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Research Article

Smoking and Infertility: Female Health-Care and Reproductive Risks Associated with Smoking.

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Abstract

Smoking has an adverse impact on several female reproductive life aspects, like oviducts function, uterus impairment, menstrual function disturbance. Moreover, smoking during pregnancy is a fundamental cause of health problems for both mother and fetus. It raises embryo implantation complexities associated with health conditions such as heart and cardiovascular diseases, pulmonary diseases, and hypertension. Smoking has an adverse impact on several female reproductive life aspects, like oviducts function, uterus impairment, menstrual function disturbance. Moreover, smoking during pregnancy is a fundamental cause of health problems for both mother and fetus. It raises embryo implantation complexities associated with health conditions such as heart and cardiovascular diseases, pulmonary diseases, and hypertension. Furthermore, several cigarette smoke compounds have toxic impacts on clinical IVF/ICSI treatment.

Keywords: Smoking and female reproductive health; Oviduct damage by smoking; Pregnancy risk associated with smoking; Impact of smoking on fertility; embryo implementation; life birth rate (ART treatment)

Introduction

The smoking rate of disability and disease is well documented, and it is spread worldwide. Accordingly, 178,000 die every year because of a smoking-attributable illness amongst women, with chronic lung disease, lung cancer, and heart disease outlining the top three causes (*Wewers et al., 2012*) [1].

The smoking rate is slightly higher in men than women; women can have a greater risk of smoking-related morbidity and mortality and encounter smoking cessation barriers that warrant intervention. The percentage of smoking amongst adolescents and adults has decreased across the past few years; still, the incidence of the drop is slowing (*Allen, Oncken and Hatsukami, 2014*). These trends differ through gender and age, such that the smoking decline rate was less in adolescent females. In contrast, in adult's females, a more significant decline has been recognised. For example, from 2009 to 2010, the smoking rate decreased by 17.5% amongst middle-school females versus a 24.4% decline among middle-school males [1]. Those data designate that further attempts to reduce smoking prev-

alence among females are warranted (*Allen, Oncken and Hatsukami, 2014*) [2]. Smoking health outcomes are enormous and well documented, as the related risk of death for current and former smokers remains to grow. Every year in the United States, 200,000 men and 180,000 women die as a consequence of smoking.

The most common associated risk of smoking is cancer, especially lung cancer. In the United States, as women started to smoke in more significant numbers, lung cancer replaced breast cancer as the leading reason for cancer death; nowadays, 90% of lung cancer deaths are linked with cigarette smoking in the US. Smoking has also been correlated with a high opportunity of cancer of the pharynx, cervix, kidney, bladder, oesophagus, and pancreas.

Smoking can also induce an increased risk of coronary artery disease. In US women under 65 years, smoking was responsible for 55% of cardiovascular deaths. Moreover, smoking also increases the risk of bronchitis, emphysema, peripheral vascular disease, cerebrovascular disease, and gastric ulcers (*Seltzer, 2000*) [3]. Furthermore, smoking impairs various aspects of reproductive health. It has an adverse impact on fertility and successful reproductive results. Smoking may further influence menstrual function and contraceptive options (*Seltzer, 2000*) [3].

This article will be discussing the potential risk of smoking on female health and reproductive function, how smoking can influence the female reproductive tract, and the effects of smoking on female fertility, pregnancy and embryo health.

Smoking and female reproductive health

Smoking can cause a reduction in ovarian function and fertility.

Extensive population-based research indicates that smoking is correlated with earlier menopause and an increased risk of osteoporosis, indicating that smoking damages the ovarian function and decreases the monthly possibility of conception in the natural cycle. Moreover, smoking also reduces the opportunities for pregnancy in assisted reproduction cycles (*Vanvoorhis et al., 1996*) [4]. Smoking influences various aspects of the female reproductive function and, consequently, natural female fertility by using several differential impacts on multiple targets, such as the ovary, oviduct, and uterus Figure 1 (*de Angelis et al., 2020*) [4].

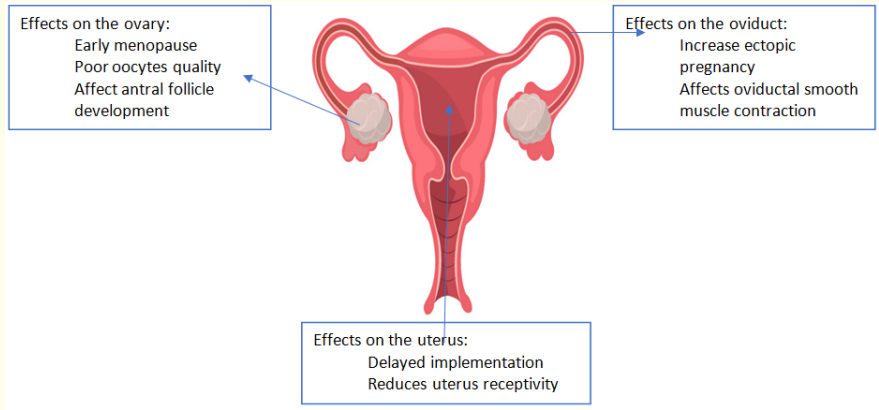

Figure 1: Overview summary of the main impact of smoking on the reproductive function in women (de Angelis et al., 2020).

Cigarette smoke comprises around 4000 compounds from a mixture of chemical classes known to be toxic, including polycyclic aromatic hydrocarbons (PAH) [e.g. benzo(a)pyrene (BaP), acenaphthene, phenanthrene, pyrene and chrysene], nitrosamines, heavy metals, alkaloids (nicotine), and aromatic amines. Those mixtures have various characteristics and different female reproductive system impacts (*Dechanet et al., 2010*) [5].

Oviduct damage by smoking

Cigarette smoke has a specific target on the oviduct, leading to ectopic pregnancy, which is defined by embryo retention inside the oviduct due to oviductal dysfunction. Researchers examined the mechanisms behind the correlation of smoking with ectopic pregnancy, focusing on oviductal smooth muscle contraction, epithelium ciliary beat frequency, oocyte adhesion to the oviductal ciliated epithelium, and oocyte pick-up percentage (*de Angelis et al., 2020)* [4]. In vivo animal models research has established that the oviduct is a target of nicotine, a principal constituent of cigarette smoke. When given to mice drinking water, nicotine (108 µmol/L) significantly reduced Na and K ion concentrations in the oviductal epithelium. Moreover, nicotine injected subcutaneously into rats showed a significant boost in lactate dehydrogenase levels in flushings of the oviduct in early pregnancy (*Talbot and Riveles, 2005*) [6].

Furthermore, in vitro study evaluated the effect of solutions comprising dissolved mainstream (MS) or sidestream (SS) cigarette smoke on ciliary beat frequencies (CBF) in hamster oviducts. All smoke solutions besides the SS particulate solution inhibited CBF. In some cases, the highest strength of MS and the whole SS smoke solution produced the most significant inhibition or entirely stopped ciliary beating. Both single-strength and 0.1-strength MS gas-phase solutions inhibited around 50% of ciliary beating. Inhibition was usually observed within 2-12 min of adding smoke solutions. In all cases, washout of smoke solution caused an increase in CBF (Knoll, Shaoulian, Magers and Talbot, 1995) [7] Figure 2.

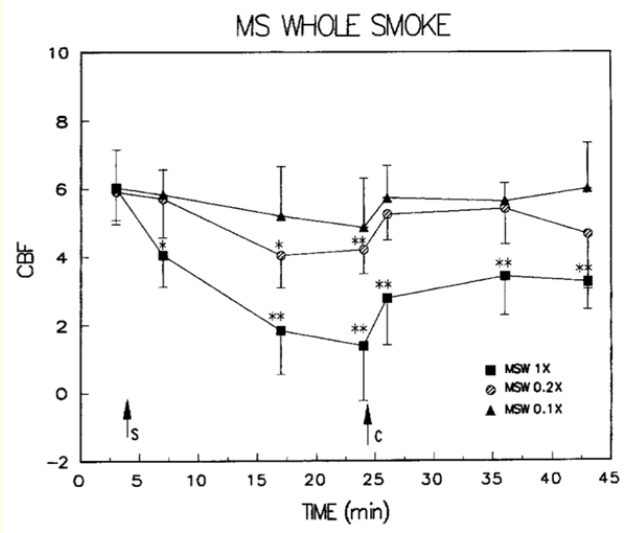

Figure 2: Effect of whole MS smoke solution on CBF, where CBF was determined after 3 min of incubation (C3). Arrow "S" indicated the time of smoke solution (MSW) introduction into the perfusion chamber, and CBF was determined after 2 (E2), 12 (E12), or 19 (E19) min of exposure. At arrow "C", EBSS- H substituted smoke solution in all groups, and CBF was determined after 2 (W2), 12 (W12), and 19 (W19) min of incubation(Knoll, Shaoulian, Magers and Talbot, 1995).

Uterus impairment by smoking

Smoking can affect the endometrium receptivity and trophoblast gene expression in the uterus. Uterine implantation requires a stable and tight interaction among a receptive endometrium and a competent blastocyst. A precisely and adequately timed remodelling of the endometrium is demanded before embryo arrival in the uterus. In addition, trophoblast gene expression can have a vital role in the endometrial lining interaction, and impaired trophoblast cannot succeed in implantation (*de Angelis et al., 2020*) [4].

Blastocyst implantation starts with the attachment of the blastocyst to the endometrium, followed by an endometrial invasion of the trophoblast cells. The endometrium helps implantation through a discrete period (cycle days 19-21) in the mid-secretory phase of the cycle, known as the "window of implantation." The endometrial glandular at the first stage changes into a secretory state, followed by numerous cytokines and growth factors production, facilitating implantation , such as CXCL12 (SDF1) and its receptor CXCR4 are applicable in numerous necessary processes in the implantation process and embryogenesis. (*Sahin Ersoy et al., 2017*) [8]. Sahin Ersoy et al., 2017 evaluate CXCL12 and FGF2 as endometrial receptivity markers both in vivo and in vitro and the effects of smoking on the endometrial receptivity. CXCL12 and FGF2 mRNA expression were significantly decreased in the smoking group, where CXCL12 was reduced to 58% of control levels and FGF2 to 6% Figure 3 (*Sahin Ersoy et al., 2017*) [8].

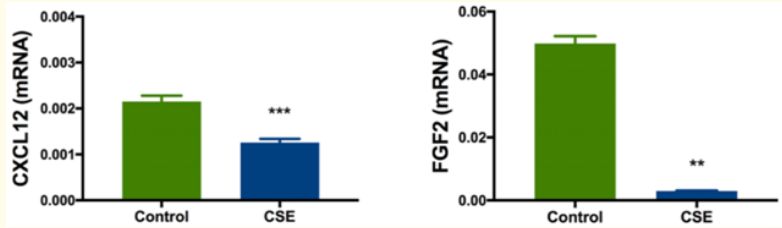

Figure 3: Effect of whole MS smoke solution on cigarette smoking extract (CSE) on endometrial CXCL12 and FGF2 expression

Moreover, they have looked into the expression of CXCL12 and FGF2 alteration after respiratory exposure to cigarette smoke in mice. It has been noted that FGF2 expression was lower in the cigarette smoke group. The intensity of FGF2 staining was reduced in the stroma to a far greater range than in the glands of the cigarette smoke group (*Sahin Ersoy et al., 2017*) [9].

Furthermore, another research studied the morphology of first-trimester chorionic villi from female smokers, as smoking-related changes in the chorionic villi size, fractional cellular, and volume of the intervillous space are seen. The fetal blood vessels inside the villus mesenchymal cores also exhibit signs of adaptive angiogenesis (*Genbacev et al., 2000)* [10] The study results showed that floating villi recorded focal defects, such as the absence of cytotrophoblast stem cells and an irregular thinning of the syncytium, in a female who smoked more than 20 cigarettes per day; Villi anchoring demonstrated a notable rise in the number of cytotrophoblast columns that couldn't enter the uterus or declined in the intervillous space (*Genbacev et al., 2000*) [10].

By smoking

Researches have shown that smokers have changes in menstrual cycle characteristics compared with non-smokers, which ultimately influence females' fertility. In addition, heavy smoking seems to be correlated with shorter and more variable cycle lengths and more changeable menses lengths (*Windham, 1999*) [10]. In Sakai and Ohashi, 2013 study, they investigated the associations between the quantity of smoking versus levels of desire for smoking, depression, and menstrual phase-associated symptoms amongst the menstrual, follicular, and luteal phases. They found that smoking craving was higher in the luteal phases than in the follicular phase without smoking cessation (*Sakai and Ohashi, 2013*) [11].

Furthermore, environmental tobacco smoke (ETS) can also lead to an increased risk of dysmenorrhea. The Chen et al., 2000 study reported that dysmenorrhea was 9.7% and 13.3% among nonexposed and exposed cycles, sequentially. Table 1 shows the number of menstrual cycles, ETS and dysmenorrhea rate, where it demonstrates that rate varied significantly by the four ETS exposure classes, with the lowest rate (9.7%) in the nonexposed group and the highest rate (16.9%) in the high ETS exposure group (Table 1)(*Chen et al., 2000*) [12].

Passive smoking (cigarettes/day)	Total cycles	Dysmenorrhea	
		No.	Percent
All cycles			
None	145	14	9.7
Low (< 0.8)	160	15	9.4
Middle (0.8–2.5)	160	22	13.8
High (> 2.6)	160	27	16.9
First cycle only			
None	33	2	6.1
Low (< 0.8)	44	5	11.4
Middle (0.8–2.7)	44	7	15.9
High (> 2.8)	44	13	29.6

Table 1: Dysmenorrhea rate in the 625 follow-up menstrual cycles by passive smoking status (Chen et al., 2000).

Moreover, they reposted a significant relation in a dose-response between ETS exposure and the risk of dysmenorrhea. It is reported that the rate of dysmenorrhea between those who did not have a history of dysmenorrhea at enrolment (*Chen et al., 2000*) [13]. It has been suggested that the biological mechanism by which cigarette smoke can induce dysmenorrhea can be that nicotine is a vasoconstrictor, which can produce a reduced endometrial blood flow, which is prevalent in women with dysmenorrhea, or that cigarette smoke might have an antiestrogenic effect (*Chen et al., 2000*) [13].

Pregnancy risk associated with smoking

Active and passive smoking is associated with decreased fertility. Different researches suggested that smoking women were more prone to have an abortion, with the total percentage of abortion increasing up to 33% (*Mund, Louwen, Klingelhoefer and Gerber, 2013*) [14]. Smoking can influence the biochemical environment of the placenta, which is an essential supply of hormones, pro-oxidant agents, and antioxidant enzymes. In a physiological pregnancy, this vital organ regulates lipid peroxidation. The maternal prenatal cigarette smoking disrupts the oxidant and antioxidant systems equilibrium, producing extra oxidative stress and increasing lipid peroxidation. Smoking throughout pregnancy develops free radical injury to the unborn fetus as well as to the mother (*Mund, Louwen, Klingelhoefer and Gerber, 2013*) [14].

Furthermore, smoking during pregnancy can be associated with health condition such as heart and cardiovascular diseases, pulmonary diseases, and Hypertension. For instance, evidence showed that maternal smoking throughout pregnancy raised the risk of congenital heart defects (CHD) in offspring, especially septal defects. Females who used to smoke through pregnancy were 44 % more prone to have offspring with a septal defect than females who did not smoke throughout pregnancy. Mechanism of smoking inducing CHDs can be that maternal smoking has antagonistic impacts on the developing fetus, such as hypoxia-induced by carbon monoxide, nicotine, and decrease in the supply of requisite nutrients to the embryonic tissues, in addition, polycyclic aromatic hydrocarbons, main cigarette smoke components, are assumed teratogens in laboratory animals and humans (*Lee and Lupo, 2012*) [15].

Pulmonary diseases, such as ischemia, can be induced by high oxidative stress generated by cigarette smoke which produces over-production of reactive oxygen species, overuse of antioxidants; consequently, it results in lipid peroxidation, chain cleavages in DNA, inactivation of specific proteins and changes in biological membranes (*Songül* Şahinli*, Marakoğlu and Kiyici, 2011)* [16]. Songül Şahinli, Marakoğlu and Kiyici, 2011 evaluated oxidative stress markers like malondialdehyde (MDA) and superoxide dismutase (SOD), vitamin A (Vit A), vitamin E (Vit E) and total antioxidant capacity (TAC) and a novel marker of ischemia – ischemia modified albumin (IMA) – to assess oxidant and antioxidant state in cord blood of smoker and non-smoker pregnant women (*Songül* Şahinli*, Marakoğlu and Kiyici, 2011*) [17].

The results showed an increase in the cord blood of the smoker women in MDA and IMA levels, SOD activities, Vit levels, and TAC (Mm Trolox) levels decreased, with a statistically significant difference. Increased IMA levels in the cord blood of smoker pregnant suggest that smoking during pregnancy causes fetal ischemia. Also, it was concluded that smoking cigarettes while gestation disrupted the balance within the oxidant and antioxidant systems and induced oxidative stress (*Songül* Şahinli*, Marakoğlu and Kiyici, 2011*) [16].

Impact of smoking on fertility, embryo implementation, and life birth rate (ART treatment)

Cigarette smoke components such as polycyclic aromatic hydrocarbons (PAHs) such as benzo(a)pyrene (BaP), nitrosamines, heavy metals, nicotine, aromatic amines and carbonyl compounds have several impacts on the female reproductive system. Nicotine shows to slow uterine decidualization, motility and migration of uterine endothelial cells in vitro (Heger, Sator, Walch and Pietrowski, 2018). Also, nicotine and BaP in cigarette smoke repress endometrial epithelial cell proliferation throughout a nitric oxide-mediated pathway in a dose and time-dependent manner. PAH derivatives modify cytochromes required in estrogen metabolism, pointing to a smoke-associated anti-estrogenic consequence. Cadmium (Cd) can decrease the size or complete loss of follicles, and damage cumulus expansion (*Heger, Sator, Walch and Pietrowski, 2018*) [16].

The impact of smoking on assisted reproduction technology has been evaluated in several types of research. An association between clinical pregnancy rate and smoking has been recorded, Lyngsø et al., 2020 reported a significant difference in the pregnancy rate of smoking and non-smoking female in all ART cycles, including IUI, IVF and ICSI (*Lee and Lupo, 2012*) [17] (Table 2).

Smoking Status	***IUI clinical pregnancy rate***	***IVF/ICSI clinical pregnancy rate***
Non-smoker	92.5%	93.3%
Smoker	7.5%	6.7%
Smoking Status	***IUI live birth rate***	***IVF/ICSI live birth rate***
Non-smoker	92.5%	93.3%
Smoker	7.5%	6.7%

Table 2: Clinical pregnancy rate and live birth rate association with smoker rand non-smoker female in different ART treatment types (Lee and Lupo, 2012).

Another study evaluated the impact of smoking on the embryo implantation process and early placentation. Results demonstrated that smoking causes endometrial maturation impairment, interrupt angiogenesis and trophoblastic invasion. In addition, cigarette components reduce uterine and endometrial vascularisation and myometrial relaxation. Thus leading to embryo implantation failure through IVF and a higher risk of miscarriage (*Dechanet et al., 2011*) [17]. Moreover, the high spontaneous abortion frequency of chromosomally normal conceptus recognised in a female who smokes proposes potential interference with placentation or implantation. Besides, nicotine therapy reduces deciduoma formation in the pseudopregnant, where the period most susceptible to nicotine repression of decidualisation appears to be during the first four days of pseudopregnancy (*Mattison, 1982*) [18].

Furthermore, embryo implantation can produce ectopic pregnancy (EP), defined as extra uterine pregnancy, resulting from embryo implantation outside the uterus, a significant element of human maternal morbidity and mortality. EP prevalences are estimated to be around 1.5%2% of all pregnancies in the Western world, and ~98% of EPs happens in the fallopian tube. Besides, females with tubal EP are at high risk for infertility and tubal EP. Smoking is considered an objective risk factor for the EP, as reported by several clinical studies, where some suggested a dose-dependent factor in the correlation between smoking and tubal EP in females (*Bouyer, 2003*) [18].

In an animal study using rats, the consequences of nicotine on preimplantation and embryonic development were evaluated. They injected a high dose of 7.5 mg nicotine twice daily from day 0 of pregnancy. The results recorded a delay in embryonic cleavage from the 2-cell stage to the 4-cell stage, in the embryonic entrance to the uterus and the ovum implantation (*Yoshinaga, Rice, Krenn and Pilot,*

1979) [19]. The four cells production delay leads to a delay to all the rest of the embryonic development stages. Nicotine treated rat induces ovum delay through the uterus entry, indicating that nicotine can cause a reduction in estrogen (E) secretion. Moreover, no blastocysts were developed in nicotine treated rats on day 8 of pregnancy (*Yoshinaga, Rice, Krenn and Pilot, 1979*) [19].

Nicotine causes implantation space crowding due to the direct impact on the uterus smooth muscles, which was noticed when a single dose of E2 was injected on the morning of day 4. (*Yoshinaga, Rice, Krenn and Pilot, 1979*) [19]. In addition, nicotine can alter the hormonal balance in the female reproductive tract, which can indirectly influence embryonic interface with the endocrine system of the mother. Furthermore, the implantation sites of nicotine treated rate differs from the rats who were injected with saline and E2 (Figure 4) (*Yoshinaga, Rice, Krenn and Pilot, 1979*) [19].

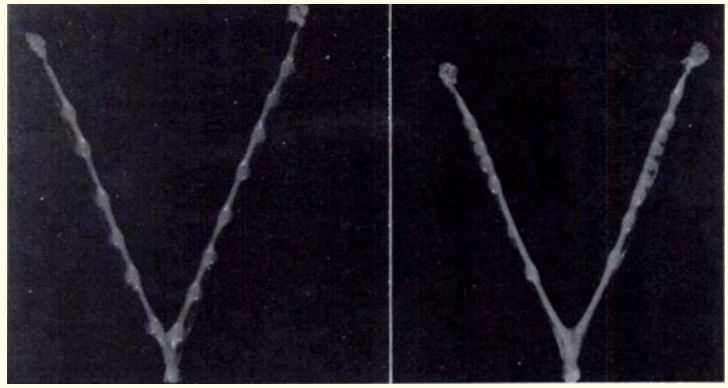

Figure 4: The disruption of implantation site in nicotine treated rate (right side), and rats who were injected with saline and E2 (left side). Nicotine treated rate showed crowded implantation sites toward the horn tubal, where the saline injected rats showed evenly disrupted implantation sits (Yoshinaga, Rice, Krenn and Pilot, 1979).

Conclusion

Most of the research suggests and recorded adverse natural fertility in current smokers and Offspring of the smoke-exposed women. Smoking has unfavourable effects on different aspects of the female reproductive tract, such as the Oviduct function and uterus. Moreover, smoking reduces clinical pregnancy rates and is associated with embryo implantation.

Acknowledgements

Objective of the Moroccan Society for Endometriosis and Reproductive Medicine (MSERM) Maintaining consistent and reliably high success rates is a monthly challenge for in IVF labs, the IRIFIV Fertility Center in Casablanca, Morocco, Department of Reproductive Medicine and Reproductive Biology and Embryology, advocacy of interdisciplinary Department of Reproductive Medicine and Reproductive Biology and Embryology study, encompassing the areas of research, collections and publishing Articles.

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