Treatment options for smoking cessation in pregnant women: A narrative review

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Abstract:

Smoking during pregnancy increases the risk for maternal and fetal adverse events including gestational hypertension, intrauterine growth restriction, low birth weight and sudden infant death syndrome. It is recommended that clinicians should discuss and prescribe smoking cessation programs to pregnant patients. In this review, the effectiveness of potential interventions including cognitive behavioral therapy (CBT) and nicotine replacement therapy (NRT) are examined and compared to the potential of exercise-aided smoking cessation programs. There is limited research available to confidently conclude that CBT on its own is an effective approach to reducing smoking during pregnancy. NRT has shown some success in reducing the total number of cigarettes smoked however the low dose of nicotine made available through NRT still poses as a risk to the developing fetus. Exercise has shown to have an acute effect on decreasing cravings and withdrawal symptoms, however there is limited research conducted for long-term cessation programs. This review provides information regarding the current gaps in literature that need to be addressed in order to confidently determine the effect exercise may have on smoking cessation during pregnancy. Additionally, the role of physicians in promoting and prescribing exercise is discussed.

1. Implications of Smoking during Pregnancy

It is well known that smoking in the general population has many negative health implications and significantly contributes to the development of chronic diseases such as lung cancer and heart disease (1). Women that smoke during pregnancy have added pregnancy related complications, impacting the health and well-being of two generations, both mother and the growing fetus.

Smoking during pregnancy has been consistently associated with the increased risk for small for gestational age (SGA, birth weight <2500g) newborns, with the average birth weight approximately 348g less than babies that were not exposed to smoking in utero (2). Babies born SGA have an increased risk for future chronic disease development including heart disease, hypertension and Type 2 Diabetes (3). Furthermore, being born SGA specifically due to maternal smoking has a twofold increase for the risk of sudden infant death syndrome (4) and delayed maturation of the respiratory system which may increase the risk for wheezing during infancy and future development of asthma (5). Birth weight is indicative of the quality of the uterine environment and specifically the efficiency of the placenta in delivering nutrients to the growing fetus (6). Smoking during pregnancy decreases placental function and promotes intrauterine growth restriction (IUGR) leading to SGA babies (2).

In 1987, Jeanty and colleagues (7) looked at 40 fetuses in the third trimester using ultrasound technology, ten were exposed to maternal smoking. The ten fetuses exposed to smoking were significantly smaller than the 30 fetuses not exposed to smoking. Specifically, length and abdominal circumference were less than non-exposed fetuses (7). Similar results were found in a large Swedish cohort (n=1,362,169) of infants born between 1983-1996, where infants exposed to maternal smoking had significantly reduced head circumference when compared to non-exposed newborns (8). Furthermore, research has shown that any amount of maternal smoking during pregnancy is associated with the increased risk of SGA babies. For instance, Vlajinac et al (9) stratified a large sample of 1011 women into one of three groups; non-smokers, those who smoked 1-9 cigarettes per day, and those who smoked 10 or more cigarettes per day. Results showed that birth weight was significantly less among women that smoked during pregnancy compared to the non-smokers with a negative correlation between number of cigarettes smoked per day and birth weight.

The increased incidence of maternal smoking may be due to a decrease in uteroplacental blood flow leading to a restriction of blood available for placental development, and oxygen and nutrient transport (10). A study that compared women that smoked (n=74) during pregnancy to non-smokers (n=69) at 35 weeks gestation found evidence for greater resistance in the uterine vasculature in the smoking group. Additionally, smoking during pregnancy causes poor flow-mediated dilation and reduces endothelial function and consequently reduces blood flow (11). Deceased placental blood flow and IUGR is also associated with fetal hypoxia (restriction of oxygen), preterm delivery and perinatal mortality (12). The incidence of IUGR and the associated adverse growth related events significantly increase with maternal smoking (12). Finally, Lucendo-Villarin et al., (13) recently published a study that examined the damage smoking causes to fetus cell development. This was an in vivo experimentation and focused on the many

psychoactive ingredients in cigarettes including cotinine. They determined that the mixture of psychoactive ingredients is more harmful in combination than many of the psychoactive ingredients alone. They concluded with the messages that the cigarette mixture effects female and male fetuses differently; in male fetuses the pathways regulating liver damaged more in comparison to female fetuses, whereas in female fetuses glucose metabolism was damaged more than the male fetuses.

Maternal smoking is a preventable risk factor for a number of pregnancy-induced complications and although quitting smoking entirely before or early in pregnancy would have the most benefit, quitting at any point will still have a positive impact on maternal and fetal health (14).

2. Prevalence of Smoking During Pregnancy and Factors Associated with Quitting

Despite the well-known benefits of quitting smoking during pregnancy, 13.8% of American and 10.5% of Canadian pregnant women continue to smoke throughout their pregnancy (15). Prevalence for smoking during pregnancy is higher among women with a pre-pregnancy body mass index of overweight or obese, low socio economic status, higher stress level and a younger age at conception (15). It should be noted however, that women attempting to quit smoking during pregnancy will spontaneously progressively reduce the number of cigarettes smoked daily with some women successfully quitting in their third trimester (16,17).

Pregnancy is a known as a 'teachable time' when women are more likely to engage in healthy behaviors including changing lifestyle habits such as increasing physical activity and healthy eating, and reducing alcohol consumption for the betterment of their health and the health of the growing baby (18). Research has shown that pregnant women want to quit smoking and hope to abstain from smoking postpartum (19). A study including 601 pregnant women who were smoking daily when they became pregnant but had quit or reduced their daily intake before their third trimester were interviewed and it was found that 29% had spontaneously quit without any intervention (20). Reasons for why women may be more successful with spontaneous quit attempts during pregnancy include aversions to the smell and taste of the cigarette (21), education on the negative health implications smoking has on fetal development (22), and if they were considering quitting smoking before becoming pregnant (19).

Spontaneous quit attempts during pregnancy however cannot be relied on to decrease smoking prevalence. Interventions are needed to support pregnant women in successfully quitting ideally before conception or early in their pregnancy. Barriers to quitting during pregnancy include a partner that smokes, lack of education on how to quit, increased maternal stress and lacking accessibility to smoking cessation support programs (23). Furthermore, research suggests that some pregnant women experience more intense cravings and withdrawal symptoms leading to relapse when compared to non-pregnant women (24). Data from 306 pregnant smokers compared to 93 non-pregnant women participating in the same smoking cessation program found that at twelve weeks post quit cravings and withdrawal symptoms were significantly higher among pregnant women (25).

Pregnant women are motivated to make healthy lifestyle changes including potentially quitting smoking. Future interventions need to address barriers to

quitting smoking during pregnancy including reducing cravings. Additionally, interventions used need to consider the impact on the fetus and assure strategies implemented do not have any potential adverse events to fetal development. The sections below will examine the effectiveness of the two most common treatments for smoking cessation for non-pregnant and pregnant populations.

3. Current Guidelines for Smoking Cessation during Pregnancy

The Clinical Practice Guideline for Treating Tobacco Use and Dependence (26) recommend that all clinicians should discuss smoking cessation with pregnant patients at their first prenatal appointment. To do this, clinicians are recommended to use the 5 A's Approach (Ask, Advise, Assess, Assist, Arrange; 27). At the first prenatal visit, clinicians should ask pregnant women about their smoking status. If they do currently smoke, the clinician needs to advise her to stop smoking by discussing the harmful effects smoking can have on the mother and growing fetus. Next the clinician should assess the patient's readiness to quit. If she is ready to quit, the clinician needs to assist her with finding a smoking cessation program. If she is not ready to quit, the clinician should provide further education on the importance of quitting for a healthy pregnancy. Finally, it is important for clinicians to arrange a follow up visit to evaluate her progress on the cessation program or her decision to begin a program (27).

In terms of what smoking cessation programs should be recommended, there is no specific guideline for clinicians to follow. It is suggested through the 2008 Clinical Practice Guideline Treating Tobacco Use and Dependence Panel that if the patient is willing to make a quit attempt then clinicians should refer to effective smoking cessation therapies and review whether these medications would be harmful during pregnancy or not (27); however no concise tool that provides this information is available. Research has shown that most physicians do not use the 5 A's approach (28–30). Most physicians will ask their patient about smoking during pregnancy (98%) and many will advise their patients to stop smoking (66%), however only 44% will assess whether their patient would like to quit, 29% will assist their patients in actually finding an effective smoking cessation program and only 6% will follow up on their progress (Jordan et al., 2006). This may be due to the fact that there are no clear guidelines for clinicians to use to determine what type of smoking cessation program would be effective and safe during pregnancy. In non-pregnant populations, behavioral therapy and nicotine replacement therapy are commonly prescribed (31).

4. Nicotine Replacement Therapy

When nicotine is consumed, the presynaptic nicotinic acetylcholine receptors (cholinergic pathways) in the ventral tegmental area, nucleus accumbens and prefrontal cortex are activated. This releases many neurotransmitters such as acetylcholine, dopamine, serotonin, glutamate, and other neurotransmitters which have a variety of consequences on an individual such as; euphuism and reward, cognitive enhancements and relief from cravings (32). Finally, nicotine prevents gamma-aminobutyric acid from down regulating the over activity of dopamine neurons allowing dopamine to be relapsed for a longer period of time (33).

Nicotine replacement therapy (NRT) is a pharmacotherapy designed to control the administration of nicotine to individuals who are attempting to quit smoking. NRT can be administered through chewing gum, lozenges, and nasal spray (absorption in the

oval or nasal cavity) and through transdermal patches worn on the skin (34). NRT attempts to maintain different levels of nicotine in the blood (depending on stage of treatment) to provide relief to the withdrawal and craving symptoms smokers' experience. Hence, the goal of NRT is to slowly cutback on nicotine levels until cessation. This is different from when an individual administers nicotine through inhalation which reaches the brain in around 15 seconds and is metabolised quickly causing spikes in nicotine blood levels (35).

To date, there is limited research available to suggest that NRT is an effective approach for supporting pregnant women with their quit attempts. In a double-blind, placebo-controlled trial including seventeen women that received NRT and thirteen women that received a placebo at 12 to 24 weeks gestation, results showed no statistical difference between the intervention and control group for quitting (36). Similarly, a large randomized controlled trial including 1051 women (521 NRT and 530 placebo), showed no significant difference in successful quit attempts after one month of the intervention and post-delivery (37). Furthermore, a systematic review including five studies (695 women) that provided pregnant women with NRT concluded that there was no statistical significance between NRT and placebo use for the smoking cessation and safety for the fetus (37). On the contrary, Coleman et al., (38) conducted a review that examined nine studies involving NRT. Results showed that NRT did increase the number of women that were smoke free late in pregnancy in comparison to a control. However, studies that included a placebo found that NRT was not statistically better. This may suggest that NRT is not as effective in the pregnant population as it is in the non-pregnant population (39). Another issue with NRT treatment in this review was the adherence to the protocol. Many pregnant women were not using the NRT as prescribed and this could be a possible reason why NRT performed similarly to that of a placebo (38). In addition, not every study determined smoking abstinence with a verified biochemical measures and relied on a self-reported measure.

The effect that nicotine may have on fetal development should also be considered before recommending NRT to pregnant women, unfortunately there is a lack of consensus in the literature regarding this as well. Primarily, the physiological effects of NRT have been compared with cigarette smoking. NRT compared to cigarettes has shown an increase in birth weight (40) and a decrease in maternal blood pressure (41). As a result, some research suggests that because NRT is less harmful than cigarette smoking, it should be recommended despite the unknown effects a low dose of nicotine may have (42). Regardless, nicotine metabolizes faster during pregnancy and therefore may have a negative impact on fetal development and may cause pregnancy related complications (43). An optimal dose amount that would not cause adverse pregnancy related events has not been determined (41). More research is needed on the safety and efficacy of NRT in the pregnant population.

In animal models (ewe), a low dose of nicotine (10 or 25 μg/kg) induces a hypoxic fetal response indicating a lack of oxygen delivery and an increase in fetal blood pressure has been observed (44,45). There is evidence that despite the low dose of nicotine in NRT options such as patches, nicotine still crosses the placenta (46). A NRT plus CBT trial was stopped early because of unreported adverse events seen in the group receiving NRT (47). Furthermore, despite literature suggesting that NRT does not increase maternal blood pressure as

much as cigarettes do, there still is an observed significant increase in maternal blood pressure and an increased risk of cardiovascular related negative effects on the fetus such as hypoxia (46). Finally, despite an increase in birth weight in NRT compared to cigarette smoking, trials that have shown this outcome have had selection bias related concerns due to differences in baseline characteristics (women that had already quit, reduced their daily intake of cigarettes or had made no change) making it difficult to confidently suggest NRT improves birth weight compared to cigarettes (46). Due to the lack of evidence confirming the efficacy of NRT during pregnancy, it is not currently recommended and warrants further research (48).

5. Behavior Therapy

Behavior therapy encompasses many different psychotherapeutic practices that try to achieve healthy behavior change goals (49), including addiction to cigarettes. One of the most common behavior therapies in the smoking cessation literature is behavioral counseling (31). Behavioral counseling involves using motivational interviewing techniques, health education and relapse prevention strategies and is normally offered over several sessions (31).

CBT is the most common type of smoking cessation therapy offered to pregnant women to support them with leading a healthy lifestyle during pregnancy by quitting smoking (39), however, there has been varying success in the use of CBT among pregnant women and there is no consensus on the best form of CBT to offer to increase the likelihood of complete smoking abstinence (39). One review, for instance, examined eights studies for the effect of isolated smoking cessation counseling programs in pregnant women and concluded that the intervention (i.e.,counseling) was not statistically better than the controls in increasing abstinences following the program, despite an overall 4% difference in cessation rates favoring the intervention groups (50). The time for each counseling session varied from 180 minutes to 600 minutes and this could be a possible reason why there was no significant difference found. There was also heterogeneity between all of the programs in information and structure. Another limitation of the included studies is that three of the eight did not validate smoking cessation biochemically and relied on self-report. The results from this review show that in isolation it does not appear that smoking cessation counseling is effective in increasing smoking cessation in pregnant women. None the less, because CBT does not include any dose of nicotine, it may be considered the more safe option. Another form of smoking cessation support that does not include any nicotine is exercise.

6. Acute Effects of Exercise on Cravings and Withdrawal in Pregnant Smokers

There is a death of evidence on the acute effects of exercise on cravings and withdrawal symptoms during pregnancy. To date, Prapavessis et al., (51) are the only research group to our knowledge to design a study examining the possibility of relieving cravings in the pregnant population with an acute bout of exercise. Pregnant women are an especially vulnerable group to withdrawal symptoms and cravings because their cravings are expedited by a faster metabolism of nicotine during pregnancy (43). Thirty pregnant female smokers were recruited to participate. They were randomized into one of two groups: a mild-to-moderate intensity exercise group (n=14, 17.80+/- 4.83 weeks pregnant) or a passive sitting group (n=16, 19.25 +/- 6.13 weeks pregnant). The mild-to-moderate intensity exercise group walked on a treadmill for

twenty minutes at 25%-55% of their heart rate reserve. The passive group would sit and watch a neutral video about gardening that was approximately 25 minutes. These interventions took place on a single day and consisted of one session only. Regardless of group assignment participants were asked to abstain from smoking tobacco for 18 hours prior to the intervention and this, was verified through a carbon monoxide reading <10 ppm. The primary outcome (cravings) and secondary outcomes (tobacco withdrawal symptoms) were measured at six different time points including; before the intervention, during, immediately following the intervention and every ten minutes for 30 minutes after the intervention. Results showed that immediately following the intervention and 10 minutes afterwards there were significant differences favoring the exercise condition for tobacco cravings ($p=0.044$, $n^2=0.16$ and $p=0.018$, $n^2=0.01$ respectively). All but one tobacco withdrawal symptom (difficultly concentrating) had large effect sizes but none reached significance between groups.

These results have been replicated at a larger scale in non-pregnant populations as seen in two meta-analysis (52,53). Increases in withdrawal symptoms and cravings have been shown to be the best predictors of failed quit attempts in non-pregnant smokers (54). Furthermore, recently Abrantes et al, (55) examined the effects of acute aerobic exercise on affect and cravings in the weeks before and during a cessation attempt in a non-pregnant population. The results indicate that aerobic exercise can provide relief from anxiety prior to a quit attempt and reduce anxiety and cravings during a quit attempt in comparison to an education control group. These findings provide evidence that the effects of acute bouts of exercise can provide relief to smokers not only immediately but throughout the entirety of a quit attempt (including the pre quit stage). Literature in non-pregnant populations provides the framework that acute exercise bouts may provide relief from withdrawal symptoms and cravings in the pregnant population as well, and further research is needed to examine the efficacy of exercise in a pregnant smoking model.

7. Physical Activity Programs and Cessation Success in Pregnant Women

Currently the use of physical activity programs for quit attempts in pregnant women in the literature is scarce. To our knowledge only one large randomized controlled multicenter trial (n=789) has been published to date (56). These investigators randomized the participants into one of two groups: a behavioral therapy alone or a behavioral therapy plus physical activity program (which included supervised exercise with physical activity consultations) for an eight-week period. Results found that the physical activity program group was not successful in decreasing the smoking rate at the end of pregnancy when compared to the control group. A limitation identified by authors was that the population recruited reported they were physically active pre-intervention and were twice as likely as the average population to reach the daily activity guidelines. Hence, a ceiling effect may have been operating for physical activity levels. Another limitation includes the frequency of supervised visits which may have not been sufficient enough to provide the participants with craving and withdrawal symptom relief, as exercise sessions were only provided twice a week for six weeks and then once a week for the final two weeks. In addition, adherence to the program was low. Participants only completed four out of fourteen sessions (29%). This may explain why Ussher et al., (56) found no significant differences in self-reported activity levels between treatment

groups. Furthermore, it was found that the small subpopulation that did receive accelerometers there was a significant over estimation of self-reported exercise. This is not uncommon as Jakicic, Polley and Wing (57) found that over 45% of women over estimate their self-reported exercise. Similar findings have been observed in non-pregnant populations (58). In short, these adherence data indicate that the exercise intervention program was not received as intended.

A possible solution to improve adherences rates to exercise-aid smoking cessation programs as seen in the non-pregnant literature, is to focus on the maintenance stage of both exercise and smoking cessation. Unfortunately, less than 10% of smokers who follow formal cessation programs receive proper maintenance assistance (59–61). All smoking cessation programs (including exercise-aided ones) show early promise followed by relapse effects at program completion and follow-up (58,62,63). Therefore, it is vital that these types of programs have both initial cessation and exercise maintenance components to initiate the behavior as well as prevent relapse in the targeted behaviors (64). This important issue has been highlighted as a primary research concern in the knowledge synthesis of exercise and smoking cessation literature (61). Future research should include objective measures of adherence to supervised long term exercise programs.

8. Summary and Conclusions

Smoking during pregnancy has adverse events the can impact both the mother and developing fetus including increased maternal blood pressure and decreased birth weight. The implications of these outcomes include future negative health outcomes for the baby such as chronic disease development, delayed maturation of the respiratory system, asthma and wheezing in infancy (5). Furthermore smoking during pregnancy has been associated with an increased risk for placental dysfunction (6) and sudden infant death syndrome (4). Most pregnant women want to quit smoking and it is important to assure they are supported with a smoking cessation program to reduce cravings and withdrawal symptoms without posing any health related risks to the mother or developing fetus.

Previously, pregnancy related smoking cessation interventions have focused on CBT and NRT. Currently there is not enough evidence to suggest that CBT on its own would be an effective intervention to recommend (50). NRT compared to cigarettes has shown an increase in birth weight (40) and a decrease in maternal blood pressure (41) and therefore it has been suggested that it would be better to recommend NRT during pregnancy to reduce the number of cigarettes smoked and increase the possibility of quitting. However, a low dose of nicotine, as found in NRT options, still has negative health implications including inducing a hypoxic fetal environment and maternal hypertension (46)

Exercise interventions have the potential to reduce cravings and withdrawal symptoms without increasing the risk for maternal or fetal adverse events. To date, only one study provides evidence that acute exercise during pregnancy reduces smoking cravings (51). The effectiveness of exercise-aided smoking cessation programs have produced mixed results in the non-smoking population and one study found no support for these type of programs in pregnant smokers wanting to quit (65). A key limitation with the current literature is the lack of adherence to the exercise program. Further research that sheds light on both the short and long term quit rates of exercise-

aided smoking cessation programs for pregnant women is needed. Finding novel and innovative ways to maximized adherence to these programs remains a high priority.

9. Physician's Role in Smoking Cessation during Pregnancy/What Physicians Need to Know?

- Current guidelines suggest that physicians should use the 5 A's (Ask, Advise, Assess, Assist, Arrange; 27) model to discuss smoking during pregnancy and support women with an effective cessation program.
- As identified in this review, there is a lack of consensus on the most effective intervention for smoking cessation that should be prescribed during pregnancy.
- CBT and NRT have been previously studied however results have not been consistent. CBT in isolation has not been successful in pregnant women and although NRT may reduce the total number of cigarettes smoked, the low dose of nicotine may still cause adverse pregnancy related events including fetal hypoxia and maternal hypertension.
- Exercise during pregnancy may be an effective approach as research has shown that exercise has an acute effect on reducing smoking cravings and withdrawal symptoms in temporary abstinent smokers
- There is no evidence in pregnancy and some evidence in the general population that exercise-aided smoking cessation programs are effective in assisting smokers quit.
- Adherence to exercise is a common problem to exercise-aided smoking cessation programs. To improve adherence to exercise, physicians should follow-up on patient progress and continue to discuss the importance of smoking abstinence during pregnancy for the health of both the mother and growing fetus.

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