann syndrome: effects of recombinant human FSH. J Clin Endocrinol Metab 102(4):1102–1111
25. Tartaglia NR, Howell S, Sutherland A, Wilson R, Wilson L (2010) A review of trisomy X (47,XXX). Orphanet J Rare Dis 5:8
26. Michala L, Goswami D, Creighton SM, Conway GS (2008) Swyer syndrome: presentation and outcomes. BJOG 115(6):737–741
27. Qin Y, Jiao X, Simpson JL, Chen ZJ (2015) Genetics of primary ovarian insufficiency: new developments and opportunities. Hum Reprod Update. 21(6):787–808
28. Lozano R, Rosero CA, Hagerman RJ (2014) Fragile X spectrum disorders. Intractable Rare Dis Res 3(4):134–146
29. Rajaratnam A, Shergill J, Salcedo-Arellano M, Saldarriaga W, Duan X (2017) Hagerman R. Fragile X syndrome and fragile X-associated disorders. F1000Res 6:2112
30. Aittomaki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J et al (1995) Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. Cell. 82(6):959–968
31. Aittomaki K, Herva R, Stenman UH, Juntunen K, Ylostalo P, Hovatta O et al (1996) Clinical features of primary ovarian failure caused by a point mutation in the follicle-stimulating hormone receptor gene. J Clin Endocrinol Metab 81(10):3722–3726
32. Aittomaki K (1994) The genetics of XX gonadal dysgenesis. Am J Hum Genet 54(5):844–851
33. Fridovich-Keil JL, Gubbels CS, Spencer JB, Sanders RD, Land JA, Rubio-Gozalbo E (2011) Ovarian function in girls and women with GALT-deficiency galactosemia. J Inherit Metab Dis 34(2):357–366
34. Crisponi L, Deiana M, Loi A, Chiappe F, Uda M, Amati P et al (2001) The putative forkhead transcription factor FOXL2 is mutated in blepharophimosis/ptosis/epicanthus inversus syndrome. Nat Genet 27(2):159–166
35. De Baere E, Dixon MJ, Small KW, Jabs EW, Leroy BP, Devriendt K et al (2001) Spectrum of FOXL2 gene mutations in blepharophimosis-ptosis-epicanthus inversus (BPES) families demonstrates a genotype–phenotype correlation. Hum Mol Genet 10(15):1591–1600
36. Fogli A, Rodriguez D, Eymard-Pierre E, Bouhour F, Labauge P, Meaney BF et al (2003) Ovarian failure related to eukaryotic initiation factor 2B mutations. Am J Hum Genet 72(6):1544–1550
37. Di Pasquale E, Beck-Peccoz P, Persani L (2004) Hypergonadotropic ovarian failure associated with an inherited mutation of human bone morphogenetic protein-15 (BMP15) gene. Am J Hum Genet 75(1):106–111

38. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J (1990) Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 322(26):1829–1836
39. Pasoto SG, Viana VS, Mendonca BB, Yoshinari NH, Bonfa E (1999) Anti-corpus luteum antibody: a novel serological marker for ovarian dysfunction in systemic lupus erythematosus. J Rheumatol 26(5):1087–1093
40. La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A (2010) Primary ovarian insufficiency: autoimmune causes. Curr Opin Obstet Gynecol 22(4):277–282
41. Welt CK (2008) Autoimmune oophoritis in the adolescent. Ann N Y Acad Sci 1135:118–122
42. Carp HJ, Selmi C, Shoenfeld Y (2012) The autoimmune bases of infertility and pregnancy loss. J Autoimm 38(2-3):J266–J274
43. Carneiro-Sampaio M, Moraes-Vasconcelos D, Kokron CM, Jacob CM, Toledo-Barros M, Dorna MB et al (2013) Primary immunodeficiency diseases in different age groups: a report on 1,008 cases from a single Brazilian reference center. J Clin Immunol 33(4):716–724
44. Cabral de Sousa D, das Chagas Medeiros MM, Trindade Viana VS, Salani Mota RM (2005) Anti-corpus luteum antibody and menstrual irregularity in patients with systemic lupus erythematosus and Hashimoto's thyroiditis. Lupus. 14(8):618–624
45. Hoek A, Schoemaker J, Drexhage HA (1997) Premature ovarian failure and ovarian autoimmunity. Endocr Rev 18(1):107–134
46. Betterle C, Volpato M (1998) Adrenal and ovarian autoimmunity. Eur J Endocrinol 138(1):16–25
47. Euthymiopoulou K, Aletras AJ, Ravazoula P, Niarakis A, Daoussis D, Antonopoulos I et al (2007) Antiovarian antibodies in primary Sjogren's syndrome. Rheumatol Int 27(12):1149–1155
48. Silva CA, Bonfa E, Ostensen M (2010) Maintenance of fertility in patients with rheumatic diseases needing antiinflammatory and immunosuppressive drugs. Arthritis Care Res 62(12):1682–1690
49. Trolle C, Hjerrild B, Cleemann L, Mortensen KH, Gravholt CH (2012) Sex hormone replacement in Turner syndrome. Endocrine. 41(2):200–219
50. Gonzalez L, Witchel SF (2012) The patient with Turner syndrome: puberty and medical management concerns. Fertil Steril 98(4):780–786
51. Shah S, Forghani N, Durham E, Neely EK (2014) A randomized trial of transdermal and oral estrogen therapy in adolescent girls with hypogonadism. Int J Pediatr Endocrinol 2014(1):12
52. Gibbons WE, Moyer DL, Lobo RA, Roy S, Mishell DR Jr (1986) Biochemical and histologic effects of sequential estrogen/progestin therapy on the endometrium of postmenopausal women. Am J Obstet Gynecol 154(2):456–461
53. Bjarnason K, Cerin A, Lindgren R, Weber T (1999) Adverse endometrial effects during long cycle hormone replacement therapy Scandinavian Long Cycle Study Group. Maturitas 32(3):161–170
54. Poirot C, Abirached F, Prades M, Coussieu C, Bernaudin F, Piver P (2012) Induction of puberty by autograft of cryopreserved ovarian tissue. Lancet. 379(9815):588
55. Ernst E, Kjaersgaard M, Birkebaek NH, Clausen N, Andersen CY (2013) Case report: stimulation of puberty in a girl with chemo- and radiation therapy induced ovarian failure by transplantation of a small part of her frozen/thawed ovarian tissue. Eur J Cancer. 49(4):911–914
56. Donnez J, Dolmans MM (2015) Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice. J Assist Reprod Genet 32(8):1167–1170
57. Demeestere I, Simon P, Dedeken L, Moffa F, Tsepelidis S, Brachet C et al (2015) Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod 30(9):2107–2109
58. Wallace WH, Critchley HO, Anderson RA (2012) Optimizing reproductive outcome in children and young people with cancer. J Clin Oncol 30(1):3–5