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Review Article

Primary ovarian insufficiency- An overview: Part 2 diagnosis and management

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ABSTRACT

Loss of normal ovarian function before the age of 40 characterizes primary ovarian insufficiency (POI), sometimes called premature ovarian failure or early menopause. Many women all around the globe deal with this serious reproductive health issue. The purpose of this study is to provide a broad perspective on how to identify and treat primary ovarian insufficiency. Clinical symptoms, hormone profiles, and ovarian imaging all play a role in making a diagnosis of POI. Genetic predisposition, autoimmune disease, and medical intervention are all possible origins. Counseling and treatment techniques for afflicted women can only be used when a timely and correct diagnosis has been made. Hormone replacement treatment (HRT) for symptom alleviation, avoidance of long-term consequences including osteoporosis and cardiovascular disease, and preservation of fertility are all part of the management of postmenopausal irritability (POI). To reduce the severity of menopausal symptoms and safeguard bone health, oestrogen replacement treatment is needed. HRT selection should be patient-specific, taking into account factors like as age, co-morbidities, and individual preferences. If a young woman is diagnosed with POI and she wants to have children in the future, she and her doctor should talk about fertility preservation strategies such oocyte or ovarian tissue cryopreservation. The latest treatments and possible revolutionary methods to POI management are also discussed in this overview. Stem cell therapy, ovarian tissue transplantation, and hormone manipulation are all examples of such unproven methods. While these treatments are still in their infancy, they show promise for the future of POI management. In conclusion, this review article gives a comprehensive, up-to-date explanation of how primary ovarian insufficiency is diagnosed and treated. Early detection, proper counselling, and individualised treatment plans are emphasised for afflicted females. The reproductive and overall health results of these people may be improved with a deeper knowledge of the processes producing POI and the development of more effective medicines.

1. Introduction

Now that we've covered the symptoms and possible causes of primary ovarian insufficiency (in Part 1 this review article), let's talk about treating and diagnosing it. Diagnosing POI requires taking into account clinical symptoms, hormonal profiles, and imaging of the ovaries. Possible causes include a genetic predisposition, an autoimmune condition, or medicinal intervention. Women may only benefit from counselling and therapy methods if they have been diagnosed with the condition in a timely manner.

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2. Diagnosis

The diagnosis of Premature Ovarian Insufficiency is based on the presence of menstrual disturbance and biochemical confirmation.[1] In a large cohort of women followed up prospectively, 0.9% experienced menopause before the age of 40 years although in this study amenorrhoea for >12 months were considered as menopause.[2] So before 40 reaching ovarian senescence is considered abnormal and often these women suffer from estrogen deficiency symptoms. It is usually FSH >40 IU/l taken to diagnose early menopause but this FSH value is not applicable for the diagnosis of POI as some women with POI has lower FSH particularly women with autoantibodies. POI due to steroidogenic cell autoimmunity had significantly lower FSH levels (range 26-64 mIU/ml, median 37 mIU/ml) compared with idiopathic POI (range 61-166 mIU/ml, median 99 mIU/ml).[3] FSH >25 IU/l is above the physiological range for FSH even at the pre-ovulatory peak. So, to include all types of POI women and exclude normal women and women with early ovarian aging a cut-off of 25 IU/l was taken. Hypoestrogenism is diagnosed when estradiol levels are below 50 pg/mL.

The diagnosis of POI is usually confirmed in women < 40 years by a combination of a 4-6 month period of amenorrhea or oligomenorrhea and two serial measurements of elevated FSH taken > 4 weeks apart.[3]

Table 1: Diagnostic criteria of POI

	Criteria to establish the Diagnosis of POI (ESHRE 2016)
Age	Less than 40 years
Menstruation	Oligo/amenorrhea for 4 months
Raised gonadotropins	An elevated FSH level > 25 IU/l on two occasions > 4 weeks apart

Inadequate anti-Müllerian hormone (AMH) may also be seen in women with regular cycles and low ovarian reserve, making POI diagnosis difficult. Follicular activity on ultrasonography can't differentiate POI from other causes since ovarian function fluctuates. Even without follicles, ovarian biopsy has resulted in pregnancy. Laparoscopy and ovarian biopsy are not recommended for POI diagnosis.

3. Investigations after Diagnosis

To determine the cause of primary ovarian insufficiency, karyotyping, adrenal antibodies, FMR1 premutation, and pelvic ultrasonography may be recommended. Every woman with these symptoms should have a pelvic ultrasound to examine endometrial thickness (oestrogen status), ovarian volume, and antral follicular count. Because 50% of women with secondary amenorrhoea and 20% with primary will experience withdrawal bleeding, a progestogen withdrawal test to assess oestrogen level is less clinically significant. This may reassure women yet mislead. Karyotyping and FMR-1 premutation analysis help young women with POI. Anti-adrenal, anti-21-hydroxylase, anti-thyroid peroxidase, and anti-thyroglobulin antibody screening is recommended. Many ovarian antigens may produce antibodies, hence antibody screening is advised. In young women with reproductive difficulties, anti-Müllerian hormone (AMH) estimate may measure ovarian reserve. Regular menstrual cycles, serum estradiol levels, and transvaginal ultrasound antral follicle count (AFC) in young women with POI or cancer therapy are extremely varied and not indicative of future fertility or hormonal output. POF women have a 50% incidence of osteopenia, hence a baseline DEXA scan is recommended.[4,5]

3.1. Management

There is no proven therapy that can restore ovarian function in women with POI. The aim of treatment is –

1. Psychological and emotional support and patient education.
2. Treatment of estrogen deficiency syndrome and to prevent long-term effects of estrogen deficiency.
3. Management of subfertility.

3.2. Patient counseling and support

The first aim of management is to help the woman deal with the diagnosis. The clinician must give this information in a sensitive and timely manner and best to inform the patient, partner, and family by having a direct conversation in the office. Adolescents with POI may show a wide range of feelings, from a lack of emotion to extremes of indifference, denial, regret, and despair. The phrase "premature ovarian failure" may be devastating to a young lady and her loved ones. In this group, "insufficiency" has replaced "deficiency" since it better accurately describes the patient's condition and allows for the potential of temporary recovery. Patients and their loved ones must be kept in the loop of how their condition could influence their future fertility. If the patient and family are interested in learning more about reproductive therapy, they should be referred to a reproductive endocrinology and infertility expert. Because of the poor self-image and isolation that may result after a verified diagnosis of primary ovarian insufficiency, this condition has been dubbed "the silent sorrow."[6] When questioned about their responses to the news, women with primary ovarian insufficiency reported significant rates of sadness, poor self-esteem, and despair, as well as a lack of tools to help them cope. Vasomotor problems partially explain this population's poor psychosocial functioning. A primary ovarian insufficiency diagnosis may be harder for adolescents to handle emotionally. Accepting a new diagnosis requires support from family and mental health professionals. Support groups such as the International Premature Ovarian Failure Association and the Daisy

Network Premature menopause support group (https://www.daisynetwork.org/) can be valuable adjuncts in helping the woman come to terms with the diagnosis.

4. Hormone Replacement Therapy in POI

If there are no contraindications, systemic hormone therapy (HT) is an effective method of treating hypoestrogenism and minimising long-term health hazards in women with primary ovarian insufficiency. Women with primary ovarian insufficiency might benefit from hormone replacement treatment since it can lessen their chances of developing osteoporosis, cardiovascular disease, and urogenital atrophy and increase their overall quality of life. The key recommendations by the American College of Obstetricians and K 9.[7]

Table 2: Key recommendations of ACOG regarding hormone replacement therapy in women with POI[7]

1.	If there are no contraindications, systemic hormone therapy (HT) is an effective method of treating hypoestrogenism and minimising long-term health hazards in women with primary ovarian insufficiency.
2.	Women with primary ovarian insufficiency might benefit from hormone replacement treatment since it can lessen their chances of developing osteoporosis, cardiovascular disease, and urogenital atrophy and increase their overall quality of life.
3.	Some of the symptoms of primary ovarian insufficiency might appear before cycle irregularity does, including hot flushes, night sweats, vaginal dryness, dyspareunia, and sleep disturbances. When prescribed, HRT is usually effective in treating these symptoms.
4.	First-line treatment should consist of HT (orally or transdermally) to reach oestrogen replacement levels. It is not advised, however, to check blood estradiol levels to track therapy progress.
5.	Combined hormonal contraceptives are more effective than HT at preventing ovulation and pregnancy, and this is important to keep in mind despite the low risk of unintended pregnancy in women with primary ovarian insufficiency.
6.	In contrast to oral progestin medication, insertion of a levonorgestrel intrauterine device provides very effective contraception for women who choose non-contraceptive oestrogen replacement.
7.	Women with primary ovarian insufficiency often have low bone mass which is best addressed with HT as opposed to bisphosphonates, which are often used as first-line therapy for postmenopausal osteopenia and osteoporosis.
8.	Primary ovarian insufficiency is treated until the typical age of natural menopause is achieved, which is between the ages of 50 and 51 for most women.

4.1. HRT – preparation

Research on the optimal HRT for women with POI is limited. HRT options for women with POI depend on types of preparation, regimens, route of administration, doses, duration, and monitoring. The following estradiol medications are effective for hormone replacement.:

1. 1–2 mg oral 17β-estradiol daily, 100 micrograms transdermal 17β-estradiol daily,
2. Conjugated equine estrogens 0.625–1.25 mg daily.
3. Synthetic ethinylestradiol (as in OCP).

The main goal of HRT for women with POI is to mimic normal physiological endocrinology concerning estrogen replacement. Oral contraceptives contain the potent synthetic estrogen ethinylestradiol, which in effect provides more steroid hormone than is needed for physiologic replacement, with unfavorable effects on lipid profile, hemostatic factors, and with an increased risk of thromboembolic events related to the progestogen and first pass effect of the liver. Various formulations of HRT are available which can be administered by the oral, transdermal, vaginal, or subcutaneous route. In the absence of any clear randomized prospective data to guide the route of administration, treatment should be individualized according to choice and risk factors. 17β-estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement.(ESHRE 2016)

Physiological sex steroid replacement with 17β-estradiol has a beneficial effect on bone mass acquisition mediated by the increased bone formation and decreased bone resorption.[8] Physiological replacement with a 17β-estradiol regimen caused lower mean blood pressure, reduced plasma angiotensin II and reduced s-creatinine without altering plasma aldosterone concentrations, compared with POI women treated with oral contraceptives.[8] No studies were identified that compared the effects of conjugated equine estrogen with ethinylestradiol or estradiol in women with POI.

Micronized natural progesterone may be preferred over synthetic progestogens is a better cardiovascular risk profile and breast cancer risk.[9] Micronized natural progesterone given in an oral dose of 200mg/day for 12 days per 28-day cycle has a similar effect as using a regimen using 10mg/day of medroxyprogesterone acetate (MPA), or 2.5mg MPA every day, for protecting the endometrium from hyperplasia caused by 0.625mg/day conjugated equine estradiol (CEE).[1] 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. (ESHRE 2016)

4.2. HRT – regimen

The estrogen therapy should be combined with appropriately dosed progestogen therapy (administered continuously or sequentially) to prevent endometrial hyperplasia and cancer. The OCP and continuous

combined HRT both decrease risk in healthy women and so are probably safe in POI women. Those desiring a pregnancy may be better treated with a sequential regimen rather than a continuous combined one, even though the risk of endometrial hyperplasia or carcinoma may be slightly higher and cyclic administration allows for earlier recognition of pregnancy. Ovulation may occur spontaneously in women with primary ovarian insufficiency, albeit it is uncommon, and in the absence of a withdrawal bleed, the patient should be urged to take a pregnancy test. A cyclical regime stimulating active functioning of the endometrium with regular proliferation and withdrawal bleedings is preferred in women aiming for pregnancy by oocyte donation.[10] Younger women are more likely to experience breakthrough bleeding with continuous combined HRT than older postmenopausal women. Women with POI who desire bleed-free HRT (and contraception) may benefit from using the levonorgestrel intrauterine system with appropriate estrogen replacement.[11]

Table 3: RT regimens for women with POI[11]

Estrogen	Progestogen	
	Continuous	**Sequential**
1–2 mg micronized 17 β-estradiol (oral)	2.5–5 mg medroxyprogesterone acetate daily (oral)	10 mg medroxyprogesterone acetate daily (oral) for 12 days each month
100 micrograms 17β-estradiol daily via transdermal route	100 mg micronized progesterone daily (oral)	200 mg micronized progesterone daily (oral) for 12 days each month
0.625–1.25 mg conjugated equine estrogen (oral)		

4.3. HRT- route of administration

When prescribing HRT, it is important to take into account the patient's contraceptive requirements and preferences regarding the route and mode of administration of each component.Compared to oral administration, the transdermal route can achieve higher plasma levels of circulating estradiol with a lower treatment dose and therefore fewer circulating estrogen metabolites, closer to matching the normal premenopausal state.[12] Transdermal HRT appears to have a beneficial effect on serum lipid profiles, inflammatory markers, and blood pressure and no effect on insulin-like growth factor I (IGF-I) concentrations and lower risk of deep vein thrombosis when compared to oral estrogen therapy.[13] Transdermal patches may irritate skin. Correct application and site rotation may help keep them in place. Cosmetic considerations may deter younger POI women from using patches. Younger POI patients may prefer oral HRT to estradiol gel. Local oestrogen therapy, such as an estrogen-releasing vaginal ring and estrogen-based vaginal creams and pessaries, is used for genito-urinary symptoms and does not cause endometrial hyperplasia. Progestogens can be administered via the oral, transdermal (as a patch), or intra-uterine routes (LNG-IUS). If the woman prefers a bleed-free regimen, local treatment with a progestogen-releasing intra-uterine system (IUS) will provide sufficient protection from endometrial hyperplasia and also contraception, with fewer side effects compared to systemic progestogen treatment.[12]

4.4. HRT-dose

The aim is to attain physiological estradiol levels as found in the serum of women with normal menstrual cycles, an average of 50-100 pg/ml (180-370 pmol/l).[13] These levels can be achieved with 100μg estradiol when given transdermally to women with POI or by oral estradiol in doses of 2 to 4 mg. Cyclical transdermal estradiol at a dose of 100μg/day week 1 then 150μg/day weeks 2 to 4 for 12 months improved bone mineral density, reduced markers of bone breakdown and increased markers of bone formation in women with POI.[14]

The purpose of progesterone supplementation is to protect the endometrium and the dose of progestogen required depends on the dose of estrogen given and the regimen used (i.e. continuous combined or sequential). Continuous regimens require a minimum dose of 1mg of oral norethisterone daily or 2.5mg medroxyprogesterone acetate (MPA) daily at the moderate to high doses of estrogen that should be provided for women with POI. Sequential regimens require 10mg MPA or 200mg micronized oral progesterone for a minimum of 10 to 12 days per month.[14]

4.5. HRT-duration

HRT should be continued at least until the age of natural menopause, or around 50 years old and Subsequently recommendations for HRT in naturally menopausal women should be followed.[15]

4.6. HRT- monitoring

There are no routine monitoring tests are required for women with POI on HRT but may be prompted by specific symptoms or concerns. Once established on therapy, women with POI using HRT should have a clinical review annually if well tolerated. If estrogen replacement or other therapy is initiated due to osteoporosis, BMD measurement (DEXA scan) should be repeated within 5 years but a decrease in BMD should prompt a review of estrogen replacement therapy and other potential causes. As in the normal population mammographic screening at the age of 45 to 50 years should be done in HRT users.

4.7. HRT- adverse effects

4.7.1. Breast cancer

Women with POI often begin HRT treatment at a much earlier age and have a substantially lower baseline risk of breast cancer than women who begin HT treatment after natural menopause. Short-term exposure to HRT has not associated with a higher chance of developing breast cancerin BRCA1 and BRCA2 carriers after risk-reducing bilateral salpingo-oophorectomy. Breast density in women with POI did not alter over periods of hypoestrogenism followed by HRT. Although women with a history of breast irradiation have a greater propensity to have breast cancer, the hypoestrogenic condition of POI may help minimise this risk, and oestrogen replacement therapy may bring it back to the same level as in women without POI. Informing POI women that HRT does not raise breast cancer risk before the onset of menopause is important.[9]

4.7.2. Endometrial hyperplasia and cancer

There is no evidence of HRT causing endometrial hyperplasia or cancer in women with POI on HRT and most of the data is extra plotted from postmenopausal women taking HRT for whom estrogen-only HRT is associated with increased risk for endometrial hyperplasia and cancer. Hence, unopposed estrogen replacement therapy is not preferred. The oral contraceptive pill reduces the risk of endometrial hyperplasia in women with normal ovaries and so it is reasonable to expect that it will have the same effect in women with POI. To safeguard the endometrium in fertile women, ESHRE (2016) advised administering progestogen with oestrogen treatment.[16]

4.7.3. Stroke and thromboembolic disease

Normal menopausal women who use HRT regularly are at little increased risk, which becomes most apparent in the first year of HRT use (absolute risk after one year's use: 7 per 1000).[16] There is one study that showed that women on HRT reaching menopause <40 years are at increased risk of VTE when compared with normal menopausal women using HRT.[17] There is no evidence that HRT increases the risk of stroke in women with POI.

Table 4: Indications for HRT in women with POI(ESHRE 2016)

Conditions	Comments
Vasomotor symptoms	Women with POI who are experiencing vasomotor symptoms may benefit from hormone replacement therapy.
Genito-urinary symptoms	Both systemic & local estrogens are effective in the treatment of genito-urinary symptoms. Where only genitourinary symptom is present then Local estrogen is preferred.
Bone protection	Bone health and osteoporosis prevention may both be supported by oestrogen replacement therapy.
Cardiovascular disease	Hormone replacement therapy with early initiation is strongly recommended in POI to control the future risk of cardiovascular disease.
Sexual function	Restoring regular sexual function is seen as possible with adequate oestrogen replacement. Dyspareunia treatment may include the use of local oestrogen.
Cognitive function*	Women with POI might consider using oestrogen replacement therapy to delay the onset of cognitive decline after menopause.
Quality of life*	Quality of life appears to be reduced: HRT may be of indirect benefit.
Life expectancy*	Life expectancy appears to be reduced due to cardiovascular mortality: HRT may be of indirect benefit.

*ESHRE 2016 guideline has stated there is conclusive evidence to HRT for these indications

5. Fertility in Women with POI

The possibility for spontaneous conception is up to 5% in women with POI[17] and thus women who don't wish to become pregnant are better to use contraception. Women with POI due to autoimmune causes should optimize their health conditions and an endocrinologist's opinion should be taken. Oocyte donation is the most successful treatment option for women with POI desiring pregnancy. Oocytes may be donated altruistically by sisters but these have a high cycle cancellation rate and should be discouraged. Oocyte-donated pregnancies have a higher incidence of pregnancy-induced hypertensive disorders, threatened miscarriage, FGR, cesarean section, and possibly postpartum hemorrhage.[17] Antenatal aneuploidy screening should be based on the age of the oocyte donor. Spontaneous pregnancies after idiopathic POI or after most forms of chemotherapy are probably not any higher risk than the general population but pelvic irradiation is associated with increased obstetric risks due to poor uterine function, especially when exposure occurred before menarche. Anthracycline chemotherapy and cardiac irradiation are associated with cardiac failure, which may become clinically apparent in pregnancy for the first time,[18] so it is better to have a full health check-up preconceptionally. A cardiologist review should be done in POI women with a history of having anthracyclines, high dose cyclophosphamide or mediastinal irradiation, and also all Turner syndrome patients. Prior to oocyte donation, women with POI should have their blood pressure, renal function, and thyroid examined, as well as their karyotype, thyroid function, and adrenal function.[18]

6. Bone Health in Women with POI

Women with POI tend to have weaker bones as evident by decrease bone mineral sensity (BMD) and are more likely to have a fracture as they age because of hypoestrogenism.

To keep their bones healthy and avoid osteoporosis, it is suggested that women take oestrogen replacement therapy in addition to consuming between 0.5 and 1.0 g of calcium and 400 to 800 IU of vitamin D daily, or a combination of the two. In order to keep their bones strong, women should stick to a healthy lifestyle that includes weight-bearing activity, avoiding smoking, and keeping their weight within a reasonable range. Some women may benefit from the OCP, however it has fewer positive benefits on bone mineral density (BMD). Women with a diagnosis of primary ovarian insufficiency should have their bone mineral density measured using dual-energy X-ray absorptiometry (DEXA). It is recommended that all women who have a diagnosis of POI have their bone mineral density (BMD) measured. Repeating a DEXA scan is not required if BMD is determined to be normal after a period of oestrogen replacement. If osteoporosis is diagnosed and treatment with oestrogen replacement or another method is begun, BMD should be measured again within 5 years. If bone mineral density (BMD) is not being maintained by hormone replacement, a referral to an osteoporosis specialist should be made. However, there is some uncertainty about the safety of bisphosphonates for women with primary ovarian insufficiency who may become pregnant on their own or with the help of donor eggs through in vitro fertilisation.[19]

7. Cardiovascular Health in Women with POI

Women are at increased risk of cardiovascular morbidity and mortality regardless of the cause of ovarian insufficiency due to metabolic and endothelial changes that occur with estrogen deprivation. Women with POI have significantly higher triglyceride and marginally lower HDL levels when compared with similar age women. Delaying menopause beyond age 39 reduces cardiovascular mortality by 2% year, according to a cohort study done in the Netherlands. All women diagnosed with POI should be advised on lifestyle modification. Hormone replacement therapy with early initiation is highly recommended in women with POI as it has beneficial effects on plasma lipids, blood pressure, insulin resistance, and endothelial function and also may reduce metabolic syndrome. The ESC's (European socity of cardiology) current recommendations recommend using a SCORE chart, although this tool is not yet accessible for patients under the age of 40.[20] But these patients require screening as it is a major health problem for them. ESHRE 2016 guideline states that cardiovascular risk should be assessed in women diagnosed with POI and at least blood pressure, weight, and smoking status should be monitored annually with other risk factors being assessed if indicated. Women diagnosed with Turner syndrome should have annual monitoring of blood pressure, smoking, weight, lipid profile, fasting plasma glucose, and HbA1c.

8. Genito-urinary and Sexual Health in Women with POI

Genito-urinary symptoms, such as vaginal dryness, irritation, urinary frequency, and incontinence, are associated with hypoestrogenism and are common in women with POI and local estrogens are effective in treatment for these. Nonhormonal like vaginal lubricants are useful for the treatment of vaginal discomfort and dyspareunia for women not using HRT. Women who are receiving adequate hormone therapy and still having genitourinary symptoms can use topical estrogen in addition to systemic hormonal therapy.[10]

POI patients may experience dyspareunia, vaginal dryness, and low libido, thus physicians should ask about their sexual health. Normalizing sexual function begins with estrogen replacement. Local estrogen gel or cream should be offered to improve sexual health and treat dyspareunia and also may benefit from short-term use of testosterone patches of 300 μg daily but prolonged should be avoided.[10]

Table 5: Treatment option for genitourinary syndrome of menopause

Hormonal treatment	Non-hormonal treatment
Systemic hormone therapy	Lubricants and moisturizers
Local estrogen therapy	Phytoestrogens
Testosterone patch	Vitamin E and D
Topical DHEA cream	2% Lidocaine gel
	5% gabapentin
	Oral pilocarpine

9. Future Therapy

Primary ovarian insufficiency (POI) treatment has the potential to be dramatically improved by new and upcoming medicines. Efforts to employ stem cell-based treatments to repair or replace damaged ovarian tissue are an exciting area of study. Emerging medicines provide promise for improving reproductive results and quality of life for women afflicted with POI, despite the fact that they are still in the early phases and need additional study and improvement.

9.1. Stem cell-based therapies

Primary ovarian insufficiency affects women for whom stem cell research holds promise for regenerating or replacing damaged ovarian tissue (POI). Many different types of stem cells are being studied for their potential to restore ovarian function by differentiating into ovarian cells. These include embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells. These treatments are aimed at increasing the number of follicles so that ovulation and spontaneous conception may resume.

9.2. Ovarian tissue transplantation

Women with POI may benefit from this procedure by receiving transplants of healthy ovarian tissue from a donor, who is often a twin or other close relative. Ovarian function may be revived by the transplanted tissue's ability to revive hormone production and follicular growth. Successful pregnancies have been recorded after ovarian tissue transplantation. Although significant progress has been made, there are still obstacles to overcome, such as graft rejection and the possibility of reinjecting malignant cells.

9.3. Hormonal manipulation

To encourage follicular growth and ovulation in women with POI, scientists are investigating innovative techniques to alter hormonal signalling pathways. To stimulate follicular development, some procedures may call for the administration of hormones such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These procedures are designed to help women conceive naturally by stimulating follicular growth rather than waiting for ovulation to occur on its own.

These medicines are in early research and need to be tested for safety, efficacy, and long-term benefits. However, they may assist primary ovarian insufficiency patients have more successful pregnancies and a better quality of life.

10. Conclusions

Secondary amenorrhea, increased gonadotrophins, and hypoestrogenic characteristics in women under 40 years old are classic presentations of premature ovarian insufficiency (POI). Depending on when rapid follicular depletion or ovarian injury occurs, POI in adolescents may manifest as either delayed puberty or amenorrhea. Although it is impossible to pinpoint a specific reason for POI, increasing scientific understanding has allowed us to correct prior misdiagnoses in many instances. Primordial follicles occur in the ovary in the early stages of POI; hence, it is critical to detect POI early in order to provide timely choices for fertility preservation. Improving quality of life and avoiding long-term repercussions of POI are the primary goals of HRT therapy.

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None.

12. Conflict of Interest

None.

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