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Nicotine Replacement Therapy (NRT) in Pregnancy

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Tobacco use during pregnancy is the most important modifiable risk factor associated with adverse pregnancy outcomes.[1-4] Tobacco contains more than 3,500 chemicals, including over 100 carcinogens and mutagens, carbon monoxide, nicotine, and hydrogen cyanide, all of which can be very harmful to fetal development.[4-7] Nevertheless, many women continue to smoke during pregnancy, with estimates of 12% in the UK, 13% in the U.S., and 15% in Australia.[7-12] These numbers may be vastly underreported due to strong social norms discouraging smoking among pregnant women, which can lead some women to fail to disclose their true smoking status. Smoking during pregnancy is most prevalent among women who have lower education levels, are socioeconomically disadvantaged, have household members who smoke, or have coexisting psychiatric or emotional problems.[3,7,13] Although some women stop smoking once learning of their pregnancy, most who smoked prior to becoming pregnant continue to smoke throughout the pregnancy.[7,14]

The first study of a smoking cessation intervention for pregnant women was published in 1976 and included brief advice from a physician to quit.[15,16] This study concluded that although their intervention encouraged some women to attempt to stop smoking, a need existed for more powerful methods of smoking cessation for pregnant women. Numerous intervention trials have been conducted since then, and results have been generally positive with regard to smoking cessation in pregnancy outcomes. However, when it comes to the use of pharmacologic therapy for smoking cessation in pregnancy, the results have been less clear in regard to pregnancy outcomes. Numerous guidelines worldwide recommend using nicotine replacement therapy (NRT) as an option for pregnant women that are considered heavy smokers or are unable to quit smoking, but conflicting study findings cloud the reliability of these recommendations. This article will focus on the use of NRT in the smoking cessation of pregnant women. It should be also be noted that any pharmacologic smoking cessation therapy for all patients should always be supplemented with cognitive behavioral therapy (CBT).[17]

IN THIS ISSUE

Effects of Smoking on Maternal and Fetal Health

Maternal smoking during pregnancy is a well-established risk factor for many adverse perinatal outcomes, including low birth weight (less than 2500 grams), preterm delivery, miscarriage, stillbirth, placenta previa, placental abruption, and sudden infant death syndrome (SIDS).[2,3,6-10,14,15,18-24] Very low birth weight newborns (birth weight <1500 grams), in particular, have exponential increases in morbidity and mortality compared to newborns of normal weight. Approximately 10% of perinatal fetal mortality and 10% of infant deaths in the U.S. may be directly attributed to maternal smoking during pregnancy. Many women who smoke recognize the risks of continuing to smoke during pregnancy, as evidenced by relatively high quit rates during the first trimester.[14] However, this smoking abstinence is usually short-lived.

Several mechanisms have been observed or proposed to explain the adverse pregnancy outcomes associated with maternal smoking, including impaired fetal oxygenation, altered fetal development and physiologic response, and toxin exposure.[4,21,22] Current theories suggest that fetal hypoxia results from nicotine and carbon monoxide intake, causing poor pregnancy outcomes by reducing either the uterine or the fetal placental blood flow.[15,21,22,25] Impaired fetal oxygenation has been observed via pathologic evaluations of the placentas of smokers, where placentas were shown to have visible structural changes as compared to those of non-smokers, including a reduction in capillary volume and increased thickness of the villous membrane.[4,5] Both of these factors may contribute to abnormal gas exchange within the placenta, resulting in compromised fetal placental blood flow and contributing to intrauterine growth restriction and a lower birth weight.[3-5,15] Nicotine has been shown to be directly responsible for acute hemodynamic effects, including increased maternal and fetal heart rate and decreased umbilical blood flow.[25] Carbon monoxide released during smoking results in the formation of carboxyhemoglobin, diminishing tissue oxygenation via competitive inhibition with normal oxyhemoglobin.[5,15] This competitive inhibition leads to decreases in systemic maternal and fetal oxygen delivery.

In addition to impairing fetal oxygen delivery acutely, nicotine exposure impacts fetal development throughout the pregnancy. Fetal exposure to nicotine results in sympathetic activation of the developing nervous system, leading to acceleration of fetal heart rate and reduction in fetal respiratory movement, both of which are used as indicators of fetal well-being. Nicotine has also been established as a neuroteratogen that compromises the development of critical neural pathways within the developing fetal brain, leading to many cognitive, emotional, and behavioral problems.[5,15,19] In animal studies, nicotine was shown to cause abnormalities of neural cell proliferation and differentiation, leading to a

TABLE 1 | Comparison of commercially-available nicotine replacement products.[3,17-19,25,28,31-34]

Product	Nicotine Gum	Nicotine Inhaler	Nicotine Lozenges	Nicotine Nasal Spray	Nicotine Patch
Delivery	Intermittent	Intermittent	Intermittent	Intermittent	Continuous
Brand Names	Nicorette®	Nicotrol inhaler®	Nicorette®, Commit®	Nicotrol NS®	Nicoderm CQ®, Nicotrol®
Availability	OTC	Rx only	OTC	Rx only	OTC and Rx
Strengths	2 mg or 4 mg (per piece)	4 mg (per cartridge)	2 mg or 4 mg (per lozenge)	0.5 mg (per spray)	7 mg, 14 mg, or 21 mg (per patch)
Starting Dosages	• <18 cigarettes/day: 2 mg • ≥18 cigarettes/day: 4 mg • 1 piece of gum every 1-2 hours; max. 24 pieces/day	• 6-12 cartridges/day for 8 weeks, then gradually decrease over four weeks	• 1st cigarette >30 mins after waking: 2 mg • 1st cigarette ≤30 mins after waking: 4 mg • 1 lozenge every 1-2 hrs; max. 20 lozenges/day	• 1-2 sprays/hour in each nostril, as needed • Maximum 40 sprays in each nostril per day	• ≥10 cigarettes/day: 21 mg • <10 cigarettes/day or weight <45 kg: 14 mg • Dose taper recommended
Common AEs	Mouth soreness; hiccups; dyspepsia; stomachache	Mouth & throat irritation; cough; rhinitis	Nausea; hiccups; heartburn	Nose & throat irritation; coughing; watering eyes	Local skin reactions ; sleep disturbances and vivid dreams
Advantages	• Reduces cravings • Available in variety of flavors • Adverse effects are generally mild, transient and can be alleviated by correcting chewing technique	• Reduces cravings • Particular suitable for patients that miss the hand-to-mouth movement of smoking • Adverse effects are generally mild and decline with continued use	• Reduces cravings • Available in mint and cherry flavors • Easy to use • Useful in patients with chewing problems or dentures	• Helps relieve sudden cravings	• Control baseline withdrawal symptoms. • Discreet, easy to apply • Preferred in heavy smokers • Acceptable to use in patients with CVD or circulatory problems
Disadvantages	• Not suitable for some patients (ie, dentures, TMJ) • Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)	• Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks) • Contraindicated in severe reactive airway disease	• Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)	• Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks) • Contraindicated in chronic nasal disorders or severe reactive airway disease	• Not for sudden cravings • Avoid in patients with severe eczema or psoriasis • 24-hour patches may cause sleep disturbances and vivid dreams
Pregnancy Category	C	D	C	C	D
Patient Instructions	• Chew slowly until taste becomes strong • Rest gum between cheek and gums to allow for absorption of nicotine • Chew gum again when taste fades, and rest gum again when taste is strong • Use new piece after 1-2 hours, if needed • Avoid food or beverages except water for 15 mins prior to/during chewing	• Load nicotine cartridge into inhaler and puff (similar to a pipe) for ~20 minutes; do not inhale like a cigarette • Puffing may be done up to 16 times/day • Avoid food or beverages except water for 15 mins prior to/during use • Keep in a warm place when not in use during cold weather seasons	• Place between cheek and gums and allow to dissolve, but do not swallow, chew, or suck on lozenge • Move from one side of the mouth to the other from time to time until fully dissolved • Avoid any foods or beverages except water for 15 minutes prior to/during use	• Spray once in each nostril, without sniffing, swallowing, or inhaling through the nose during sprays • Should not be used while driving due to sneezing and watering eyes occurring shortly after administration	• Place unwrapped patch on hairless skin area; wash hands after application • Remove old patch, fold sticky side in, and dispose of before applying new patch • Rotate patch site to avoid skin irritation • If skin irritation occurs, apply hydrocortisone 1% cream • Do not cut patches

AEs = adverse effects; **CVD =** cardiovascular disease; **MI =** myocardial infarction; **OTC =** over-the-counter; **Rx =** prescription; **TMJ =** temporomandibular joint dysfunction.

reduced number of neurons and altered synaptic activity.[1,7] Beyond nicotine and carbon monoxide, smoking exposes the mother and fetus to a multitude of toxins.[4,6,7,24] Although most of these toxins have not been studied in humans, certain toxins have known harmful effects.[3,21,22] For example, lead is a known neurotoxin and some polycyclic aromatic hydrocarbons have been found to be mutagenic.

The association with major congenital abnormalities is not very clear as multiple studies have produced mixed results.[9,15,22,23] Hackshaw et al. (2011) conducted a large systematic literature review that analyzed 172 studies conducted from 1959 to 2010 to determine if an association between maternal smoking and major congenital abnormalities existed. The mechanisms through which maternal tobacco use triggers these congenital malformations is currently unknown, but several theories suggest that the hypoxia and/or toxin exposure interfere with fetal cell proliferation and migration, specifically at critical periods for organogenesis. Combined with different thresholds for damage in fetal tissues, these detriments may determine which organs or systems are affected and to what extent. Although the literature review concluded that no association was found for all congenital abnormalities, some system-specific abnormalities were associated with maternal tobacco use, including cardiac defects, musculoskeletal defects, gastrointestinal defects, orofacial clefts, and cryptorchidism.

The risks of maternal smoking during pregnancy extend beyond pregnancy-related complications. Children born to mothers who smoke during pregnancy were found to have increased susceptibility to behavioral, learning, and attention disorders, asthma, upper and lower respiratory infections, infantile colic, and childhood obesity.[1,3,5,10,15,19-21,24,26] Affected children, as well as those exposed to secondhand smoke, were also found to have an increased risk of numerous adverse cardiovascular, respiratory, endocrine, and metabolic outcomes during their adult years. For children born with major congenital abnormalities, most of these malformations have significant physical and psychological morbidity for both the children and their parents, in addition to significant and often lifelong healthcare service costs.[22] Despite awareness of the health consequences of smoking during pregnancy, the majority of women who smoke will continue to smoke throughout pregnancy.[7,14]

Nicotine Replacement Therapy Options

Nicotine replacement therapy is considered a first-line option for smoking cessation for all smokers.[10,17] Although the use of behavioral intervention alone is preferable to the use of pharmacologic agents, CBT alone yields quit rates that rarely exceed 18%.[7,15] Nicotine replacement is estimated to double or triple the success rate of behavioral interventions.[6,11,17,18] A recent meta-analysis of 267 studies from 12 Cochrane reviews determined that significantly higher rates of smoking cessation were associated with patients receiving CBT and NRT (17.6%), as compared with the those receiving CBT and placebo (10.6%).[27]

For consistent smokers, when nicotine blood levels fall, withdrawal symptoms develop, such as restlessness, increased appetite, inability to concentrate, irritability, dizziness, constipation, or "just feeling awful."[19,28] These symptoms begin within a few hours after the last cigarette and worsen if not relieved by another cigarette. By providing relief of these withdrawal symptoms, NRT has helped improve smoking cessation among patients, although exact estimates are unclear due to variations in different reports.

A comparison of available NRT products is summarized in **Table 1**. Products are widely available both over the counter and by prescription. In terms of selecting which NRT formulation to use, evidence does not suggest that one particular type is more effective than another.[28-30] Patient preference and smoking characteristics usually determines which formulations would provide the most benefit to the patient.

Combination NRT therapy, which uses a continuous NRT product together with an intermittent product, may be considered for patients that are considered heavy smokers (≥20 cigarettes/day), have relapsed multiple times, or have particularly bad withdrawal symptoms.[10,17,27-29,33,35] The most common combination is an NRT patch (for continuous nicotine replacement) with gum or spray (taken periodically to ease sudden cravings). Evidence from multiple studies suggests that combination NRT therapy provides a significant increase in smoking cessation success rates (31.5%) as compared with use of a single NRT product (17.6%).[27] A common concern of patients, particularly those using combination NRT therapy, is addiction to the NRT, although the actual risk of becoming dependent on NRT is small. About 1 in 20 people using this smoking cessation option continue to use the NRT beyond the manufacturers' recommendations, although the safety of NRT for these extended durations is not yet known.

Nicotine Replacement Therapy in Pregnancy

Considerable interest has been placed in the use of NRT to improve smoking cessation rates in pregnant smokers.[2,3,10,14,19,23-25] Evidence suggests that NRT use during pregnancy is not more harmful to the fetus than smoking and may provide a significant benefit to certain pregnant women.[11,17-19] Several guidelines currently recommend NRT as a second line option for pregnant smokers who have failed CBT alone or as a first line option for pregnant smokers who smoke >10 cigarettes/day, in addition to continued CBT.[15,20,36] These recommendations also state that this therapy should be undertaken with close physician supervision and a thorough discussion of the risks of continued smoking and the potential benefits and risks of NRT.

Nicotine replacement therapy may have two major potential benefits during pregnancy. The first is to reduce or eliminate fetal exposure to the other toxins in cigarette smoke.[3,19,25] It can be argued that NRT use in pregnancy, if it leads to smoking cessation, would eliminate maternal and fetal exposure to hundreds or thousands of other potentially harmful chemicals in tobacco smoke.[5] While NRT may double the quit rates compared to no pharmacologic interventions in non-pregnant patients, conflicting findings have been reported as to whether NRT is a safe and effective option for smoking cessation in pregnancy.[7] **Table 2** lists selected studies of NRT in pregnancy that provide evidence of efficacy and safety in this patient population.

In Wisborg et al. (2000) and Oncken et al. (2008), a reduction in the number of cigarettes smoked by patients in the groups receiving NRT was noted, but not significant differences in smoking cessation.[6,7] In Pollak et al. (2007), the group receiving NRT had a statistically significant difference in smoking cessation during pregnancy, but confirmed quit rates at 3-months postpartum were not significantly different between groups.[14] In Coleman et al. (2012), no significant differences in smoking cessation between the placebo and NRT groups were identified, but, despite being one of the largest randomized control trials conducted in this research topic, this study was severely limited by poor compliance rates.[2] Similar to Pollak, El-Mohandes et al. (2013) also initially

TABLE 2 | Selected studies of nicotine replacement therapy during pregnancy.

Study	Patient Characteristics	Exclusion Criteria	Study Arms	Objectives and Outcomes	Results

Oncken, et al.[25] (1996)	• 24-36 wks gestation
	• Smoked ≥10 cigarettes/day
	• Attempted to reduce or quit smoking during pregnancy
		• History of heart, liver, or kidney disease, HTN or DM, Illicit drug or smokeless tobacco use, TMJ
		• Placenta previa
		• Fetal growth restriction
		• Non-heavy smokers (cotinine <85 ng/mL)
			• Control group (no intervention) (n=10)
			• NRT group (n=19)
				• Compare effects of multiple doses of nicotine gum
				• Measurement of cotinine levels[a]
				• Changes in maternal and fetal hemodynamic parameters
					• Cotinine levels:
					  • No change in control group
					  • Significantly decreased in experimental group
					• No statistically significant changes in maternal and fetal hemodynamics

Wright, et al.[18] (1997)	• Singleton pregnancy • Maternal age <35 years old • 27-38 wks gestation • Smoked ≥½ pack/day • Unwilling or could not quit	• Obstetric or medical problems • Medications (other than prenatal vitamins or iron supplements) • Fetal, placental, or amniotic fluid abnormalities	• All patients received nicotine patches (n=6)	• Safety of transdermal nicotine patch • Changes in maternal and fetal characteristics • Control of nicotine withdrawal symptoms	• No apparent maternal or fetal adverse effects • Uncomplicated delivery in 5 of 6 patients • No change in maternal and fetal characteristics • No nicotine withdrawal symptoms in 5 of 6 patients
Wisborg, et al.[6] (2000)	• <22 wks gestation • Smoked ≥10 cigarettes/day	• Non-singleton pregnancies	• NRT group (n=124) • Placebo group (n=126)	• Smoking cessation at end of treatment and end of pregnancy • Effect on birth weight and preterm delivery	• Non-significant differences in smoking cessation, possibly be due to low adherence rates in both groups • Higher birth weights in NRT group • No significant difference in preterm delivery rates

Pollak, et al.[14] (2007)	• Maternal age ≥18 years
	• 13-25 wks gestation
	• Smoked ≥100 cigarettes in their lifetime
	• Smoked ≥5 cigarettes/day
	• Spoke English
		• Maternal cognitive or mental health problems
		• Drug, alcohol addiction
		• Poorly controlled HTN
		• Cardiac arrhythmia
		• MI in previous 6 mos
		• Hx of placental abruption
		• Congenital abnormalities in previous pregnancy or family history of congenital abnormalities
			• CBT only (n=58)
			• CBT + NRT (n=113)
				• Smoking cessation rates at 7 wks after randomization, 38 wks gestation, and 3 months postpartum
				• Differences in fetal characteristics
				• Serious adverse events
					• NRT +CBT improved smoking cessation
					  • Greater follow-up in CBT + NRT
					  • Greater smoking abstinence in CBT + NRT at 7 wks and 38 wks
					  • No difference in smoking abstinence at 3 months postpartum
					• No difference in fetal birthweight or gestational age
					• Increased serious adverse events in CBT + NRT arm

Oncken, et al.[7] (2008)	• Smoked ≥1 cigarette/day • ≤26 wks gestation • Maternal age ≥16 years • Spoke English or Spanish • Living in a stable home	• Evidence of current alcohol, illicit drug use. • Non-singleton pregnancy • Unstable psychiatric or medical problem • Medical condition that would interfere with study participation	• CBT only (n=94) • CBT + NRT (n=194)	• Smoking cessation after 6 wks of gum use and at the end of pregnancy • Efficacy and safety of NRT • Effects on birth weight • Changes in smoking status	• CBT + NRT: non-statistically significant lower risk of serious adverse events • Stopped at 6 wks due to lack of efficacy in smoking cessation (only 7% quit rate in CBT and 14% quit rate in CBT + NRT at 6 wks) • CBT + NRT: statistically significant increases in birth weight and gestational age • CBT + NRT: statistically significant decrease in number of cigarettes/day and cotinine concentrations

[a]Many studies use cotinine (a principal metabolite of nicotine) as a biomarker for nicotine due to the longer half-life of cotinine (15 hrs) as compared to nicotine (2 hrs).[1,5,7,11,18,25]

CBT = cognitive behavioral therapy **DM =** diabetes mellitus; **HTN =** hypertension; **MI =** myocardial infarction; **NRT =** nicotine replacement therapy; **TMJ =** temporomandibular joint dysfunction.

TABLE 2 (cont'd) | Selected studies of nicotine replacement therapy during pregnancy.

Study	Patient Characteristics	Exclusion Criteria	Study Arms	Objectives and Outcomes	Results
Coleman, et al.[2] (2012)	• Agreed to set a quit date • Maternal age 16-50 years • 12-24 wks gestation • Smoke ≥5 cigarettes/ day	• Known major fetal abnormalities • Drug, alcohol dependence • Contraindications to NRT	• NRT group (n=521) • Placebo group (n=529)	• Prolonged smoking cessation • Differences in birth outcomes	• No differences in smoking cessation (9.4% prolonged abstinence in NRT group vs. 7.6% in placebo group) • Low adherence rates in both groups (7.2% in NRT group vs. 2.8% in placebo group)
Brose, et al.[10] (2013)	• Attempted to quit smoking • Enrollment in Stop Smoking Services in England	• Follow-up data missing or not yet completed • Missing maternal age • Smoking cessation medication other than NRT • Missing due date • Data entry errors	• Control group with no intervention (n=588) • Single NRT (n=1166) • Combination NRT (n=2126)	• Smoking Cessation • Differences in efficacy between single and combination NRT	• Single NRT was not associated with improved abstinence rates vs. control group at 4-wk follow-up • Combination NRT was strongly associated with greater abstinence at 4-wk follow-up
El-Mohandes, et al.[11] (2013)	• Spoke English • Identified as African-American • Maternal age ≥18 years • <30 wks gestation • Willing to quit smoking • CO concentration ≥8 ppm • Salivary cotinine ≥20 ng/ml or urinary cotinine ≥100 ng/ml	• Psychiatric illness • Alcohol or drug abuse	• CBT only group (n=26) • CBT + NRT group (n=25)	• Smoking cessation rates • Differences in birth weights	• Non-statistically significant increase in smoking cessation in the CBT+NRT group • Non-statistically significant increase in birth weights in CBT+NRT group
Cooper, et al.[1] (2014)	• Maternal age 16-45 years • 12-24 wks gestation • Smoked ≥5 cigarettes/ day	• Fetal or postnatal infant death • Non-singleton pregnancies	• NRT group (n=445) • Placebo group (n=446)	• Effects of maternal NRT use on child outcomes at 2 years old	• Less developmental impairments infants of mothers in NRT group compared to placebo
Dhalwani, et al.[9] (2015)	• Within The Health Improvement Network (THIN) • Maternal age 15-49 years • Live birth between January 2001 and December 2012	• Live births resulting in minor congenital abnormalities • Live births with congenital abnormalities caused by other known teratogens	• NRT group: NRT use 4 wks before conception and/or during 1st trimester (n=2,677) • Smoking group: no NRT use (n=9,980) • Control group: non-smokers (n=179,841)	• Association between early pregnancy exposure to NRT with overall and system-specific major congenital abnormalities in live births	• Association between NRT use and overall major congenital abnormalities was not statistically significant • No evidence of association between NRT and system-specific major congenital abnormalities except for a small increased risk of respiratory anomalies.

CBT = cognitive behavioral therapy **DM =** diabetes mellitus; **HTN =** hypertension; **MI =** myocardial infarction; **NRT =** nicotine replacement therapy; **TMJ =** temporomandibular joint dysfunction.

showed positive smoking cessation rates, but concluded at the end of their study that the differences in smoking cessation between the NRT and non-NRT group were not significant.[11] Overall, these studies suggest that NRT may be effective in short-term abstinence, but not as effective for sustained smoking cessation.[1]

The second major potential benefit for NRT use during pregnancy is to reduce the overall dose and duration of exposure to nicotine.[3,19,25] Nicotine concentrations achieved with NRT are much lower than those seen in cigarette use.[18] In Oncken et al. (1996), peak and trough concentrations of cotinine, an active metabolite of nicotine, were significantly lower in patients using nicotine gum, both in comparison to their baseline cotinine concentration prior to starting the gum, as well as compared to the cotinine concentration of the control group.[25]

Use of NRT products appears to reduce adverse perinatal outcomes compared to non-pharmacologic interventions. For example, patients receiving NRT had greater infant birth weights.[6] Similarly, despite poor patient compliance, Oncken et al. (2008) showed that the NRT group had a lower risk of preterm delivery and greater infant birth weights as compared to those of the placebo group.[7] In contrast, Pollak et al. (2007) had better compliance rates, but had no significant differences in infant birth weight or preterm delivery between the NRT group and the non-NRT group.[14] El-Mohandes et al. (2013) also similarly showed a non-significant difference in the two groups.[11]

Prior to 2015, very few studies showed if NRT use was associated with major congenital abnormalities.[9,22,23] Evidence of safety in relation to congenital abnormalities was limited to one observational study, which did not find an increased risk, and two small randomized controlled trials, which found a reduced risk, but were not adequately powered. Dhalwani et al. (2015) was a population-based pregnancy cohort study and currently the largest published study to date that investigated whether exposure to NRT increased the risk of major congenital abnormalities.[9] This study determined that NRT use was not associated with any major congenital abnormalities other than a small increase in respiratory anomalies.

Similar to smoking, nicotine exposure from NRT use during pregnancy has been associated with several adverse effects for the children of these pregnancies, including respiratory problems, attention deficit hyperactivity disorder (ADHD) and learning disabilities, as well as putting the child at risk for nicotine addiction in the future.[19] Cooper et al. (2014) was a study that examined maternal NRT use and potential long-term developmental effects on the children from those pregnancies.[1] In comparison to placebo, this study found that the children of the mothers in the NRT group had less developmental impairments at two years old.

A major limitation of many studies involving NRT in pregnant women is low adherence rates, as can be seen in Wisborg et al. (2000), Oncken et al. (2008), and Coleman et al. (2012).[2,6,7] Multiple reasons for these low NRT adherence rates can be concluded, such as lack of efficacy, maternal concern about medication use during pregnancy, nicotine-withdrawal symptoms, adverse effects, or societal/cultural stigma.[2,8]

Lack of efficacy may be a significant problem, as the metabolism and clearance of nicotine is accelerated during pregnancy, theoretically making the same amount of NRT less effective than in non-pregnant smokers.[8,10] To optimize efficacy, some clinicians have suggested that higher doses of NRT or even combination NRT may be needed in pregnant smokers. Increased nicotine levels from NRT have been associated with adverse fetal effects in animal studies, but this association has not been seen in human trials.[18] In comparison to the intermittent forms of NRT, which are Pregnancy Category C, transdermal nicotine patches are Pregnancy Category D due to a higher amount of nicotine delivered over the course of the patch versus each individual intermittent product. Wright et al. (1997) examined the safety of transdermal patches and showed no apparent maternal or fetal adverse effects. Despite this finding, transdermal patches remain Pregnancy Category D. Brose et al. (2013) compared the use of single NRT to combination NRT and determined that combination NRT was associated with greater smoking abstinence rates than single NRT.[10] A major limitation of this study was the lack of data on safety outcomes. Given that nicotine is a neuroteratogen both in animals and humans, it is imperative that nicotine exposure during the use of NRT does not exceed the nicotine exposure during smoking.[8,25] Combination NRT exposes the fetus to higher levels of nicotine than single NRT, but is unlikely to reach the levels found in tobacco smoking, as well as with the added benefit of not having carbon monoxide and the multitude of other toxins absorbed from cigarette smoke.[10]

Conclusion

Pregnancy provides a unique opportunity for healthcare provider intervention for smoking cessation because women in prenatal care see their physicians frequently during their pregnancy, allowing for multiple opportunities to assess and reinforce abstinence.[37] All pregnant women or women planning to become pregnant should be asked regularly about tobacco use, including what types of products and how often she uses them. These interventions can lead to significant reductions in the number of women smoking during pregnancy, although counseling alone is associated with only a modest improvement in smoking abstinence.[15,20,36] Use of pharmacologic therapy, in combination with CBT, has higher cessation rates than the use of CBT alone. For the pregnant women unable to quit on their own, using NRT may improve smoking cessation rates during pregnancy.[14]

Until definitive safety and efficacy data becomes available, the long-term risk-benefit ratio of NRT in pregnancy is unclear.[5] Because any form of nicotine use during pregnancy may be deleterious to the mother and the fetus, pregnant women should ideally try to quit smoking without nicotine replacement.[25] The short-term risk/benefit ratio of the use of NRT, when necessary, seems favorable for women who are unable to stop smoking.

Clinicians are recommended to use the lowest dose necessary to achieve success in order to minimize fetal nicotine exposure.[17,28] Intermittent forms of NRT products (i.e., gum, lozenge, or spray) are preferred to patches due smaller nicotine concentrations delivered than continuous NRT products (i.e., patches). If a patch is used, limiting the duration of patch use (i.e., 16 hours rather than 24 hours) is recommended. Although some may recommend that NRT be reserved for those patients who are unable to quit without pharmacologic therapy, this recommendation should be weighed against the risks of continued smoking and the benefits of smoking cessation or reduction.

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Personalized Medicine Corner

HLA-B pharmacogenetics and carbamazepine: Who, when, and how to test

The anti-seizure agent carbamazepine (*Tegretol*, *Equetro*, others) has been strongly associated with potentially fatal adverse skin reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS). The risk of serious dermatologic reactions with carbamazepine is linked to the presence of a variant of the *HLA-B* gene.

What is the HLA-B gene?

Human leukocyte antigen B (HLA-B) is a gene that encodes a cell surface protein involved in presenting antigens to the immune system.[1] In some cases and with certain medications, this presenting process triggers an inappropriate immune reaction and leads to serious dermatologic adverse events. In individuals who are primarily Caucasian, these reactions occur in about 1 to 6 per 10,000 people. But this risk is increased 10-fold in patients predisposed to carry the at-risk genetic variant, *HLA-B*15:02*, predominantly patients of Han Chinese ancestry and those from India and Southeast Asia.[1-3]

Who should I test?

The FDA recommends *HLA-B*15:02* testing before initiating carbamazepine in patients with ancestry in at-risk populations.[4] Clinical guidelines define at-risk populations as those of Han Chinese descent, followed by those with ancestry in Vietnam, Cambodia, the Réunion Islands, Thailand, India (specifically Hindus), Indonesia, Malaysia, and Hong Kong.[1] While the frequency of *HLA-B*15:02* is low in other populations, patients may be unaware of or fail to disclose a relevant ancestry. Patients are considered *HLA-B*15:02*-positive if they have one or more copies of this allele, while patients who test negative have no copies present.

*How do I order an HLA-B*1502 test?*

Several commercial laboratories offer the *HLA-B*15:02* test, including Pathway Genomics and ApolloGen Inc. Find additional information about commercially available tests through the National Institutes of Health Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/).

*What should I do if the patient is HLA-B*1502 positive?*

Because SJS and TEN usually manifest in the first three months of therapy, providers can cautiously consider continued use of carbamazepine in patients who have taken it for more than 3 months with no cutaneous adverse reactions.[1] Carbamazepine-naïve patients who test positive for *HLA-B*15:02* should not be started on carbamazepine. Phenytoin and fosphenytoin should also be avoided in phenytoin-naïve *HLA-B*15:02*-positive individuals because this variant has also been linked to adverse events with phenytoin use.[5]

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