International Journal of Science and Healthcare Research
Vol.8; Issue: 1; Jan.-March 2023
Website: ijshr.com
Review Article *ISSN: 2455-7587*

Primary Ovarian Insufficiency and Hormone Replacement Therapy: A Review Article

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DOI: https://doi.org/10.52403/ijshr.20230132

ABSTRACT

An uncommon but significant cause of ovarian hormone deficit and infertility in women is Primary Ovarian Insufficiency (POI). In addition to leading to infertility, POI is linked to many health problems, including troublesome menopausal symptoms, lower bone density and an increased risk of fractures, early cardiovascular disease development, a potential early reduction in cognition, and dry eye syndrome. It is essential to provide women with POI with the proper Hormone Replacement Treatment (HRT) to replace premenopausal levels of ovarian sex steroids and reduce the health concerns that come with them. Using HRT formulations that nearly resemble natural ovarian hormone production is advised in this evaluation. HRT should be continued until the typical age of natural menopause, 50 years old.

Keywords: Primary Ovarian Insufficiency, Hormone Replacement Treatment, Menopausal Symptoms

INTRODUCTION

An uncommon but significant cause of sex steroid deficit and infertility in premenopausal women is primary ovarian insufficiency (POI). According to Golezar et al., 3.7% of women globally have the disease. Primary amenorrhea (PA), secondary amenorrhea (SA), and oligomenorrhea of 4 months before the age of 40 are characteristics of POI. Women who display these findings after the age of 40 but before the age of 45 are termed to be in the early menopausal stage because the typical age of natural menopause is 50–51 years are all signs of POI. Long-term side effects in POI patients include osteoporosis, fractures, cardiovascular conditions, a potential early reduction in cognition, and dry eye syndrome. Since POI is sometimes discovered too late, the fertility and general health of the affected women are permanently harmed. According to recent evidence, POI is linked to high morbidity and mortality.[(1),(2),(3)]

Elevated follicle-stimulating hormone is the primary indicator of POI-associated hypogonadotropic hypogonadism (FSH). Transvaginal ovarian ultrasound (US) with antral follicular count and antiMüllerian hormone (AMH) measurement can both be used to assess the ovarian reserve (OR). Genetic, autoimmune, mitochondrial, iatrogenic (including chemotherapy, radiation, and surgery), and environmental variables contribute to POI, a diverse condition. Additionally, a sizable portion of POI patients has idiopathic conditions with unknown causes. There are various techniques to cure POI. Hormone replacement therapy (HRT) should be viewed as a physiological replacement for estrogen and progestin, although it cannot restore ovarian function. In vitro activation (IVA), mitochondrial activation, stem cell and exosome therapy, biomaterials techniques, and intra-ovarian platelet-rich plasma infusion are the most often employed innovative approaches (PRP).[(2),(3)]

In this review, we will primarily discuss the advantages and disadvantages of HRT therapy in women with early menopause and POI.

PRIMARY OVARIAN INSUFFICIENCY (POI)

After ovulation, monthly menstruation is crucial for female health and reproduction. The generation of sex steroids, essential for the genital tract's growth, appropriate bone density, and overall health, depends on healthy ovarian function. Health and reproductive issues may arise for women who do not have regular menstrual periods. We believe primary ovarian insufficiency may represent a variety of decreased ovarian functions. In addition to ovarian problems, endocrine issues such as polycystic ovary syndrome, hypothalamic-pituitary abnormalities, and adrenal dysfunction may also impair ovarian function. The triad of amenorrhea for at least four months, sex steroid deficiency, and two measurements of serum follicle-stimulating hormone (FSH) concentrations of more than 40 IU/L taken at least one month apart in a woman under the age of 40 is what defines primary ovarian insufficiency. The end-stage of primary ovarian insufficiency, menopause, occurs several years before age 40 and is a non-physiological illness. The individual variability of menopausal age and the degree of fertility reduction vary significantly among women of the same period.[(2),(4)]

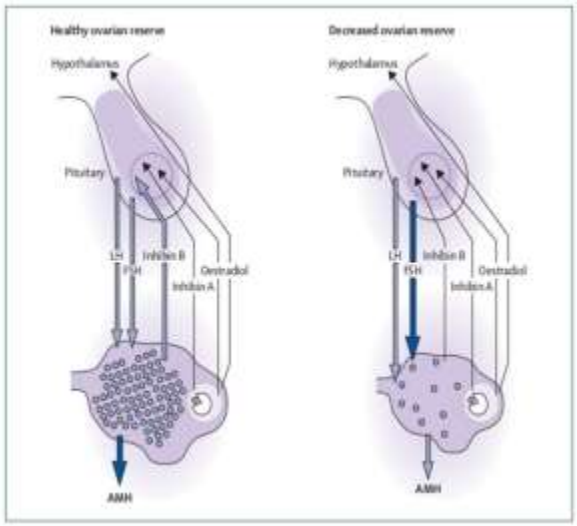

Figure 1. Healthy and decreased ovarian follicular reserve with age and variations in ovarian and hypothalami pituitary hormone concentrations.(2)

Etiology

The etiology of POI is complicated and has many contributing factors, including idiopathic, X-chromosome abnormalities, autosomal genetic diseases, radiation treatment, infections, immunosuppressive medications, and autoimmune oophoritis. Autoimmune illness is characterized by autoreactive T-cells and the presence of both organ- and non-organ-specific autoantibodies. Women with histologically inflammatory characteristics in an ovary biopsy and circulating ovarian and adrenal autoantibodies can be diagnosed with autoimmune oophoritis. Autoimmune ovarian insufficiency can happen in three ways: in conjunction with an adrenal autoimmune disorder, an autoimmune disorder unrelated to the adrenals, and isolated cases. According to epidemiology, 1-2% of women will develop POI. Most patients—60–80%—of autoimmune oophoritis, which affects 5% of these women, are thought to be caused by the adrenal glands. Furthermore, autoimmune diseases, particularly autoimmune thyroiditis and type 1 diabetes mellitus, are present in 10 to 30% of women with POI.[(1),(4),(5)]

Clinical characteristics and indicators of ovarian reserve

Generally speaking, autoimmune oophoritis has no symptoms. However, adnexal mass, enlarged ovarian cysts, and severe stomach discomfort have all been noted. The characteristic of POI, according to clinical definition, is amenorrhea; however, irregular periods can occur before menstruation ceases entirely. Common symptoms include infertility, hot flashes, vaginal atrophy, and dyspareunia. In addition to lowering the quality of life in terms of health, early menopause raises the risk of osteoporosis, cardiovascular mortality, and sexual dysfunction. Low estrogen levels, often less than 50 pg/mL, and elevated serum FSH levels, typically above 40 IU/L on at least two occasions, are used in laboratories to diagnose POI.[(1),(3),(4)]

AMH and AFC are now the top non-dynamic assays for predicting ovarian function in human reproductive therapy. Granulosa cells of early-stage follicles generate AMH, which has the benefit of being FSH-independent. An ovary ultrasound is part of the ovarian reserve test to evaluate AFC. AFC comprises all antral follicles with a mean diameter of 2 to 10 mm in both ovaries that were counted by transvaginal ultrasound during the early follicular phase.[(1),(3)]

Criteria for Autoimmune POI Diagnosis

Women with ovarian, adrenocortical, and/or steroidogenic autoantibodies in their serum, as well as POI patients with autoimmune Addison's disease and adrenocortical and/or steroidogenic autoantibodies, may have their ovarian histology confirm this autoimmune abnormality. In particular, genetics, prior ovarian surgery, systemic chemotherapy, and pelvic radiation must all be ruled out as potential causes of POI. Sustained amenorrhea, elevated blood FSH levels typically more significant than 40 IU/L on at least two occasions, and low estrogen levels typically lower than 50 pg/mL are all symptoms of POI.[(1),(4),(6)]

Autoimmune POI	Autoantibody	Autoimmune disease	Ovarian histology
Possible	Antibodies that are ovarian or adrenocortical and steroidogenic (such as anti-17-hydroxilase, cytochrome P450 side chain cleavage enzyme, and 21-hidroxylase) include anti-LH receptor, anti-FSH receptor, anti-zona pellucida, and anti-corpus luteum.	No	Not available.
Probable	Ovarian antibodies	Systemic lupus erythematosus, Sjögren's syndrome, immune thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, vitiligo, alopecia areata, celiac disease, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis, and myastenia gravis are among the autoimmune thyroid disorders.	Not available.
Confirmed	Adrenocortical or steroidogenic antibodies. Ovarian or, adrenocortical or steroidogenic antibodies	Autoimmune Addison's disease (APS type I or II) With or without autoimmune disease	Not available. Oophoritis (generally with lymphocytic infifiltration)

Table 1. Diagnostic criteria of autoimmune primary ovarian insufficiency (POI).[(1)]

HORMONE REPLACEMENT THERAPY

Benefits And Risks if HRT in Women with POI and Early Menopause

Sexual Function and Menopausal Symptoms

Common complaints from women with early menopause and POI center on inconvenient menopausal symptoms, which can appear gradually or unexpectedly. These women suffer the same symptoms as women who go through menopause naturally, which might include hot flashes. Flashes, night sweats, inability to sleep, and sexual dysfunction were brought on by dyspareunia and decreased desire. These symptoms are caused by a decrease in ovarian E2 production and, to some extent, ovarian T production. Menopausal symptoms are reduced with appropriate physiologic estrogen replacement, and it may also help with sexual dysfunction brought on by vaginal dryness, dyspareunia, and low libido. Some studies have shown that T replacement increases the positive benefits of estrogen treatment on sexual function in women with POI after oophorectomy.[(3),(7),(8)]

Cardiovascular Disease

According to a recent meta-analysis, women who go through menopause before age 45 are more likely to develop coronary heart disease, die from cardiovascular causes, and die overall than women who go through menopause after age 50. Women with sPOI

show impaired vascular endothelial function, an early indicator of atherosclerosis, when compared to age-matched ordinary women. Endothelial function in these women was dramatically enhanced after treatment with HRT for six months. Regardless of the reason, women with POI are at higher risk for ischemic stroke and CVD. Regular CVD risk assessments and risk-reduction strategies are recommended when taken as a whole. These include changes to one's way of life, control over blood pressure and cholesterol levels, and the early start of physiologic HRT. Women with POI are crucial for maintaining long-term cardiovascular health. [(3),(9),(10),(11)]

Cognitive Function

An early estrogen deficit would potentially increase a woman's risk for cognitive decline and dementia because research shows that estrogen is neuroprotective. Studies on human neuroimaging activities indicate that estrogen increases the brain's processing of memories. ERT is protective against dementia development, especially when begun early in the menopausal transition, and is taken for more than ten years, according to many studies in older postmenopausal women. However, the only postmenopausal groups with data on the advantages of HRT for cognition are older, and there is no evidence that HRT has any direct benefits for awareness in young women with POI. [(3),(12)]

Bone Mineral Density and Fracture Risk

Numerous studies have demonstrated a link between lower bone mineral density (BMD) and enhanced fracture risk in women with POI or early menopause. Several of these studies also showed that using HRT to treat women with POI or early menopause lowers the risk of fractures. Women reach their optimum bone mass by age 30, after which continuous estrogen insufficiency causes early bone loss. In young women with POI, early BMD loss or failure to reach peak bone density increases the risk of fracture, especially if proper HRT therapy is not started promptly after illness onset. Compared to women of comparable age and regular menstrual cycle, a cohort of young women with 46, XX sPOI (mean age 32 years) showed significantly lower BMD z-scores. A femoral neck BMD z-score less than 1.0 and sPOI in 67% of the women with sPOI identified within 1.5 years. The high prevalence of low BMD in newly diagnosed women may be caused by gradual declines in ovarian hormone production that took place before the diagnosis of sPOI. Women with POI are at increased risk due to delayed diagnosis. In one POI research, more than 50% of women who complained of menstruation irregularities had to see three or more separate doctors before having their FSH levels checked. The menstrual cycle should be viewed as a crucial indicator of bone health, and any anomalies should be quickly investigated. Women with POI must ensure enough calcium and vitamin D consumption and maintain a regular exercise schedule involving weight-bearing. [(13),(14)]

Popat et al. discovered that 58% of women with POI had insufficient blood 25-hydroxy vitamin D levels, 49% had inadequate calcium consumption, and nearly one out of four had no regular exercise routine. To improve bone health, women with POI should consume 1,000–2,000 IU of vitamin D3 (cholecalciferol) daily, combined with 1200 mg of elemental calcium, either from food sources or supplements. Older age, earlier age at POI diagnosis, and lower body mass index are additional risk factors for reduced BMD in women with POI. Women with POI need physiologic HRT and good lifestyle practices to maintain bone density and lower fracture risk. The National Institutes of Health (NIH) Intramural Research Program studied young women with 46, XX sPOI for three years to determine the effects of a conventional HRT regimen on BMD. In the trial, physiologic E2 replacement therapy was employed with cyclic oral progestin (100 mg/d transdermal E2 with 10 mg oral medroxyprogesterone

every day for 12 days each month). The addition of transdermal T replacement to the regimen of oral medroxyprogesterone acetate and transdermal E2 produced no other positive impact on BMD. There is substantial data to suggest that physiologic HRT (transdermal E2 and cyclic progestin) is superior to ongoing combination treatment with oral contraceptives for preserving bone health in young women with POI (OCPs). [(3),(13)]

For instance, a study in women with POI comparing the effectiveness of 12 months of combined OCP (30 mg ethinyl E2 and 1.5 mg norethisterone daily for three weeks per month) to 12 months of physiologic HRT (100-150 mg/d transdermal E2 plus cyclic progestin) showed that physiologic HRT was superior to OCPs in protecting and improving BMD. Physiologic E2 replacement (2 mg oral E2 and 0.075 mg levonorgestrel daily) and combination OCP (0.030 mg ethinyl E2 and 0.150 mg levonorgestrel administered daily for 21 days followed by a 7-day break) were evaluated in a 2-year open-label randomized experiment in women with POI. With the use of physiologic E2 replacement, the results showed a much more significant rise in lumbar spine BMD. These findings suggest using physiologic E2 and progestin HRT rather than chronic combined contraceptive steroids to preserve bone health in POI women. [(13),(14)]

Dry Eye Syndrome

Dry eye syndrome affects 20% more women with POI than age-matched control women with normal ovarian function. Women with POI do not experience diminished tear production from dry eye syndrome, unlike older people (>65 years) who are more frequently impacted by this ocular surface ailment. Ocular surface tissues include sex hormone receptors, which offer a potential method by which ovarian hormones might change function. [(3),(15)]

Infertility

The most unfortunate consequence of POI for many women is infertility. Ovarian follicles are still present in the ovary in almost three out of four POI patients. POI is often not an ovarian "failure," but rather an unexpected, intermittent ovarian function that might last for decades. However, the tonic elevation in blood LH levels results in early luteinization of developing antral follicles, which reduces the likelihood of spontaneous ovulation or a positive response to ovarian stimulation. The use of physiologic HRT, such as transdermal E2 combined with cyclic medroxyprogesterone, can improve ovarian follicles' capacity to avoid early luteinization, respond to an endogenous or exogenous stimulation from gonadotropins, proceed through follicular maturation, and ovulate. This possible effect of HRT comes from its capacity to reduce serum LH levels into the premenopausal range, which may lessen the unwarranted luteinization of follicles brought on by persistently increased LH levels and enhance ovulation rates. Reducing chronically increased FSH levels, which have been found to inhibit granulosa cell FSH receptors, it is hypothesized that E2 may increase fertility rates. Treatment with estradiol may enable the regeneration of FSH receptors, improving the responsiveness to exogenous gonadotropins in the pool of surviving ovarian follicles. [(3),(8)]

In a randomized controlled experiment examining the impact affecting fertility in sPOI-afflicted women who get physiologic estrogen replacement, oral E2 therapy for six weeks reduced blood LH levels and properly elevated E2 concentrations. However, during that brief trial, E2 had no impact on folliculogenesis, ovulation, or pregnancy rates. Another randomized placebo-controlled study looking at the effects of estrogen pretreatment on ovarian responsiveness to gonadotropin therapy in POI women found treatment with 0.05 mg ethinyl E2 three times daily compared to placebo, two weeks before stimulation of

ovulation, ovulation rates were considerably more significant. Only in women with blood FSH levels of 15% mIU/mL did follicle growth and ovulation occur, indicating that suppression of endogenous gonadotropins by E2 increased response rates. In that research, four of the eight ovulating women with E2 pretreatment and gonadotropin-assisted ovulation induction went on to get pregnant.[8],[16]

Transdermal or Transvaginal Estradiol

Hormone replacement treatment is hormone "replacement," whereas hormone "extension" therapy is the hormone "replacement" for young women with E2 insufficiency. According to recent research, 52% of young women with POI either never start HRT, start it years after their diagnosis, or stop taking it before age 45. Transdermal or transvaginal E2 treatment is now the preferred first-line HRT for young women with POI or early menopause, according to the weight of the evidence. Long-term ovarian sex steroid replacement is necessary for young women who develop POI. Some patients will need this treatment for years. The ideal replacement would replicate healthy ovarian function. An artificial ovary created to imitate endogenous ovarian output during a menstrual cycle would be constructed to administer a continuous parenteral infusion of the proper hormone combination. The first crude step in this approach is the vaginal ring and transdermal patch, which supply 0.100 mg E2 daily. The average serum E2 levels produced by these formulations, which replicate the daily ovarian E2 production rate, are 100 pg/mL throughout the menstrual cycle, the group that women with typical ovarian function experience daily.[17],[18]

The transdermal and transvaginal modes of delivery transfer hormone directly into the circulation, avoiding difficulties related to the first-pass impact on the liver when estrogen is administered orally. However, an equivalent dosage of oral E2 is also a viable alternative. Comparing the use of oral estrogen to the use of transdermal estrogen, the risk of venous thromboembolism is raised. Unlike oral estrogens, transdermal HRT does not negatively affect cardiovascular disease or thromboembolic risk indicators. The risk of venous thromboembolism linked with oral estrogen is increased even higher in women with underlying obesity or coagulation problems, reaching 5-8 times the risk reported in nonusers or users of transdermal estrogen preparations. To prevent ovulation in women with regular menstrual cycles, steroidal hormone agents—developed as contraceptives—deliver supraphysiologic amounts of synthetic estrogen and progestin. In addition to increasing cardiometabolic risk, including an increase in blood pressure and unfavorable lipid profiles, contraceptive steroid hormone drugs have also been linked to an increased risk of thromboembolism, stroke, subarachnoid hemorrhage, and other cardiovascular events. Additionally, oral contraceptives typically have a 1-week "pill-free" phase once every month (or once every three months with preparations for three months), which causes a consistent temporary estrogen deficiency condition. [3],[17]

Transdermal E2 with cyclic progestin medication versus treatment with a combined oral contraceptive was examined for its cardiovascular effects in a recent randomized controlled cross-over experiment in young women with POI. Transdermal physiologic HRT for 12 months dramatically lowered blood pressure compared to oral contraceptives, improved renal function, and decreased renin-angiotensin-aldosterone system activation. This data demonstrates that transdermal physiologic HRT promotes cardiovascular health more effectively in young women with POI than in combination with oral contraceptives. [17],[18]

Testosterone

Endogenous T production in premenopausal women is 300 mg daily, with 50% generated by the ovaries and 50% by the adrenal glands. As a result, women with POI have

impairments in ovarian T production and ovarian estrogen and P production. T deficit in women, even those with POI, cannot currently be diagnosed or treated due to a lack of reliable data. Treatment with 1.5 mg of oral methyl T for a year improved BMD in little research involving young women with Turner syndrome. There were benefits in neurocognitive parameters (attention and memory), libido, overall quality of life, and cardiometabolic risk factors, in addition to a favorable safety profile (improved lipid profiles, lower fat mass, and increased lean body mass). T replacement at physiologic amounts may ultimately benefit women with POI, given their weak ovarian androgen production and the combination of these factors. [(3),(19)]

Dehydroepiandrosterone

Ovarian folliculogenesis is aided by dehydroepiandrosterone, an endogenous androgen generated by the adrenals and ovaries. Androstenedione levels in POI women are lower than in women who cycle regularly. The currently available information does not support the regular replacement of DHEA for women with POI. Yilmaz et al. showed that six weeks of DHEA supplementation (25 mg taken three times daily) in women with occult ovarian insufficiency enhanced serum FSH, antimullerian hormone, and inhibin B levels as well as slightly increased the number of antral follicles. However, the results of DHEA's fertility-enhancing benefits in women with ovarian insufficiency are still debatable and, at most, indicate a slight therapeutic advantage.[(3),(20)]

Progestins

It is recommended to replace estrogen and progestin as most women with POI still have an intact uterus. For endometrial protection, cyclical progestin is advised. The NIH trial of HRT in POI combined oral medroxyprogesterone acetate (10 mg/d for 12 days each month) with transdermal E2 (100 mg/d). The regimen was well tolerated. Only medroxyprogesterone acetate, when administered in regular monthly cycles, has the potential to fully generate secretory endometrium when combined with a total dosage of estrogen, according to the existing data. To reduce the danger of endometrial hyperplasia and perhaps endometrial cancer, it is not advised to cycle progestin treatments more frequently than once per month. Unlike the 19 norprogestins, which may also have related androgenic effects, medroxyprogesterone acetate is not produced from T and is a 21-carbon "pure" progestin. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Group did not look at the effectiveness of oral micronized P to efficiently promote secretory endometrium in conjunction with a total replacement dose of estrogen. [(3),(21)]

In addition, it is not advised to use a progestin-containing intrauterine device (PIUD) as the progestin component of an HRT regimen in young women with POI, given that PIUD-induced endometrial suppression has only been studied in older postmenopausal women with intact uteri who need a progestin along with low postmenopausal doses of E2. Additionally, the PIUD would stop regular menses and prevent conception. It would be an undesired outcome for many young women with POI who want their HRT regimen to help "normalize" their reproductive life. The lower P level in the range designated for a typical functional corpus luteum is where the P peak level is located, as independently verified by mass spectrometry. This implies that, in the presence of a total replacement dosage of E2, the integrated progestin action at the endometrium level would not be sufficient to promote complete maturation with this dose of oral micronized P. [(3),(21)]

Before oral micronized P may be suggested as the first-line progestin for this clinical scenario, more proof is required regarding its effects at the endometrial level in the presence of a total replacement dosage of E2. Medroxyprogesterone acetate and micronized P treatment may differ considerably in their relation to the emergence of breast cancer, but there is

inadequate data to make that determination. Micronized P may be provided to women who cannot take medroxyprogesterone acetate, although they need to do so at least yearly to be checked for endometrial suppression. Medroxyprogesterone acetate and micronized P reduce cardiovascular risk when combined with E2, lowering blood pressure, fibrinogen levels, and serum levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL). The risk of venous thromboembolism is unaffected by adding micronized P or medroxyprogesterone acetate to HRT regimens. But using norpregnane derivatives (such as promegestrol acetate and promegestone) can boost the risk of venous thromboembolism by a factor of four. [21]

CONCLUSION

The effects of primary ovarian insufficiency on overall health are extensive and include reduced fertility. Clinicians could differentiate between pathological ovarian follicular depletion and early physiological menopause, two potentially distinct entities with different origins, using improved ovarian reserve testing. Genetic research will be essential for this advancement. Several methods, such as adoption or egg donation, are frequently accessible for reproductive-sparing goals. Human oocytes or embryos from women at risk for primary ovarian insufficiency can be cryopreserved after hormonal stimulation. Women with primary ovarian insufficiency are highly urged to use hormone replacement treatment since the early loss of sufficient estrogen production is linked to skeletal, cardiovascular, and cognitive issues.

The HRT of choice should closely resemble natural ovarian steroid hormone production and offer enough E2 to lessen menopausal symptoms, preserve bone density, diminish the psychological effects of estrogen insufficiency, and guard against the onset of CVD and dementia early in life. To safeguard the endometrium, the progestin component of HRT for women with POI should be cyclical and cause frequent withdrawal bleeding. When a woman reaches the age of natural menopause, HRT should be continued. At that point, the dose may be decreased to postmenopausal levels or discontinued, depending on the woman's individual needs and risks.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Ervina Pratiwi. Primary ovarian insufficiency and hormone replacement therapy: a review article. *International Journal of Science & Healthcare Research.* 2023; 8(1): 225-233. DOI: *https://doi.org/10.52403/ijshr.20230132*

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