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Premature ovarian insufficiency: decoding oxidative stress, metabolic pathways, epigenetic regulation, and the therapeutic role of yoga

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Abstract: Premature ovarian insufficiency (POI) is a heterogeneous multifactorial disorder characterized by amenorrhoea, hypoestrogenism and elevated serum gonadotropins in women below 40 years. Genetic predisposition, infections, iatrogenic, autoimmune conditions and endocrinopathies are few of the known causes of POI, but majority cases of POI are idiopathic which is attributed to be due to environmental factors, epigenetic changes, oxidative DNA damage or faulty DNA repair mechanisms. These epigenetic changes and cumulative oxidative DNA damage can pass transgenerationally to subsequent generations. Management of POI involves hormone replacement to alleviate the symptoms of hypoestrogenism and in some cases treatment for infertility, comorbid stress and depression. The broad spectrum of decreased quality of life and psychosocial impact of the medical condition is less often addressed. Lifestyle modification and yoga can act as adjunct therapy in conjunction with the standard treatment protocol to alleviate the stress, anxiety and depression. YBLI exerts immunomodulatory effects and provides a natural way to decrease oxidative stress, DNA damage, inflammation, restoring hormonal normality and in turn protect accelerated oocyte atresia.

Keywords: epigenetics, premature ovarian insufficiency, oxidative stress, reactive oxidative species, yoga.

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Introduction

Premature ovarian insufficiency (POI) is a heterogeneous medical condition which is classically defined as the cessation of ovarian function below 40 years of age. It is characterized by the triad of biochemical manifestations of amenorrhoea, hypoestrogenism and raised serum gonadotropins which may also result in infertility [1]. Some may also exhibit follicle-stimulating hormone (FSH), estradiol, and anti-mullerian hormone (AMH) levels equivalent to menopausal age group [2]. In majority of the cases however the cause of POI including molecular pathogenesis remains undetermined [3].

Recent view about POI indicates it to be a medical condition wherein there occurs depletion of ovarian follicles and cessation of the reproductive and endocrine functions of ovary in women below 40 years of age [4]. Approximately 1–2% of females below 40 years and 0.1% of females below 30 years are affected by this condition. The clinical manifestations of POI range from absent pubertal development and primary amenorrhea in its severe form to secondary amenorrhea with faulty folliculogenesis [5]. The affected females present with menopausal symptoms of hot flashes, chills, night sweats, vaginal dryness, sleep problems, mood changes etc. and infertility and increased risk of osteoporosis.

A myriad of etiological factors such as genetic, autoimmune; e.g. anti-ovarian antibodies, iatrogenic; e.g. pelvic surgery, chemotherapy, radiotherapy, environmental; e.g. infections, toxin exposure, oxidative stress etc. are implicated. Genetic aetiologies like single gene mutations, cytogenetic alterations like chromosomal rearrangements and X-chromosome aneuploidies are often found. Genetic factors can be the cause themselves or may put the individual at more risk to the condition [6]. Despite the fact that it has heterogeneous causations, studies indicate that greater than 50% of the cases of POI continue to be idiopathic, underlying molecular mechanisms remain unclear and they can present in either sporadic or familial form.

Methods

A thorough review of the literature was performed using the PubMed/Medline, Scopus, Embase and Google Scholar databases. We included the following combination terms and keywords, while searching the databases 'premature ovarian insufficiency,' 'premature ovarian failure,' 'one-carbon metabolism,' 'MTHFR deficiency,' 'epigenetics of premature ovarian insufficiency' and 'premature ovarian failure and yoga.' The full-length articles on human subjects and in experimental animals published in international peer reviewed journals with no restriction to time of publication were included. Finally, a total of 47 articles were selected for the narrative review. All the relevant data were analysed by manual methods and cited in the text.

Oxidative stress and POI

Everyone dreams and aspires of longevity without aging. In fact, the average human longevity has experienced a considerable escalation in the past few decades. However, it is not accompanied by prolonged healthy span and thus older age is accompanied by increased incidence of complex lifestyle diseases [7]. Ovaries too experience aging much earlier than the aging of other organs. Ovarian aging is an ongoing process right from the beginning of oocyte death that starts in embryos at 20 weeks gestation [8]. Diminished ovarian reserve (DOR) is a strong determinant of ovarian aging, which is defined as quantitative and qualitative depletion of oocytes with age. Ovarian aging is linked with the occurrence of type 2 diabetes, cardiovascular diseases, cancers, and other age-related diseases leading to poor quality of life. Ovarian aging is also associated with infertility and failure in assisted reproduction techniques (ARTs) [9]. Enhanced longevity in the old mice has been seen with transplantation of ovaries from young mice, which suggests that ovary plays a role in maintaining overall health and contributes to longevity [10]. Healthy and 'young' ovaries are crucial as actively functioning ovaries in aged mice have shown positive reinforcement in cardiovascular, renal, immune, and cognitive functions.

Apoptosis, shortening of telomeres, inflammation, dysfunctional mitochondria, oxidative stress etc. are postulated to be the underlying culprit for accelerated ovarian aging [11, 12]. The free

radical mediated injury being the central point of the aging process highlights elevated reactive oxygen species (ROS) to be the most remarkable benefactor of the mammalian cellular senescence and aging. Female germ cells are residing and developing in a relatively hypoxic condition in the ovarian cortex as compared to the ovarian medulla due to less vascularity of the cortex, although it is practically impossible to measure site specific differential oxygen concentration. It is further evidenced histologically by relative absence of developing oogonia near blood vessels [13]. Nevertheless, the developing oogonia are prone for damage by supraphysiological levels of ROS. Elevated ROS induces oxidative DNA damage in the mitochondrial DNA leading to mitochondrial dysfunction, which may hinder oxidative phosphorylation yielding low ATP. Oxidative DNA damage leads to decline in mitochondrial function by affecting the replication and transcription of mtDNA which in succession promote enhanced ROS production and added injury to mtDNA [14]. Ovarian ageing and consequent POI are undoubtedly linked to the considerable impact of oxidative stress. However, the exact molecular mechanisms responsible in the pathogenesis are not fully deciphered yet. Pilot studies conducted in idiopathic POI patients revealed increased occurrence of mutations in the mitochondrial ATP synthase gene (*mtATP6*), cytochrome-C oxidase1 gene (*mt-CO1*). Additionally genetic mutations in mitochondria, increased OS coupled with decreased efficiency of the oxidative phosphorylation pathway have also been linked with POI [15]. In experimentally designed aging-based mice models treated with coenzymeQ10, an important regulatory enzyme for optimal functioning of TCA cycle, it was found that CoQ10 administration could arrest onset of POI [16]. Therefore, elevated ROS with resultant mitochondrial DNA damage may result in faulty oogenesis, truncated oocyte number and eventual POI.

ROS encompasses H_2O_2 and superoxide anions having strong oxidising abilities which can be either free radicals or non-free radicals. They are continuously produced during the routing metabolic processes in eukaryotic cells. Physiological level of ROS is required for normal cell proliferation, differentiation, and survival and essential for cellular signal transduction. However, supraphysiological ROS levels can overwhelm the cellular antioxidant defence mechanisms and cause oxidative damage. OS causes DNA fragmentation in the nuclear/mitochondrial genome, and causes dysregulation in levels of transcripts. Mitochondria-derived ROS increases inflammatory damage via TNF-α, NF-β and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [17]. mtDNA does not have DNA repair mechanisms and no protection by histones as compared to nuclear DNA. So, the mitochondrial genome is highly susceptible to mutagenesis as compared to nuclear DNA. Also, the oxidative damage to mitochondrial DNA is more severe and sustained as compared to nuclear DNA as mitochondria are targets of free radicals. The elevated ROS can bring about oxidative damage to most bio-molecules including nuclear or non-nuclear DNA, proteins, lipids etc. which over a period result accelerated early onset of complex lifestyle diseases [18]. These oxidative damages to nuclear and mitochondrial DNA can even pass on to the subsequent generations if damage is extensive and oocyte repair mechanism suboptimal as in delayed parenthood. OS mediates the damage to the intra-ovarian milieu through lipid peroxidation that affects folliculogenesis, gametogenesis and the ovulation [19]. It is to be noted that all the primary oocytes of a female's entire lifetime are present by the fifth week of intrauterine life. These oocytes remain dormant till puberty arrested in first meiotic division; due to which they are quite vulnerable to chronic oxidative insults and dysfunction errors. It is known that elevated intra-ovarian ROS might lead to decline in oocyte quality and it induces early apoptosis of granulosa cells. It also hinders the cross talk between granulosa cells and oocytes thereby affecting pre-ovulatory maturation of oocytes [20].

The intra-ovarian ROS levels correspond well with the age of females, in whom germ cells are essentially more vulnerable to the additive effect of chronic OS [21]. Elevated ROS levels are seen in the follicular fluid and oocyte of elderly females undergoing ART, and the rate of ART success among them is found to be relatively low [22]. There are antioxidant defence mechanisms in biological systems, the important enzyme systems among them being the superoxide dismutases (SODs), glutathione peroxidase (GPX) and catalases (CAT) systems. The antioxidant levels in the intra ovarian milieu decreases with age, reducing the overall ROS scavenging capacity thus rendering the oocyte more vulnerable to oxidative damage. SOD-I and CAT levels in the cumulus oophorus cells surrounding ovulated oocytes were observed to be diminished with advancing female age and its diminished activity was linked with IVF failure [23]. To summarize it can be stated that the ROS-antioxidant balance is crucial for optimum intra-ovarian milieu and its derangement may lead to decline in oocyte quality and result in accelerated atresia of oocyte and manifests as POI.

The one carbon metabolism, MTHFR and POI

One carbon (1C) metabolism pathway is the integration point of several biochemical events involving nutritional signal folate, nucleotide biosynthesis, maintenance of cellular redox environment and epigenetics. The naturally occurring B vitamin folate is the central metabolite and 5,10-methylenetetrahydrofolate reductase (MTHFR) is the key enzyme of this 1C metabolism pathway. This pathway is involved in nucleotide biosynthesis, methylation reactions through the interlinked folate-homocysteine pathway to generate S-adenosyl methionine (SAM). The homocysteine generated in the pathway is further metabolized to yield and maintain a steady reservoir of the master antioxidant glutathione within the cellular environment [24].

Moreover, gene polymorphisms of enzymes of the 1C pathway especially *MTHFR* are found to be associated with diminished ovarian reserve, inadequate response to follicular stimulation and may impair the female fecundity [25, 26]. MTHFR and methionine synthase reductase are two important key enzymes responsible for remethylation of homocysteine to methionine in the pathway. Erstwhile studies indicate that serum level of homocysteine is associated with ovarian reserve, therapeutic ovarian stimulation outcome and overall result of ARTs. Hyperhomocysteinemia in women is seen to be associated with higher risk of pregnancy loss. Researches involving the most commonly studied polymorphisms of *MTHFR* 677C>T (rs1801133), 1298A>C (rs1801131) and *MTRR* 66A>G (rs1801394) indicate that polymorphic variants render these enzymes inactive thereby increasing the blood homocysteine levels [27]. Hyperhomocysteinemia is a known risk factor for cardiovascular diseases, renal diseases, cancers etc. Presence of these polymorphisms may also put a woman more susceptible to suffer from infertility, recurrent pregnancy loss and implantation failure. Recent systematic reviews by Wu *et al.* found increased risk of depression in Asian adults with *MTHFR* 677C>T variant and Cho *et al.* observed similar propensity among white women with *MTHFR* 1298A>C polymorphisms, possibly due to hyperhomocysteinemia associated with impaired folate metabolism [28]. However, only limited data are available at present about the *MTHFR* gene polymorphism among females with POI. *MTHFR* 1298A>C polymorphism was reported to be linked with low therapeutic response to ovarian stimulation along with high serum gonadotropins [29]. Strong association was reportedbetween*MTHFR*677C>T polymorphism with idiopathic POI and it was also postulated to be a useful novel genetic marker for risk prediction [30]. More data is yet to be gathered to establish a concrete association, but the defective 1C metabolism clearly contributes to weak cellular antioxidant defence mechanisms.

Base excision repair and POI

Increased oxidizing agents or ROS have been found to be associated with increased incidence of POI. Various differentiation and developmental events take place in the ovarian system during puberty that may lead to increased oxidative stress and further immune dysregulation. Increased levels of oxidative stress marker, *malondialdehyde* (MDA) and decreased level of antioxidants like SOD and glutathione peroxidase have been found to be associated with POI [31]. Increased OS causes oxidative damage and deregulation of metabolism and signaling cascades that can cause reduction of folliculogenesis [32]. Further, it is now a known fact that increased oxidative stress leads to increased DNA damage and accumulation of oxidative DNA adducts. Oxidative marker, 8-Hydroxydeoxyguanosine (8-OHdG) can induce both mutations and epimutations and thus the burden of genetic and epigenetic disease in the offspring. DNA double strand break is the most severe form of DNA damage that can lead to ovarian senescence, apoptotic cell death or carcinogenesis. Oocytes have extensive DNA repair mechanisms. Base excision repair (BER) is one of the important mechanisms of avoiding oxidative DNA damage. Damaged DNA strands can be removed via excision repair processes in which complementary DNA is used to replace individual excised DNA strands. Small mutations due to oxidative damage can be repaired via the BER. BER mechanism becomes less efficient with ageing and repeated oxidative damage leading to accumulation of oxidative DNA adducts. Key enzyme of BER, DNA polymerase beta (Pol-β) has been found to be linked with oocyte senescence [33]. BER starts with excision of the improper base by DNA glycosylase and then breakage of DNA backbone by Apurinic/Apyrimidinic Endonuclease 1 (APE1) forming abasic sites further repaired by short patch BER (SP-BER) or long patch BER (LP-BER). Pol-ß plays a key role in SP-BER by adding a single base to the 3'-end of this nicked site. It also mediates strand displacement synthesis in LP-BER. Further events take place by XRCC1/ Ligase III a, FEN1, DNA ligase seals Nick I. Any mutations interfering with the ability of Pol-ß to carry out its function can impair BER activity [34]. Association between oxidative DNA damage and BER gene expression has also been found in couples with recurrent pregnancy loss [35]. So, defective BER genes due to any cause can lead to increased accumulation of DNA adducts and early oocyte senescence or in turn cause POI. Further, if damaged DNA is not repaired in time, it will not only cause early oocyte senescence or ovarian failure, but can also transmit the defect to next generations [36].

Epigenetics and POI

POI is thought to be caused by genetic alterations like chromosomal abnormalities and single gene mutations. But these changes are only found in 4–20% of cases. Rest of the cases of POI may have multifactorial causes and epigenetic change is one of them. Gametogenesis involves epigenetic reprogramming through DNA and histone methylation. Epigenetic changes due to environmental factors like nutritional abnormalities, stress, and exposure to harmful exogenous or endogenous toxic chemicals, unhealthy lifestyle habits like smoking, during fetal and early postnatal development can cause adult-onset diseases in later life. These epigenetic changes not only affect F0 generation but can get transferred transgenerationally to F1 and F3 generations and may cause adult-onset disease in those. Same is the case with POI. These are mainly caused by DNA methylation errors leading to great impact on epigenetic programming and imprinting. There is linkage between DNA methylation and gametogenesis. Primordial germ cells are initially demethylated,

and these are methylated in females during postnatal development. Hypermethylation of androgen receptor genes causing decreased levels of androgen receptors (ARs) have been found in patients of POI [37]. Transgenerational epigenetic alterations in F1 and F3 generations have also been found in one of the studies where the F0 generation gestating females were exposed to fungicide, a pesticide mixture, a plastic mixture, dioxin, and hydrocarbon mixture [38]. Environmental factors like endocrine disruptors generate OS and induce epigenetic transgenerational alterations through uncharacteristic DNA methylation [39]. To avoid epigenetic changes in offspring, methyl donors can be administered which will restore the methylation pattern. It can also solve some idiopathic infertility problems related to methylation process [40]. It has also been found that critical region 1 (CR1) of X_q is responsible for methylation pattern of POI patients. Further CR1 region also down-regulates genes for oocytes and ovarian follicle maturation [41]. Fragile X mental retardation 1 (FMR1) gene is one of the key regulatory gene in occurrence of POI. It has been found that regulation of FMR1 gene is done by highly dynamic gene expression and histone modification indicating a role of epigenetics in POI molecular pathophysiology [42]. So, it is critical to think and avoid the modifiable environmental and lifestyle factors which lead to these types of unwanted epigenetic changes, which not only hamper the physiology of the current generation but also harm the successive generations. Yoga based lifestyle intervention is an adjunctive way, which can help in improving these epigenetic changes. All the mechanisms affecting causation or progression of POI have been highlighted via a line diagram in Figure 1.

Yoga Based Lifestyle Intervention and POI

POI is idiopathic in most of the cases. Oxidative stress, DNA damage, DNA repair mechanisms and epigenetics play a key role in this disease. Oxidative stress, DNA damage and epigenetic changes can be modified by lifestyle changes. Avoiding environmental factors like toxic chemical exposure, decreased use of plasticizers, or adopting healthy lifestyle habits and choosing a wholesome nutritious diet can modify these factors to some extent. Further, it has been found in many studies that yoga plays a key role in improving many of these harmful factors. Yoga is a profound science of wellbeing which includes structured physical activity, pranayama, and meditation. Decrease in the reactive oxygen species and oxidative DNA damage was observed after adopting Yoga-Based Lifestyle Intervention (YBLI) even after a brief period 10 days [43, 44]. Decreased oxidative stress and DNA damage can have profound effects on prevention of oocyte senescence and ovarian failure. Further, yoga has been found to significantly change the expression of BER genes, which are essential and highly active for prevention of any DNA damage in oocytes. Changes in BER genes OGG1 and PARP 1 have been found after 21 days YBLI [45]. YBLI has positive effects on telomerase length, telomerase activity, increased neurotransmitters like β-endorphins, melatonin, BDNF, immunomodulators like sHLA-G levels. It also decreases inflammatory markers like IL-6, TNF-α, IL-17A, CRP. It also has a role as immunomodulators apart from decreasing oxidative DNA damage [46]. Yoga improves mitochondrial health through up-regulation of mtDNA, mitochondrial activity markers and transcripts that maintain mitochondrial integrity. This is carried out by improving COX-II activity, regulation of circadian rhythm, and increase in level of melatonin. Melatonin is a potent antioxidant and a key molecule which maintains homeostasis and circadian rhythm and increases expression levels of transcripts that maintain mitochondrial integrity. COX-II is an important component of complex IV, and increased COX-II levels by yoga stabilize the cytochrome C oxidase

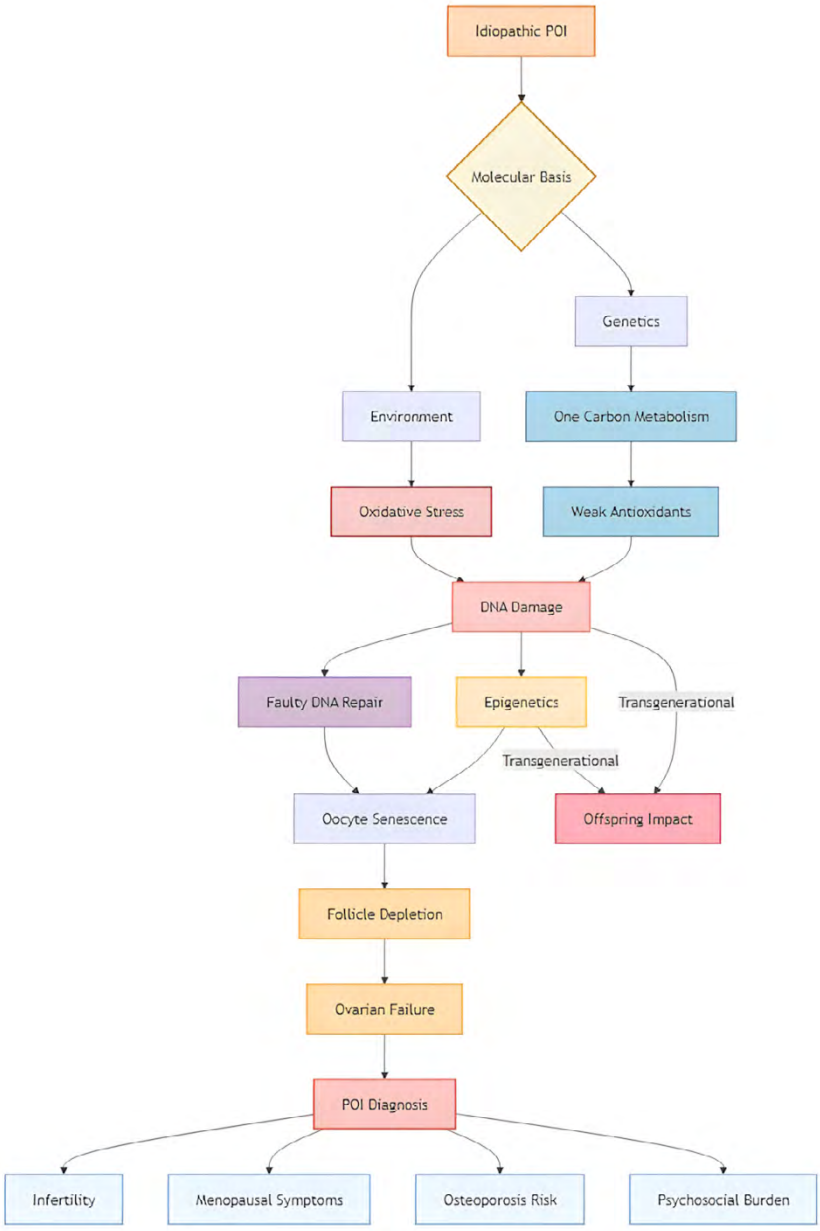

Fig. 1. Pathogenesis of Premature Ovarian Insufficiency (Diagram illustrates the complex interplay of genetic, environmental, and molecular factors leading to Premature Ovarian Insufficiency (POI), encompassing oxidative stress, DNA damage, and epigenetic alterations that contribute to oocyte senescence and ovarian failure. It also highlights the potential for transgenerational impacts and the subsequent clinical consequences of POI.)

super-complex. It also affects signal transduction and gene transcription by causing genome wide hypo-methylation and thus causes changes in the epigenome. YBLI also causes significant increase in NAD+ levels. NAD+ acts as a central metabolic cofactor having an important role in biological processes including energy homeostasis, DNA repair, gene expression and calcium-dependent second messenger signalling. YBLI causes decline in reduced expression levels of pro-inflammatory genes like TNF-α, nuclear factor kappa B subunit 1 (NFKB1), IL-6 and upregulation in anti-inflammatory genes [17].

YBLI has been shown to significantly decrease DNA fragmentation index (DFI). YBLI also helps in the epigenetic modification by histone modifications and changes in DNA methylation pattern. YBLI has been found to be associated with methylation changes in approximately 400 genes including several genes related to optimum fertility and genomic integrity. Therefore, it is associated with epigenetic change by altering the DNA methylation status, which in turn directly impact gene expression levels [47]. YBLI benefits both the mind and the body by decreasing stress and improving quality of life. Delay in oocyte senescence may improve reproductive potential and decrease incidence of POI. So, YBLI may be considered as adjunctive therapy in case of idiopathic POI. Effect of YBLI on POI has been illustrated via a line diagram in Figure 2.

Summary and Conclusion

POI is a clinical condition recognized in women below 40 years of age in whom there occurs cessation of ovarian function and clinically characterized by amenorrhoea, hypoestrogenism and elevated serum gonadotropin levels. Genetic cause of POI has only been implicated in up to 40% of cases. Rest of POI has multifactorial etiological factors like epigenetic changes, oxidative DNA damage, damage to DNA repair mechanisms etc. and further many of the epigenetic changes are transgenerational. Currently management of POI rely on conservative symptom relieving medications viz. hormone replacement with estrogen and progestin and exogenous steroids. Other supporting measures include calcium and vitamin D rich diet with risk factor avoidance to target prevention of osteoporosis especially in the estrogen depleted patients. The psychological stress and decreased quality of life too needs timely intervention which is a major challenge in treating these women. But many POI patients may present with infertility and with significant associated morbidity because of the sequel of steroid inadequacy as the condition is often diagnosed late.

Given the tremendous impact of POI on women's quality of life, we propose that integration of YBLI may help in restoring the one carbon pathway reserves, change in expressions level of BER enzymes thereby boosting the antioxidant defence mechanism of body leading to decreased DNA damage or correction of already produced DNA adducts. Also embracing healthy lifestyle habits like cessation of smoking, healthy diet, exercise, and decreased exposure to environmental pollutants can decrease oxidative DNA damage. These lifestyle interventions not only benefit the present generation but also protect further generations by reducing transmission of the abnormal epigenetic changes. This also helps in decreasing oocyte senescence thus protecting the early occurrence of POI.

Author contribution

Conceptualization: R.K., R.D.; Writing — original draft preparation: R.K., D.B.; Writing — review and editing: R.K., D.B., R.D.; Supervision: R.D.

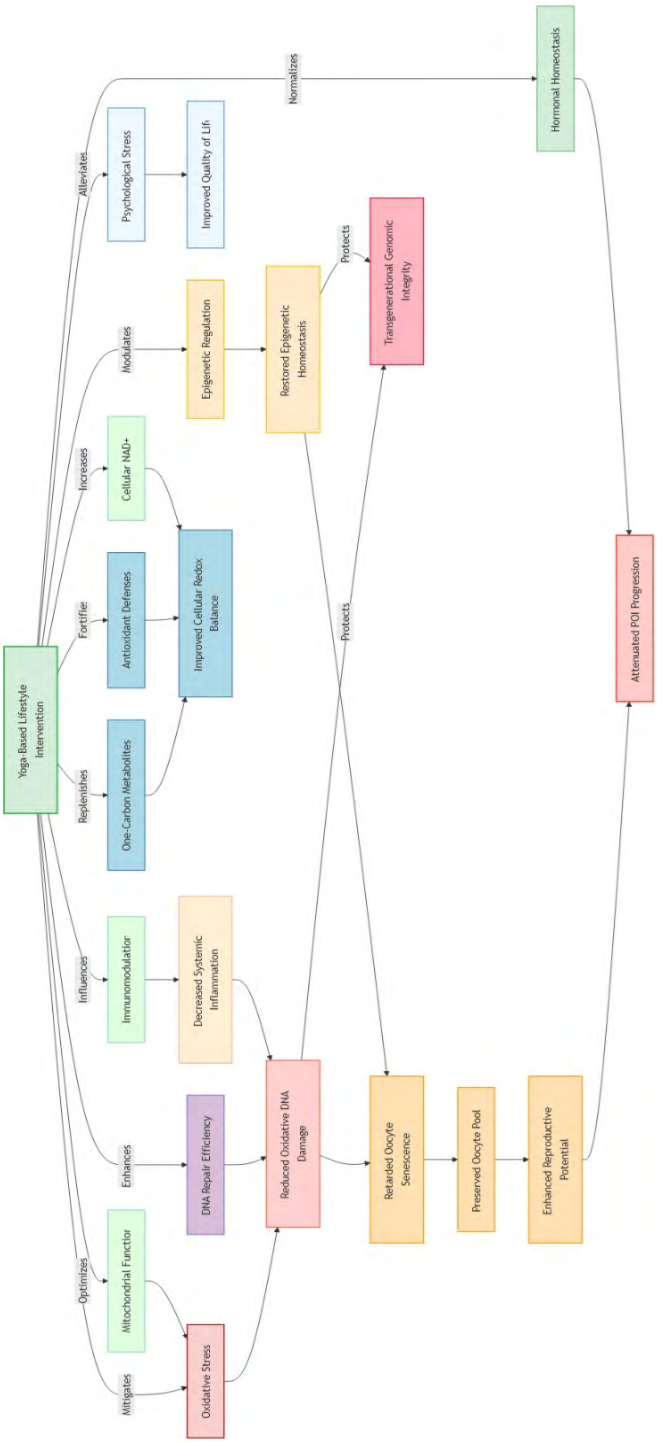

Fig. 2. Impact of Yoga-Based Lifestyle Intervention on premature ovarian insufficiency (Diagram illustrates how Yoga-Based Lifestyle Intervention (YBLI) positively influences various physiological pathways, including mitigating oxidative stress, enhancing DNA repair, and modulating epigenetic regulation, ultimately leading to improved hormonal homeostasis and attenuated POI progression. The comprehensive benefits of YBLI extend to improving reproductive potential, quality of life, and protecting against transgenerational genomic damage.)

Statements and Declarations

The authors declare they have no financial interests. The authors have no competing interests to declare that are relevant to the content of this article.

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Conflict of interest

None declared.

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