

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



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J. Reproduktionsmed. Endokrinol 2015; 12 (4), 274-278

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Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



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FÜR KLINIK & PRAXIS

20.-21. März 2026

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Primary Ovarian Insufficiency

R. Baber^{1,3}, M. Kwik^{2,3}

Primary Ovarian Insufficiency (POI) is a distressing condition that affects 1% of women under the age of 40 years. The diagnosis should be considered in young women with secondary amenorrhoea or oligomenorrhoea of more than 4 months and although tests should be performed to elucidate the cause of POI, the cause is often not found. A multidisciplinary approach is required to help women with the emotional aspect of losing their fertility, and the management of hormone replacement to mitigate the long term health risks associated with the condition. **J Reproduktionsmed Endokrinol Online 2015; 12 (4): 274–8.**

Key words: primary, ovarian, insufficiency, premature, menopause

■ Introduction

The menopause is a physiological event that occurs in women between 45 and 55 years of age (average 51 years of age) [1]. Menopause is described as premature when it occurs before age 40. This condition has been the subject of confusing terminology for many years but is now known as Primary ovarian insufficiency (POI) and idiopathic POI is estimated to affect 1% of women under the age of 40. POI is associated with a range of long-term health consequences if not managed appropriately. POI has been shown to be associated with an increased risk of cardiac morbidity and mortality [2–4], as well as an increased risk of morbidity and mortality associated with osteoporotic fractures [5]. It is generally agreed that replacing estrogen up to the normal age of a physiological menopause is important for the long-term health of patients with POI [6]. For most women this will be given as menopausal hormone therapy (MHT) but it may also be delivered via the combined oral contraceptive pill [7].

POI is a major cause of female infertility, associated with significant psychological and emotional anguish for the women and their families. The inability of women to generate more eggs once the ovarian reserve has been depleted often leaves oocyte or embryo donation as the only options for conception.

■ Diagnosis

The diagnostic criteria for POI include hypergonadotropic amenorrhoea in a

woman < 40 years of age. Two FSH levels should be obtained, six weeks apart. Some women may experience vasomotor symptoms in association with irregular periods, and other causes of oligomenorrhoea should be excluded, including thyroid dysfunction, hyperprolactinaemia, polycystic ovarian syndrome, hypothalamic amenorrhoea and pregnancy. An AMH level will assist in determining ovarian reserve and a pelvic ultrasound scan will assist in the diagnosis of autoimmune oophoritis. In 10–15% of sufferers there may be a family history of early menopause, particularly in younger women and those with a history of mental illness in male relatives suggestive of the FMR1 premutation

Upon diagnosis of POI, other investigations should attempt to elucidate the cause. Although the majority of cases will be idiopathic, a karyotype and FMR1 premutation studies should be performed together with screening tests for autoimmune disease.

■ Causes of Primary Ovarian Insufficiency

In most cases of POI, the exact cause will not be found. POI may occur due to a reduced ovarian reserve at birth, an acceleration of follicular atresia resulting in earlier depletion of ovarian reserve, or rare conditions affecting growth factors and their receptors resulting in the inability of follicles to be recruited into a menstrual cycle [8, 9].

Of cases where there is a clear cause, iatrogenic causes are the most common [10].

■ Iatrogenic Causes

Improvements in the treatment of malignant diseases of childhood and adolescence have resulted in many young women surviving their cancers but at the expenses of their ovarian reserves. Not all chemotherapeutic agents are toxic to the ovaries, and the agents of highest risk are the alkylating agents, as their effect is not dependent on cell-cycles [11, 12]. The dose of pelvic irradiation required to cause POI is not high and is related to the background ovarian reserve. A woman with an excellent ovarian reserve will be able to withstand some damage from chemotherapy and radiation, however, a woman who already has a low ovarian reserve will have a much higher chance of POI as a result of identical treatment [13, 14]. The use of GnRH agonists to suppress ovarian function prior to chemotherapy may reduce the chance of POI following treatment [14]. Transposition of the ovaries out of the radiation field is also an effective way of reducing the risk of POI from treatment [15].

■ Surgery

The other iatrogenic cause of POI is surgical oophorectomy, most commonly performed to treat pelvic malignancy, or performed prophylactically to avoid hormone based cancers. Surgical menopause is often associated with an acute reduction in hormones, and therefore a severe onset of vasomotor symptoms that may be difficult to manage. Unilateral oophorectomy has been shown to result in an earlier onset of menopause [16].

Received and accepted: May 8th, 2015

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Pelvic surgery for benign conditions has also been shown to decrease ovarian reserve, possibly as a result of reduced blood supply to the ovary in the case of hysterectomy and salpingectomy [17, 18]. Surgery on the ovary will also cause damage to primordial follicles, and there is a decline in ovarian reserve following ovarian cystectomy [19]. Bilateral endometrioma surgery is associated with a 2.4% chance of POI post-operatively [20].

■ Genetic Causes

Genetic factors represent the most commonly identified cause of POI. In most cases the genetic origin remains unknown and there are many candidate genes. Defects of the X chromosome are the most common identifiable genetic cause of POI and may be found in up to 15% of cases [21, 22]. The X chromosome contains genes that regulate normal ovarian function and structural abnormalities such as complete or partial absence of the X chromosome I (Turner Syndrome), X linked mutations and translocations may also result in aberrant gene expression and consequent ovarian failure.

Turner Syndrome

Turner Syndrome affects 1 in 2500 live births [23]. Features of Turner Syndrome include short stature, webbed neck and wide carrying angle. Women who are mosaic for Turner Syndrome (45XO/46XX) are more likely to undergo spontaneous puberty, but then will almost certainly go through POI.

Early identification of these young women allows for the option of ovarian stimulation for oocyte retrieval and cryopreservation. The risk of transmission of Turner Syndrome to offspring is dependent on the exact karyotype and structure of the maternal X chromosome [24]. However, women with Turner Syndrome are more likely to have associated thyroid dysfunction, deafness, skeletal issues, renal or cardiovascular abnormalities, and have an increased risk of pregnancy related morbidity and mortality associated with aortic root dissection. For some women these risks will be too high in which case surrogacy should be considered [25].

In women with Turner Syndrome who undergo POI prior to puberty, puberty should be induced. It is generally accepted that estrogen is started at a low dose,

and slowly increased to mimic the natural rise in estrogen over a few years. Once breast development has started, cyclical progestogens are then introduced [26].

Fragile X Mental Retardation 1 (FMR 1)

The FMR 1 gene is an unstable region on the X chromosome that contains CGG trinucleotide repeats. These repeats expand unpredictably in offspring, and those with 55–200 repeats are considered to be a permutation carrier [27]. Fragile X is the most common cause of mental retardation, and affects males more than females. Premutation carriers may develop POI, and should be aware that the FMR1 gene may be passed on to their offspring. As it is impossible to predict how the FMR1 gene will expand in subsequent generations, preimplantation screening may be performed to ensure that the patient does not have a child affected by Fragile X.

Uncommon Genetic Causes

There are other key gene mutations that may lead to POI, and these are all extremely rare.

Mutations in the ATM gene causes a deficiency in protein kinase, resulting in cell cycle dysregulation and immune deficiency seen in ataxia telangiectasia, an autosomal recessive condition [8].

Mutations in the Forkhead box L2 (FOXL2) gene causes Blepharophimosis-ptosis-epicanthus-inversus syndrome, an autosomal dominant condition.

Mutations in the GALT enzyme results in galactosemia, a condition that affects 1 in 30,000–1 in 50,000 [28]. FSH and LH receptor mutations are extremely rare, and will also result in POI [29]. Mutations in Bone Morphogenic Protein 15 (BMP 15), a member of the Transforming Growth Factor Beta (TGF Beta) family may cause dysregulation of the follicular granulosa cells thus increasing the risk of POI [30]. Finally, mice studies have shown that mutations in the Kisspeptin receptor (Kiss1r) affect follicular response to gonadotropins [31].

■ Autoimmune Causes of POI

Up to a third of women with POI will have other autoimmune markers [32,

33], and women with POI have a higher risk of also having autoimmune thyroiditis, inflammatory bowel disease, coeliac disease, Type I diabetes mellitus, systemic lupus erythematosus, Sjogrens Syndrome, and Addison's disease [34–36].

Screening for ovarian antibodies is unreliable and not recommended. In consequence, attempted treatment of autoimmune oophoritis is regarded as controversial [37] since by the time women present with signs of POI irreversible depletion of primordial follicles has already occurred.

■ Infectious Causes

Viral infections, notably, mumps, herpes simplex, herpes zoster and cytomegalovirus have been implicated in the aetiology of POI. Other documented infections include tuberculosis, shigella and malaria.

■ Management of POI

POI often has far-reaching effects, and the initial presenting symptoms of menstrual irregularity and vasomotor symptoms should be managed in conjunction with counseling with respect to bone and cardiovascular health, fertility, and emotional distress.

A multi-disciplinary team approach is often the most effective way of helping patients and their families through this difficult time, and experienced counselors are important for psychological support. Ideally patients should have ready access to support groups and expert care. Coordination of care should be via the family physician with access to fertility, reproductive endocrinology and psychiatric care available.

■ Vasomotor and Urogenital Symptoms

The most acute presenting symptoms for women with POI are vasomotor symptoms, which may be extremely distressing, particularly in women who have had sudden ovarian failure, such as that caused by oophorectomy or chemotherapy.

Menopausal Hormone Therapy (MHT) is the most effective treatment of vasomotor symptoms and should be contin-

ued at least until the normal age of menopause [6]. For women with POI, the benefits of MHT will far outweigh the risks and concerns regarding increased risk of breast cancer and cardiovascular disease should not be applied to this age group. Any increased risk of venous thromboembolic disease (VTE) may be reduced by the use of non oral therapy due to the avoidance of hepatic first pass metabolism [38, 39]. Progestogens should be used where the uterus is intact, to protect against endometrial hyperplasia [40].

Urogenital symptoms occur as a direct effect of the hypoestrogenic state causing thinning of the vaginal epithelium. This in turn contributes to vaginal dryness and irritation, and may also lead to superficial dyspareunia. Whilst various vaginal moisturisers and lubricant will provide some relief, it is estrogen replacement which will offer the most benefit. For some women systemic estrogens will not be sufficient to alleviate these symptoms and the use of locally acting vaginal estrogens should be considered in these cases.

Although MHT remains the cornerstone of treatment of POI there will be some women, notably survivors of hormone dependent cancers who cannot take, or choose not to take MHT.

Management of vasomotor symptoms in this group of women is problematic. Many will try complementary and alternative therapies, of which there is limited evidence of efficacy. Pharmaceutical options include clonidine, an alpha-adrenergic agonist, several SSRIs and SNRIs notably venlafaxine, desvenlafaxine, escitalopram, citalopram and paroxetine. Paroxetine should not be prescribed for women who are also taking tamoxifene as it interferes with the latter's metabolism. Gabapentin and pregabalin are also moderately effective in alleviating VMS. There is little evidence of benefit from Yoga, relaxation therapy or exercise and data on acupuncture is mixed [41].

■ Cardiovascular Health

Women who have POI are at an increased risk of premature death, largely due to an increased risk of cardiovascular disease [2–4], with women undergoing a surgical menopause at greatest risk [4]. In women with surgical POI, the risk of car-

diovascular disease was higher in those who did not take HRT [42], however, a large cohort study found that even if women with POI take HRT, they are still at increased risk of coronary heart disease over premenopausal women [43].

Women who have POI are also at an increased risk of ischaemic cerebral infarcts, and the administration of MHT may reduce this risk [44]. A recent systematic review and meta analysis found that POI resulted in an increased risk of developing or dying from ischaemic heart disease (RR 1.69, 95%-CI: 1.29–2.21) and total cardiovascular disease (RR 1.61, 95%-CI: 1.22–2.12) but no increased risk of stroke [45].

■ Bone Health

Women with POI are at a 6-fold increased risk of osteoporosis [5]. Estrogen deficiency at a young age leads to lower peak bone density and increased risk of osteoporotic fractures which are in turn associated with increased morbidity and mortality. Women with a diagnosis of POI should have a baseline Bone Mineral Density test and should be screened for vitamin D deficiency, thyroid disease and coeliac disease.

To improve bone density, women should be encouraged to partake in regular weight bearing exercise, consume adequate amounts of dietary calcium, consider vitamin D supplementation, and start MHT. MHT is a very effective way of increasing bone density and reducing fracture risk in addition to cardioprotection and alleviation of vasomotor and urogenital symptoms [46].

■ Psychological Health

Many women find the premature loss of ovarian function distressing. As investigations will most often fail to find a cause for the diagnosis, women are left with unanswered questions as to how and why this has happened. This frustration is often associated with a sense of failure as they may be unable to conceive without assistance, and guilt that they are letting their partner down. They are therefore more prone to depression and anxiety disorders, and effective counsellors and support groups are important to validate their feelings and help them deal with the diagnosis [47].

■ Fertility

For many women, the diagnosis of POI will be made more difficult by the impact that POI has on fertility.

Women are born with a finite quantity of oocytes, and are unable to generate new eggs once the ovarian reserve has been depleted. The chance of spontaneous conception following idiopathic POI is low (5%), but may still occur due to random spontaneous ovulation even after the diagnosis of POI has been made. Although the chances of spontaneous conception are low, women with POI who are wishing to conceive should be started on MHT rather than the oral contraceptive pill, as MHT will not inhibit ovulation.

Fertility options for women with POI include accepting the small chance of spontaneous conception, accepting their childlessness, adopting or fostering children, or using assisted reproductive techniques (ART) to conceive either with their own oocytes, or with donated oocytes or embryos [48]. ART is also able to screen for genetic causes of POI, particularly if the woman has a chromosomal abnormality or is a carrier of the FMR1 premutation.

It is important to note that the small chance of pregnancy may, for some women, be undesirable and appropriate contraceptive measure should be discussed in these cases.

For women who require chemotherapy or radiotherapy which will place them at high risk of POI, options for fertility preservation include oocyte/embryo cryopreservation, cryopreservation of ovarian cortex, or ovarian transposition out of the radiation field [49]. As modern day cancer treatments are so effective, the long term survival rates for many cancers are excellent, and many cancer survivors eventually find that infertility associated with POI becomes a real issue.

Embryo and mature oocyte cryopreservation, and ovarian transposition are the only fertility preservation techniques endorsed by the American Society of Reproductive Medicine [49]. Approximately 2–3 weeks are required to stimulate the ovaries with exogenous FSH,

and oocytes are retrieved transvaginally. To minimize the risk of ovarian hyperstimulation syndrome, a GnRH antagonist protocol should be used, with a GnRH agonist trigger for oocyte maturation [50]. Mature oocytes are vitrified, and once these oocytes have thawed successfully, the chances of a live birth are equivalent to that of a fresh oocyte [51]. As an alternative, oocytes that are fertilized may be vitrified as embryos.

Laparoscopic ovarian cortex biopsy is an experimental procedure that is mostly performed when there is not enough time available for a stimulated IVF cycle to harvest eggs prior to gonadotoxic treatment, eg haematological malignancies. Ovarian cortex biopsies may also be performed in pre-pubertal girls, and the tissue containing many primordial follicles is frozen for later transplantation back to the patient. The main issues faced with this technology involve the large number of follicles that perish in the thawing process, and also in the revascularisation process following transplantation. Therefore, there is difficulty in using this tissue for long-term hormone production, as after transplantation, the tissue does not function in vivo for very long. There have not been many babies born from this technique (approximately 30 babies worldwide), and there is also concern that the ovarian tissue may re-introduce malignancy (particularly haematological malignancy) into the patient.

Conclusions

Premature Ovarian Insufficiency is uncommon but not rare, occurring in perhaps 5% of women < 40 years of age, due to a variety of causes. The diagnosis should be considered in any young women with secondary amenorrhoea or oligoamenorrhoea of more than four months duration. POI is a chronic condition, often associated with co-morbidities, and management should involve support groups and clinicians from multiple disciplines. Hormone replacement therapy, when not contraindicated is the cornerstone of treatment and should be continued until the normal age of menopause (51 years).

Causes of Primary Ovarian Insufficiency

Genetic. Monosomy X (Turner Syndrome), Trisomy X, Fragile X Syndrome (FMR 1 premutation), Deletions, Translocations, FSH and LH Receptor defects, GALT gene, Inhibin, FOXL-2

Autoimmune. Hashimoto's thyroiditis, Addison's disease, Coeliac disease, Diabetes, Rheumatoid arthritis, Autoimmune Polyglandular syndromes 1 & 2, Myasthenia Gravis, Sjogren Syndrome, Thymic aplasia

Metabolic. Galactosemia, 17-Hydroxylase deficiency, Aromatase enzyme deficiency

Infectious. Mumps, H Zoster, H simplex, Cytomegalovirus, Malaria, Shigella, Tuberculosis

Anatomical. Gonadal Dysgenesis, GD plus Cerebellar ataxia, GD plus multiple malformations

Iatrogenic. Ovarian Surgery, Chemotherapy, radiotherapy

Conflict of Interest

R. J. Baber has received honoraria for lectures at meetings sponsored by Abbott pharma and Bayer Pharma. M. Kwik has received a honorarium for a lecture at a meeting sponsored by Bayer Pharma.

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