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# Molecular hydrogen therapies and the benefits for menopausal and perimenopausal women: An aphoristic review

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## Abstract

Women account for half of the global population, yet, when applying of the principles of legislation to women's health and gender-based research there is a void pertaining to women-specific healthcare as they age. Hydrogen therapies such as oxy-hydrogen (HHO, $H_2/O_2$) inhalation act as a novel, non-toxic, antioxidant and anti-inflammatory compounds, with clinical and empirical research confidently suggesting such therapies may be beneficial to human reproductive health. This aphoristic review highlights the need for medical evidence-based research into female-focused age conditioning and offers an explanation as to why HHO therapies may be effective in combatting menopausal and perimenopausal symptoms.

**Keywords:** Molecular Hydrogen; Menopause; Oxy-hydrogen; Perimenopause

## 1. Introduction

Human reproductive health is an integral part of personal wellbeing, one that can markedly impact upon individuals, couples, families, and the wider society. And whilst women account for 49.6% of the global population [1] when applying of the principles of legislation to women's health and gender-based research there is a void pertaining to women-specific healthcare, particularly as they age. Despite progress being made in recent years, when understanding both the aging process and gender-specific medicine [2] the application of the principles behind the legislation to women's health and gender-based research have not been well applied. This disparity is particularly noticeable when considering the physiological adaptations that occur during the transition from fertility to maturity. Therefore, a better understanding of how to manage such adaptations is needed if women are to be able to effectively be diagnosed and treated for menopause-associated complications.

In women >45-years, menopausal diagnosis is based on symptomatic experiences alone, there is, as yet no definitive test that can identify the onset of the menopause. In the <45-year age-group a simple blood test that detects elevated levels of follicle-stimulating hormone (FSH) can be used [3]. This method, however, cannot be fully relied upon because of inherent fluctuations in hormone levels during the perimenopause and women experiencing menopausal or perimenopausal symptoms risk facing acute physiological changes without an accurate medical diagnosis.

## 2. Discussion

As established, symptoms of the perimenopause have yet to be well delineated, and often medical professionals misunderstand the condition, diagnosing anxiety or depression as a result of lifestyle and environment, instead of a

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naturally occurring hormone imbalance [3]. It is clear that the current trajectory of ignorance encourages and enforces typical female stereotypes, and that such philistinism should not continue to be a barrier to female health.

The perimenopause is a time before the menopause (defined as the full cessation of menses), when female hormones begin to decline. Profound changes in the hormone-producing endocrine system during this time are known to have severe consequences upon the individual's confidence and quality of life. For some, this period of transition can last for a decade or more [4] and present with symptoms that include epidermal distress, hot flushes and mild cognitive impairment, alongside an increased susceptibility to cardiovascular disease, neurodegenerative conditions and urogenital dystrophy [5]. Although research into this area of women's health is wholly insufficient, numerous reports, spanning decades, highlight a concordance between the decline in oestrogen production, and an increase in systemic oxidative stress (OxS) and persistent low-grade inflammation [4,6-8]. Depreciating levels of steroidal oestrogen derivatives; estrone (E1), 17β-oestradiol (E2), estriol (E3), as well as progesterone, testosterone and prolactin are known to affect fundamental biochemistry including antioxidant potential [4], immunological responses [3,7], insulin resistance [9], lipid profiling [3] and neurotransmitter release [10], all of which add to the physiological and psychological symptoms associated with transition. To illustrate the extreme depletion of gender-based hormones, before perimenopause the bioavailability of E2 ranges between 100 and 250 picograms per mL, whilst post-menopausal levels have been recorded as low as 10 picograms per mL [4]. Such a significant decline in E2 is likely to be responsible for the increase in OxS, epidermal thinning, reduced serotonin production and decreased bone density. E2 is a major regulator of the reduction/oxidation status of cells and acts to upregulate endogenous antioxidant enzyme expression, catalase (CAT) and superoxide dismutase (SOD) for example and small redox molecules such as glutathione (GSH), without which cells can 'switch' to a pro-oxidative, pro-inflammatory, state that is detrimental to health.

Oxy-hydrogen (HHO, or $H_2/O_2$) is an emerging medical gas, generated from the electrolysis of water. HHO is a mixture of molecular hydrogen ($H_2$) and molecular oxygen ($O_2$), delivered in a 2:1 ratio [11]. Inhalation is a non-invasive therapy administered via a nasal cannula or mask, allowing the gas mixture to directly enter the blood-stream via the respiratory tract. Research into $H_2$ and hydrogen-related therapies, including oxy-hydrogen, as natural pharmaceuticals (nutraceuticals) is now well developed, with in excess of 1500 clinical and laboratory studies attesting to the favourable anti-allergy, anti-apoptotic, anti-inflammatory and antioxidant qualities of such treatments. $H_2$ is often described as an inert, colourless, non-toxic, odourless and tasteless gas, however, empirical reports reveal $H_2$ is capable of influencing many cellular functions including signal modulation, energy metabolism, protein phosphorylation and gene expression [12,13]. A host of studies have also described $H_2$, the primary component of oxy-hydrogen, as having salubrious anti-inflammatory and anti-oxidant effects, and initial clinical studies show increasingly promising results [14-16].

As an antioxidant, $H_2$ acts in a similar way to oestrogen derivatives, through upregulating the endogenous expression of antioxidant enzymes and peptides, including CAT, GSH and SOD. In contrast, well-known antioxidants such as vitamins C (L-ascorbic acid) and E (alpha tocopherol), although effective in the short-term can accumulate in the body of susceptible individuals, leading to adverse effects including digestive distress and improper kidney or liver function if taken for a prolonged time, or in large doses [17]. As HHO is a mixture of biocompatible gases, excesses are easily eliminated from the body either by simply diffusing away, or by exhaling in our breath [18]. Such qualities make HHO an ideal therapeutic for targeting dysfunctional intracellular processes such as metabolic dysregulation and redox homeostasis, irregularities that are deemed significant to both pathogenesis and progression of menopause-associated symptoms.

In addition to oxidative stress, HHO has a propitious anti-inflammatory profile, typically through inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signalling pathway, again in similarity with oestrogen and its derivatives [19]. In addition to this, reductions in immune cell activation have also been extensively observed [20-22]. These factors are important as the cycle of inflammation underpins many complaints associated with the climacteric transition, with clinical research linking cellular inflammation with the progression of neurological decline (e.g., Alzheimer's Disease, emotional instability), metabolic diseases (e.g., Diabetes, Hyperlipidaemia) and both muscle and joint degeneration (e.g., Arthritis, Sarcopenia) [4]. Many reports describe an anti-inflammatory effect of $H_2$ treatments, and supporting scientific evidence suggests that $H_2$-inhalation therapies, in particular, are able to suppress biological markers of oxidative stress and pro-inflammatory peptides (e.g., malondialdehyde [MDA]; cytokines (e.g.,TNF-α) and interleukins (e.g., IL-1β, IL-6), respectively) [23-25]. Recent reports into the effects of $H_2$ as a medical gas describe the significant reduction in pro-inflammatory cytokine production, reduced neutrophil infiltration and activity, and decreased oxidative damage to DNA after administration, all of which strongly imply that HHO is an ideal natural therapy for targeting the myriad of complaints women endure as they age.

As stated previously, $H_2$ is an inert, colourless, non-toxic, odourless and tasteless gas that acts as a natural and novel antioxidant. $H_2$ gas is also endogenously produced through fermentation of nutrients by intestinal micro-organisms

such as *Escherichia coli* [26]. Endogenous $H_2$, however, is not found in significant quantities to be therapeutically advantageous and research shows inhalation of $H_2$ gas to be beneficial in humans [15, 18, 24, 25, 27-30]. To illustrate, high exposure to $H_2$ (96%), in conjunction with 4% oxygen ($O_2$), has been used as a treatment to prevent decompression sickness in deep-sea divers since 1944 [27]. Further clinical trials investigations into the safety and effectiveness of HHO inhalation in combatting debilitating symptoms associated with such diseases as Cancer (NCT03818347) [28], COPD (NCT04000451) [29], and COVID-19 (NCT04378712) [30] demonstrate no serious or long-lasting side-effects regarding HHO treatments.

## 3. Conclusion

During the menopausal transition OxS and chronic inflammation are known to contribute to and exacerbate the pathogenesis and progression of numerous menopausal symptoms. Through modulation of the redox environment (via direct and indirect mechanisms), attenuating aberrant immunological responses, and the inherent safety of $H_2$ as a biocompatible compound, it is evidential that HHO regimens are likely to be highly beneficial as an adjunctive, or an alternative, to prevalent therapeutic strategies for women experiencing exuberant symptoms of climacteric transition.

## Compliance with ethical standards

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A. Nenov is a board member of Water Fuel Engineering. G. Russell declares no conflict of interest.

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