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Inhaling Risk: Smoking Impact on Male and Female Reproductive Health

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Smoking is still prevalent around the world, even though there is evidence that it has negative consequences for both general health and fertility. Concern over smoking-related illnesses and their detrimental impacts, particularly reproductive health, has long existed. Each year, about 8 million individuals die as a result of smoking. The majority of these deaths occur in nations with low and moderate incomes. Specifically, estimates suggest that cigarettes harbor nearly a thousand of harmful substances and toxins. Research demonstrates that smoking causes fragmentation of sperm DNA and lowers semen parameters in male smokers. Smoke's constituents can influence spermatogenesis and cause varying degrees of harm to germ cells. Female smokers face various problems, such as early loss of reproductive function, hormonal imbalance, mutagenesis of gametes, and earlier menopause. It has also been associated with spontaneous abortion and ectopic pregnancy. It has been demonstrated in both men and women that smoking can affect an offspring's normal development, result in a variety of inborn abnormalities, and affect their long-term health outcomes. It is, therefore, important to create awareness among expectant mothers and their families about the detrimental consequences of cigarette smoke. Reducing the fetus's exposure to hazardous substances during pregnancy is possible when the mother quits smoking. This review offers a thorough examination of current research that explores the relationship between smoking and fertility.

Keywords: cigarette smoke, epigenetics, hormonal imbalance, infertility, offspring health, pregnancy complications, semen quality, smoking cessation.

The global health problem of cigarette smoking persists. Cigarettes are the most popular way of consuming tobacco worldwide.[1] Apart from cigarettes, other major products used are bidis, cigars, pipe tobacco, cigarillos, roll-your-tobacco, and e-cigarettes.[1] Smokers typically inhale smoke into their mouths and lungs from the combustion of tobacco.[2] There is classification of tobacco smoke: mainstream, which comes from filter tips; side-stream, which comes from burning cigarettes; and side-stream, or second-hand smoke, also referred as passive smoking or ambient tobacco smoke.[3] Tobacco smoke contains thousands of chemicals that are known to be harmful, such as heavy metals, nitrosamines, polycyclic aromatic hydrocarbons, nicotine, aromatic amines, and a trace quantity of radioactive materials.[4] Humans primarily metabolize nicotine, the primary psychoactive

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component in tobacco, into cotinine, which they then further convert into trans-3'-hydroxy cotinine.[5] Figure 1 provides simplified representation of primary metabolic pathway of nicotine. Tobacco-related diseases cause over eight million deaths annually, with 1.2 million deaths attributed to smoke exposure.[1] The economic cost of tobacco usage worldwide totals 1,436 billion dollars, or 1.8% of the global GDP per year.[6] During the reproductive years, young males have a higher prevalence of smoking. In 2019, there were 120 countries where men aged 15 to 24 were more likely to smoke than women in 40 countries.[7] Male smokers frequently exhibit poor semen characteristics, such as volume, density, motility, and lower reproductive potential.[8,9] Smoking and the increased risk of erectile dysfunction are significantly correlated.[10] Numerous reviews have extensively covered the impact of the various components of smoke on the reproductive health of females.[9,11] An increased risk of infertility was linked to female smokers.[12] Other reproductive problems experienced by female smokers include early menopause, ectopic pregnancy, and abortion.[13] Pregnancy-related smoking, or second-hand smoke, can result in an underdeveloped fetus.[2] Low body weight, poor lung development, and a cleft lip and palate are among the birth abnormalities that affect newborns.[14] Further, figures 2 and 3 illustrate the summarized effects of smoking on male and female reproductive health.

METHODOLOGY

Study design and types of paper

The study adopted a narrative review as the study design. This review includes systematic reviews, meta-analyses, review articles, cross-sectional studies, cohort studies, experimental studies (In Vivo and In Vitro), public health reports from World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and National Center for Complementary and Integrative Health (NCCIH).

Literature search strategy

A literature search was conducted across Google Scholar, PubMed, and Tobacco in Australia to identify all relevant studies published between 2010 and 2024. To ensure that relevant studies were included, search results were refined using Boolean operators (AND, OR). The search involved ("cigarette smoke" OR "smoking exposure" OR "tobacco smoke") AND ("infertility" or "reproductive dysfunction"), AND ("male fertility" OR "semen quality" OR "sperm parameters"), AND ("hormonal imbalance" OR "endocrine disruption"), AND ("epigenetics" OR "gene expression changes" OR "DNA methylation"), AND ("adverse pregnancy outcomes" OR "pregnancy complications"), AND ("child health" OR "offspring health" OR "fetal development") AND ("smoking cessation" OR "nicotine withdrawal" OR "quit smoking").

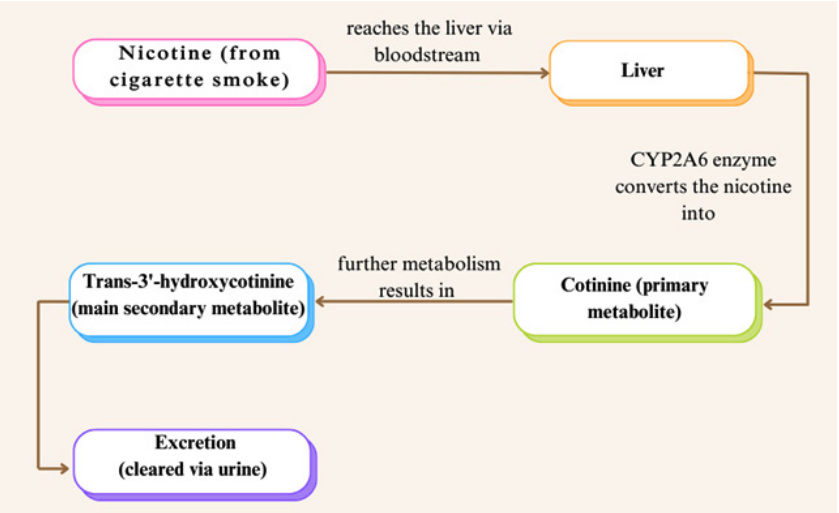

Fig. 1. Primary metabolic pathway of nicotine

Additionally, reference lists of selected papers were screened to find more relevant publications.

Inclusion Criteria

• Publications between 2010 and 2024
• Peer-reviewed articles
• Studies on both human and animal
• Relevant studies related to topic irrespective of their geographical focus.
• Publications in English language

Exclusion Criteria

• Blogs, editorials and news reports
• Non- English language publications

Factors Affecting Male Fertility

Smoking effect on semen quality

A meta-analysis found that smokers tend to have oligozoospermia and spermatozoa with morphological defects. However, the spermatozoa's pH or motility remained unaffected.[15] Likewise, other research revealed that smoking did not significantly affect sperm motility.[16,17] However, the results on sperm motility remain controversial, because several other articles reported a negative impact.[18,19] Compared to fertile, infertile nonsmoking subjects, infertile smokers who smoked a maximum of ten cigarettes per day showed adverse effects on sperm morphology, motility, and pH.[20] Among the 50 smokers, 20 cases of asthenozoospermia and seven cases of oligospermia were found, with an insignificant p-value of 0.9223.[21] In a semen analysis, smoking significantly affected the concentration of sperm and semen volume.[16,22,23] Antioxidant enzyme expression levels and heat-shock response-related protein expression levels can be used to determine

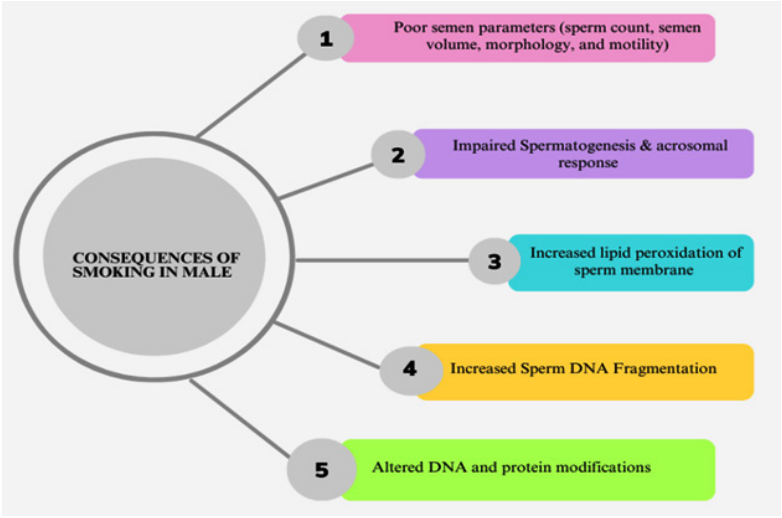

Fig. 2. Male associated reproductive damages

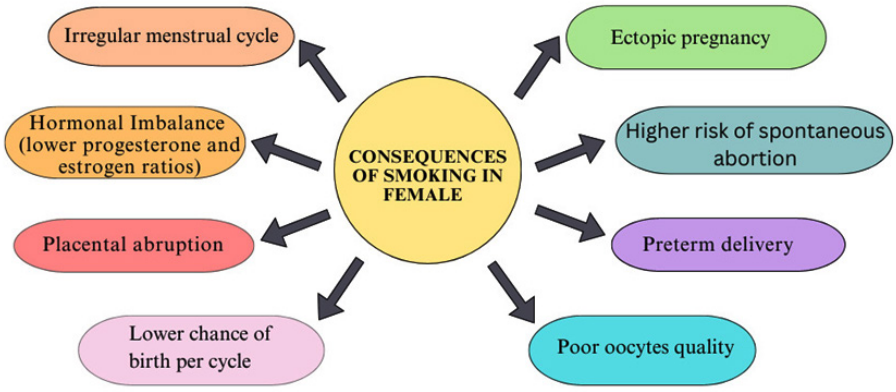

Fig. 3. Female associated reproductive damages

if stress response pathways are activated in sperm cells.[23] Henriques states that smoking is connected to higher amounts of p-HSP27 and HSP27 in sperm cells. The overall detrimental effect of stress response pathway activation in sperm cells on male fertility and semen quality measures is evident.[23]

Smoking effect on functional integrity of sperm

Exposure to condensate from cigarette smoke altered glucose transporter production and reduced 2-deoxyglucose absorption in male germ cells, potentially affecting sperm motility.[24] In vitro, excessive nicotine concentration causes spermatozoa to undergo premature acrosome responses and reduces their motility and viability.[25] Smoking changes the expression of the nicotinic receptor in human sperm, resulting in the presence of additional subunits (alpha 7) that are not present in non-smokers, allowing researchers to examine the damage smoking causes to sperm.[26] The proposed mechanism suggests that nicotine damages the blood-testis barrier in the testis by decreasing Nrf2 transcription, which further inactivates the downstream pathway, thereby contributing to ferroptosis.[27] In the study of 15 males, benzo-á-pyrene (BaP) was found to make sperm move more slowly and affect other functions of sperm, such as lipid peroxidation, chromatin compactness, and DNA fragmentation.[28] A further in vitro investigation has revealed a direct relationship between BaP dose, the rate of hyperactivation, and acrosome responses.[29] According to the study, cigarette smoking and functional polymorphisms of genes causes impaired spermatogenesis through inflammatory pathways.[30]

Smoking and Oxidative damage of sperm

Reactive oxygen species (ROS) determine the sperm's ability to fertilize, including acrosome response and capacitation.[31] Nevertheless, elevated ROS levels cause oxidative stress, which damages seminal characteristics (motility, viability, and sperm morphology) and the lipids in the sperm membrane.[31] Smokers who were infertile had low antioxidant levels in their seminal plasma, but significant quantities of cigarette toxicants in their semen.[32] Studies in vitro and in silico showed that cadmium has a clear effect on reactive oxygen species, which in turn affects sperm shape and results in male infertility.[32] Heavy smokers may exhibit reduced sperm resistance due to high ROS and reduced antioxidant activity. Malondialdehyde, a byproduct of lipid peroxidation, can also impair sperm motility and have a deleterious effect on the fertilization process.[33] When treated with BaP, rats had high concentrations of lipid peroxidation, hydrogen peroxide, and superoxide anions in their testis and epididymis.[34] Heavy smokers had lower glutathione levels, higher iron and lipid reactive oxygen species (ROS) levels, and higher ferroptosis levels in their seminal plasma, all of which affected semen quality.[35] In vitro exposure of BaP also increases the percentage of spermatozoa exhibiting intracellular oxidative signals and causes

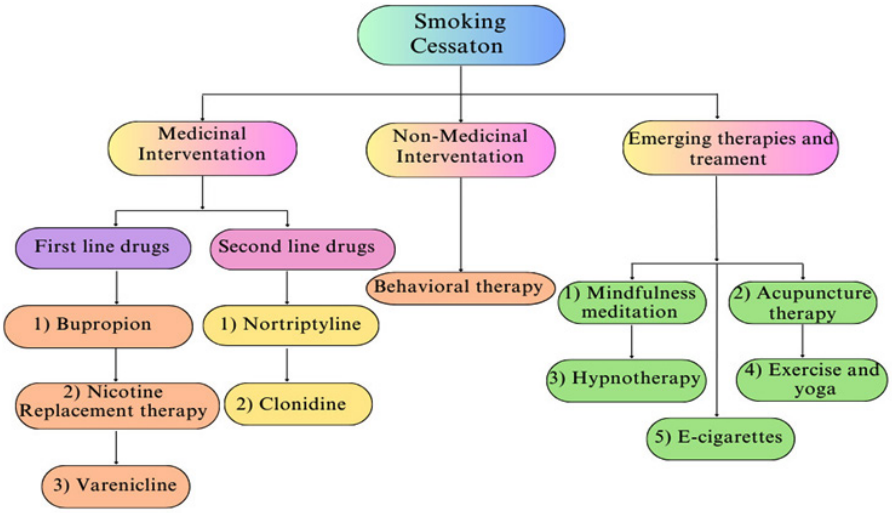

Fig. 4. Approaches to smoking cessation

sperm DNA fragmentation.[29] Using less than ten cigarettes per day had a significant alteration and increase in cotinine levels, capase-3 marker, and sperm fragmentation.[20] However, there was no evidence linking nicotine or polycyclic aromatic hydrocarbon exposure to the sperm DNA fragmentation index.[36]

Smoking induced genetic alterations

Tobacco smoke contains toxic substances, potentially causing male infertility and genetic mutations in spermatozoa, leading to altered reproductive parameters in both smokers and offspring.[37] Smoking exposure largely disrupts the methylation of DNA, which causes low semen quality and sperm count.[38] Smoking impacts the CHD5 gene's methylation pattern; smokers had poorer semen parameters and higher methylation levels than non-smokers.[39] These results function as biomarkers to assess semen quality and identify variables that increase the likelihood of infertility.[39] Cigarette smoking may change the protein profile of the testes. Furthermore, DNA methylation of phosphatidylethanolamine-binding protein 1 may have an impact on ERK activation and may harm mouse spermatogenesis.[40] Asthenozoospermia and oligozoospermia were linked to hypomethylation of H9-ICR, whereas teratozoospermia and asthenozoospermia were linked to hypermethylation of SNRPN-ICR.[41] Alteration in sperm protein profiles could potentially affect energy production pathways, as demonstrated by significant changes in citrate synthase and fructose-bisphosphate aldolase A proteins in mouse and human samples.[42] In vitro studies have shown that nicotine limits seminal fructose content, which in turn lowers tyrosine phosphorylation levels in capacitated spermatozoa.[43] Nicotine's hypermethylation of the Sord gene (encodes for sorbitol dehydrogenase) indicates a compromise in the secretory processes of the mouse epididymis, potentially impeding sperm maturation and capacitation. However, further research is required to support this theory.[43]

Paternal smoking effect on offspring health

Paternal smoking during early adolescence increases the progeny's asthma incidence.[44] Research strongly links adolescent exposure to parental smoke with an increased susceptibility to obesity and overweight.[45] Studies have also revealed that pre-conceptional paternal smoking raises the risk of many malignancies in children.[46] When a parent rat is exposed to nicotine, the progeny exhibits persistent neurobehavioral changes.[47] The altered imprinted gene methylation levels brought about by paternal BaP exposure may indicate sensitivity to environmental toxicants. The F2 generation of mice showed less pronounced changes, while the F1-2 generations showed similar changes, suggesting potential transgenerational impacts.[48] Research has revealed DNA methylation signals in male smokers' cord blood and offspring blood.[49] Paternal smoking, both before conception and during adolescence, contributed to DNA methylation at specific locations in the offspring, which were hypermethylated and competent for gene silencing in the promoter region.[50] The outcomes of their children, such as weight, BMI, asthma, and wheezing, are associated with many of these hypermethylated sites.[50]

Factors Affecting female Fertility

Smoking, hormones and menstruation

The study found that higher smoking rates were connected with lower progesterone and estradiol (PE) ratios.[51] They also came to the conclusion that the progesterone and estradiol ratios were the most accurate indicators of smoking habits when compared to other hormonal measurements.[51] Researchers examined possible variations in resting-state functional connectivity (rsFC) in natural cycling women who rely on cigarettes at different stages of their menstrual cycle.[52] When a person is at rest, meaning they are not engaged in any particular task or stimulus, rsFC measures the temporal correlation between various brain areas.[52] Women who were dependent on cigarettes had weaker resting-state functional connectivity (rsFC) during the follicular phase (FP) of their periods.[52] This could mean that they have less cognitive control over their smoking habits, which could make them more likely to keep smoking and relapse.[52] According to a meta-analysis, a substantial connection exists between dysmenorrhea and smoking.[53] Another study found that smokers have a 1.45-fold higher chance of dysmenorrhea than non-smokers.[54] Early smoking initiation (around 19 years old) and a high pack-year history (>5 years) also had a close relationship with premature menopause in postmenopausal women.[54]

Smoking effect on uterus, fallopian tube, and ovary

Cigarette smoke inhibits the development of endometrial cells via a process mediated by nitric oxide.[55] Kida et al[56] found that cigarette smoke causes potential cellular stress and inflammation in the endometrium. It has been associated with changes in morphology and function of cells that may affect the development of an ectopic pregnancy.[57] These include alteration in the turnover of tubal epithelial cells. When pregnant women were exposed to low doses of nicotine (1 mg/kg/d), the placenta and amniotic fluid colonization decreased, and inflammation inside the uterus increased.[58] Mid-dose nicotine exposure (3 mg/kg/d) decreased fetal inflammation in a rat model.[58] Cigarette smoke exposure in rats showed increased apoptosis and DNA damage, which reduced follicular cells of ovaries in female offspring.[59] It was discovered that the effect of smoke exposure on ovarian follicles growth persisted even after the exposure was stopped.[60] There were fewer follicles available for ovulation in ovaries of mice that had been exposed to cigarette smoke because of higher levels of oxidative stress, the death of antral follicle oocytes, and a loss of primordial follicles.[61] According to Mai et al[62], mice exposed to cigarette smoke produced smaller, lower-quality oocytes.

Smoking and pregnancy associated issues

Aliyu et al[63] showed a positive relationship between placenta-associated symptoms (PAS) and tobacco smoking during pregnancy. Tikkanen et al[64] found female smokers who experienced placental abruption had greater levels of cotinine. The study also indicates that smoking can lead to the breakdown of the placenta's double-strand DNA.[65] It was found that smokers' placentas had a lot of phosphorylated H2AX-positive cells in the syncytial knot nuclei and villous syncytiotrophoblast. These cells damaged DNA, making the placenta less stable.[65] Former smokers showed less DNA damage than nonsmokers, even those who had stopped smoking just over 4 weeks before giving birth.[65] The incidence of spontaneous abortion was high among pregnant women who smoked or were exposed to environmental smoke.[66] Smoking led to a two-fold decrease in norepinephrine levels in the umbilical cord, which may contribute to pregnancy-related issues such as cesarean section, postpartum hemorrhage, and breathing difficulties.[67] The research found no link between smoking and gestational diabetes mellitus risk (GDM), but differences in oral glucose test tolerance and HbA1c were observed among women with and without GDM.[68] Pregnant women who smoked and had gestational diabetes mellitus were significantly more likely to have a cesarean delivery.[69] The presence of lead, cadmium, and cotinine in tobacco smoke significantly impacts fetal development and umbilical cord morphology, causing severe intrauterine growth restriction.[70] While stopping smoking reduces the chance of stillbirth, it also raises the risk of hypertensive disorder of pregnancy (HDP) and excessive weight gain.[71]

Smoking induced preterm delivery

Smoking was associated with gestation of less than 28 weeks in moderate smokers.[72] For smokers, taking an omega-3 supplement may help prevent low birth weight and subsequent spontaneous premature deliveries.[73] Low production of hydroxyprostaglandin dehydrogenase, an enzyme that regulates prostaglandin metabolism, has been linked to maternal smoking. This could result in elevated prostaglandin levels and premature labor.[74] Preterm birth (PTB) and maternal smoking have a dose-response relationship.[75] Pregnancy-related morbidity increases with the amount and duration of a woman's smoking.[75] The study found that reducing smoking during the early stage of pregnancy, even one or two cigarettes per day, increases the risk of premature delivery.[76] Based on available data, there is no suggested smoking threshold or safe trimester for pregnant women. The majority of women who give birth to preterm infants have male babies, suggesting that fetal gender also contributes to preterm birth.[77] Women between the ages of 25 and 29 who are white, non-Hispanic, first-time mothers, and who smoke one to nine cigarettes a day are more inclined to give birth preterm. Quitting smoking reduces the risk to 7.8 percent at the beginning of pregnancy and 9.0 percent in the subsequent trimester.[78] In rural Chinese couples where only the women smoked, the adjusted hazard ratio for preterm birth was 1.04; for only men, it was 1.08; in both cases, it was 1.11.[79] Among 21,540 women, 34% had smoked during their initial pregnancy and had quit; this group saw a 26% drop in the incidence of premature delivery in subsequent pregnancies.[81] A study

investigated the impact of maternal cigarette use during pregnancy on volumetric brain MRI findings in 13-year-old very preterm adolescents.[80] Gray matter volume in certain brain regions was smaller in exposed groups.[81] There were no appreciable differences in absolute volumes, curvature, or cortical thickness when compared to unexposed groups.[81]

Maternal smoking and offspring health

As mentioned in the introduction, female smoking during pregnancy adds to the overall health burden of diseases affecting infants. It is also found that newborns exposed to tobacco smoke prenatally are associated with hypoactivity in inhibitory regions of the brain and decreased brain volume in cortical, white matter, or subcortical sections of the brain. These may result in a decreased impulse control and disruptive behavior in the offspring.[82] Tobacco smoke increases blood levels of carbon monoxide in arteries, which inhibits the transport of oxygen to the fetus, results in fetal hypoxia, and causes anemia, low birth weight, and irregular placental flow.[83] By means of epigenetic mechanisms, tobacco use during pregnancy may result in fetal growth restriction.[84] Smoking also raises homocysteine levels and lowers folic acid levels in the umbilical cord, which may make the fetus more vulnerable to vascular disease.[85] Emerging research suggests that maternal exposure to tobacco smoke may result in long-term metabolic abnormalities in offspring, increasing their risk of chronic diseases.[86] The research suggests that a biological mechanism associated with mother smoking may influence the likelihood of conduct disorder symptoms in infants.[87] Because of altered placental NR3C1 promoter methylation, newborns had a reduced baseline and level of reactive cortisol in the month following delivery.[88]

Placental DNA methylation at specific loci may mediate the connection between reduced birth weight and maternal smoking.[89] Prenatal nicotine exposure caused low steroidogenesis in the testis and heritability in male progeny rats.[90] The most well-researched and probable mechanism for smoking-induced epigenetic modifications is altered gene expression due to changes in DNA methylation, which can occur either in the placenta or fetus. Other mechanisms of smoking-induced epigenetic changes include RNA-mediated gene regulation and histone modification.[91-92] The recent study found that maternal smoking changes the levels of sex steroids, which results in low levels of estradiol and progesterone in the cord blood serum.[93] This is due to the interaction between cadmium and lead present in smoke with iron in the mother's placenta and fetus. These sex steroid levels in the umbilical cord may serve as predictor of future disease burden.[93]

Smoking cessation

Medicinal and non-medical interventions

First- and second-line medications are useful for helping people quit smoking.[94] The three first-line medications are bupropion, varenicline and nicotine replacement therapies (NRT), while clonidine and nortriptyline are included in second-line medications.[94] Available nicotine replacement therapies include chewing gum, transdermal patches, lozenges, and nasal sprays.[95] Nicotine replacement therapy (NRT) does not fully alleviate withdrawal symptoms due to the lack of rapid nicotine delivery in available devices.[96]

It is safe and more beneficial, according to strong evidence, to combine a faster-acting NRT form, like a lozenge, with a longer-acting NRT form, like a patch.[97] Non-medicinal interventions consist of counseling and behavioral therapy.[95] Providing behavioral assistance over the phone or in person increases the likelihood of successfully quitting smoking. Research estimates that behavioral support enhances the effectiveness of smoking cessation.[98] An evaluation of combination medications indicates that behavioral therapy and varenicline complement each other more effectively than other pharmaceutical treatments.[99] Figure 4 provides a concise summary of smoking cessation strategies.

Emerging therapies and treatment

The most successful strategy to quit smoking is to combine behavioral support with first-line medications and follow-up.[100] In addition to evidence-based treatment methods, many individuals attempting to stop smoking are interested in novel and alternative therapies like mindfulness meditation, acupuncture, exercise, or hypnotherapy.[101]

Mindfulness meditation: According to Westbrook et al[102], self-reported data from participants indicated that mindful attention decreased cravings for cigarettes. Furthermore, it was found to decrease neuronal activity in a craving-related brain region during imaging studies. Reducing the prevalence of cigarette

smoking may benefit greatly from mindfulness training.[103]

Acupuncture therapy: When it comes to aiding smokers in quitting, auricular acupressure has been proven to be more successful than sham aurical acupressure., although there was no apparent distinction in the rates of short- or long-term cessation. Further research is necessary.[105] The varying methodologies employed in meta-analyses regarding the effectiveness of acupuncture in helping smokers quit have likely contributed to their contradictory findings.[106]

Hypnotherapy: The study found that both hypnotherapy (HT) and cognitive-behavioral therapy (CBT) showed similar success rates in helping people quit smoking, with CBT having a higher rate of 21.2%.[107]

Exercise and yoga: Short-term smoking cessation can be facilitated by aerobic exercise, whether or not natural replacement therapy is used.[108] Researchers who compared the impacts of yoga and aerobic exercise discovered that the former reduced cravings for cigarettes while the latter did not.[109]

E-cigarettes: According to a summary of studies, there is low to very low certainty regarding e-cigarettes' risks and low to moderate certainty regarding their benefits, which could help increase the smoking cessation rate. To comprehend the long-term benefits and potential drawbacks, more research is required.[110]

CONCLUSION

Smoking clearly and significantly harms both men's and women's reproductive systems. Numerous studies have explained the various ways that tobacco smoking negatively affects fertility and reproductive outcomes. Tobacco smoke exposure in adult males can cause carcinogenic and mutagenic effects, damaging sperm quality, altering genetic integrity, and causing long-lasting epigenetic changes that impact subsequent generations. Cigarette smoking in women leads to reproductive issues such as irregular menstruation, increased miscarriage, pregnancy-related problems, subfertility, and premature birth, affecting egg quality, implantation, and newborn weight. Quitting smoking has several benefits for reproductive health. Studies have verified the significance of quitting smoking for those who are pregnant or planning to conceive. Promoting a smoke-free lifestyle is essential for both individual health and the health of next generations. In response to the pervasive trend of smoking-related reproductive dangers, we require public fitness initiatives, support systems, effective tobacco control legislation, and awareness campaigns. To fully understand these intricate negative effects and, more importantly, to improve our current data on longer-term repercussions for both men and women, more extensive study to understand mechanisms and find potential remedies is required. Essentially, coordinated efforts in education, assistance in quitting, and further medical research can help to mitigate the severe impacts of smoking on reproductive health indices.

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