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The Impact of Cigarette Smoking on Female Hormonal Health and Reproductive Outcomes: A Comprehensive Review

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ABSTRACT: Smoking remains one of the most significant preventable health threats, with over 193 million female smokers globally. Despite its well-documented associations with numerous reproductive and chronic health issues, the impact of smoking on female hormonal levels continues to be an area of active research. This review aims to provide current knowledge on the effects of smoking on female reproductive hormones, including estrogen, progesterone, gonadotrophins, androgens, and its influence on thyroid function and overall reproductive health. A comprehensive review of the literature was conducted using online tools such as Google Scholar and PubMed, focusing on studies that investigate the impact of smoking on ovarian hormones (estrogen and progesterone), androgens, gonadotrophins (LH, FSH), anti-Müllerian hormone (AMH), and thyroid hormones. Studies were selected based on their relevance to smoking and hormonal levels, with a focus on findings from both active and passive smokers.

KEYWORDS: Cigarette smoking, Ovarian hormones, gonadotrophins, Thyroid hormones, Reproductive health.

I. INTRODUCTION

Smoking remains a major preventable health threat, with 193 million female smokers globally, a number that's rising despite known health risks. Smoking is associated with reproductive issues such as infertility, spontaneous abortion, and early menopause, as well as chronic diseases including cervical and lung cancers, cardiovascular disorders, and osteoporosis. Notably, female smokers face a 25% higher prevalence of coronary heart disease compared to their male counterparts[1].

The menstrual cycle, consisting of the follicular and luteal phases, lasts 21 to 37 days. It begins with menstruation marking Day 1 of the follicular phase, where follicle-stimulating hormone (FSH) peaks, promoting follicular growth and estrogen release. Elevated estrogen levels trigger a luteinizing hormone (LH) surge, leading to ovulation. Post-ovulation, the corpus luteum releases estrogen and progesterone, which regulate FSH and LH through negative feedback[2].

Cigarette smoke contains over 7,000 chemicals, including 72 carcinogens[3]. Nicotine, the primary alkaloid, is metabolised into cotinine and broken down. These chemicals disrupt female reproductive health by interfering with aromatisation, folliculogenesis, and luteinization. Studies show that tobacco smoke reduces the conversion of androgens to estrogens, diminishes estrogen and progesterone production in granulosa cells, and impairs luteal cell progesterone release[4,5]. Exposure to tobacco compounds like Benzo[a]pyrene (BaP) also results in decreased follicular development and reduced hormone levels.

II. LITERATURE REVIEW

Ovarian hormones and smoking:

In the present review, we included literature about the impact of smoking on different ovarian hormones; estrogen, and progesterone. Estrogen and progesterone are the two main ovarian hormones crucial for female reproductive health and serve as important indicators of reproductive homeostasis disturbances. Estrogen is primarily produced in ovaries,

where androgens convert into estrogens through aromatisation. The three primary estrogens in the female body are estrone (E1), estradiol (E2), and estriol (E3)[6].

Whitcomb et al.[7] and MacMahon et al. [8] studied estrogen levels throughout the menstrual cycle, including the follicular and luteal phases and they found that tobacco smoking is associated with decreased estrogen levels in premenopausal women. Szkup et al. [9], Soldin et al. [10] studied estrogen levels in the follicular phase (specifically the 2nd or 3rd day), and Chen et al. [11] in the luteal phase of the menstrual cycle reported reduced estrogen levels in female smokers.

Two main mechanisms explain this antiestrogenic effect. First, tobacco may decrease the aromatization process. Studies involving human granulosa cells exposed to tobacco alkaloids like nicotine, cotinine, and anabasine have shown that these substances compete for aromatase enzymes, thereby reducing the conversion of androgens to estrogens[5,12]. Second, smoking promotes the 2-hydroxylation of estrogens, resulting in 2-hydroxy estrogens that cannot perform typical estrogen functions[10,13]. Despite these explanations, the mechanisms behind tobacco's antiestrogenic effects remain a topic of ongoing debate. Verkasalo et al. [14] found increased estradiol concentrations in premenopausal female smokers. In contrast to the above studies, Caserta et al. [15], Dafopoulos et al. [16], Freour et al. [17], Lucero et al. [18], Law et al. [19], Thomas et al. [20], Daniel et al. [21], Key et al. [22], and Zumoff et al. [23] did not find any significant differences in estrogen levels between female smokers and non-smokers.

Progesterone, a hormone secreted by the corpus luteum after ovulation through a process called luteinization, plays a crucial role in fertility by maintaining the uterine lining (Endometrium) and supporting embryo development. Miceli et al. [4] and Gocze et al. [12] exposed human luteal cells and granulosa cells respectively, to cigarette smoke components and observed a reduction in progesterone production. Berta et al. [24] found that smokers had lower progesterone levels than non-smokers during the luteal phase. Tobacco smoking has been shown to disrupt folliculogenesis and the formation and function of the corpus luteum, leading to decreased progesterone levels in female smokers.

In 2022, Florek et al. [25] recently conducted a study on 153 women of reproductive age. They observed increased levels of progesterone during the luteal phase and elevated levels of LH and FSH during the follicular phase. They concluded that higher levels of LH and FSH might lead to abnormal follicle growth, affect the function of the corpus luteum, and increase the length of the menstrual cycle. In contrast, studies by Dafopoulos et al. [16], and Key et al. [22] found no significant difference in progesterone levels between smokers and non-smokers. Khalid et al. [26] studied the effect of second-hand smoke on progesterone and estrogen levels in women who experienced recent abortions and did not find any difference in hormonal levels.

Studies have indicated that tobacco may reduce the risk of breast and endometrial cancer in female smokers due to its antiestrogenic effects[13,27,28]. However, decreased estrogens in women cause different health complications which include, infertility, spontaneous abortion, osteoporosis, depression, atherosclerosis, endometriosis and Alzheimer's[29].

Ovarian hormones and smoking behaviour:

Saladin et al. [30] and Schiller et al. [31] highlighted the significant roles of estrogen and progesterone in smoking abstinence. Previous research indicates that estrogen enhances reward perception and contributes to smoking reinstatement, while progesterone reduces drug-seeking behaviour[32]. Additionally, higher ratios of progesterone to estrogen have been associated with improved success in overcoming nicotine addiction. Farris et al. [33] also found that female smokers are more likely to successfully quit during the early follicular phase, which is characterized by lower estrogen levels.

Smoking and gonadotrophins:

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels typically rise with age. Their secretion is regulated by ovarian hormones and gonadotropin-releasing hormone (GnRH). A decrease in ovarian hormone levels can disrupt the negative feedback mechanism, leading to elevated FSH and LH levels in female smokers[34].

The studies conducted on the impact of smoking on LH and FSH levels have been controversial. Whitcomb et al. [7] conducted a study on samples collected throughout the menstrual cycle (conducted 8 visits) and found significantly

higher LH and FSH levels in current smokers except for the late follicular phase. Florek et al. [25] collected samples on the 1st, 14th, and 21st days of the menstrual cycle and observed increased LH and FSH levels in the early follicular phase (on the 1st day) in smokers compared to second-hand smokers and non-smokers. Caserta et al. [15] noted increased FSH levels during the follicular phase in smokers but found no differences in LH levels. In contrast, Szkup et al. [9] investigated the effects of smoking on FSH, estrogen levels, and lipid metabolism and reported that non-smoking women had higher FSH levels compared to smoking women. However, Dafopoulos et al. [16], Law et al. [19], and Thomas et al. [20] studied LH and FSH levels in smokers but did not find significant differences between smokers and non-smokers.

However, Freour et al. [17], Lucero et al. [18], Windham et al. [34], and Kline et al. [35] focused on FSH levels in the follicular phase without accounting for LH levels in smokers and all the investigators except for Freour et al. (2008), reported higher FSH levels in smokers. Zumoff et al. [23], did not find significant differences in LH levels between smokers and non-smokers.

Smoking and androgens:

Dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione (A4) are the primary pro-androgens in females. These hormones can be converted into testosterone (T) and dihydrotestosterone (DHT), which bind to androgen receptors [36]. In females, androgens are predominantly produced in the ovaries and adrenal glands. Luteinizing hormone (LH) regulates androgen production from theca cells in the ovaries. These androgens are converted into estrogens through a process called aromatization, which involves a two-cell, two-gonadotrophin mechanism [37]. Previous research has suggested that nicotine metabolites may interfere with androgens during aromatisation [5,10,12]. This competition can inhibit the conversion of androgens to estrogens, potentially resulting in higher levels of androgens in female smokers.

Sowers et al. [39] investigated testosterone levels during the early follicular phase in 611 premenopausal women and found that current smokers had significantly higher testosterone levels compared to former and never smokers. Soldin et al. [10] measured steroid hormone and cotinine levels in current, passive, and non-smokers and discovered elevated levels of DHEA and DHEAS in second-hand smokers during the follicular phase, relative to non-smokers. In contrast, studies by Law et al. [19], Thomas et al. [20], Daniel et al. [21], and Key et al. [22] did not find statistically significant differences in androgen levels between smokers and non-smokers among premenopausal women.

Smoking and Anti-Müllerian Hormone (AMH):

Anti-Müllerian hormone (AMH) plays a critical role in male sex differentiation by inhibiting the development of Müllerian ducts, which form the fallopian tubes, uterus, and upper parts of the vagina during fetal development. In females, AMH is not present in primordial follicles but is expressed in growing follicles within the ovary [40,41]. Ovarian age is typically assessed by evaluating the primordial follicle pool. Since direct detection of primordial follicles is not possible, this pool is indirectly represented by the growing follicle pool, which can be assessed through AMH levels [42]. Cigarette smoke contains various reactive oxygen species (ROS) such as carbon dioxide, hydrogen peroxide, and nitrogen oxides, which can cause apoptosis of primordial follicles in the ovaries [43]. This, in turn, leads to reduced AMH levels in smokers. An AMH level of less than 0.1 ng/mL is considered indicative of diminished ovarian reserve (DOR) [44].

Plante et al. [45] reported decreased levels of AMH in female smokers during their early follicular phase. In contrast, Dafopoulos et al. [16], Kline et al. [35], Oladipupo et al. [44] and Hawkins Bressler et al. [46] found no differences in AMH levels between smokers and non-smokers.

Smoking and thyroid hormones:

Thyroid disorders are more common in women, with female smokers being particularly susceptible to conditions such as hyperthyroidism, goitre, autoimmune hypothyroidism, and Graves' disease. The exact impact of smoking on thyroid function remains unclear.

Goiter, characterized by the enlargement of the thyroid gland, can be classified as diffuse, multinodular, or nodular and may be associated with either hypo- or hyperthyroidism. Iodine deficiency is a primary cause of goitre. Knudsen et al. [47] found a positive correlation between multinodular goitre and smoking. Peter Vestergaard et al. [48] also reported a 28% increased risk of goitre and a 23% increased risk of autoimmune hypothyroidism in female smokers. This study suggests that thiocyanate in cigarette smoke may have antithyroid effects by interfering with iodine organification, potentially leading to hypothyroidism. In contrast, Knudsen et al. [47] observed a lower risk of hypothyroidism among female smokers.

Jamshid Farahati et al. [49] conducted a study with 370 women and found significant associations between goitre and factors such as iodine deficiency, parity, and older age, but did not find a link between smoking and goitre in females. Graves' disease, an autoimmune disorder where the body's antibodies attack thyroid antigens, results in excessive thyroid hormone secretion and gland enlargement. Vestergaard et al. [48] noted a 45% increased risk of Graves' disease among women who had ever smoked.

Multiple studies have reported that smoking is associated with. These studies observed significantly lower TSH levels and elevated thyroid hormone levels in smokers[50-56]. Zhang et al. [51] and Horton et al. [57] suggested that thiocyanate (SCN-) in cigarette smoke interferes with thyroid hormone binding to thyroid-binding globulin (TBG), leading to increased free thyroid hormone levels. Rehan et al. [54] proposed that nicotine metabolites, such as cotinine, trans-3'-hydroxycotinine, and 5'-hydroxycotinine, compete with thyroid hormones for TBG binding, which could also raise thyroid hormone levels and lower TSH. Conversely, Meral et al. [58] found no statistically significant differences in fT3, fT4, tT3, tT4, and TSH levels between smokers and non-smokers, indicating no clear association between smoking and thyroid function.

Smoking and Female Reproductive Health:

As mentioned earlier current smoking has a severe impact on female reproductive health that includes ectopic pregnancy, spontaneous abortion, infertility, pre-ovary insufficiency, and early menopause.

Ectopic pregnancy is defined as the implantation of an embryo on other sites instead of the endometrium of the uterus. If the ectopic pregnancy continues it might cause the death of the person that carrying it. Gaskins et al. [59] mentioned that smoking is associated with a 22% increased risk of ectopic pregnancy in smokers compared to non-smokers. Ashraf Moini et al. [60] reported that passive smoking also involved with increased risk of ectopic pregnancy by 1.7 times. Andrew Hyland et al. [61] conducted a cross-sectional analysis on 80,762 women and concluded that women who ever smoked during their reproductive age faced a higher risk for ectopic pregnancy, spontaneous abortion, and unexplained infertility. Shiqi Lin et al. [62] reported an association between passive smoking and vitamin D deficiency with an increased risk of spontaneous abortions by 1.76 times. Long Wang et al. [63] conducted a population-based study on rural Chinese women who are exposed to tobacco smoke through passive smoking and observed an increased risk of spontaneous abortions in Passive smokers compared to never-smokers.

Menopause is the end of regular menstruation and it is a natural process experienced by all women. Menopause is experienced at different ages based on ethnicity, genetics, and habits[64]. The average age for menopause is between 48 and 52. Cessation of menstruation below 45 is considered as early menopause which is linked with long-term health consequences. A cross-sectional study by Sevcan Arzu et al. [65] concluded that smoking was found to increase the risk of early menopause by 1.34 times. Hee Jung Yang et al. [66] also observed early menopause in smokers compared to past and never smokers. A population-based study (12-month follow-up) was carried out by Olof Lindquist et al. [67] on 1462 women aged 38 to 60 years and reported adverse effects of smoking on reproductive age. Further, they observed earlier menopause in premenopausal women who were smokers.

III. CONCLUSION

Cigarette smoking presents a significant preventable threat to female reproductive health, impacting a wide range of hormonal and physiological processes. While there is substantial evidence indicating that smoking negatively affects female reproductive health through various mechanisms, the findings are not entirely consistent across all studies. The complex interactions between smoking and hormonal regulation require further investigation to fully understand the

underlying processes. Addressing smoking as a modifiable risk factor is crucial for improving women's reproductive health outcomes and overall well-being.

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