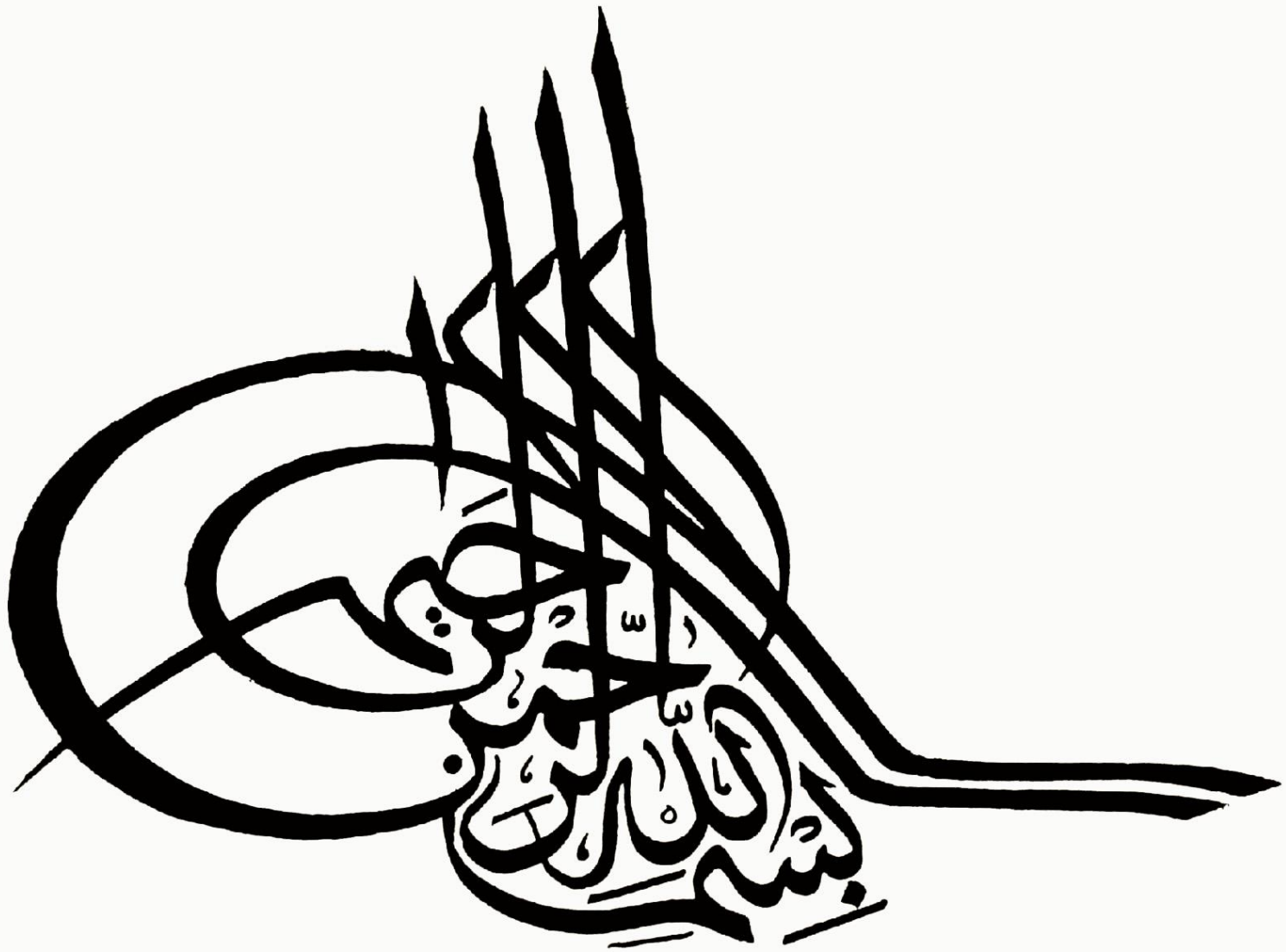
بسم الله الرحمن الرحيم

Premature ovarian insufficiency

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Definition premature ovarian insufficiency

Although proper diagnostic accuracy in POI is lacking, the GDG recommeeds the following diagnostic criteria:

- Premature ovarian insufficiency is a clinical syndrome defined by loss of ovarian activity before the age of 40.
- oligo/amenorrhea for at least 4 months
- an elevated FSH level > 25 IU/l on two occasions > 4 weeks apart.

It is recommend the term “insufficiency” instead of “failure”. It is felt that “insufficiency” more accurately describes the fluctuating nature of the condition, and does not carry the negative connotation of “failure”

The prevalence of POI is approximately 1%. Population characteristics such as ethnicity may affect the prevalence

The prevalence of early menopause (in the 40 to 44 age group) is ten times higher

Causes of premature ovarian insufficiency

- chromosomal and genetic defects

- Chromosomal and genetic abnormalities
- Autoimmune processes
- Fragile-X mutation
- Chemotherapy,
- Radiation
- Infections
- Surgery,
- Idiopathic.

how should POI be investigated?

- Chromosomal analysis should be performed in all women with non-iatrogenic Premature Ovarian Insufficiency.
- Gonadectomy should be recommended for all women with detectable Y chromosomal material.
- Fragile-X premutation testing is indicated in POI women.
- The implications of the fragile-X premutation should be discussed before the test is performed.

how should POI be investigated? cont:

- Autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).

- Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be considered in women with POI of unknown cause or if an immune disorder is suspected.
- Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison's disease.

- Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected.
- In patients with a positive TPO-Ab test, thyroid stimulating hormone (TSH) should be measured every year.

how should POI be investigated? cont:

- There is insufficient evidence to recommend routinely screening POI women for diabetes.
- There is no indication for infection screening in women with POI.
- The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.
- Although no causal relation has been proved for cigarette smoking and POI, there is a relation to early menopause. Therefore, women who are prone to POI should be advised to stop smoking.
- In a significant number of women with POI, the cause is not identified and these women are described as having unexplained or idiopathic POI.

How often should tests for autoantibodies be repeated? What do you do in case of a positive test result for autoantibodies?

- If 21OH-Ab/ACA and TPO-Ab are negative in women with POI, there is no indication for re-testing later in life, unless signs or symptoms of these endocrine diseases develop.

Untreated POI is associated with reduced life expectancy, largely due to cardiovascular disease.

Women with POI should be advised on how to reduce cardiovascular risk factors by not smoking, taking regular exercise, and maintaining a healthy weight.

All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease.

hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.

What are the implications for relatives of women with POI?

- Relatives of women with the fragile-X premutation should be offered genetic counselling and testing
- Relatives of women with non-iatrogenic premature ovarian insufficiency who are concerned about their risk for developing POI should be informed that:
- currently there is no proven predictive test to identify women that will develop POI, unless a mutation known to be related to POI was detected
- there are no established POI preventing measures
- fertility preservation appears as a promising option, although studies are lacking
- their potential risk of earlier menopause should be taken into account when planning a family.

What are the consequences of POI for life expectancy?

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What are the consequences of POI for fertility?

- Women with POI should be informed that there is a small chance of spontaneous pregnancy.

- Women with POI should be advised to use contraception if they wish to avoid pregnancy.

What fertility interventions are effective?

- Inform women with POI that there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates.
- Oocyte donation is an established option for fertility in women with POI.
- Inform women considering oocyte donation from sisters that this carries a higher risk of cycle cancellation.
- stem cell therapy
- ovarian tissue cryopreservation
- intra ovarian infusion of autologous platelet rich plasma
- In women with established POI, the opportunity for fertility preservation is missed

What are the obstetric risks associated with POI?

- Women should be reassured that spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population.

- Oocyte donation pregnancies are high risk and should be managed in an appropriate obstetric unit. Women and their partners should be encouraged to disclose the origin of their pregnancy with their obstetric team.
- Antenatal aneuploidy screening should be based on the age of the oocyte donor.

What are the obstetric risks associated with POI?

- Pregnancies in women who have received radiation to the uterus are at high risk of obstetric complications and should be managed in an appropriate obstetric unit.
- Pregnancies in women with Turner Syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with cardiologist involvement.
- A cardiologist should be involved in care of pregnant women who have received anthracyclines and/or cardiac irradiation.

How should fitness for pregnancy be assessed in women with POI?

- Women presenting for oocyte donation who are suspected of having POI should be fully investigated prior to oocyte donation, including thyroid and adrenal function as well as karyotype.
- Women previously exposed to anthracyclines, high dose cyclophosphamide or mediastinal irradiation should have an echocardiogram prior to pregnancy, and referral to a cardiologist if indicated.
- Women with Turner Syndrome should be assessed by a cardiologist with a specialist interest in adult congenital heart disease and should have a general medical and endocrine examination.
- Women with POI should have their blood pressure, renal function, and thyroid function assessed prior to pregnancy.
- Pregnancy in some women can be of such high risk that clinicians may consider oocyte donation to be life threatening and therefore inappropriate.

What are the consequences of POI for bone health?

- POI is associated with reduced bone mineral density (BMD).
- Reduced BMD is very likely to indicate that POI is associated with an increased risk of fracture later in life, although this has not been adequately demonstrated.

What are the treatment options for bone protection and improvement?

- Women should maintain a healthy lifestyle, involving weight-bearing exercise, avoidance of smoking, and maintenance of normal body weight to optimize bone health.
- A balanced diet will contain the recommended intake of calcium and vitamin D. Dietary supplementation may be required in women with inadequate vitamin D status and/or calcium intake, and may be of value in women with low BMD.

- Estrogen replacement is recommended to maintain bone health and prevent osteoporosis; it is plausible that it will reduce the risk of fracture.
- The combined oral contraceptive pill may be appropriate for some women but effects on BMD are less favourable.
- Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist. Particular caution applies t women desiring pregnancy.

How should bone health be monitored in women with POI?

- It is important to consider bone health at diagnosis in POI, and during ongoing care.
- Measurement of BMD at initial diagnosis of POI should be considered for all women, but especially when there are additional risk factors.
- If BMD is normal and adequate systemic estrogen replacement is commenced, the value of repeated DEXA scan is low.
- If a diagnosis of osteoporosis is made and estrogen replacement or other therapy initiated, BMD measurement should be repeated within 5 years.
- A decrease in BMD should prompt review of estrogen replacement therapy and of other potential factors. Review by a specialist in osteoporosis may be appropriate.

What are the consequences of POI for the cardiovascular system?

- Women with POI are at increased risk of cardiovascular disease and should be advised of risk factors that they can modify through behavioural change (e.g. stopping smoking, taking regular weight-bearing exercise, healthy weight).

- All women diagnosed with Turner Syndrome should be evaluated by a cardiologist with expertise in congenital heart disease.

Is estrogen replacement cardio-protective?

- Despite lack of longitudinal outcome data, hormone replacement therapy with early initiation is strongly recommended in women with POI to control future risk of cardiovascular disease; it should be continued at least until the average age of natural menopause.

Should cardiovascular risk factors be monitored?

- Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight and smoking status should be monitored annually with other risk factors being assessed if indicated.

- In women with Turner Syndrome, cardiovascular risk factors should be assessed at diagnosis and annually monitored (at least blood pressure, smoking, weight, lipid profile, fasting plasma glucose, HbA1c).

What are the consequences of POI on psychological wellbeing and quality of life?

- A diagnosis of POI has a significant negative impact on psychological wellbeing and quality of life.

- Psychological and lifestyle interventions should be accessible to women with POI.

What are the management options for the effects of POI on sexuality?

- Adequate estrogen replacement is regarded as a starting point for normalising sexual function. Local estrogen may be required to treat dyspareunia.
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- Women with POI should receive adequate counselling about the possibility of using testosterone supplementation so that they can make an informed choice, in the knowledge that long-term efficacy and safety are unknown.

What treatments are available for genito-urinary symptoms in POI?

- Local estrogens are effective in treatment of genito-urinary symptoms.
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- Clinicians should be aware that despite seemingly adequate systemic hormone replacement therapy (HRT), women with POI may experience genito-urinary symptoms. Local estrogens may be given in addition to systemic HRT.
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- Lubricants are useful for treatment of vaginal discomfort and dyspareunia for women not using HRT.

What are the consequences of POI on neurological function?

- The possible detrimental effect on cognition should be discussed when planning hysterectomy and/or oophorectomy under the age of 50 years, especially for prophylactic reasons.
- Estrogen replacement to reduce the possible risk of cognitive impairment should be considered in women with POI at least until the average age of natural menopause.
- Women with POI should be advised to take lifestyle measures (e.g. exercise, cessation of smoking, maintaining a healthy weight) to reduce possible risks for cognitive impairment.

HORMONE REPLACEMENT THERAPY (HRT)

- Hormone replacement therapy is indicated for the treatment of symptoms of low estrogen in women with POI.

- Women should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system and for bone protection.

What are the risks of hormone replacement therapy?

- Women with POI should be informed that HRT has not been found to increase the risk of breast cancer before the age of natural menopause.

- Progestogen should be given in combination with estrogen therapy to protect the endometrium in women with an intact uterus.

What are the options for hormone replacement therapy?

- 17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.

- Women should be informed that whilst there may be advantages to micronized natural progesterone, the strongest evidence of endometrial protection is for oral cyclical combined treatment.

- Patient preference for route and method of administration of each component of HRT must be considered when prescribing, as should contraceptive needs.

HRT in women with POI and special issues

- *Turner Syndrome* Girls and women with POI due to Turner Syndrome should be offered HRT throughout the normal reproductive lifespan.
- *BRCA gene mutation or after breast cancer* HRT is generally contra-indicated in breast cancer survivors.HRT is a treatment option for women carrying BRCA1/2 mutations but without personal history of breast cancer after prophylactic bilateral salpingo-oophorectomy (BSO).
- *Endometriosis* For women with endometriosis who required oophorectomy, combined estrogen/progestogen therapy can be effective for the treatment of vasomotor symptoms and may reduce the risk of disease reactivation.
- *Migraine* Migraine should not be seen as a contraindication to HRT use by women with POI. Consideration should be given to changing dose, route of administration or regimen if migraine worsens during HRT. Transdermal delivery may be the lowest-risk route of administration of estrogen for migraine-sufferers with aura.

HRT in women with POI and special issues cont:

- *Hypertension* Hypertension should not be considered a contraindication to HRT use by women with POI. In hypertensive women with POI, transdermal estradiol is the preferred method of delivery.

- *Obesity* Transdermal estradiol is the preferred method of delivery for women with POI requiring HRT who are obese or overweight.

- *Fibroids* Fibroids are not a contraindication to HRT use by women with POI.

What complementary treatments are available in POI?

Women should be informed that for most alternative and complementary treatments evidence on efficacy is limited and data on safety are lacking.

How should puberty be induced?

- Puberty should be induced or progressed with 17β-estradiol, starting with low dose at the age of 12 with a gradual increase over 2 to 3 years.

- In cases of late diagnosis and for those girls in whom growth is not a concern, a modified regimen of estradiol can be considered.
- Evidence for the optimum mode of administration (oral or transdermal) is inconclusive. Transdermal estradiol results in more physiological estrogen levels and is therefore preferred.
- The oral contraceptive pill is contra-indicated for puberty induction.

- Begin cyclical progestogens after at least 2 years of estrogen or when breakthrough bleeding occurs.