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. 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. Nevertheless, many women continue to smoke during pregnancy, with estimates of 12% in the UK, 13% in the U.S., and 15% in Australia. 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. Although some women stop smoking once learning of their pregnancy, most who smoked prior to becoming pregnant continue to smoke throughout the pregnancy.

The first study of a smoking cessation intervention for pregnant women was published in 1976 and included brief advice from a physician to quit. 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).

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). 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. 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. 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. 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. 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. Nicotine has been shown to be directly responsible for acute hemodynamic effects, including increased maternal and fetal heart rate and decreased umbilical blood flow. Carbon monoxide released during smoking results in the formation of carboxyhemoglobin, diminishing tissue oxygenation via competitive inhibition with normal oxyhemoglobin. 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 neurotoxin that compromises the development of critical neural pathways within the developing fetal brain, leading to many cognitive, emotional, and behavioral problems. In animal studies, nicotine was shown to cause abnormalities of neural cell proliferation and differentiation, leading to a
<table>
<thead>
<tr>
<th>Product</th>
<th>Nicotine Gum</th>
<th>Nicotine Inhaler</th>
<th>Nicotine Lozenges</th>
<th>Nicotine Nasal Spray</th>
<th>Nicotine Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Intermittent</td>
<td>Continuous</td>
</tr>
<tr>
<td>Brand Names</td>
<td>Nicorette®</td>
<td>Nicotrol inhaler®</td>
<td>Nicorette®, Commit®</td>
<td>Nicotrol NS®</td>
<td>Nicoderm CQ®, Nicotrol®</td>
</tr>
<tr>
<td>Availability</td>
<td>OTC</td>
<td>Rx only</td>
<td>OTC</td>
<td>Rx only</td>
<td>OTC and Rx</td>
</tr>
<tr>
<td>Strengths</td>
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<tr>
<td>&lt;18 cigarettes/day: 2 mg (per piece)</td>
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<tr>
<td>≥18 cigarettes/day: 4 mg</td>
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<td>1 piece of gum every 1-2 hours; max. 24 pieces/day</td>
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<td>Starting Dosages</td>
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<tr>
<td>&lt;18 cigarettes/day: 2 mg (per lozenge)</td>
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<tr>
<td>≥18 cigarettes/day: 4 mg</td>
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<tr>
<td>1 piece of gum every 1-2 hours; max. 24 pieces/day</td>
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<tr>
<td>Common AEs</td>
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</tr>
<tr>
<td>Mouth soreness; hiccups; dyspepsia; stomachache</td>
<td>Mouth &amp; throat irritation; cough; rhinitis</td>
<td>Nausea; hiccups; heartburn</td>
<td>Nose &amp; throat irritation; coughing; watering eyes</td>
<td>Local skin reactions; sleep disturbances and vivid dreams</td>
<td></td>
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<tr>
<td>Advantages</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduces cravings</td>
<td>Available in variety of flavors</td>
<td>Reduces cravings</td>
<td>Reduces cravings</td>
<td>Helps relieve sudden cravings</td>
<td></td>
</tr>
<tr>
<td>Adverse effects are generally mild, transient and can be alleviated by correcting chewing technique</td>
<td>Available in mint and cherry flavors</td>
<td>Easy to use</td>
<td>Useful in patients with chewing problems or dentures</td>
<td>Control baseline withdrawal symptoms</td>
<td></td>
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<tr>
<td>Disadvantages</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Not suitable for some patients (ie, dentures, TMJ)</td>
<td>Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)</td>
<td>Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)</td>
<td>Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)</td>
<td>Not for sudden cravings</td>
<td></td>
</tr>
<tr>
<td>Caution in CVD, especially serious arrhythmias, unstable angina, or acute MI (prev. 2 weeks)</td>
<td>Contraindicated in severe reactive airway disease</td>
<td>Contraindicated in severe reactive airway disease</td>
<td>Contraindicated in chronic nasal disorders or severe reactive airway disease</td>
<td>Avoid in patients with severe eczema or psoriasis</td>
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<tr>
<td>Patient Instructions</td>
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<tr>
<td>Chew slowly until taste becomes strong</td>
<td>Load nicotine cartridge into inhaler and puff (similar to a pipe) for ~20 minutes; do not inhale like a cigarette</td>
<td>Place between cheek and gums and allow to dissolve, but do not swallow, chew, or suck on lozenge</td>
<td>Spray once in each nostril, without sniffing, swallowing, or inhaling through the nose during sprays</td>
<td>Place unwrapped patch on hairless skin area; wash hands after application</td>
<td></td>
</tr>
<tr>
<td>Rest gum between cheek and gums to allow for absorption of nicotine</td>
<td>Puffing may be done up to 16 times/day</td>
<td>Move from one side of the mouth to the other from time to time until fully dissolved</td>
<td>Remove old patch, fold sticky side in, and dispose of before applying new patch</td>
<td>Remove old patch, fold sticky side in, and dispose of before applying new patch</td>
<td></td>
</tr>
<tr>
<td>Chew gum again when taste fades, and rest gum again when taste is strong</td>
<td>Avoid food or beverages except water for 15 mins prior to/during use</td>
<td>Avoid any foods or beverages except water for 15 minutes prior to/during use</td>
<td>Rotate patch site to avoid skin irritation</td>
<td>Rotate patch site to avoid skin irritation</td>
<td></td>
</tr>
<tr>
<td>Use new piece after 1-2 hours, if needed</td>
<td>Keep in a warm place when not in use during cold weather seasons</td>
<td>Keep in a warm place when not in use during cold weather seasons</td>
<td>If skin irritation occurs, apply hydrocortisone 1% cream</td>
<td>If skin irritation occurs, apply hydrocortisone 1% cream</td>
<td></td>
</tr>
<tr>
<td>Avoid food or beverages except water for 15 mins prior to/during use</td>
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</tr>
</tbody>
</table>

**AEs** = adverse effects; **CVD** = cardiovascular disease; **MI** = myocardial infarction; **OTC** = over-the-counter; **Rx** = prescription; **TMJ** = temporomandibular joint dysfunction.
helped improve smoking cessation among patients, although exact
by prescription. In terms of selecting which NRT formulation to
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
detrimental effects 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 to-
acco use, including cardiac defects, musculoskeletal defects, gas-
trointestinal defects, oro-facial clefts, and cryptorchidism.

The risks of maternal smoking during pregnancy extend be-
yond pregnancy-related complications. Children born to mothers
who smoke during pregnancy were found to have increased sus-
ceptibility 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, en-
docrine, and metabolic outcomes during their adult years. For
children born with major congenital abnormalities, most of these
malformations have significant physical and psychological mor-
bidity for both the children and their parents, in addition to signif-
ificant and often lifelong healthcare service costs.22 Despite aware-
ness of the health consequences of smoking during pregnancy, the
majority of women who smoke will continue to smoke through-
out pregnancy.3,14

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 phar-
macologic 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, with-
drawal 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

### 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 cur-
cently 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 cessa-
tion, 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 ef-
ective 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 re-
ceiving 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 Colema 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 re-
search topic, this study was severely limited by poor compliance
rates.5 Similar to Pollak, El-Mohandes et al. (2013) also initially

http://pharmacy.ufl.edu/pharmanote/
### TABLE 2 | Selected studies of nicotine replacement therapy during pregnancy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics</th>
<th>Exclusion Criteria</th>
<th>Study Arms</th>
<th>Objectives and Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncken, et al.²⁶</td>
<td>24-36 wks gestation</td>
<td>History of heart, liver, or kidney disease, HTN or DM, illicit drug or smokeless tobacco use, TMJ</td>
<td>Control group (no intervention) (n=10) NRT group (n=19)</td>
<td>Compare effects of multiple doses of nicotine gum Measurement of cotinine levels clears Changes in maternal and fetal hemodynamic parameters</td>
<td></td>
</tr>
<tr>
<td>(1996)</td>
<td>Smoked ≥10 cigarettes/day</td>
<td>Placenta previa</td>
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<td></td>
<td>No change in control group Significantly decreased in experimental group No statistically significant changes in maternal and fetal hemodynamics</td>
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<tr>
<td></td>
<td>Attempted to reduce or quit smoking during pregnancy</td>
<td>Fetal growth restriction</td>
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<tr>
<td></td>
<td></td>
<td>Non-heavy smokers (cotinine &lt;85 ng/mL)</td>
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<tr>
<td>Wright, et al.¹⁸</td>
<td>Singleton pregnancy</td>
<td>Obstetric or medical problems</td>
<td>All patients received nicotine patches (n=6)</td>
<td>Safety of transdermal nicotine patch Changes in maternal and fetal characteristics Control of nicotine withdrawal symptoms</td>
<td></td>
</tr>
<tr>
<td>(1997)</td>
<td>Maternal age &lt;35 years old</td>
<td>Medications (other than prenatal vitamins or iron supplements)</td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>27-38 wks gestation</td>
<td>Fetal, placental, or amniotic fluid abnormalities</td>
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<td></td>
<td>Smoked ≥½ pack/day</td>
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<td></td>
<td>Unwilling or could not quit</td>
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<tr>
<td>Wisborg, et al.⁰⁰</td>
<td>&lt;22 wks gestation</td>
<td>Non-singleton pregnancies</td>
<td>NRT group (n=124) Placebo group (n=126)</td>
<td>Smoking cessation at end of treatment and end of pregnancy Effect on birth weight and preterm delivery</td>
<td>Non-significant differences in smoking cessation, possibly due to low adherence rates in both groups Higher birth weights in NRT group No significant difference in preterm delivery rates</td>
</tr>
<tr>
<td>(2000)</td>
<td>Smoked ≥10 cigarettes/day</td>
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<tr>
<td>Pollak, et al.¹⁴</td>
<td>Maternal age ≥18 years</td>
<td>Maternal cognitive or mental health problems</td>
<td>CBT only (n=58) CBT + NRT (n=113)</td>
<td>Smoking cessation rates at 7 wks after randomization, 38 wks gestation, and 3 months postpartum Differences in fetal characteristics Serious adverse events</td>
<td></td>
</tr>
<tr>
<td>(2007)</td>
<td>13-25 wks gestation</td>
<td>Drug, alcohol addiction</td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Smoked ≥100 cigarettes in their lifetime</td>
<td>Poorly controlled HTN</td>
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<td></td>
<td>Smoked ≥5 cigarettes/day</td>
<td>Cardiac arrhythmia</td>
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<td></td>
<td>Spoke English</td>
<td>MI in previous 6 mos</td>
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<td>Hx of placental abruption</td>
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<td></td>
<td>Congenital abnormalities in previous pregnancy or family history of congenital abnormalities</td>
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<tr>
<td>Oncken, et al.⁷</td>
<td>Smoked ≥1 cigarette/day</td>
<td>Evidence of current alcohol, illicit drug use.</td>
<td>CBT only (n=94) CBT + NRT (n=194)</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>(2008)</td>
<td>≤26 wks gestation</td>
<td>Non-singleton pregnancy</td>
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<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Maternal age ≥16 years</td>
<td>Unstable psychiatric or medical problem</td>
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<tr>
<td></td>
<td>Spoke English or Spanish</td>
<td>Medical condition that would interfere with study participation</td>
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<tr>
<td></td>
<td>Living in a stable home</td>
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</tbody>
</table>

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²Many 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).¹,³,⁴,⁵,¹¹,¹³,¹⁸,²⁹

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.\textsuperscript{11} Overall, these studies suggest that NRT may be effective in short-term abstinence, but not as effective for sustained smoking cessation.\textsuperscript{1}

The second major potential benefit for NRT use during pregnancy is to reduce the overall dose and duration of exposure to nicotine.\textsuperscript{3,19,25} Nicotine concentrations achieved with NRT are much lower than those seen in cigarette use.\textsuperscript{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.\textsuperscript{25}

<table>
<thead>
<tr>
<th>Study</th>
<th>Exclusion Criteria</th>
<th>Study Arms</th>
<th>Objectives and Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman, et al.\textsuperscript{2} (2012)</td>
<td>Known major fetal abnormalities; Drug, alcohol dependence; Contraindications to NRT</td>
<td>NRT group (n=521)</td>
<td>Prolonged smoking cessation; Differences in birth outcomes</td>
<td>No differences in smoking cessation (9.4% prolonged abstinence in NRT group vs. 7.6% in placebo group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo group (n=529)</td>
<td></td>
<td>Low adherence rates in both groups (7.2% in NRT group vs. 2.8% in placebo group)</td>
</tr>
<tr>
<td>Brose, et al.\textsuperscript{10} (2013)</td>
<td>Follow-up data missing or not yet completed; Missing maternal age; Smoking cessation medication other than NRT; Missing due date; Data entry errors</td>
<td>Control group with no intervention (n=588)</td>
<td>Smoking Cessation; Differences in efficacy between single and combination NRT</td>
<td>Single NRT was not associated with improved abstinence rates vs. control group at 4-wk follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single NRT (n=1166)</td>
<td></td>
<td>Combination NRT was strongly associated with greater abstinence at 4-wk follow-up</td>
</tr>
<tr>
<td>El-Mohandes, et al.\textsuperscript{11} (2013)</td>
<td>Psychiatric illness; Alcohol or drug abuse</td>
<td>CBT only group (n=26)</td>
<td>Smoking cessation rates; Differences in birth weights</td>
<td>Non-statistically significant increase in smoking cessation in the CBT+NRT group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBT + NRT group (n=25)</td>
<td></td>
<td>Non-statistically significant increase in birth weights in CBT+NRT group</td>
</tr>
<tr>
<td>Cooper, et al.\textsuperscript{1} (2014)</td>
<td>Fetal or postnatal infant death; Non-singleton pregnancies</td>
<td>NRT group (n=445)</td>
<td>Effects of maternal NRT use on child outcomes at 2 years old</td>
<td>Less developmental impairments infants of mothers in NRT group compared to placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo group (n=446)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dhalwani, et al.\textsuperscript{9} (2015)</td>
<td>Live births resulting in minor congenital abnormalities; Live births with congenital abnormalities caused by other known teratogens</td>
<td>NRT group: NRT use 4 wks before conception and/or during 1\textsuperscript{st} trimester (n=2,677)</td>
<td>Association between early pregnancy exposure to NRT with overall and system-specific major congenital abnormalities in live births</td>
<td>Association between NRT use and overall major congenital abnormalities was not statistically significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking group: no NRT use (n=9,980)</td>
<td></td>
<td>No evidence of association between NRT and systems-specific major congenital abnormalities except for a small increased risk of respiratory anomalies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group: non-smokers (n=179,841)</td>
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CBT = cognitive behavioral therapy; DM = diabetes mellitus; HTN = hypertension; MI = myocardial infarction; NRT = nicotine replacement therapy; TMJ = temporomandibular joint dysfunction.
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.8 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.9 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.10 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.3,2,23 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.28

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.19 A major limitation of this study was the lack of data on safety outcomes. Given that nicotine is a neurotoxigen 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.29 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.

References


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

The anti-seizure agent carbamazepine (Tegretol, Eqnoa, 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. 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*1502, predominantly patients of Han Chinese ancestry and those from India and Southeast Asia.1-3

Who should I test?

The FDA recommends HLA-B*1502 testing before initiating carbamazepine in patients with ancestry in at-risk populations. Clinical guidelines define at-risk populations as those of Han Chinese descent, followed by those with ancestry in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindu), Indonesia, Malaysia, and Hong Kong. While the frequency of HLA-B*1502 is low in other populations, patients may be unaware of or fail to disclose a relevant ancestry. Patients are considered HLA-B*1502-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*1502 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. Carbamazepine-naive patients who test positive for HLA-B*1502 should not be started on carbamazepine. Phenytoin and fosphenytoin should also be avoided in phenytoin-naive HLA-B*1502-positive individuals because this variant has also been linked to adverse events with phenytoin use.5

References:

Co-Editors: Larisa Cavallari, PharmD; Kristin Weitzel, PharmD; Associate Editor: Siegfried O. Schmidt, MD, PhD; Assistant Editor: Dyson Wake, PharmD

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