Smoking in pregnancy: pathophysiology of harm and current evidence for monitoring and cessation

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Review

Smoking in pregnancy: pathophysiology of harm and current evidence for monitoring and cessation

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Key content

- Smoking in pregnancy is a risk factor for miscarriage, stillbirth, placental abruption, preterm birth, low birthweight and neonatal morbidity and mortality.
- The adverse effects of cigarette smoke are primarily driven by carbon monoxide, tar and nicotine.
- Psychosocial interventions are effective in helping women to quit smoking during pregnancy.
- There is weak evidence that nicotine replacement therapy (NRT) with behavioural support can improve cessation rates in pregnancy.
- Electronic cigarettes are more popular among smokers, but evidence of their safety and effectiveness in pregnancy are lacking.

Learning objectives

- To understand the pathophysiology of harm from cigarette smoking.
- To describe the role of exhaled carbon monoxide testing among pregnant women.
- To review the evidence on the safety and use of NRT and electronic cigarettes as methods of cessation.

Keywords: carbon monoxide monitoring / electronic cigarettes / nicotine replacement therapy / pregnancy / smoking

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Introduction

Cigarette smoking in pregnancy has an adverse impact on maternal and fetal health; smoking cessation is advocated to eliminate this risk factor and improve pregnancy outcome. Smoking has long been associated with increased rates of miscarriage, stillbirth, placental abruption, preterm birth and low birthweight.[1] Emerging evidence suggests that in utero exposure to smoking has long-term neonatal adverse outcomes such as impaired neurological development, endocrine dysfunction and oncogenesis. These continue to manifest into early and late childhood with a higher incidence of sudden infant death syndrome, attention deficit hyperactivity disorder, poor academic performance in school and future smoking in adulthood.[2–4]

In England, the prevalence of smoking at the time of delivery has steadily declined from 15.1% in 2006/07 to 10.4% in the first quarter of 2018, with a target of 6% or less by 2022.[5] Smoking strongly correlates with lower socio-economic status and is a major cause of the health and life expectancy inequalities encountered by women from deprived backgrounds. Pregnant smokers are more likely to be younger, be unemployed, have low educational attainment, have a lack of social support and have increased incidence of mental illness.[6] Women experiencing depression are four times more likely to smoke than other women, and this presents a challenge to smoking cessation services.[7]

The pathophysiology of harm from smoking

Cigarette smoke is a complex, heterogeneous mixture of more than 4000 compounds, including nicotine, carbon monoxide, carcinogens and heavy metals. In pregnancy, cigarette smoke negatively impacts the fetus globally – restricting the supply of oxygen and nutrients, altering its growth and affecting the development of organs such as the brain and lungs.[8]

Carbon monoxide

Carbon monoxide is a colourless and odourless gas produced by the combustion of tobacco. The quantity of carbon monoxide entering the system is influenced by the type of tobacco product smoked and the depth and frequency of

inhalation.[9] Tobacco smoke is approximately 45 000 parts per million (ppm) carbon monoxide, a concentration of 4.5% by volume. Absorbed carbon monoxide rapidly binds to haemoglobin, forming carboxyhaemoglobin, where each iron atom binds a molecule of carbon monoxide at the expense of a molecule of oxygen. A smoker is exposed to 400–500 ppm carbon monoxide over the time taken to smoke a cigarette, producing a baseline carboxyhaemoglobin of 4% (range 3–8%). This is in contrast with non-smokers, who have an average 1% carboxyhaemoglobin in their blood. Heavy smokers may have a carboxyhaemoglobin level of up to 15%.[9] As the concentration of carbon monoxide increases, there is a left shift of the oxygen–haemoglobin dissociation curve, reflecting the greater affinity of haemoglobin for carbon monoxide. This left shift impairs oxygen delivery to the myometrium and fetoplacental unit.[10] Chronic exposure to carbon monoxide through sources other than smoking – for example air pollution – is also associated with fetal growth restriction and preterm birth.[11,12]

Tar

Tar is the combusted particulate matter contained in cigarette smoke which forms a residue on the skin, mucous membranes and lungs of smokers. Tar damages the respiratory tract by mechanical and biochemical mechanisms. It contains the majority of carcinogenic compounds, such as polycyclic aromatic hydrocarbons, aromatic amines and nitrosamines. These compounds interfere with biochemical pathways and macromolecules, leading to a pro-inflammatory state with widespread oxidative damage.[13] The fetotoxic and teratogenic nature of these compounds has been established in animal studies,[8] but little research has been performed on their effects on the human fetus. The heavy metal cadmium, contained in cigarette smoke, is known to accumulate in the placenta and has been associated with fetal growth restriction.[14] The effect of other compounds and the many additives to cigarettes remains unclear.

Nicotine

Nicotine is an addictive alkaloid derived from tobacco and is a potent stimulant of the parasympathetic nervous system. It readily crosses the placenta and has a direct effect on the fetus and the placental vasculature, in addition to its effect on the maternal circulation.[15] Nicotine has been classed as a neuro-teratogen and is known to bind nicotinic acetylcholine receptors in the fetal brain, disrupting neurotransmitter function and altering normal brain development.[16] These developmental insults are thought to lead to the cognitive, emotional and behavioural problems seen in children of smokers, such as attention deficit hyperactivity disorder and learning disabilities.[17] Additionally, exposure to nicotine during fetal development is thought to increase the later likelihood of addictive behaviours, including smoking itself.[8]

Carbon monoxide monitoring in pregnancy

The National Institute for Health and Care Excellence[18] recommends that all pregnant women be asked about their smoking status at their maternity booking visit and at regular intervals during their pregnancy and puerperium. It also recommends biochemical screening of all pregnant women via exhaled carbon monoxide. This identifies non-disclosing smokers who can be referred on an 'opt-out' basis for smoking cessation support. Referring all women with a positive exhaled carbon monoxide reading results in larger numbers accessing help and support, although it does not necessarily result in higher numbers of biochemically verified quitters.[19–21]

Currently in the UK, a midwife or health support worker administers the exhaled carbon monoxide test to women presenting for their booking appointment. The test is explained in advance and the result interpreted by the midwife or health support worker and explained to the patient. All current smokers, occasional smokers and smokers who have quit in the previous 2 weeks are referred to their local NHS Stop Smoking Services on an opt-out basis. Women with high exhaled carbon monoxide levels (>4 ppm) who deny smoking are referred to NHS Stop Smoking Services for advice on second-hand smoking and smoke-free homes.[18] Rarer causes of a high carbon monoxide reading in the absence of smoking are exposure to carbon monoxide through faulty gas appliances, air pollution and lactose intolerance.

Non-disclosure of smoking status during pregnancy prevents women from accessing appropriate smoking cessation support and can lead to significant underestimation of smoking prevalence. This non-disclosure can be a result of recall bias, whereby the woman is unable to accurately recall exposure, or of unwillingness to disclose smoking status because of the negative social perception of smoking in pregnancy.[22,23]

A high carbon monoxide reading may help to motivate some women to stop smoking as a form of feedback intervention, with the subsequent referral to NHS Stop Smoking Services acting as a 'final push' for cessation. In a similar manner, a normal carbon monoxide reading is an encouraging finding appreciated by women undergoing a cessation attempt.[21]

Before the introduction of carbon monoxide screening, concerns had been expressed about the impact of discussing smoking status on the relationship between the midwife and the woman. Some suggested midwives prioritised a good relationship with the patient over provision of smoking cessation advice.[24] In the setting of a booking visit, there were

concerns about having sufficient time and resources for carbon monoxide screening and smoking cessation advice, especially when dealing with other issues such as alcohol use and domestic violence.[24,25] However, since the introduction of carbon monoxide screening, midwives report favourable views towards providing smoking cessation advice and see it as integral to their role, with high motivation levels expressed.[26] Health support workers have found universal carbon monoxide screening easy to implement and well received by women, with screening now seen as part of the daily routine.[21]

Smoking cessation during pregnancy

The cessation rate in pregnancy is much higher than that of the general population, with between 27% and 47% of smokers quitting within the first trimester.[27] Many women report quitting spontaneously when pregnancy is confirmed, often within the first few days.[28] Factors associated with spontaneous cessation include living in a household with a non-smoking partner, smoking fewer cigarettes per day, a previously successful quit attempt and more awareness of the negative consequences of smoking.[6,29,30] Women who quit in early pregnancy are more likely to maintain cessation than are those who quit later.[31]

Prospective longitudinal data suggest there is little change in smoking status from the second trimester onwards, and in fact intention to quit falls as the pregnancy progresses and in the postpartum period.[29] Nonetheless, women may be planning to quit at any time during pregnancy and therefore smoking status and motivation to quit should be re-addressed at each visit.

Postpartum relapse

Unfortunately, there is a high rate of relapse, with many women smoking again before the end of pregnancy and in the early postnatal period.[29,31,32] Less than a third of spontaneous quitters in pregnancy remain abstinent 1 year postpartum.[33] Women who are single, who are parous, who have a partner or household member who smokes, those with high depression scores, and those with a heavier smoking habit prepregnancy are most likely to relapse in the postpartum period.[32–34] Breastfeeding mothers are less likely to relapse.[32] Behavioural interventions are generally unsuccessful in preventing long-term postpartum relapse. Incentive-based therapies, while effective in the short term, are associated with relapse once the incentive is withdrawn.[35] In non-pregnant women, bupropion and nicotine replacement therapy (NRT) individually have shown promising results in preventing relapse after an initial period of abstinence.[36] However, there are no clinical trials using pharmacological agents specifically to prevent postpartum relapse, and such treatments should be used with caution in breastfeeding mothers because of a lack of safety data.[37]

Psychosocial interventions

Psychosocial interventions such as counselling, feedback and provision of incentives are effective at achieving cessation in pregnancy. Moreover, psychosocial interventions reduce the incidence of low birthweight and neonatal intensive care unit admission.[6] Such interventions are seen as positive by most women, with evidence of an improved sense of wellbeing without negative physical or psychological consequences.

All healthcare professionals should be comfortable in asking about smoking status and providing basic smoking cessation advice to their patients. Successful interventions for smoking cessation begin with the identification of smokers, giving clear advice to quit, and provision of assistance for a cessation attempt. A useful strategy is to use the five As approach to smoking cessation interventions (Box 1).[38]

Meta-analysis of counselling interventions has shown most to be effective in achieving cessation in late pregnancy, particularly when used in conjunction with other therapies, or when tailored to the individual woman. However, it is unclear which type of counselling (cognitive behavioural therapy, motivational interviewing, psychotherapy or other) is most effective.

Feedback interventions consist of providing women with individual measurements of tobacco use (such as salivary or urinary cotinine or exhaled carbon monoxide) and information on fetal status in relation to smoking. Feedback has been shown to be effective when provided with other interventions such as counselling.[6]

Financial incentives have been shown to improve smoking cessation rates during pregnancy, but their use is controversial.[39] Health education alone, social support from

Box 1. The five As for brief smoking cessation interventions[38]

Ask: Identify and document tobacco use status for every woman at every visit. Ask about previous quit attempts.
Advise: In a clear, strong, and personalised manner, urge every smoker to quit.
Assess: Determine willingness to quit. Asking a readiness score can be a useful way of assessing readiness to quit, e.g. 'on a scale of 1 to 10 how ready are you to quit smoking?'.
Assist: For the woman willing to make a quit attempt, refer to in-house smoking cessation services or a local NHS Stop Smoking Service. Discuss methods of cessation including counselling and the use of nicotine replacement therapy.
Arrange: Schedule follow-up contact, usually a week after the quit date. If the woman has quit, congratulate them and discuss any obstacles and how to overcome them. For those still smoking, revisit the five As and encourage to set a new quit date.

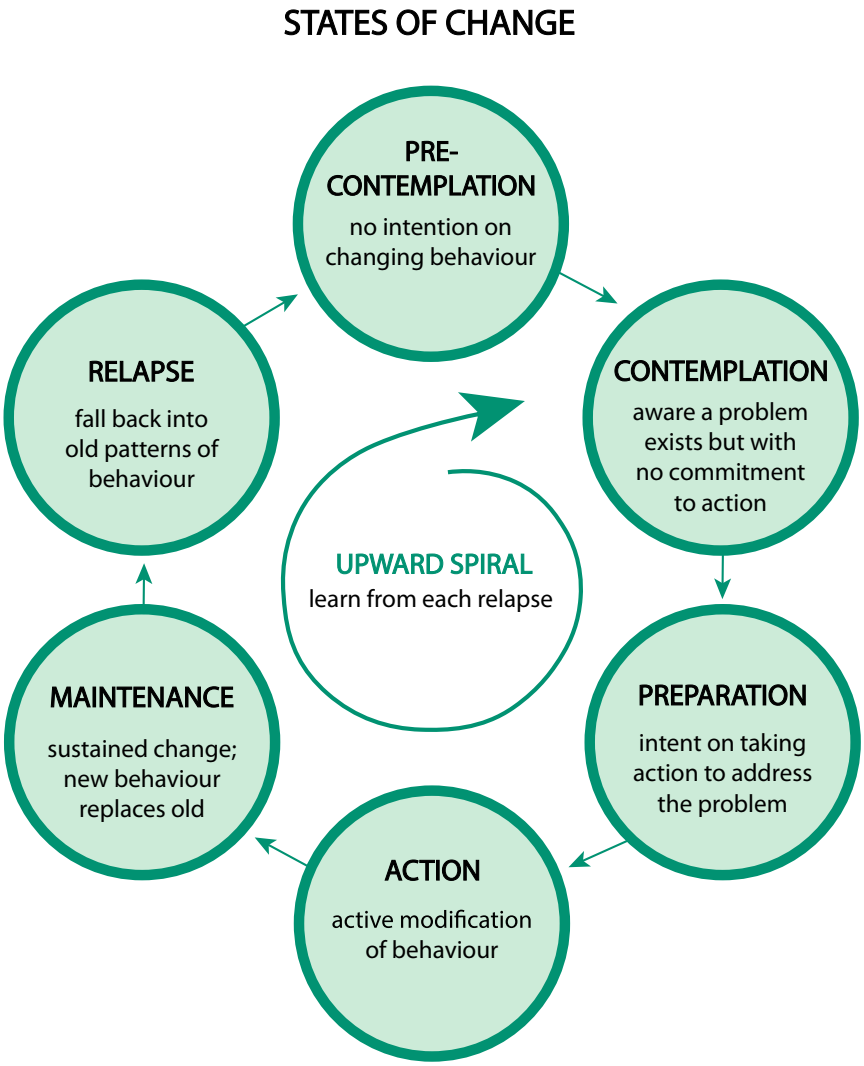

Figure 1. The Transtheoretical Model of Intentional Behaviour Change. Adapted from Pacheco.[40]

a family member or peer, or exercise interventions are of less certain benefit as a means of cessation.[6]

It is important to recognise that some women are not prepared to stop smoking in pregnancy. The Transtheoretical Model of Intentional Behaviour Change can provide a useful starting point for the categorisation of the pregnant smoker (Figure 1).[40,41]

Nicotine replacement therapy

NRT seeks to replace cigarette smoking, with its harmful tar, carbon monoxide and other compounds, with clean nicotine delivered in a safe manner. The dose of NRT is gradually reduced until a user can stop the therapy without excessive psychological or physiological withdrawal symptoms.[18] Nicotine undergoes first pass metabolism in the liver, limiting its oral bioavailability. NRT is therefore delivered via mucosal or transdermal routes. Available forms of NRT include transdermal patches, lozenges, chewing gum, oral sprays, microtabs and inhalers.[42] Transdermal patches deliver nicotine slowly over the course of a day, in contrast with the other products that are faster acting and aim to counter acute cravings. Accelerated metabolism of nicotine in pregnancy results in lower serum concentrations of nicotine and its metabolite cotinine, making sufficient dosage of NRT an issue in a pregnant population.[43] Additionally, use of NRT does not lead to the high serum levels of nicotine rapidly achieved by smokers.

The use of NRT is a proven method of smoking cessation in non-pregnant adults, with an increase of 50–60% in

cessation rate, regardless of the setting.[42] The evidence suggests that NRT use in pregnancy does not influence pregnancy outcomes such as birthweight or preterm labour. Occasional mild adverse effects are encountered with patches, such as skin irritation and headaches, but in general NRT is well tolerated. Clinical trials have not detected an increase in serious adverse events either during pregnancy or in the neonatal period. Two-year-old children born to users of NRT were more likely to survive without a developmental impairment than were those born to women who smoked and used placebo NRT.[42,44,45] Therefore, NRT use in pregnancy may improve developmental outcomes for the offspring of smokers.

Most trials of NRT use in pregnancy have used it as an adjunct to behavioural support, with fewer comparing it alone with placebo. There is weak evidence that NRT with behavioural support can improve cessation rates in pregnancy.[43] A 2018 Cochrane meta-analysis on NRT found a significantly higher rate of cessation at the end of pregnancy, but with no effect on postpartum cessation.[42] The National Institute for Health and Care Excellence[18] and the Royal College of Obstetricians and Gynaecologists recommend the use of NRT in pregnancy as an adjunct to a smoking cessation attempt in those who have not quit with a psychosocial intervention alone.

Electronic cigarettes

Electronic cigarettes use a battery-powered element to heat a solution of water, propylene glycol or glycerine, nicotine and flavourings. This solution becomes aerosolised and is inhaled by the user. Electronic cigarette use results in a rapid rise of serum nicotine levels, reaching higher values than those achieved by NRT. The use of electronic cigarettes mimics the behavioural and psychosocial aspects of conventional cigarette smoking, without the associated harm. Electronic cigarettes do not contain tobacco and do not combust their contents. They therefore do not contain the carbon monoxide and tar found in cigarette smoke.[46] Electronic cigarettes have been regulated by UK and European Union law since 2016, with the aim of standardising their form, content and marketing. New-generation electronic cigarettes emit minimal carcinogens, such as aldehydes, when tested under conditions that mimic real use.[47]. Other purported negative health effects appear to be minimal, and in studies to date, they have not been associated with serious adverse events in short-term to medium-term follow-up.[8] It is estimated that electronic cigarettes have a theoretical harm reduction of 95% compared with smoking cigarettes, however, this estimate is not based on real-world use and the true risks or benefits of electronic cigarette use are still unknown.[9] Additionally, longitudinal data on safety and the effects on pulmonary and cardiovascular health are lacking.

Approximately 5.5% of the adult population in England use electronic cigarettes, with their use increasing year on year. The decline in the prevalence of cigarette smoking has been mirrored with a rise in electronic cigarette use among adults. There are currently approximately 2.6 million electronic cigarette users in Great Britain, compared with 9 million tobacco smokers. The most frequently cited reasons for using electronic cigarettes are health, wanting to cut down, and wanting to quit smoking. The majority of electronic cigarette users consider them safer than cigarettes.[46] Concerns have been raised that electronic cigarettes may re-normalise smoking or perhaps lead to non-smokers taking up smoking through a 'gateway drug' effect. However, almost all electronic cigarette users are current or ex-smokers, with 'never-smoker' users of electronic cigarettes accounting for only 0.2% of total users. It is noteworthy that electronic cigarettes are the most common smoking cessation aid used in the UK today.[46]

Studies of electronic cigarettes as a method of cessation are heterogeneous, due to the constantly changing nature of the technology. There have been no trials of electronic cigarettes for smoking cessation compared with the recommended regimen of behavioural support and NRT/medication. Clinical trials of electronic cigarettes for smoking cessation in non-pregnant adults have demonstrated their effectiveness in reduction in cigarette consumption and smoking cessation compared with placebo alone.[50–52] There is also evidence that electronic cigarette use can encourage smoking cessation even in smokers who do not want to quit.

The National Centre for Smoking Cessation and Training recommends that smoking cessation services be open to electronic cigarette use among non-pregnant smokers, particularly those who have tried to quit with other methods and failed. Multi-sessional behavioural support is recommended to improve their chances of quitting.

There is a lack of safety data on the use of electronic cigarettes in pregnancy, and their effectiveness for smoking cessation in pregnancy has not been established.[43] There are no randomised controlled trials of electronic cigarette use for cessation in pregnancy and no published observational data on obstetric outcomes in pregnant users of electronic cigarettes. Women perceive electronic cigarettes as useful aids for reducing cigarette consumption and achieving cessation, while being less harmful than conventional cigarettes.[53] In the limited research conducted to date, many pregnant electronic cigarette users report dual use of electronic cigarettes and cigarettes. One US study[54] found that over half of pregnant women entering a smoking cessation trial had previously used electronic cigarettes, with these women reporting a higher cigarette consumption prepregnancy and more failed quit attempts. Fourteen

percent of women entering the trial were actively using electronic cigarettes in pregnancy and had similar characteristics, leading the authors to conclude that women who find it more difficult to quit smoking are more likely to use electronic cigarettes. In the UK, 'Helping pregnant smokers quit' is a National Institute for Health Research multicentre randomised controlled trial currently recruiting pregnant smokers for a clinical trial comparing electronic cigarettes versus usual care (behavioural support and NRT), with the results expected in 2021.

Conclusion

Smoking in pregnancy is a major preventable risk factor for maternal and neonatal morbidity. Maternal smoking rates are declining, with a higher proportion of continued cigarette smoking encountered in lower socio-economic groups. The harm from cigarette smoking is primarily from carbon monoxide and tar, which contribute to the complications seen during pregnancy. Nicotine alters fetal brain development and contributes to behavioural disorders in the offspring of smokers.

Smoking cessation in pregnancy is a key part of the NHS England initiative *Saving Babies' Lives*, a care bundle for reducing stillbirths, and all healthcare professionals should be comfortable with providing smoking cessation advice.

The relatively high smoking cessation rate in pregnancy is tempered by a high rate of relapse in the postnatal period, with less than one-third of spontaneous quitters remaining abstinent at 1 year postpartum. There is weak evidence that NRT with behavioural support can improve cessation rates in pregnancy, but with no effect on postpartum cessation.

The use of electronic cigarettes is becoming more common, as women perceive them to be less harmful than cigarettes. However, there is a lack of safety and efficacy data on their use in pregnancy, and no data on obstetric outcomes in pregnant users.

Further research is needed on pregnancy-specific cessation methods – for example, use of higher-dose NRT, electronic cigarettes or pharmacotherapy – as well as methods of preventing postpartum relapse. More data are also needed on outcomes in pregnant users of electronic cigarettes. Clinical trials for new methods of smoking cessation should consider the inclusion of pregnant women, because they are a group particularly at risk from continued smoking.

Disclosure of interests

There are no conflicts of interest.

Contribution to authorship

BPM researched and wrote the article; CR critically revised and edited the article. Both authors approved the final version.

Supporting Information

Additional supporting information may be found in the online version of this article at http://wileyonlinelibrary.com/journal/tog

Infographic S1. Smoking in pregnancy.

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