GMR
The Original

PREMATURE OVARIAN INSUFFICIENCY: EXPLORING PATHOPHYSIOLOGY, DIAGNOSIS, AND THE IMPACT ON WOMEN'S HEALTH

Dr. Seetesh Ghose[1]

[1]Dean and Professor, O&G Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry. Email id: seetesh@mgmcri.ac.in, ORCID-0000-0002-2465-555X

ABSTRACT:
Background: This review aims to explore the pathophysiology, diagnostic approaches, and extensive impact of premature ovarian insufficiency (POI) on women's health.
Methods: A comprehensive literature search was conducted across databases including PubMed, Embase, Cochrane Library, and Google Scholar, utilizing keywords related to POI, including its causes, consequences, and treatment strategies. Articles published between January 2000 and October 2023 were included, focusing on studies that provide insights into the multifactorial aspects of POI.
Results: POI is characterized by the loss of ovarian function prior to age 40, resulting from genetic, autoimmune, and environmental factors. Diagnosis typically involves clinical evaluation and hormonal blood tests, primarily measuring elevated follicle-stimulating hormone (FSH) and low estradiol levels. The consequences of POI extend beyond reproductive health, significantly increasing risks for cardiovascular disease, osteoporosis, and mental health challenges such as anxiety and depression. Management strategies include hormonal replacement therapy (HRT), fertility preservation through oocyte or embryo cryopreservation, and tailored psychosocial support. Lifestyle modifications, including diet and exercise, also play a critical role in patient care.

KEYWORDS: Premature ovarian insufficiency, diagnosis, pathophysiology, women's health, hormone replacement therapy.

INTRODUCTION

Premature ovarian insufficiency (POI), defined as the cessation of ovarian function before the age of 40, is a significant health concern affecting approximately 1% of women under 40 years of age. It results in diminished estrogen production, leading to various physical and psychological complications, including infertility, bone density loss, and increased risk of cardiovascular disease. (1) POI can arise from various causes, including genetic factors, autoimmune disorders, and surgical interventions, and its multifactorial nature complicates both diagnosis and treatment. (2) The pathophysiology of POI is complex and not fully understood. Research indicates that genetic mutations, such as those affecting the FOXL2 (Forkhead Box L2), FSHR (Follicle Stimulating Hormone Receptor), and GALT (Galactose-1-Phosphate Transferaseuridylyl) genes, may predispose women to POI. (3) Additionally, autoimmune mechanisms can contribute, with antibodies against ovarian tissues being detected in some patients. (4) Environmental factors, such as chemotherapy and radiation exposure, are also known to harm ovarian function, leading to POI. (5) As a result, the clinical manifestations of POI are diverse and can occur abruptly, leading to significant lifestyle changes and health-related concerns for affected women.

The diagnosis of POI often involves a combination of clinical evaluation and laboratory tests. Women presenting with symptoms such as irregular menstrual cycles, hot flashes, and vaginal dryness may undergo hormonal assessments, including serum follicle-stimulating hormone (FSH) and estradiol levels. (6) Elevated FSH levels along with low estradiol levels are indicative of reduced ovarian reserve, thus supporting a diagnosis of POI. However, it is essential to consider secondary causes of amenorrhea and rule out other reproductive endocrine disorders. (7) Misdiagnosis or delayed diagnosis can occur, leading to inadequacies in treatment and support, which further emphasizes the necessity for heightened awareness and knowledge among healthcare providers regarding the signs and symptoms of POI.

The implications of POI extend beyond reproductive health, impacting the overall well-being of women. Studies indicate a high prevalence of psychological distress among women with POI, including increased rates of depression and anxiety compared to their peers. (8) The sudden loss of reproductive potential can lead to feelings of grief and loss, significantly affecting self-esteem and quality of life. Furthermore, the long-term consequences of decreased estrogen levels can result in severe health issues, such as osteoporosis and cardiovascular problems. (9) Consequently, women with POI may require comprehensive care that addresses both the physiological and psychological aspects of the condition.

Management strategies for POI are variable and tailored to individual needs. Hormonal replacement therapy (HRT) is often employed to mitigate symptoms related to estrogen deficiency and to provide protection against long-term

sequelae such as osteoporosis. (10) Additionally, fertility options such as egg donation and assisted reproductive technologies (ART) are increasingly being explored for women wishing to conceive. (11) Supportive measures, including counseling and education about POI and its effects, are crucial for providing holistic care to these patients, thereby improving their quality of life.

Methods: A comprehensive search was performed using multiple databases (PubMed, Embase, Cochrane library , Web of Science and Google scholar) to capture a wide range of studies. The search was conducted using a combination of controlled vocabulary and keywords related to POI i.e., POI, ovarian failure, pathophysiology, diagnosis, women's health, infertility using Boolean operators (AND, OR). The search included studies published from January 2000 to May 2024, ensuring a focused and relevant time frame for the literature reviewed. Inclusion criteria were peer reviewed articles including original research, systematic reviews, clinical trials and meta-analyses focusing on POI. Articles published in English were used to ensure clarity and comprehension for the review team. Exclusion criteria were editorials, letters to the editor, conference abstracts, and case reports that do not provide substantive analysis or data. A standardized data extraction template was developed to facilitate the systematic collection of relevant information from the included studies. Extracted data were synthesized into a narrative structure highlighting patterns, gaps in knowledge, and emerging themes in the literature on POI. Statistical analysis was not performed, as the review aimed to provide a descriptive synthesis rather than quantitative results.

Pathophysiology of Premature Ovarian Insufficiency

Premature ovarian insufficiency (POI), characterized by the loss of normal ovarian function before the age of 40, involves a complex interplay of genetic, autoimmune, and environmental factors that contribute to its pathophysiology. Understanding these mechanisms is crucial to developing effective diagnostic and therapeutic strategies for women affected by this condition.

Genetic factors

Genetic predisposition plays a significant role in the development of POI. Several chromosomal abnormalities have been implicated, including Turner syndrome, which is caused by the absence of all or part of one X chromosome. (12) Women with Turner syndrome often present with ovarian dysfunction at an early age, leading to POI. Additionally, mutations in specific genes involved in ovarian function, such as FOXL2, FSHR, and GALT, have been identified in patients with idiopathic POI. (3) For instance, mutations in FOXL2 are associated with altered folliculogenesis and premature depletion of the ovarian reserve, while FSH receptor (FSHR) mutations can affect follicular development. (3) Genetic testing can aid in identifying these mutations, allowing for better management of the condition.

Autoimmune factors

Autoimmunity is another critical element in the pathophysiology of POI. Studies have found that women with POI often exhibit high titers of ovarian antibodies, suggesting an autoimmune process that leads to the destruction of ovarian tissue. (13) Conditions such as autoimmune polyglandular syndrome (APS) can co-occur with POI, indicating a shared predisposition for autoimmune conditions affecting multiple endocrine organs. (14) The presence of autoantibodies, including anti-ovarian and anti-FSH receptor antibodies, can impair ovarian function and contribute to hormone dysregulation. (15) Understanding these autoimmune mechanisms underscores the importance of screening for other autoimmune disorders in women diagnosed with POI.

Environmental factors

Environmental factors also significantly influence the onset and progression of POI. Exposure to chemotherapy and radiation, particularly in the treatment of various cancers, is known to damage ovarian reserve and induce premature ovarian failure.(16) Furthermore, exposure to endocrine-disrupting chemicals, such as bisphenol A and phthalates, commonly found in plastics, has been linked to adverse reproductive health outcomes, including POI.(17) Lifestyle factors such as smoking, which accelerates follicular depletion and affects hormone levels, may also contribute to the risk of developing POI. (18) Therefore, awareness of these risk factors can help in devising preventive strategies for women at risk.

Follicular dysfunction

At a more cellular level, the pathophysiology of POI is marked by follicular dysfunction and loss of oocytes. In normal ovarian physiology, a pool of primordial follicles undergoes a controlled process of recruitment and maturation, leading to ovulation. In POI, however, this process is disrupted, resulting in follicular arrest and atresia.(19) Studies have shown that primordial follicles are depleted prematurely, leading to an inadequate ovarian reserve. (20) This follicular disruption is associated with decline in sex hormone production not only disrupts the menstrual cycle but also contributes to symptoms of hypogonadism and increased health risks, such as osteoporosis and cardiovascular disease

Diagnostic Approach

The accurate diagnosis of premature ovarian insufficiency (POI) is vital for effective management and optimal patient outcomes. A systematic approach, combining clinical evaluation and laboratory testing, guides clinicians in diagnosing POI and differentiating it from other related menstrual irregularities and reproductive health issues.

Clinical Evaluation

The diagnostic process for POI begins with a comprehensive medical history and physical examination. Physicians should inquire about a range of factors, including the patient's menstrual history, family history of ovarian dysfunction, autoimmune disorders, and previous surgical interventions affecting the ovaries. (1) Women typically present with symptoms such as amenorrhea (the absence of menstruation), irregular menstrual cycles, and symptoms of estrogen deficiency, such as hot flashes, night sweats, and vaginal dryness. (21)

Menstrual irregularities, particularly in younger women, warrant further investigation to establish a clear diagnosis. In some cases, POI can be mistaken for hypothalamic amenorrhea or other endocrine disorders like polycystic ovary

syndrome (PCOS). Therefore, clinicians must differentiate POI from these conditions through thorough assessments to avoid delays in treatment. (22)

Laboratory Testing

Once clinical signs suggestive of POI are identified, laboratory investigations are performed to confirm the diagnosis and evaluate the underlying causes. The cornerstone of diagnosing POI lies in serum hormone testing, particularly measuring follicle-stimulating hormone (FSH) and estradiol levels.

1.Follicle-Stimulating Hormone (FSH) Levels: In POI, reduced ovarian function leads to elevated serum FSH levels. FSH stimulates ovarian follicles to produce estrogen, and when ovarian resistance occurs, elevated FSH levels are typically accompanied by low estradiol levels . According to the current guidelines, an FSH level greater than 25 mIU/mL on day 3 of the menstrual cycle is indicative of POI. (23) However, since women with POI can sometimes have fluctuating hormone levels, testing should be performed at least twice to confirm persistently elevated FSH levels.

2.Estradiol levels: In conjunction with FSH measurements, serum estradiol levels are assessed. In healthy reproductive-age women, estradiol levels are generally elevated, particularly in the follicular phase of the menstrual cycle. In contrast, women with POI present with low estradiol levels along with high FSH levels. A combination of high FSH and low estradiol confirms ovarian insufficiency and reflects diminished ovarian reserve .

3.Anti-Mullerian Hormone (AMH): Anti-Müllerian hormone is an emerging biomarker for ovarian reserve. AMH is produced by granulosa cells of developing follicles, and its levels correlate with the number of antral follicles. In women with POI, significantly low AMH levels correspond to diminished follicular development. (24) Though not routinely used for the diagnosis of POI, AMH may provide additional insight into residual ovarian function.

4.Thyroid Function Test: Since thyroid disorders can present with similar symptoms to POI, it is essential to assess thyroid function through serum TSH (thyroid-stimulating hormone) and free T4 measurements. (25) An underlying thyroid disorder can contribute to menstrual irregularities and should be managed concurrently if present.

5.Autoimmune Screening: Given the association between POI and autoimmune conditions, screening for relevant autoantibodies may be warranted, particularly if there are clinical signs of an autoimmune disorder. Common tests include anti-thyroid antibodies, anti-adrenal antibodies, and anti-ovarian antibodies. A significant proportion of women with POI may have autoantibodies that can contribute to ovarian dysfunction. (14) In addition to antibodies, checking for conditions such as Addison's disease or type 1 diabetes may be important, as these conditions frequently co-occur with POI. (26)

6.Genetic testing: Genetic evaluation can help identify inheritable conditions associated with POI. Karyotyping is often performed to check for chromosomal abnormalities, particularly in cases suggesting Turner syndrome. (12) Targeted genetic testing may also be indicated for specific gene mutations related to POI, including mutations in the FSHR and FOXL2 genes. Identification of genetic causes can provide valuable prognostic information and allow for informed decisions regarding management and counseling. (3)

Imaging techniques

While hormonal assessments are primarily used in the diagnosis of POI, imaging studies may be employed to evaluate the structural and functional aspects of the ovaries. Transvaginal ultrasound can provide insights into the morphology and the presence of any ovarian lesions. In women with POI, ultrasound may demonstrate the absence of antral follicles, which is consistent with reduced ovarian reserve. Though imaging studies are not always necessary for diagnosing POI, they may be useful in cases where anatomical abnormalities are suspected

Impact on Women's Health

Premature ovarian insufficiency (POI) has profound and multifaceted effects on women's health, extending beyond the reproductive system. The cessation of ovarian function before the age of 40 results in a decrease in estrogen production, leading to a myriad of physical, psychological, and social consequences. Understanding these impacts is crucial for healthcare providers to offer comprehensive care to affected women.

Reproductive Health Consequences

One of the most immediate effects of POI is infertility. Women diagnosed with POI experience reduced ovarian reserve, often leading to anovulation and the inability to conceive naturally. (1) The emotional toll of infertility can be significant, as many women with POI face the distressing reality of not being able to fulfill reproductive plans. This challenge is compounded by the limited options available for fertility preservation, which may include oocyte retrieval and cryopreservation prior to the onset of POI. (27) In cases where oocyte retrieval is not feasible, assisted reproductive technologies such as donor oocyte IVF may be necessary but are emotionally and financially taxing. (11)

Physical Health Risks

The decline in estrogen levels associated with POI has lasting implications for physical health. One of the most significant concerns is the increased risk of developing osteoporosis. Estrogen plays a vital role in maintaining bone density, and women with POI face a higher likelihood of bone mineral density loss, leading to an elevated risk of fractures. Studies indicate that women with early menopause or POI can experience bone density loss at rates two to four times higher than their peers, underscoring the importance of early screening and preventive measures such as calcium and vitamin D supplementation, as well as engaging in weight-bearing exercises. (28,29)

In addition to osteoporosis, POI can negatively impact cardiovascular health. Estrogen is known to exert protective effects on the cardiovascular system by influencing lipid profiles and vascular function. Women with POI may have an unfavorable lipid profile, resulting in increased risk factors for cardiovascular disease. (30) Research has shown that those with POI may have a higher incidence of hypertension and atherosclerosis, conditions typically associated with aging and menopause. (31) As such, regular cardiovascular screening is recommended for women diagnosed with POI to mitigate the risk of long-term cardiovascular complications.

Psychological impact

The psychological ramifications of POI can be profound and are often overlooked. Women with POI frequently report higher levels of anxiety and depression compared to their peers in the general population. (32) The loss of reproductive potential, accompanied by the physical symptoms of estrogen deficiency such as hot flashes and mood swings, can exacerbate feelings of loss, grief, and inadequacy.(33) Furthermore, the social stigma surrounding infertility can lead to feelings of isolation and distress, adversely affecting interpersonal relationships and overall quality of life.(34) Supportive counseling and mental health resources are essential components of comprehensive care for women with POI. Engaging in support groups or therapy can provide valuable emotional support, helping women navigate the psychological challenges posed by their condition.

Quality of Life Considerations

The cumulative effects of POI on physical and mental health significantly impact the overall quality of life for affected women. Lifestyle factors, including diet, exercise, and stress management, play a critical role in managing the health implications of POI. (34) Healthcare providers should work with patients to develop individualized lifestyle modifications aimed at minimizing risks associated with POI. These may include interventions targeting bone health, cardiovascular fitness, and mental well-being.

Current management strategies

The management of premature ovarian insufficiency (POI) encompasses a multi-faceted approach that addresses the reproductive, physical, and psychological needs of affected women. Due to the diverse implications of POI, treatment strategies must be tailored to each individual's circumstances, including age, symptom severity, desire for children, and overall health. Current management strategies for women with POI can be broadly categorized into hormonal replacement therapy (HRT), fertility preservation options, psychosocial support, and lifestyle modifications.

Hormone Replacement Therapy (HRT)

One of the primary management strategies for POI is hormonal replacement therapy. Given that POI results in decreased production of estrogen and progesterone, hormone replacement is utilized to mitigate the effects of these hormonal deficiencies. Oestrogen replacement can help relieve many symptoms associated with POI, including hot flashes, vaginal dryness, and mood swings. (1). HRT can be administered in various forms, including oral tablets, transdermal patches, and vaginal creams, which allow for flexibility based on patient preference and tolerability. It is generally recommended that women with POI initiate HRT to protect against the long-term health consequences of hypoestrogenism, including osteoporosis and cardiovascular disease). Current guidelines suggest that HRT should be continued until the average age of natural menopause, typically around 51 years, to optimize health outcomes. (35) It's essential to monitor and regularly reassess the need for HRT, as well as adjust dosages according to individual responses and any emerging health concerns. While many women tolerate HRT well, it is critical to consider contraindications such as a history of hormone-sensitive cancers or thromboembolic disorders. (36)

Fertility Preservation Options

For women with POI who wish to conceive, fertility preservation strategies are also essential components of management. Given the spontaneous resolution of POI can be rare, early intervention is crucial.

1.Oocyte cryopreservation: This is the preferred option for women of reproductive age before the onset of POI. Oocyte retrieval can be performed during ovarian stimulation, followed by cryopreservation for future use . Studies indicate that the success rates of IVF using frozen oocytes remain competitive and offer hope for women with POI. (37,38)

2.Donor Oocytes: For those who have not undergone oocyte cryopreservation prior to the diagnosis of POI, the use of donor oocytes is a viable option. Many women with POI achieve pregnancy through in vitro fertilization (IVF) using oocytes from younger donors, yielding higher success rates compared to using their own oocytes. (39, 40)

3.Embryo cryopreservation: For women undergoing IVF, cryopreservation of embryos can also be offered, particularly for those who respond well to stimulation protocols, as this may increase the likelihood of successful conception in the future.

Psychological support

The psychological impact of POI can be profound and multifaceted, encompassing feelings of loss and grief over reproductive potential, anxiety about health risks, and depression related to hormonal imbalances. Thus, incorporating psychosocial support is critical in the management of women with POI. (8)

Counseling and psychotherapy can help women navigate the emotional challenges associated with infertility and hormonal changes. Support groups can also provide a safe space for women to share experiences and foster connections with others facing similar challenges. (41) Involving partners and families in counseling can enhance support systems and improve coping strategies, contributing positively to mental well-being.

Healthcare providers should refer patients to mental health professionals specializing in reproductive health issues when necessary. Regular screening for anxiety and depressive symptoms can be beneficial in identifying those who may require additional support. (8,42)

Lifestyle Modification

Integrating lifestyle modifications into the management plan for women with POI is essential for overall health and well-being. Addressing diet, exercise, and stress management can enhance physical health and improve the quality of life.

1.Nutrition: Emphasizing a nutrient-dense diet rich in calcium, vitamin D, and phytoestrogens can help support bone health and mitigate some consequences of estrogen deficiency. (43, 44) Women should be encouraged to consume a balanced diet filled with fruits, vegetables, whole grains, and lean proteins.

2.Exercise: Regular weight-bearing exercise is vital for maintaining bone density and cardiovascular health. (44) Recommendations generally include a mix of aerobic and strength-training exercises, ideally aiming for at least 150 minutes of moderate-intensity exercise weekly

3.Stress management: Techniques such as mindfulness, yoga, and meditation can help improve emotional resilience and reduce stress, which is particularly important for women coping with the implications of POI. (34,45)

4.Regular health screening: Given the increased risk of osteoporosis and cardiovascular disease, regular health check-ups, including bone density tests and cardiovascular assessments, are essential components of healthcare for women with POI. (28,30,46,47) Conclusion

In conclusion, premature ovarian insufficiency (POI) represents a significant health concern that affects a small but critical percentage of women, with profound repercussions on their reproductive health, overall well-being, and quality of life. As a complex condition characterized by the loss of normal ovarian function before the age of 40, POI can lead to infertility and a range of physical and psychological symptoms. The journey from diagnosis to management necessitates a comprehensive and individualized approach that addresses the multifaceted aspects of the condition.

The diagnostic process for POI is essential in establishing a clear understanding of the underlying pathophysiology, which includes genetic, autoimmune, and environmental factors. Healthcare providers must remain vigilant in recognizing the clinical signs and symptoms of POI, as timely diagnosis can significantly affect treatment outcomes. Through careful evaluation of hormonal profiles and other diagnostic tools, clinicians can confirm the presence of POI and initiate appropriate interventions.

Hormonal replacement therapy (HRT) is the cornerstone of managing the symptoms of POI, providing vital estrogen and progesterone to alleviate hormonal deficiencies and decrease the risk of long-term health complications such as osteoporosis and cardiovascular disease. For women desiring to conceive, various fertility preservation options are available, including oocyte and embryo cryopreservation, alongside the use of donor oocytes. The success of assisted reproductive technologies offers hope for many women with POI, enabling them to achieve their family-building goals.

However, the impact of POI extends beyond the physical realm, significantly influencing the psychological well-being of affected individuals. Feelings of grief, loss, and anxiety are common, and healthcare providers must prioritize psychosocial support alongside medical treatment. Engaging in counseling and joining support groups can help women navigate the emotional challenges associated with POI and infertility, fostering resilience and enhancing quality of life.

Lifestyle modifications play a crucial role in the overall management of POI. Women should be educated on the importance of maintaining a healthy diet, engaging in regular physical activity, and implementing stress-reducing practices to promote both physical and emotional health. Regular health screenings are essential to monitor potential complications and ensure timely intervention when needed.

As the recognition and understanding of POI continue to evolve, there is a growing need for comprehensive and multidisciplinary approaches to care. This includes an emphasis on education, research, and collaboration among healthcare providers, mental health professionals, and patients. By enhancing awareness and understanding of POI, we can ensure that affected women receive the support and resources they need to thrive.

In summary, the complexities of premature ovarian insufficiency necessitate a tailored approach that encompasses hormonal management, fertility options, psychosocial support, and lifestyle interventions. As we advance our understanding of this condition, it is vital to empower women with the knowledge and tools to make informed healthcare decisions. By prioritizing the well-being of women with POI, we can improve their quality of life and promote healthier futures for those affected by this challenging condition.

CONCLUSIONS

Understanding the intricate details of POI is essential for improving the quality of life and long-term health outcomes for affected women. A multidisciplinary approach to management can provide comprehensive care that addresses the reproductive, physical, and psychological implications of this condition.

REFERENCES

1. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360(6):606-14. doi:10.1056/NEJMcp0808697.
2. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet. 2010 Sep 11;376(9744):911-21. doi: 10.1016/S0140-6736(10)60355-8. Epub 2010 Aug 11. PMID: 20708256.
3. Fortuño C, Labarta E. Genetics of primary ovarian insufficiency: a review. J Assist Reprod Genet. 2014 Dec;31(12):1573-85. doi: 10.1007/s10815-014-0342-9. Epub 2014 Sep 18. PMID: 25227694; PMCID: PMC4250468.
4. Szeliga A, Calik-Ksepka A, Maciejewska-Jeske M, Grymowicz M, Smolarczyk K et al. Autoimmune Diseases in Patients with Premature Ovarian Insufficiency-Our Current State of Knowledge. Int J Mol Sci. 2021 Mar 5;22(5):2594. doi: 10.3390/ijms22052594. PMID: 33807517; PMCID: PMC7961833
5. Verp, M, Glob. libr. women's med.,(ISSN: 1756-2228) 2008; doi:10.3843/GLOWM.10357
6. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-müllerian hormone from conception to menopause. PLoS One. 2011;6(7):e22024. doi: 10.1371/journal.pone.0022024. PMID: 21789206
7. Rahman R, Panay N. Diagnosis and management of premature ovarian insufficiency. Best Pract Res Clin Endocrinol Metab. 2021 Dec;35(6):101600. doi: 10.1016/j.beem.2021.101600. Epub 2021 Nov 16. PMID: 34823999.
8. Xi D, Chen B, Tao H, Xu Y, Chen G. The risk of depressive and anxiety symptoms in women with premature ovarian insufficiency: a systematic review and meta-analysis. Arch Womens Ment Health. 2023 Feb;26(1):1-10. doi: 10.1007/s00737-022-01289-7. Epub 2023 Jan 27. PMID: 36705738; PMCID: PMC9908676.

9. Shelling AN. Premature ovarian failure. Reproduction. 2010;140(5):633-41. doi: 10.1530/REP-09-0567. Epub 2010 Aug 17. PMID: 20716613.
10. Laura G L, Najwa M T, Paula C L, Mariana F A, Isadora M F, Eriston V G. Hormone replacement therapy: Risk and Benefit. Integr J Med Sci.2020;7:3p.doi: 10.15342/ijms.7.242
11. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019 Dec;112(6):1022-1033. doi: 10.1016/j.fertnstert.2019.09.013. PMID: 31843073.).
12. Fukami M. Ovarian dysfunction in women with Turner syndrome. Front Endocrinol (Lausanne). 2023 Mar 23;14:1160258. doi: 10.3389/fendo.2023.1160258. PMID: 37033245; PMCID: PMC10076527
13. Domniz N, Meirow D. Premature ovarian insufficiency and autoimmune diseases. Best Pract Res Clin Obstet Gynaecol. 2019 Oct;60:42-55. doi: 10.1016/j.bpobgyn.2019.07.008. Epub 2019 Jul 29. PMID: 31495598.
14. Kauffman RP, Castracane VD. Premature ovarian failure associated with autoimmune polyglandular syndrome: pathophysiological mechanisms and future fertility. J Womens Health (Larchmt). 2003 Jun;12(5):513-20. doi: 10.1089/154099903766651649. PMID: 12869299.
15. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update. 2006 Nov-Dec;12(6):685-718. doi: 10.1093/humupd/dml034. Epub 2006 Aug 4. PMID: 16891297.
16. Rodriguez-Wallberg KA, Jiang Y, Lekberg T, Nilsson HP. The Late Effects of Cancer Treatment on Female Fertility and the Current Status of Fertility Preservation-A Narrative Review. Life (Basel). 2023 May 17;13(5):1195. doi: 10.3390/life13051195. PMID: 37240840; PMCID: PMC10224240.
17. McLachlan JA, Simpson E, Martin M. Endocrine disrupters and female reproductive health. Best Pract Res Clin Endocrinol Metab. 2006 Mar;20(1):63-75. doi: 10.1016/j.beem.2005.09.009. PMID: 16522520.
18. El-Nemr A, Al-Shawaf T, Sabatini L, Wilson C, Lower AM, Grudzinskas JG. Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer. Hum Reprod. 1998 Aug;13(8):2192-8. doi: 10.1093/humrep/13.8.2192. PMID: 9756295.
19. Conti M, Hsieh M, Zamah AM, Oh JS. Novel signaling mechanisms in the ovary during oocyte maturation and ovulation. Mol Cell Endocrinol. 2012 Jun 5;356(1-2):65-73. doi: 10.1016/j.mce.2011.11.002. Epub 2011 Nov 12. PMID: 22101318; PMCID: PMC4104635.
20. Revelli A, Delle Piane L, Casano S, Molinari E, Massobrio M, Rinaudo P. Follicular fluid content and oocyte quality: from single biochemical markers to metabolomics. Reprod Biol Endocrinol. 2009 May 4;7:40. doi: 10.1186/1477-7827-7-40. PMID: 19413899; PMCID: PMC2685803.
21. Falzone L, Scandurra G, Lombardo V, Gattuso G, Lavoro A, Distefano AB, Scibilia G and Scollo P: A multidisciplinary approach remains the best strategy to improve and strengthen the management of ovarian cancer (Review). Int J Oncol. 2021;59(1) doi.org/10.3892/ijo.2021.5233
22. Kovanci E, Schutt AK. Premature ovarian failure: clinical presentation and treatment. Obstet Gynecol Clin North Am. 2015;42(1):153-61.
23. doi: 10.1016/j.ogc.2014.10.004. PMID: 25681846.
24. Practice Committee of the American Society for Reproductive Medicine. Committee opinion no. 618: Ovarian reserve testing. Obstet Gynecol. 2015 Jan;125(1):268-273. doi: 10.1097/01.AOG.0000459864.68372.ec. PMID: 25560143.
25. Bedenk J, Vrtačnik-Bokal E, Virant-Klun I. The role of anti-Müllerian hormone (AMH) in ovarian disease and infertility. J Assist Reprod Genet. 2020 Jan;37(1):89-100. doi: 10.1007/s10815-019-01622-7. Epub 2019 Nov 21. PMID: 31755000; PMCID: PMC7000586.
26. Saran S, Gupta BS, Philip R, Singh KS, Bende SA, Agroiya P,. Effect of hypothyroidism on female reproductive hormones. Indian J Endocrinol Metab. 2016 Jan-Feb;20(1):108-13. doi: 10.4103/2230-8210.172245. PMID: 26904478; PMCID: PMC4743370.
27. Ebrahimi M, Akbari Asbagh F. The role of autoimmunity in premature ovarian failure. Iran J Reprod Med. 2015 Aug;13(8):461-72. PMID: 26568748; PMCID: PMC4637110.
28. Męczekalski B, Maciejewska-Jeske M, Podfigurna A. Reproduction in premature ovarian insufficiency patients - from latest studies to therapeutic approach. Prz Menopauzalny. 2018 Sep;17(3):117-119. doi: 10.5114/pm.2018.78554. Epub 2018 Sep 30. PMID: 30356967; PMCID: PMC6196776..
29. Jones AR, Enticott J, Ebeling PR, Mishra GD, Teede HT, Vincent AJ. Bone health in women with premature ovarian insufficiency/early menopause: a 23-year longitudinal analysis. Hum Reprod. 2024 May 2;39(5):1013-1022. doi: 10.1093/humrep/deae037. PMID: 38396142; PMCID: PMC11063537.
30. Silva de Sá MF. Premature Ovarian Insufficiency and Bone Health Care: A Concern of the Gynecologist. Rev Bras Ginecol Obstet. 2018 Jun;40(6):305-308. doi: 10.1055/s-0038-1667112. Epub 2018 Jul 6. PMID: 29980158; PMCID: PMC10316913
31. Roeters van Lennep JE, Heida KY, Bots ML, Hoek A; collaborators of the Dutch Multidisciplinary Guideline Development Group on Cardiovascular Risk Management after Reproductive Disorders. Cardiovascular disease risk in women with premature ovarian insufficiency: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016 Jan;23(2):178-86. doi: 10.1177/2047487314556004. Epub 2014 Oct 20. PMID: 25331207.
32. Daan NM, Muka T, Koster MP, Roeters van Lennep JE et al. Cardiovascular Risk in Women With Premature Ovarian Insufficiency Compared to Premenopausal Women at Middle Age. J Clin Endocrinol Metab. 2016 Sep;101(9):3306-15. doi: 10.1210/jc.2016-1141. Epub 2016 Jun 14. PMID: 27300572.

33. McDonald IR, Welt CK, Dwyer AA. Health-related quality of life in women with primary ovarian insufficiency: a scoping review of the literature and implications for targeted interventions. Hum Reprod. 2022 Nov 24;37(12):2817-2830. doi: 10.1093/humrep/deac200. PMID: 36102839; PMCID: PMC9989734.
34. Golezar, S., Keshavarz, Z., Ramezani Tehrani, F. et al. Primary ovarian insufficiency quality of life scale (POIQOLS): development and psychometric properties. BMC Women's Health 22, 481 (2022). doi.org/10.1186/s12905-022-02008-1
35. Li XT, Li PY, Liu Y, Yang HS et al. Health-related quality-of-life among patients with premature ovarian insufficiency: a systematic review and meta-analysis. Qual Life Res. 2020 Jan;29(1):19-36. doi: 10.1007/s11136-019-02326-2. Epub 2019 Oct 16. PMID: 31620985; PMCID: PMC6962283.
36. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril. 2016 Dec;106(7):1588-1599. doi: 10.1016/j.fertnstert.2016.09.046. PMID: 27912889; PMCID: PMC5137796.
37. Plu-Bureau G, Maitrot-Mantelet L, Hugon-Rodin J, Canonico M. Hormonal contraceptives and venous thromboembolism: an epidemiological update. Best Pract Res Clin Endocrinol Metab. 2013 Feb;27(1):25-34. doi: 10.1016/j.beem.2012.11.002. Epub 2012 Dec 21. PMID: 23384743.
38. Oktay K, Bedoschi G. Oocyte cryopreservation for fertility preservation in postpubertal female children at risk for premature ovarian failure due to accelerated follicle loss in Turner syndrome or cancer treatments. J Pediatr Adolesc Gynecol. 2014 Dec;27(6):342-6. doi: 10.1016/j.jpag.2014.01.003. Epub 2014 Sep 10. PMID: 25214440; PMCID: PMC4252563.
39. Cacciottola L, Donnez J, Dolmans MM. Ovarian tissue and oocyte cryopreservation prior to iatrogenic premature ovarian insufficiency. Best Pract Res Clin Obstet Gynaecol. 2022 May ;81:119-133. doi: 10.1016/j.bpobgyn.2021.09.010. Epub 2021 Nov 15. PMID: 34887172.
40. Chae-Kim JJ, Gavrilova-Jordan L. Premature Ovarian Insufficiency: Procreative Management and Preventive Strategies. Biomedicines. 2018 Dec 28;7(1):2. doi: 10.3390/biomedicines7010002. PMID: 30597834; PMCID: PMC6466184.
41. Sun B, Li L, Zhang Y, Wang F, Sun Y. Pregnancy outcomes in women with primary ovarian insufficiency in assisted reproductive technology therapy: a retrospective study. Front Endocrinol (Lausanne). 2024 Apr 29;15:1343803. doi: 10.3389/fendo.2024.1343803. PMID: 38745952; PMCID: PMC11092371.
42. Groff AA, Covington SN, Halverson LR, Fitzgerald OR, Vanderhoof V, Calis K, Nelson LM. Assessing the emotional needs of women with spontaneous premature ovarian failure. Fertil Steril. 2005 Jun;83(6):1734-41. doi: 10.1016/j.fertnstert.2004.11.067. PMID: 15950644.
43. Tian Y, Zhang X, Xin Z, Li CR, Zhang F, Deng H, . Premature Ovarian Insufficiency Is Associated with Increased Risk of Depression, Anxiety, and Poor Life Quality: A Systematic Review and Meta-analysis. Alpha Psychiatry. 2024 Mar 1;25(2):132-141. doi: 10.5152/alphapsychiatry.2024.231501. PMID: 38798816; PMCID: PMC11117423.
44. Shelling, A. N., & Ahmed Nasef, N. The Role of Lifestyle and Dietary Factors in the Development of Premature Ovarian Insufficiency. Antioxidants. (2023). 12(8), 1601. https://doi.org/10.3390/antiox12081601
45. Han Q, Chen ZJ, Du Y. Dietary supplementation for female infertility: Recent advances in the nutritional therapy for premature ovarian insufficiency. Front Microbiol. 2022 Nov 17;13:1001209. doi: 10.3389/fmicb.2022.1001209. PMID: 36466679; PMCID: PMC9712792.
46. McDonald IR, Welt CK, Dwyer AA. Health-related quality of life in women with primary ovarian insufficiency: a scoping review of the literature and implications for targeted interventions. Hum Reprod. 2022 Nov 24;37(12):2817-2830. doi: 10.1093/humrep/deac200. PMID: 36102839; PMCID: PMC9989734.
47. Rezende GP, Dassie T, Gomes DAY, Benetti-Pinto CL. Cardiovascular Risk Factors in Premature Ovarian Insufficiency using Hormonal Therapy. Rev Bras Ginecol Obstet. 2023 Jun;45(6):312-318. doi: 10.1055/s-0043-1770088. Epub 2023 Jul 21. PMID: 37494573; PMCID: PMC10371067.
48. Podfigurna A, Męczekalski B. Cardiovascular health in patients with premature ovarian insufficiency. Management of long-term consequences. Prz Menopauzalny. 2018 Sep;17(3):109-111. doi: 10.5114/pm.2018.78551. Epub 2018 Sep 30. PMID: 30357009; PMCID: PMC6196783.