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Review Article

DIMINISHED OVARIAN RESERVE: BIOMEDICAL PATHOPHYSIOLOGY, CLINICAL SPECTRUM, AND AYURVEDIC INTERPRETATIONS

Maya Balakrishnan[1], Sreelakshmi K[2]*

[1]Professor & HOD, Dept. of Prasutitantra and Striroga, Government Ayurveda College, Tripunithura.
*[2]PG Scholar, Dept. of Prasutitantra and Striroga, Government Ayurveda College, Thiruvananthapuram, Kerala.

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ABSTRACT

Diminished ovarian reserve is a condition marked by a decline in both the quantity and functional competence of primordial follicles, resulting in reduced fertility potential and poorer reproductive outcomes. In modern reproductive medicine, diminished ovarian reserve possess critical diagnostic and therapeutic challenges, frequently encountered during assisted reproductive techniques. Contemporary scientific understanding attributes follicular depletion to advancing age, oxidative stress, mitochondrial damage, endocrine disruptors, and genetic alterations. In Ayurveda, although diminished ovarian reserve is not described as an independent biological entity, its clinical manifestations and reproductive consequences may be explained through the concepts of *Artava Kshaya, Nashtartava*, and *Dhatukshaya Vandhya*. The underlying *Samprapti* represents a *Vata*-predominant *Tridosha* imbalance involving the *Artavavaha Srotas,* driving *Beeja kshaya* and progressive localized *Dhatukshaya*. Understanding the interface between biomedical ovarian physiology and Ayurvedic concepts offers valuable integrative insights into reproductive health and tissue rejuvenation.

INTRODUCTION

WHO recognizes infertility as an important global public health concern, impacting nearly 48 million couples and around 186 million individuals globally. Among the various causes of female infertility, ovarian ageing plays a significant role. It involves a progressive reduction in the quantity as well as the functional competence of primordial follicles, ultimately reducing reproductive potential and contributing to considerable social and economic challenges.

Diminished ovarian reserve (DOR) is a condition seen in women of reproductive age in which the ovarian reserve is reduced and the ovaries respond poorly to gonadotropin stimulation, commonly associated with raised basal FSH levels, reduced AMH levels, and a lower antral follicle count [1].

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DOR is frequently encountered, with prevalence rates reported between 6% and 64% depending on population characteristics and diagnostic criteria.[2]

Management of DOR remains a serious problem in reproductive medicine, particularly in assisted reproductive techniques. Although in vitro fertilization remains a standard treatment modality, Women with DOR commonly exhibit a suboptimal response to ovarian stimulation, along with lower chances of achieving successful pregnancy outcomes[3].

DOR can be interpreted as a condition involving *Artava kshaya* and infertility associated with DOR as *Dhatukshaya vandhya*. As diminished ovarian reserve can be considered an early *Jara* condition in Ayurveda, therapies possessing *Rasayana*, *Brimhana*, and *Vatahara* properties may help preserve and support reproductive function.

This review examines the biomedical concepts of DOR and explores its interpretation through relevant Ayurvedic concepts.

MATERIALS AND METHODS

The present article is a narrative review based on a comprehensive review of biomedical literature

and classical Ayurvedic texts related to diminished ovarian reserve (DOR). Relevant scientific literature was reviewed to explore the definition, etiology, pathophysiology, clinical manifestations, diagnostic methods, and emerging therapeutic approaches for DOR. Classical Ayurvedic references from *Charaka Samhita, Sushruta Samhita,* and *Ashtanga Sangraha*, along with relevant secondary literature, were examined to explore its possible correlations with *Artava Kshaya, Nashtartava, Dhatukshaya Vandhya,* and *Yoni Shushkata*. The findings were descriptively synthesized to develop a conceptual understanding of DOR and its probable *Samprapti* from an Ayurvedic perspective.

Diminished Ovarian Reserve

DOR is characterised by ovaries with lower number of oocytes than expected for female chronologic age, marked by biochemical abnormalities (increased serum FSH levels, decreased serum AMH levels) and/or ultrasound findings (low antral follicle count) associated with ovarian ageing, reduced response to ovarian stimulation, and female infertility[4].

Ovarian reserve refers to the total number of oocytes remaining within the ovaries, essentially reflecting the quantity of a woman's reproductive potential. Females are born with a limited reserve of ovarian follicles. Physiological ovarian reserve is a phenomenon where ovarian reserve declines with advancing age and it is characterized by increased basal FSH levels, decreased AMH levels, reduced AFC, and reduction in the number as well as viability of oocytes, consequently impairing reproductive capacity. Female reproductive potential typically starts to diminish in the early thirties and decreases more significantly after the age of 35. This decline is mainly associated with reduced egg quality and a higher likelihood of chromosomal irregularities, which can contribute to difficulties in conception, pregnancy loss, and developmental abnormalities in offspring.[5,6]

DOR and related Ovarian Conditions

DOR should be distinguished from Premature ovarian insufficiency (POI), Poor ovarian response (POR), and Resistant ovarian Syndrome.

Poor Ovarian Response (POR) [7,8]

A standardized definition for POR has not yet been universally established, and treatment approaches for women with a prior history of POR differ considerably across clinical settings. Nevertheless, the most widely accepted diagnostic criterion for POR is the retrieval of a low number of oocytes despite adequate ovarian stimulation during an assisted reproductive cycle. POR has been more clearly defined through established criteria, while DOR remains a broader clinical diagnosis based on ovarian reserve testing and clinical judgment.

According to the Bologna criteria formulated by the European Society of Human Reproduction and Embryology, a diagnosis of poor ovarian response is made when at least two of the following features are observed:

1. Advanced maternal age (≥ 40 years) or risk factors for poor ovarian response.
2. Previous history of poor ovarian response with retrieval of ≤3 oocytes following controlled ovarian stimulation.
3. Abnormal ovarian reserve test results: AFC < 5–7 follicles; AMH < 0.5–1.1ng/ml.

The working group further proposed that a patient may be identified as having poor ovarian response if two separate cycles show inadequate ovarian response despite the use of maximum stimulation protocols, even when additional diagnostic indicators are not present.

Premature Ovarian Insufficiency (POI)[7]

POI is a disorder characterized by loss of normal ovarian function before the age of 40 years. It may result from depletion of the ovarian follicular pool, accelerated follicular loss, or impaired follicular development. Clinically, POI is associated with hypoestrogenism, presenting initially with menstrual irregularities such as oligomenorrhea and prolonged cycles, which may eventually progress to secondary amenorrhea. In cases where ovarian dysfunction occurs before puberty, it may manifest as primary amenorrhea. Biochemically, POI is characterized by hypergonadotropic hypogonadism.

The condition is estimated to affect approximately 3.5% of individuals, and its causes are diverse, including genetic defects, autoimmune conditions, metabolic disorders, infections, and treatment-related factors such as ovarian surgery, chemotherapy, and radiotherapy. However, in many patients, the underlying cause remains unknown and is considered idiopathic. Women affected by POI require individualized evaluation and management because of the diverse clinical and reproductive implications associated with the disorder.

POI has been described using various terms in the literature, such as premature ovarian failure, early ovarian failure, premature ovarian dysfunction, and hypergonadotropic amenorrhea. However, the term "Premature Ovarian Insufficiency" is now preferred and recommended by professional bodies like the European Society of Human Reproduction and Embryology (ESHRE) and the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO). This terminology emphasizes that POI differs from physiological menopause and therefore requires a distinct diagnostic and therapeutic approach.

Diagnostic Criteria: The diagnosis of POI is based on finding elevated serum FSH levels exceeding

25mIU/mL, confirmed on two different tests performed at least four weeks apart.

Resistant Ovary Syndrome (ROS)[9]

Resistant Ovary Syndrome (ROS), also referred to as Savage syndrome or ovarian insensitivity syndrome, is a rare gynecological disorder with varied etiological backgrounds. It was first described by de Moraes-Ruehsen and Jones. Clinically, affected women often present with primary or secondary amenorrhea before 30 years of age and demonstrate little to no response of the ovaries to exogenous gonadotropin stimulation. Endocrine assessment generally demonstrates increased endogenous gonadotropin concentrations together with reduced estrogen production.

Although these hormonal abnormalities are present, most patients exhibit a normal chromosomal pattern and maintain an intact ovarian reserve. This is usually indicated by normal levels of AMH and inhibin B, together with a typical count of small antral follicles observed on transvaginal ultrasound and confirmed through histological evaluation of the ovaries.

Based on the World Health Organization classification system, ROS is included under type III amenorrhea associated with hypergonadotropic hypogonadism. In clinical practice, distinguishing ROS from POI or POF can be challenging, and for this reason it is often regarded as a variant or subtype of these disorders.

Symptomatology [10-15]

Most women with DOR have no clear symptoms, and the condition is usually detected incidentally through laboratory tests such as AMH and follicle stimulating hormone, or transvaginal ultrasound for AFC, rather than specific clinical complaints. Menstrual changes may occur over time, such as a shorter cycle length (for example, a 28-day cycle decreasing to 24–25 days), reflecting early follicular phase shortening and advancing ovarian aging, although these cycle changes are not always present and cannot be used alone to diagnose DOR. As ovarian function declines further and oestrogen levels fall, many women develop symptoms of oestrogen deficiency, including hot flashes, disturbed sleep, vaginal dryness, and irregular or missed periods; in this setting, low oestrogen can also lead to dyspareunia secondary to vaginal atrophy and poor lubrication, similar to what is seen in premature ovarian insufficiency. Infertility or recurrent early pregnancy loss is frequently the initial clinical presentation of DOR, thereby lowering likelihood of natural conception and live birth.

Etiology of Diminished Ovarian Reserve [16-24]

This may be grouped under five broad categories: Iatrogenic causes, Spontaneous causes, Ovarian Tissue Cryopreservation and Transplantation, Environmental factors, Epigenetics.

Iatrogenic Causes

Iatrogenic causes of DOR arise due to medical or surgical interventions that damage ovarian tissue. Common causes include chemotherapy, radiation therapy, ovarian surgeries and repeated ovarian stimulation all of which can lead to follicular depletion and reduced ovarian function, thereby affecting fertility potential.

- **Chemotherapy:** Chemotherapy is a well-established cause of iatrogenic diminished ovarian reserve. Among the chemotherapeutic agents, alkylating drugs such as cyclophosphamide are particularly gonadotoxic, as they can directly damage primordial follicles by interfering with DNA replication through crosslinking, triggering apoptosis of granulosa cells and eventually resulting in follicular atresia. Other agents like cisplatin and doxorubicin also contribute to ovarian toxicity by inducing DNA damage, generating oxidative stress, and disrupting cellular repair pathways, all of which can accelerate the loss of ovarian follicles and lead to reduced ovarian reserve.
- **Radiation Therapy:** Radiation exposure has a harmful effect on ovarian tissue, damaging granulosa cells and promoting stromal fibrosis, which disrupts the normal ovarian microenvironment. Primordial follicles are particularly sensitive to radiation, and even low doses can markedly reduce the follicular pool. As the radiation dose increases, the risk of premature ovarian insufficiency also rises, leading to earlier depletion of ovarian function and potential long term fertility impairment.
- **Ovarian Surgery:** Surgical excision of endometriomas, especially via cystectomy, may diminish ovarian reserve, as normal ovarian tissue surrounding the cyst wall can inadvertently be removed along with the lesion. In addition to direct tissue loss, mechanical trauma during surgery, thermal injury from electrocautery, and postoperative inflammatory changes can further damage the surrounding follicles, resulting in additional follicular depletion and a potential decline in overall ovarian function.
- **Repeated Ovarian Stimulation:** Repeated cycles of superovulation may negatively impact ovarian function by depleting the pool of primordial follicles and lowering serum AMH levels. It has also been linked to a reduced antral follicle count, changes in the expression of genes regulating follicular activation, and a higher rate of follicular atresia. In addition, repeated stimulation may reduce circulating FSH, LH, and estradiol levels, while increasing apoptosis-related gene expression in

granulosa cells, indicating an imbalance between cell survival and death.

Spontaneous Causes

Spontaneous causes of DOR occur due to inherent or naturally developing conditions that impair ovarian function. These include genetic abnormalities and endometriosis. All of which can accelerate follicular depletion and reduce reproductive potential.

- **Genetic Factors:** Turner syndrome, which results from partial or complete loss of one X chromosome, is associated with accelerated follicular depletion early in life, leading to markedly reduced ovarian reserve. Women with mosaic karyotypes may retain some reproductive capacity, but they often still show diminished ovarian function compared to those with normal karyotypes. In addition, mutations in the BRCA1 and BRCA2 genes have been linked to lower ovarian reserve, likely due to impaired DNA repair mechanisms in oocytes that compromise follicular survival. Similarly, premutations in the FMR1 gene are associated with earlier menopause and a tendency toward reduced ovarian reserve, further highlighting the role of genetic factors in ovarian aging.
- **Endometrioma:** Endometriosis can negatively affect ovarian reserve by promoting inflammatory processes, generating oxidative stress, and causing mechanical compression of ovarian tissue. The fluid within endometriotic cysts often contains elevated levels of reactive oxygen species and inflammatory mediators, which damages nearby follicles, accelerate follicular atresia, and contribute to stromal fibrosis, thereby reducing the overall functional ovarian tissue.

Ovarian Tissue Cryopreservation and Transplantation

Ovarian tissue cryopreservation is an evolving fertility preservation method that involves freezing ovarian tissue for future use. However, substantial follicular loss can occur during the processes of freezing, thawing, and transplantation, limiting the number of viable follicles available after grafting. Following transplantation, reduced blood supply and slow restoration of circulation can lead to additional loss of primordial follicles. This damage may negatively affect the longevity of ovarian activity and lower the likelihood of restoring fertility over time.

Environmental Factors

Exposure to endocrine disrupting chemicals, particularly compounds leaching from plastics and synthetic materials, may adversely affect ovarian reserve. These compounds may interact with hormone-related receptors, including the aryl hydrocarbon (AHR) and estrogen receptor (ER), thereby interfering with normal follicle development and the synthesis of steroid hormones. Continuous or long-term exposure to these agents can hasten ovarian aging and may gradually impair reproductive capacity.

Microplastics and DOR: Tiny plastic particles, known as microplastics and nanoplastics (MNPs), can build up in reproductive organs and may even be transferred from one generation to the next. This has raised growing concerns about their possible long-term effects on fertility and the health of future offspring. People can come into contact with these particles in several ways, such as by consuming contaminated food or water, breathing in particles present in the air, or through direct contact with the skin. Common sources such as plastic packaging, synthetic textiles, and degraded consumer products contribute to continuous lowlevel exposure, increasing the potential for these particles to reach and persist in reproductive tissues.

Recent research has found Microplastics and Nanoplastics (MNPs) in several human biological samples, including blood, brain tissue, urine, feces, lung tissue, and even the placenta. Scientists have also identified these particles in reproductive tissues like the endometrium and semen, leading to increasing concern about their potential impact on reproductive health. In the ovary, exposure to polystyrene nanoparticles has been shown to lead to their deposition within ovarian tissue, disrupting normal oestrous cyclicity, altering hormonal balance, and impairing follicular development. This results in fewer healthy developing and mature follicles, increased follicular atresia, and, over time, contributes to the development of diminished ovarian reserve.

Epigenetics

Epigenetic biomarkers, particularly DNA methylation patterns, are being explored as potential predictors of ovarian reserve and reproductive lifespan. DNA methylation helps regulate genes involved in folliculogenesis and steroid hormone production, and changes in these methylation profiles can disrupt granulosa cell function and promote follicular depletion. Histone modifications also influence chromatin structure and control the activation of primordial follicles. In addition, noncoding RNAs such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are key regulators of ovarian cell differentiation and programmed cell death, and their abnormal expression has been linked to impaired oocyte development and accelerated ovarian aging. N6methyladenosine RNA modifications further contribute to the age-related decline in oocyte quality, highlighting the growing role of epigenetic mechanisms in ovarian function and fertility.

Pathophysiology [25-46]

The pathophysiology of DOR involves progressive depletion of ovarian follicles and decline in oocyte quality due to aging, oxidative stress, hormonal

imbalance, genetic factors, environmental influences, and chronic stress. These factors impair follicular development, increase apoptosis, disrupt ovarian hormone production, and alter the ovarian microenvironment, ultimately reducing fertility potential.

- **Decrease in Follicular Count:** Total number of oocytes at 20 weeks of intrauterine life is about 6-7 million. At birth, the total number of primordial follicles is estimated to be about 2 million. The primary oocytes do not finish the first meiotic division until puberty is reached. At puberty, some 4,00,000 primary oocytes are left behind, the rest become atretic. During the entire reproductive period, some 400 are likely to ovulate. The degeneration starts in the intrauterine life and continues throughout childhood and the child bearing period. As a result, no more follicles with ova can be detected in menopausal women. Most follicles are naturally lost through apoptosis, a programmed cell death process that occurs as part of normal ovarian aging. However, factors such as oxidative stress and exposure to environmental pollutants can speed up this decline. In addition, lifestyle habits like smoking, alcohol use, unhealthy dietary patterns, and contact with harmful chemicals may further accelerate follicular loss, potentially lowering fertility and increasing the likelihood of early menopause.
- **Hormonal dysregulation:** Declining follicle numbers lead to reduced secretion of key ovarian hormones, particularly inhibin B and AMH. As levels of inhibin B fall, the negative feedback on the pituitary gland weakens, resulting in elevated serum FSH. This sustained rise in gonadotropins, especially FSH, further accelerates the loss of remaining follicles.
- **Cellular Oxidative Imbalance and Mitochondrial Damage:** Oocytes rely heavily on healthy mitochondrial function to produce ATP, which provides the energy needed for demanding cellular processes. With advancing age, mitochondrial DNA in oocytes accumulates damage in the form of mutations, oxidative base lesions, and altered copy number, which together impair mitochondrial function and reduce oocyte quality and fertility potential. Primary oocytes remain arrested in prophase I of meiosis from fetal life until meiotic resumption in selected preovulatory follicles, resulting in an exceptionally long resting phase. This prolonged quiescence increases the susceptibility of oocyte mitochondria to cumulative genetic damage, further contributing to age related decline in reproductive capacity.
- **Reactive oxygen species:** ROS are naturally produced during normal mitochondrial metabolic activities as part of the cell's energy production process, but excess ROS can damage DNA, promote follicular atresia, and impair oocyte quality. Lifestyle habits such as smoking and alcohol consumption further increase ROS production, exacerbating oxidative stress in the follicle. Antioxidants like vitamin C, vitamin E, and dimethyl fumarate may help reduce cellular stress by maintaining the body's redox balance. Additionally, proteins such as sirtuin 1 and sirtuin 3 play an important role in protecting the ovaries by strengthening antioxidant defenses and supporting DNA repair processes, which can help maintain the health and integrity of follicles and oocytes.
- **Genetic factors:** Several genetic mutations linked to POI affect important proteins involved in normal ovarian function. These include changes in the FSH receptor, the steroidogenic acute regulatory (StAR) protein, and forkhead box protein L2 (FOXL2). In particular, mutations in FOXL2 can interfere with the proper development of granulosa cells and disturb normal follicle growth. As a result, follicle survival may decrease, leading to a faster decline in the ovarian follicle reserve.
- **Microenvironmental Alterations:** As the ovary ages, its internal environment gradually changes. There is an increase in fibrous tissue within the stroma, reduced formation of new blood vessels, ongoing mild inflammation, and a greater presence of immune cells. These changes can make it harder for follicles to survive because they limit the supply of oxygen, nutrients, and growth signals needed for normal development. Factors such as oxidative stress, hormonal shifts, repeated ovulation cycles, natural aging, and exposure to environmental toxins all contribute to making this environment increasingly unfavorable over time. Recent single-cell RNA sequencing research has also shown that certain pro-fibrotic immune cells, particularly macrophages, become more common in the ovarian stroma with age, highlighting the role of immune-driven changes in the gradual decline of ovarian reserve.

Consequences Associated with DOR [47-54]

DOR can adversely affect reproductive, psychological, and systemic health. It is associated with reduced fertility, poor pregnancy outcomes, hormonal imbalance, increased risk of miscarriage and pregnancy complications, as well as depression and anxiety.

- Systemic Health Effects: Lower levels of AMH are inversely related to cardiovascular disease risk, indicating a potential association between ovarian aging and overall systemic health.

- Other Reproductive Disorders: Coexists with POI, POR, and recurrent pregnancy loss.
- Risk of Aneuploidy and Miscarriage: Chromosomal abnormalities leading to aneuploidy are a major cause of first-trimester abortion. Probability of such abnormalities tends to rise with advancing maternal age and diminished ovarian reserve.
- Risk of Hypertensive Disorders in Pregnancy: Evidence indicates that women with diminished ovarian reserve may be at a higher risk of hypertensive disorders during pregnancy, suggesting potential involvement of both endocrine and vascular mechanisms.
- Depression in DOR: Women with DOR have a significantly higher risk of developing depression and anxiety compared with healthy individuals, with studies indicating that their risk of depression may be about 3–6 times greater.
- Anxiety Disorders in DOR: Anxiety is frequently seen in women with diminished ovarian reserve and is closely associated with reduced levels of both serotonin and oestrogen. Lower serotonin availability alters the function of key brain regions such as the amygdala, which is involved in threat processing, thereby amplifying anxiety responses.

Dietary Modification and DOR [55-59]

Diet has a significant influence on ovarian function and overall reproductive health. Nutrients that help lower oxidative stress, inflammation, and hormonal imbalance may support the maintenance of ovarian reserve and enhance fertility outcomes in women with DOR. Therefore, thoughtful dietary changes along with suitable nutritional supplementation may help improve ovarian health and reproductive potential.

- MedDiet - protective action: The Mediterranean dietary pattern is largely based on plant-derived foods, including fruits, vegetables, legumes, nuts, whole grains, and olive oil, with moderate intake of fish and dairy products, and limited consumption of red and processed meats. This diet is rich in antioxidants, anti-inflammatory compounds, and beneficial fats such as monounsaturated and polyunsaturated fatty acids. Owing to these properties, it may promote ovarian health by reducing oxidative stress and inflammation, both of which are important factors in ovarian aging and reproductive dysfunction.
- Vitamin D administration: In women with both DOR and vitamin D deficiency, vitamin D supplementation has been shown to reduce FSH levels, indicating a potential role in enhancing fertility outcomes in these cases.

Measures of ovarian reserve [60-75]

Evaluating ovarian reserve in DOR is essential for understanding both the number and functional quality of the remaining follicular pool. It supports early identification of the condition, helps estimate reproductive potential and likely response to fertility treatments, and guides appropriate counselling and management decisions. Ovarian reserve assessment mainly involves hormonal (biochemical) investigations as well as ultrasound-based imaging techniques.

1. Biochemical markers
2. Ultrasound based imaging techniques

Biochemical Markers

Hormonal assessment of ovarian reserve is generally divided into three groups: early follicular phase tests such as FSH, estradiol, and inhibin B; cycle-independent evaluation using AMH; and dynamic or stimulation-based tests like the clomiphene citrate challenge test. Though not routinely used AMH and inhibin B are regarded as more direct indicators of ovarian reserve since they are produced by growing ovarian follicles.

Basal Serum FSH and Estradiol: Elevated basal FSH levels, usually measured during days 2–4 of the menstrual cycle, are commonly associated with DOR. Although a high FSH value is considered fairly specific for detecting DOR, its sensitivity is limited because FSH levels may vary significantly between menstrual cycles. Estradiol alone is not regarded as a reliable screening marker for ovarian reserve; however, it has an important supportive role in the interpretation of FSH values. An early rise in estradiol levels can suppress FSH concentrations into the normal range, thereby masking underlying ovarian dysfunction. Therefore, the presence of normal FSH levels in association with elevated estradiol levels may still indicate reduced ovarian reserve.

Clomiphene Citrate Challenge Test (CCCT): The Clomiphene Citrate Challenge Test assesses ovarian responsiveness by measuring FSH levels before and after administration of clomiphene citrate. Although the CCCT may improve the sensitivity of detecting reduced ovarian reserve, it has not shown significant advantages over simpler and more commonly used methods such as basal FSH measurement or antral follicle count.

Anti Mullerian Hormone: AMH is secreted by granulosa cells of pre-antral and small antral follicles and serves as an indicator of the growing follicular population within the ovaries. Its levels peak in the mid-twenties and progressively decrease with increasing age, often becoming very low or undetectable in the years leading up to menopause. Because AMH is produced in the early stages of follicle development and is minimally influenced by gonadotropins, its serum concentration remains relatively constant throughout the menstrual cycle, allowing testing at any point. It is commonly measured using ELISA-based methods, particularly the Gen II ELISA assay, while newer automated platforms offer

improved accuracy, reproducibility, and faster turnaround time.

Ultrasound Based Imaging Techniques

Ultrasound-based imaging techniques used in the assessment of ovarian reserve include transvaginal ultrasound for the evaluation of AFC and measurement of ovarian volume.

Antral Follicle Count: AFC refers to the total number of small follicles present in both ovaries, assessed by transvaginal ultrasound during the early follicular phase of the menstrual cycle, usually between day 2 and day 4. Antral follicles are defined as follicles measuring 2–10mm in diameter in the largest two-dimensional section of the ovary. AFC is considered a reliable marker of ovarian reserve because it demonstrates minimal inter cycle variation and good consistency when assessed by experienced observers. Clinically, an AFC of less than 5–7 suggests low ovarian reserve or poor ovarian response, an AFC between 8 and 24 indicates normal ovarian reserve, and an AFC greater than 24 is commonly associated with high ovarian reserve, as seen in PCOS. Due to its good reproducibility and relatively low inter-observer variability, AFC is widely used in routine clinical practice. The number of antral follicles reflects the remaining follicular pool and assists clinicians in estimating ovarian responsiveness to gonadotropin stimulation during assisted reproductive procedures. A reduced AFC is strongly associated with poor ovarian response during IVF cycles, indicating diminished ovarian reserve. The specificity of AFC in predicting non-pregnancy ranges from 64% to 98%, whereas its sensitivity ranges from 7% to 34%, suggesting that AFC is more effective in identifying women unlikely to conceive rather than confirming successful pregnancy outcomes. However, AFC has certain limitations. Follicles counted within the 2–10 mm range may include atretic follicles, which can lead to overestimation of the number of follicles capable of responding to FSH stimulation. In addition, although AFC values remain relatively stable across menstrual cycles, its accuracy may be influenced by technical factors such as ultrasound resolution and patient-related factors including extreme body weight.

Table 1: Antral Follicle Count (AFC) and Clinical Interpretation

Antral Follicle Count (AFC)	Clinical Interpretation
< 5–7	Low ovarian reserve (DOR / poor responder)
8 – 24	Normal ovarian reserve
> 24	High ovarian reserve (Polycystic Ovary Syndrome)

Ovarian Volume: Ovarian volume assessment is an ultrasound-guided method used in the evaluation of ovarian reserve. Ovarian volume generally decreases with advancing age due to the progressive decline in follicular population. However, because of considerable interindividual variability and its relatively low sensitivity, ovarian volume is not considered a highly reliable standalone marker and is therefore less commonly used for routine clinical decision-making in the assessment of diminished ovarian reserve.

Possible therapeutic approaches [76-80]

Various emerging therapeutic approaches are being explored for the management of diminished ovarian reserve. These include stem cell therapy, in vitro activation, platelet-rich plasma therapy, ovarian tissue transplantation, electroacupuncture, and other supportive therapies such as DHEA, testosterone supplementation, antioxidants, and traditional medicine approaches.

Stem Cell Therapy: These therapies have shown promising results in experimental models of ovarian insufficiency. Animal studies have demonstrated that mesenchymal stem cells derived from amniotic tissue, bone marrow, and menstrual blood can improve follicular development, increase AMH levels, and help restore hormonal balance. Despite these encouraging findings, clinical evidence in humans remains limited, and further studies are required to validate their safety and effectiveness.

In Vitro Activation: This technique involves the activation of dormant ovarian follicles through modulation of intracellular signaling pathways, particularly the PI3K-Akt and Hippo pathways. By activating the remaining ovarian follicles, this approach seeks to promote follicular development and improve fertility potential in women with diminished ovarian reserve or ovarian insufficiency. While some successful pregnancies have been documented with its use, the evidence base remains limited, and there are ongoing concerns that it may hasten the depletion of the existing follicular pool.

Platelet-Rich Plasma (PRP): PRP is rich in growth factors and cytokines that may support tissue healing and regeneration. In reproductive medicine, direct intraovarian injection of PRP has been investigated as a possible treatment to improve ovarian function in women with diminished ovarian reserve. Early studies indicate potential improvements in ovarian reserve indicators such as AMH levels and AFC. Nevertheless, although the initial results are encouraging, robust large-scale controlled trials are still needed to confirm its true efficacy, especially in terms of increasing pregnancy and live birth rates.

Ovarian Tissue Transplantation: Transplantation of cryopreserved ovarian tissue has shown potential in

restoring hormonal function and fertility in women with ovarian insufficiency. However, a significant loss of follicles may occur during the transplantation process, which can affect the overall success of the procedure. Although the technique appears promising, its long-term effectiveness and outcomes are still under investigation.

Electroacupuncture: Studies suggest that electroacupuncture may improve ovarian function by helping to normalize reproductive hormone levels, including reducing elevated FSH and LH levels while enhancing the effective utilization of estrogen (E2). These effects are believed to occur partly through modulation of the PI3K/AKT/mTOR signaling pathway, thereby contributing to restoration of the HPO axis.

Others: Various therapeutic approaches, including testosterone supplementation, dehydroepiandrosterone (DHEA), antioxidant agents such as resveratrol, and interventions from traditional Chinese medicine, are currently being explored for their potential to enhance ovarian function and delay the decline in ovarian reserve. However, their efficacy and the precise biological mechanisms underlying their effects are not yet fully established and require further scientific investigation.

Interpretation of DOR on the basis of ayurvedic concepts

Diminished ovarian reserve is not described as an independent disease entity in Ayurveda; however, its clinical manifestations and consequences can be correlated with several Ayurvedic conditions. Menstrual irregularities, reduced menstrual flow, and shortening of the menstrual cycle may be correlated with *Artava Kshaya* (reduced menstruation) and *Nashtarthava* (absence of menstruation). The progressive decline in ovarian function, depletion of follicular reserve, and reduced reproductive capacity reflect *Dhatu Kshaya* (depletion of body tissue*)* i.e.: *Artava Dhatu Kshaya*. Consequences of DOR such as infertility can be understood under *Dhatukshaya Vandhya,* while symptoms arising due to oestrogen deficiency, including vaginal dryness and dyspareunia is mentioned under *Yoni Shushkata*.

Artava Kshaya **[81-82]**

From *Rasa (Dhatu)*, the *Rakta* named *Raja* is formed. *Rakta* reaching uterus and coming out for three days in every month is called *Artava*.

Artava Kṣhaya is derived from two terms, *Artava* and *Kṣhaya*. The word *Kṣhaya* originates from the root "*Kṣi*," which signifies reduction, depletion, or diminution. According to the *Visala Sabda Kosa Sagara*, *Kṣhaya* is defined as *Nyunata* or *Apacaya*, meaning loss or wasting of tissue. In classical descriptions, *Artava Kṣhaya* is characterized by delayed onset of menstruation, scanty menstrual flow, and pain in the vaginal region. Thus, it refers to a pathological condition involving both quantitative and qualitative reduction of *Artava*. Sushruta has described eight types of *Artava Duṣṭi*, among which the seventh type, *Kṣhiṇa Artava* (also referred to as *Artava Kshaya*), indicates reduced menstrual bleeding.

Nashtartava **[83-85]**

Nashtartava literally refers to the destruction or absence of menstrual fluid and clinically corresponds to the non-occurrence of menstruation. According to the Sushruta Samhita, the condition is explained by the statement *"Doshairavrutamargatvad artavam nashyati striyah,"* meaning that in many cases the *Artava* is not truly destroyed but its channels are obstructed by aggravated *Doshas*, particularly *Kapha* and *Vata*, preventing its normal flow. This obstruction leads to functional loss of menstruation. The involvement of *Artava-vaha Srotas (Srotovedha*-injury to *Strotas*) manifests as infertility (*Vandhyatva),* pain or intolerance during sexual intercourse *(Maithuna-asahishnutva)*, and complete cessation of menstruation (*Artava-nasha*). Among the causative factors, *Kapha* and *Vata* are considered primary, where *Kapha* produces obstruction due to its heavy and cold qualities, while *Vata,* especially *Apana Vayu*, becomes vitiated and unable to facilitate downward movement of *Artava* results in absence of menstruation.

Vandhya

According to Sushruta, *Vandhya* is specifically described as a woman in whom *Artava* is completely absent or destroyed, leading to absolute infertility.

Classification of *Vandhya*

Charaka has classified infertility into three categories [86]:

- *Vandhya*– Absolute sterility caused by severe congenital or irreversible factors such as *Beejopaghata*.
- *Apraja*– Infertility where conception becomes possible only after appropriate treatment (primary infertility), or where conception occurs but does not result in successful continuation of pregnancy.
- *Sapraja* – Secondary infertility.
- Harita has elaborated six distinct types of *Vandhya*[87] (based on the clinical presentation):
- *Kakavandhya*– Inability to conceive even after the birth of one child.
- *Anapatya*– Primary sterility, where conception has never occurred.
- *Garbhasravi*– Repeated pregnancy loss due to recurrent abortions.
- *Mritavatsa*– Recurrent intrauterine deaths, stillbirths or perinatal losses.
- *Balakshaya*– Infertility resulting from loss of strength or depletion *Dhatu*.

- *Ajata rajas*– Infertility arising from coitus before menarche leading to constriction of reproductive organs, causing delayed or difficult conception.

Yoni Shushka (Yoni Shushkata) [88]

Yoni Shushkata refers to abnormal dryness of the vaginal canal caused predominantly by aggravated *Vata Dosha*, leading to loss of lubrication, roughness, pain, and discomfort during sexual intercourse. In some cases of DOR symptoms of hypo oestrogenism may be seen, like as in *Yoni sosha*.

DISCUSSION

Table 2: Correlation between Clinical Features of DOR and Ayurvedic Manifestations

Clinical Features / Symptomatology of DOR	Ayurvedic Correlation	Basis of Correlation
Shortened menstrual cycle, reduced menstrual flow, delayed or scanty menstruation	*Artava Kshaya / Ksheena Artava (Vata pitta)*	Represents diminution of *Artava* in quantity and quality, reflecting depletion of reproductive potential. Classical features include delayed menstruation, scanty flow, and reduced duration of bleeding.
Complete cessation of menstruation in advanced ovarian decline	*Nashtartava*	Comparable to premature menopausal state with *Artava Nasha*.

Two entities resulting in reduced *Artava* described in Ayurveda are *Artava Kshaya* and *Nashtartava.* Among these, *Nashtartava* is explained as a condition caused by obstruction in the pathways responsible for the production and flow of *Artava*, whereas *Artava Kshaya* occurs due to the depletion of *Artava* or of the factors responsible for its production. Among the factors essential for the production of *Artava*, the presence of healthy ovarian follicles is considered highly important. Therefore, depletion of ovarian follicles itself can lead to reduced *Artava;* hence, DOR may be more closely correlated with *Artava Kshaya*. Infertility resulting from DOR can be understood under *Dhatukshaya Vandhya*.

Probable *Samprapti* (Pathogenesis) of DOR

Table 3: Probable *Samprapthi* Of DOR

Nidanas		
Nija	***Agantu***	
Beeja dushti	**Iatrogenic causes**	**Environmental factors**
Turner syndrome, BRCA1 and BRCA2 mutations, and FMR1 permutations	Ovarian surgeries, chemotherapy, and radiotherapy, repeated ovarian stimulation,	Microplastics, nanoplastics (polystyrene nanoparticles) endocrine disrupting chemicals
↓	↓	↓
Vata pradhana tridosha	*Vata pradhana tridosha*	*Dushivisha*
		↓
		Tridosha

↓

Selective *Dhatukshaya* (depletion of oocytes)

Arthava kshaya — *Vandhyatwa*

Maithuna asahishnutwa

Arthava nasha

The *Samprapti* is a *Vata-pradhana Tridosha dushti* affecting the *Artava vaha srotas* and ovarian reserve. Due to exposure to etiological factors, all three *Doshas* become vitiated, with predominance of *Vata*, leading to *Beeja kshaya* and progressive *Dhatukshaya*, which further results in *Artava Kshaya*. This sequence predominantly manifests as localized *Dhatu dushti* at the level of the ovary rather than systemic *Dhatu dushti*. On analysis of the *Nidanas*, these factors primarily produce localized tissue degeneration and functional impairment within the ovarian milieu rather than causing generalized systemic involvement.

The pathology develops mainly through 2 major pathways: *Nija and Agantuja*.

***Nija* Pathway (Intrinsic pathway)**

The *Nija* pathway involves *Beeja Dushti*, where genetic and epigenetic abnormalities affect ovarian function and produce *Beejakshaya*, progressive *Dhatukshaya* (localised) and *Arthavakshaya*. In Turner

syndrome (45,X or mosaic forms), ovarian development is disrupted in fetal life due to accelerated loss of oogonia and primordial follicles along with absence of key X-linked genes, resulting in streak ovaries with markedly reduced follicular reserve and low AFC. BRCA1/BRCA2 mutations impair DNA repair in oocytes and granulosa cells, leading to DNA damage accumulation, oxidative stress, increased apoptosis, and accelerated follicular atresia, thereby reducing AMH and AFC. In FMR1 premutation carriers, elevated toxic mRNA disrupts granulosa cell function and PI3K/AKT signaling, causing premature follicular activation and accelerated depletion of ovarian reserve. In addition, epigenetic alterations such as DNA methylation changes, histone modifications, and abnormal microRNA expression disturb the regulation of genes responsible for oocyte maturation, hormonal signaling, follicular survival, and cellular repair. These abnormalities result in defective follicular growth, accelerated degeneration, and depletion of ovarian reserve, ultimately leading to *Artava Dhatu Kshaya*. Such molecular defects can be correlated with *Beeja Dushti* in Ayurveda. Since the pathology involves the *Beeja* itself, reversal becomes extremely difficult, making it an almost *Asadhya Avastha*.

Agantuja Pathway (Extrinsic pathway)

Agantuja factors involved in DOR include iatrogenic causes, repeated ovarian stimulation, and environmental influences. Iatrogenic causes produce direct injury to the ovarian tissue and reproductive channels, resulting in structural and functional damage. Ovarian surgeries, chemotherapy, and radiotherapy can cause localized ovarian injury leading to fibrosis, vascular compromise, oxidative stress, and destruction of follicles. This results in obstruction and dysfunction of the *Artava Vaha Srotas,* causing impaired nourishment of *Artava Dhatu* and localised *Dhatukshaya*. Consequently, progressive depletion of ovarian follicles and oocytes occurs due to loss of proper tissue nutrition and degeneration of reproductive structures.

Repeated ovarian stimulation, particularly controlled ovarian hyperstimulation used in assisted reproductive techniques, can also be considered an *Agantuja Nidana* contributing to ovarian stress and progressive *Dhatukshaya*. It is reported that repeated superovulation disturbs normal follicular homeostasis by accelerating primordial follicle activation and increasing follicular atresia, thereby depleting ovarian reserve. Collectively, these changes accelerate follicular exhaustion and contribute to progressive *Dhatukshaya*.

Environmental and endocrine disruption also play an important role in the pathogenesis of DOR. Chronic exposure to microplastics, nanoplastics, endocrine-disrupting chemicals, pollutants, and environmental toxins can be considered as *Dushivisha* (Residual toxic substance), producing slow and cumulative toxic effects within the ovary. These toxins aggravate *Tridosha*. Persistent exposure to *Dushivisha* induces chronic inflammation, oxidative stress, mitochondrial dysfunction, endocrine imbalance, and cellular toxicity. This gradually weakens *Artava Dhatu*, impairs cellular repair mechanisms, and promotes *Beeja kshaya* & localised *Dhatukshaya*. The resulting degeneration accelerates follicular depletion, oocyte loss, and premature ovarian aging, ultimately leading to reduced ovarian reserve and infertility.

CONCLUSION

Diminished ovarian reserve is characterized by a decline in the quantity of ovarian follicles in women of reproductive age, resulting in a reduced response to gonadotropin stimulation. It is commonly associated with elevated basal FSH levels, decreased Anti mullerian hormone levels, and a reduced antral follicle count. Multiple factors including aging, genetic influences, environmental exposures, oxidative stress, hormonal imbalance, and chronic stress contribute to its development and progression. DOR is closely associated with infertility, poor reproductive outcomes, psychological disturbances, and systemic health effects. Early assessment through biochemical markers and ultrasound-based imaging techniques plays an important role in diagnosis and management. Although current treatment options are limited, emerging therapeutic approaches such as stem cell therapy, PRP, ovarian tissue transplantation, and electroacupuncture show promising potential for improving ovarian function and fertility outcomes.

From an Ayurvedic perspective, DOR may be interpreted as *Artava Kshaya*, premature *Jara avastha*, and *Dhatukshaya Vandhya* arising from a localized *Vata*-predominant *Tridoshic* imbalance to the *Artavavaha Srotas*. Recognizing these parallels provides a robust conceptual foundation for holistic reproductive health management.

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***Address for correspondence**
Dr. Sreelakshmi K
PG Scholar,
Dept. of Prasutitantra and Striroga
Government Ayurveda College
Thiruvananthapuram, Kerala.
Email: sreelakshmik000@gmail.com

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