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Premature ovarian insufficiency: A review on the role of tobacco smoke, its clinical harm, and treatment

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Abstract

Background: Premature ovarian insufficiency (POI) is the cessation of normal ovarian function before the age of 40 and is associated with infertility, hypoestrogenism, and increased risk of chronic disease. In environmental and lifestyle factors, cigarette smoking is a modifiable risk factor accelerate ovarian aging.

Objective: This systematic review evaluate the association between tobacco smoke exposure and POI in women of reproductive age by reviewing findings from original studies assessing ovarian reserve markers, reproductive hormone profiles, and fertility outcomes.

Methods: A literature search was conducted in (PubMed, Scopus, and Web of Science) for studies published between 2010 and 2025. Eligible studies included human participants aged 18 to 45, with exposure to active or passive cigarette smoking through self-report or biochemical markers. Included outcomes were anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), in vitro fertilization (IVF) parameters, and natural fecundability. Studies were selected through a two phase screening process and analyzed qualitatively due to methodological heterogeneity.

Results: Six original studies were included. Smoking was associated with lower AMH levels, higher FSH levels, and diminished ovarian reserve. Active smoking was linked to fewer oocytes retrieved, poorer embryo quality, and reduced pregnancy rates during IVF. Long-term or high-dose smokers show reduced fecundability in natural cycles. One study found no significant difference in IVF outcomes in smokers with normal ovarian reserve.

Conclusion: Cigarette smoking negatively affects ovarian reserve and fertility. Smoking cessation should be advised to preserve reproductive health and prevent POI.

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Keywords: Premature ovarian insufficiency; Cigarette smoking; Ovarian reserve; Anti-Müllerian hormone; Fertility; Reproductive aging; Tobacco exposure

1. Introduction

Premature ovarian insufficiency (POI) is characterized by the loss of normal ovarian function before the age of 40, presented as as menstrual irregularity, infertility, and hypoestrogenism. POI affect 1–3% of women, POI has multifactorial etiology, including genetic, autoimmune, iatrogenic, and environmental causes. In modifiable lifestyle factors, cigarette smoking is a significant contributor to accelerated ovarian aging and affect reproductive dysfunction (Budani et al. 2017).

Cigarette smoke contains over 4,000 chemical compounds, some of which are ovotoxic, which include polycyclic aromatic hydrocarbons, cadmium, and nicotine metabolites. These substances interfere with folliculogenesis, promote oxidative stress, induce apoptosis, and form DNA adducts within ovarian cells, leading to follicle depletion and reduced ovarian reserve (Budani et al. 2017). Studies detect measurable concentrations of cotinine and benzo[a]pyrene in follicular fluid, which indicate direct ovarian exposure and support a biological basis for smoke-related reproductive damage (Budani et al. 2017).

Smoking is associated with reduced levels of anti-Müllerian hormone (AMH), elevated follicle-stimulating hormone (FSH), and poorer in vitro fertilization (IVF) outcomes (Freour et al. 2008; Oladipupo et al. 2022). Altered hormonal profiles also observed in healthy premenopausal smokers, with phase-specific elevations in FSH and luteinizing hormone (LH), which suggest early endocrine disruption (Waylen et al. 2010). Not all studies found differences in IVF success rates (Wright et al. 2006), and longitudinal evidence indicates a dose-dependent decline in fecundability in smokers (Radin et al. 2014).

This systematic review aims to evaluate the association between tobacco smoke exposure and premature ovarian insufficiency. We aim to provide clinicians and reproductive health specialists with evidence based insights into the effect of smoking on ovarian reserve, reproductive hormones, and fertility outcomes.

2. Methodology

This systematic review was conducted to examine the association between tobacco smoke exposure and POI, with a focus on ovarian reserve indicators and reproductive outcomes in women. A comprehensive search of electronic databases (PubMed, Scopus, and Web of Science) was performed to identify relevant articles published between 2010, and 2025. The search strategy combined both MeSH terms and keywords which include: *premature ovarian insufficiency, ovarian reserve, anti-Müllerian hormone, AMH, inhibin B, FSH, follicle-stimulating hormone, smoking, cigarette, tobacco, fertility, and IVF outcomes.*

We include original research conducted on female participants aged 18 to 45 years; examined exposure to active or passive cigarette smoking, verified through self-report or biochemical assessment (urinary cotinine levels); assessed outcomes related to ovarian reserve (AMH, FSH, inhibin B, antral follicle count), fecundability, or assisted reproductive technology (ART) outcomes. Observational studies (cross-sectional, cohort, or case-control) and interventional trials were eligible. We exclude animal or in vitro studies, reviews, editorials, case reports, and conference abstracts. We also exclude articles not reporting smoking exposure or ovarian outcomes, duplicates or those involving overlapping datasets.

The selection of studies was carried out in two phases. First two independent reviewers screened the titles and abstracts of all retrieved articles. Then full texts of potentially eligible studies were reviewed for inclusion based on the criteria. Disagreements were resolved through discussion or consultation with a third reviewer to reach consensus.

Data from the selected studies were extracted using a predesigned template. Information recorded included: author, publication year, country of study, study design, sample size, participant demographics, method of smoking exposure assessment, outcome measures, and major findings. We also exatrct information on adjustment for confounders and statistical significance.

Due to the heterogeneity in study designs, populations, outcome definitions, and measurement methods, a qualitative synthesis was performed. The results were grouped and presented under thematic categories which include hormonal

biomarkers, IVF-related outcomes, and fecundability. Studies were summarized and compared to identify consistent parameters and divergences.

3. Results

This review included six original studies about the relationship between cigarette smoking and various indicators of ovarian function, including ovarian reserve, reproductive hormones, fecundability, and IVF outcomes. Sample sizes differ from 111 to 3,773 participants, and all studies focused on women of reproductive age undergoing fertility evaluation, treatment, or planning pregnancy.

Evidence supported a negative association between active smoking and ovarian reserve markers. In a study of 207 women in fertility care, a dose-dependent relationship was observed between the number of cigarettes smoked and the low ovarian reserve (defined as AMH <1 ng/mL), even after adjusting for polycystic ovary syndrome (PCOS) and genetic variability in NAT2 acetylator phenotype (Oladipupo et al. 2022). A retrospective analysis of 111 IVF patients show that active smokers had fewer mature oocytes retrieved, lower AMH levels, and reduced clinical pregnancy rates compared to non-smokers (Freour et al. 2008).

Hormonal assessments reflected the effect of tobacco exposure on ovarian aging. In a retrospective database analysis of reproductive-aged women, lower inhibin B concentrations were found in smokers compared to non-smokers. These hormone alterations indicate accelerated ovarian aging in smokers (Waylen et al. 2010). An earlier study examining ovarian reserve through the clomiphene citrate challenge test found that smokers had a higher incidence of abnormal FSH responses in compareson to non-smokers, which indicate a faster progression toward low ovarian reserve. IVF outcomes were similar in smokers and non-smokers who had normal ovarian reserve, which suggest that the fertility decline in smokers is mediated through ovarian reserve depletion (Sharara et al. 1994).

A larger retrospective cohort study of 389 first-cycle IVF patients showed no significant differences in peak estradiol levels, number of oocytes retrieved, fertilization rate, or live birth rates between smokers, former smokers, and non-smokers. These results indicate that smoking not directly impair IVF success in well-managed clinical settings (Wright et al. 2006). However, the inconsistency due to varying definitions of smoking exposure, sample sizes, and outcome measures. A prospective cohort study of 3,773 pregnancy planners found that cumulative smoking exposure (≥10 years) was associated with reduced fecundability, as measured by the cycle-specific probability of conception. Smokers with a history of heavy smoking exhibited reduced fecundability regardless of when they had quit, while passive smoking showed no association with delayed conception (Radin et al. 2014).

Findings in studies converge to show that cigarette smoking is associated with measurable adverse effects on ovarian function, mainly through the reduction of ovarian reserve markers and fecundability. While IVF success rates may not uniformly decline in all smokers, the underlying depletion of follicular reserve and hormonal alterations indicate a biologically plausible mechanism by which tobacco accelerates reproductive aging and reduces fertility potential.

Table 1 Summary of studies on smoking and premature ovarian insufficiency

Citation	Study Design	Study Aim	Sample Size	Inclusion Criteria	Methodology
Sharara et al., 1994	Retrospective comparative study	To test if reduced fecundity in smokers is due to accelerated low ovarian reserve	Part 1: 65 smokers, 145 non-smokers; Part 2: 29 smokers, 73 non-smokers	Women aged 35–39; infertility evaluation; no prior ovarian surgery; strict tubal factor infertility	Clomiphene citrate challenge test (FSH on days 3 and 10); IVF outcome comparisons in tubal infertility cases
Waylen et al., 2010	Retrospective analysis	To investigate if smoking affects early follicular serum concentrations of inhibin B, FSH, and AMH	Not specified (retrospective database of women undergoing ovarian reserve testing)	Women of reproductive age; menstrual cycle 27–34 days; off contraceptives for 1+ month	Serum hormone levels measured on day 2–3; ELISA for inhibin B, AMH, FSH; analyzed by smoking status

Wright et al., 2006	Retrospective cohort study	To assess effect of smoking on IVF outcomes	389 women undergoing first IVF cycle	Women undergoing first IVF/ICSI cycle; no donor oocyte cycles	Comparison of E2, oocytes, embryo quality, pregnancy/live birth between smokers and non-smokers
Freour et al., 2008	Retrospective cohort study	To evaluate smoking's effect on ovarian reserve and IVF outcome	111 women (40 smokers, 71 non-smokers)	Women undergoing IVF; smoking and passive exposure reported	Day 2/3 FSH, AMH, estradiol; ovarian response, embryo development, and pregnancy outcomes measured
Radin et al., 2014	Prospective cohort study	To assess association between active/passive smoking and fecundability	3,773 women (Denmark)	Aged 18–40, planning pregnancy, no fertility treatment, in stable relationship	Questionnaires; urinary cotinine; fecundability ratios calculated with proportional probabilities model
Oladipupo et al., 2022	Cross-sectional study	To assess association of smoking with ovarian reserve and NAT2 genotype effect modification	207 women	Women ≥21 years seeking fertility care; not pregnant; able to consent; English proficiency	Smoking status by cotinine levels; serum AMH levels; regression analysis by PCOS status and NAT2 genotype

Table 2 Demographics and outcomes of included studies

Citation	**Demographic Characteristics**	**Main Findings**	**Outcomes**
Sharara et al., 1994	Women aged 35–39; infertility evaluation population; U.S. military tertiary center	Higher incidence of low ovarian reserve in smokers (12.3%) vs. non-smokers (4.8%)	Smoking accelerates diminished ovarian reserve; no difference in IVF outcome among women with normal reserve
Waylen et al., 2010	Women of reproductive age; UK; cycle length 27–34 days	Lower inhibin B in smokers; non-significant lower AMH and FSH	Trend toward advanced ovarian aging in smokers
Wright et al., 2006	389 U.S. women undergoing first IVF cycle; stratified by age <35 vs. ≥35	No significant differences in pregnancy or live birth outcomes among smokers vs. non-smokers	Smoking had no measurable impact on IVF outcome
Freour et al., 2008	111 French women (40 smokers, 71 non-smokers) undergoing IVF	Smokers had fewer oocytes and lower AMH and pregnancy rates	Smoking associated with reduced ovarian reserve and IVF success
Radin et al., 2014	3,773 Danish pregnancy planners (18–40 years)	Smoking ≥10 years linked to reduced fecundability; passive smoking not significant	Long-term and heavy smoking delays conception
Oladipupo et al., 2022	207 U.S. women seeking fertility care; evaluated for PCOS and NAT2 genotype	Each cigarette/day and pack-year increases odds of diminished ovarian reserve	Smoking dose-dependently reduces ovarian reserve; NAT2 genotype not a modifier

4. Discussion

Most studies find that there is association between active smoking and reduced ovarian reserve, which indicated by lower levels of AMH and AFC. Reductions in AMH in smokers compared to non-smokers were associated with diminished ovarian response during IVF cycles (Freour et al. 2012; Oladipupo et al. 2022). This finding is corroborated by a meta-analysis showing lower pregnancy and live birth rates in ART cycles (Waylen et al. 2009).

In addition to ovarian reserve, cigarette smoking alter important reproductive hormones. One study observed higher follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels during specific menstrual phases in smokers, reflecting compensatory responses to declining ovarian function (Whitcomb et al. 2010). Evidence indicated that smoking leads to chromosomal and DNA damage in oocytes, compromising viability and meiotic competence (Zenzes 2000).

The effects of smoking are not limited to oocyte health. It's also affected by endometrial receptivity and uterine environment, as high-quality embryos failed to implant at comparable rates in smokers, which indicate that uterine factors contribute to poor reproductive outcomes (Ben-Haroush et al. 2011). This supports the idea that the harmful effects of smoking are systemic and not ovarian (Ben-Haroush et al. 2011).

A systematic review concluded that benzopyrene and cadmium disrupt folliculogenesis through oxidative stress, apoptosis, and DNA adduct formation, reinforcing the biological plausibility of smoking-induced POI (Budani et al. 2017).

Environmental exposures related to smoking was associated with reproductive aging. Higher levels of organochlorine compounds such as DDE correlated with shorter menstrual cycles and luteal phase durations, indicative of compromised ovarian endocrine function (Windham et al. 2005).

These findings align with earlier research that show the effect of environmental and lifestyle factors including smoking on reproductive health (Feichtinger 1991), which supports an integrative view of POI etiology, of both behavioral and environmental determinants (Feichtinger 1991).

The literature provides support for the assertion that cigarette smoking negatively affect ovarian reserve, oocyte quality, and overall reproductive potential. While some inconsistencies exist mainly in studies that did not control for confounding lifestyle variables, the preponderance of data affirms the detrimental effects of tobacco exposure on female fertility. Public health messaging and clinical counseling should emphasize smoking cessation as a critical step in preserving reproductive health and delaying the onset of POI.

Abbreviations

POI, Premature Ovarian Insufficiency; AMH, Anti-Müllerian Hormone; FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; AFC, Antral Follicle Count; IVF, In Vitro Fertilization; ART, Assisted Reproductive Technology; PCOS, Polycystic Ovary Syndrome; DOR, Diminished Ovarian Reserve; DDE, Dichlorodiphenyldichloroethylene; PAHs, Polycyclic Aromatic Hydrocarbons; NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone; BaP, Benzo[a]pyrene; NOS, Newcastle-Ottawa Scale.

5. Conclusion

Cigarette smoking negatively affect ovarian function. Smoking is associated with reduced AMH levels, elevated FSH, and low ovarian reserve. It also alters reproductive hormones, which indicate early ovarian dysfunction. IVF outcomes compromised, mainly in active smokers, due to lower oocyte yield and embryo quality. One study found no significant impact on live birth rates, but reduced fecundability was observed in long-term smokers. Smoking cessation should be advised to preserve fertility and prevent POI.

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