REVIEW ARTICLE

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Artículo 137.159

Nicotine Replacement Therapy During Pregnancy

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In spite of the fact that smoking is the main cause of obstetric morbidity and mortality, 20% of North American women smoke during pregnancy. In Spain, this figure is as high as 30% to 35%. Treating smoking addiction in these patients should be the first and most important therapeutic measure undertaken by health professionals responsible for the care of pregnant women. All experts recommend the use of nicotine replacement therapy when more conservative treatments have failed. This article reviews the indications and contraindications for nicotine replacement therapy during pregnancy as well as other issues relating to the safety of this type of treatment.

Key words: *Smoking. Pregnancy. Nicotine replacement therapy.*

Tratamiento sustitutivo con nicotina durante el embarazo

El consumo de tabaco durante el embarazo es la principal causa de morbimortalidad obstétrica. A pesar de ello, el 20% de las mujeres norteamericanas fuman cuando están embarazadas, cifra que llega a ser de hasta el 30-35% en nuestro país. El tratamiento del tabaquismo en la mujer embarazada debe ser la primera y principal medida terapéutica que los profesionales sanitarios deben adoptar cuando prestan asistencia sanitaria a la embarazada. Todos los expertos recomiendan la utilización del tratamiento sustitutivo con nicotina en los casos en que hayan fracasado tratamientos más conservadores. A lo largo de este artículo se abordan las indicaciones y contraindicaciones del tratamiento sustitutivo con nicotina durante el embarazo, así como aspectos relativos a su seguridad de uso.

Palabras clave: *Tabaquismo. Embarazo. Tratamiento sustitutivo con nicotina.*

Introduction

Although smoking during pregnancy is the leading preventable cause of fetal morbidity and mortality and obstetric disease,[1] many pregnant women continue to smoke. In fact, very often they are not even advised by their doctor, gynecologist, or midwife that they should stop smoking and do not receive the help they need to quit.[2]

According to international studies, approximately 12% of North American women smoke during pregnancy.[1] However, this figure rises to 20% or even 25% when a survey is validated by carbon monoxide pulse oximetry or the measurement of cotinine in bodily fluids.[3] In other words, the results of surveys targeting this special subgroup of smokers are not very reliable. In Spain, very few large studies on smoking in pregnancy have been undertaken, but several surveys of small groups have been carried out. In general, the prevalence of smoking among pregnant women in Spain has been found to be between 30% and 35%. Since almost none of the Spanish surveys have been validated physiologically, it would appear reasonable to suppose that the real prevalence of smoking during pregnancy in this country is actually higher than the estimated figure.[4-6]

In view of the high prevalence of smoking among pregnant women and the fact that smoking cessation represents an excellent preventative measure in these circumstances, the treatment of tobacco addiction in this group is one of the health interventions that should be accorded the highest priority by health care professionals. Treating the patient's addiction to tobacco should be the first and most important therapeutic intervention of any health care professional providing care for a pregnant smoker. A minimum intervention consisting of a motivational interview and psychological treatment have been shown to be effective in helping pregnant smokers to quit. Many women who smoke actually quit spontaneously when they learn that they are pregnant. It has been reported in the United States of America that between 25% and 60% of pregnant smokers quit spontaneously.[7] Nonetheless, many women continue to smoke throughout pregnancy even after receiving the interventions mentioned above. In such cases, the use

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Manuscript received September 17, 2005. Accepted for publication September 27, 2005.

of nicotine replacement therapy (NRT) may be indicated.

Smoking during pregnancy exposes the fetus to large amounts of the toxic substances present in tobacco smoke in addition to high levels of nicotine. Using NRT during pregnancy exposes the fetus to lower levels of nicotine than smoking cigarettes does and, moreover, eliminates exposure to other toxic substances such as carbon monoxide, tars, nitrosamines, and toxic oxygen radicals. This is why in recent decades there has been a marked increase in research into the safety and efficacy of NRT as an aid to tobacco cessation during pregnancy.

We will review the risks to the health of the fetus posed by the nicotine absorbed by the mother as a result of smoking and compare these to the risks to the fetus of maternal NRT treatment. We also analyze the efficacy of NRT in this subgroup of smokers and close with a description of the indications for its use in pregnant women.

Preliminary Clarifications

Before moving on to an explanation of the fetal damage caused by nicotine, 3 important points should be made:

1. Pregnant women who smoke expose the fetus to over 4500 toxic substances, which include carbon monoxide, nitrosamines, tars, and the oxidizing components of tobacco smoke, all of which have a high capacity to cause serious lesions to the placenta and fetal tissue.[8] By contrast, in pregnant women who use NRT as an aid to tobacco cessation, the fetus is only exposed to nicotine.

2. We know that the effects of nicotine on the fetus are dependent on the route of administration, the frequency of consumption, and the dose.[9] The faster the route of administration, the more pronounced and intense are the cardiovascular effects of the nicotine. Smoking cigarettes is the most rapid form of delivery of nicotine followed, at a distance, by nasal sprays, nicotine gum, oral inhalers, lozenges, and, last of all, nicotine patches.[9]

3. It should be remembered that the pharmacokinetic characteristics of nicotine in the fetus and in the mother are different. Since nicotine enters the fetus via the placenta, peak nicotine levels in the fetus occur between 15 and 30 minutes after the substance is consumed by the mother.[10] Moreover, most of the nicotine that enters the fetus returns to the maternal circulation to be eliminated by the mother in the normal way. However, a certain quantity of nicotine is eliminated by the fetus into amniotic fluid via urine. As a result, high concentrations of nicotine and cotinine accumulate in the amniotic fluid of the pregnant smoker because the content eliminated by the fetus is added to the nicotine and cotinine coming from the blood vessels of the amniochorionic membrane.[11] The fetus is, therefore, exposed to high levels of nicotine even after concentrations in maternal blood have decreased.

Fetal Damage Caused by Nicotine

Our understanding of how nicotine damages a fetus has been obtained principally through animal research. Very few studies have been carried out in humans using pure nicotine.

Mechanisms of Nicotine-Related Fetal Damage

Three mechanisms by which nicotine can damage the fetus have been described. The following is a brief review.

One of the most studied mechanisms is based on the effect of nicotine on the uteroplacental vascular system. According to this hypothesis, nicotine constricts the uteroplacental blood vessels by releasing catecholamines and reducing the release of nitric oxide (both known effects of nicotine).[12] This uterine and placental vasoconstriction reduces the delivery of oxygen and nutrients to the fetal tissue, an effect that could retard fetal growth and give rise to placental abnormalities. This hypothesis is supported by the results of studies carried out by Resnik et al[13] and Suzuki et al,[14] who produced significant reductions in the uteroplacental blood flow of pregnant monkeys and ewes using very high doses of nicotine (much higher than those used by NRT). The reduction in blood flow gave rise to acidosis and hypoxia in the fetuses. However, certain other studies contradict this theory. We know that uteroplacental circulation is a low pressure system capable of resisting an intense uterine contraction (during labour for example) while maintaining an adequate blood flow to the fetus. Furthermore, this circulatory system has an adequate reserve capacity and, even during the third trimester of pregnancy after the fetus has grown considerably, the placenta has sufficient blood in reserve to supply the necessary nutrition to the fetus.[15] Nor is it clear that the hemodynamic effects produced by nicotine are sufficiently serious to cause abnormalities in fetal growth.[8,15]

Studies in animals rapidly injected intravenously with high doses of nicotine have demonstrated that nicotine can cause platelet activation and thereby give rise to the formation of thrombi.[16] It has been hypothesized that this could be a pathological mechanism in the uteroplacental circulation of pregnant smokers. However, studies in humans using both nicotine patches and cigarettes have not shown nicotine to be capable of causing platelet activation.[17]

In vitro studies have demonstrated that nicotine, cotinine, and other toxins found in tobacco smoke (such as anabasine) inhibit aromatase, an enzyme that plays a role in the conversion of androstenedione to estrogen. This would explain why plasma estrogen titers are lower in pregnant smokers than in nonsmoking pregnant women, and would suggest another mechanism of nicotine-related fetal damage.[18,19]

The Effects of Nicotine on the Fetus

Nicotine can damage the lungs, heart, and above all the central nervous system of the fetus.

It is undoubtedly the fetal central nervous system that is most susceptible to nicotine damage. It has even been ascertained that the toxic effects of nicotine persist after administration has stopped. In the course of the embryonic development of the central nervous system, certain neurotransmitters play a fundamental role in activating and arresting cell proliferation, differentiation, migration, and apoptosis. Nicotine stimulates the production of cholinergic receptors. The appearance of such receptors at an inappropriate time during the development of the nervous system (for example, when adequate quantities of acetylcholine are not present) can prematurely arrest cell proliferation and trigger cellular differentiation in the central nervous system, thereby reducing the number of neurons present in certain areas of the brain.[9,20] The administration of nicotine to experimental animals during gestation has been associated with harmful effects on the synthesis and release of various neurotransmitters, such acetylcholine, noradrenaline, dopamine, and serotonin.[21] Moreover, alterations have been observed in the type and density of certain receptors of various different neurotransmitters at nerve endings.[9] In experimental animals, certain abnormalities attributable to these alterations in brain development have been detected using various types of behavioral and cognitive tests. A positive dose-response relationship has even been found for such abnormalities.[22]

The administration of nicotine during gestation provokes an increase or decrease in fetal heart rate. However, these alterations are slight and, of course, less intense when they are the result of NRT than when they are caused by smoking during pregnancy.[9]

Studies in monkeys have demonstrated that the administration of nicotine during pregnancy increases the development of $\alpha 7$ nicotine receptors in certain cells implicated in lung development. Pulmonary hypoplasia and other abnormalities in pulmonary and bronchial development were found in the offspring of experimental animals after exposure to nicotine during gestation.[23] Probably owing to this effect (or to other, as yet undefined, disorders affecting pulmonary and bronchial development in fetuses exposed to nicotine), newborn infants of mothers who have smoked tobacco during their pregnancy tend to be hypoxic. The response of these newborn infants to hypoxia is also deficient. In rats that have not been exposed to nicotine, hypoxia triggers the rapid release of catecholamines in the adrenal medulla, thereby stimulating heart rate and increasing blood flow to the brain. In contrast, in rats that have been exposed to intrauterine nicotine, hypoxia triggers only a very scant release of catecholamines and impairs the adequate supply of oxygen to the brain. This mechanism may facilitate the onset of processes such as sudden infant death syndrome,[24] which is reported more often in the children of mothers who smoked during pregnancy than in infants never exposed to nicotine.[25]

Alterations in the Metabolism of Nicotine During Pregnancy

The metabolism of nicotine and cotinine changes during pregnancy. An understanding of these changes is necessary because they have important clinical and therapeutic repercussions.

The metabolic clearance of nicotine is increased in pregnant women. Dempsey et al[26] studied 10 women who received intravenous nicotine during pregnancy and postpartum. The mean clearance of nicotine during pregnancy was 26 mL/min/kg as compared to 16 mL/min/kg in the postpartum period. Since pregnancy produces an increase in heart rate that gives rise to an increase in liver blood flow, hepatic metabolism of nicotine increases and clearance is accelerated. The therapeutic and clinical repercussions of this accelerated clearance are important. Firstly, it leads us to suppose that NRT should be administered at higher doses during pregnancy than under normal circumstances (and the fact that normal doses have been used in the studies undertaken to date may explain the lack of efficacy observed).[27] Secondly, it highlights the need for monitoring of nicotine concentrations in blood when NRT is used during pregnancy in order to ensure an appropriate regimen is used and avoid either a too low or a too high dose.

Metabolic clearance of cotinine also increases during pregnancy. In the study mentioned above, Dempsey et al[26] found cotinine clearance in women to be 1.5 mL/min/kg during pregnancy and only 0.5 mL/min/kg in the postpartum period.[26] Since cotinine is a substance that metabolizes very slowly, its rapid clearance during pregnancy cannot be explained by an increase in liver blood flow. The phenomenon appears rather to be due to an increase in the production and activity of certain enzymes directly related to the metabolism of cotinine. While the half-life of cotinine under normal circumstances is approximately 17 hours, this figure falls to around 9 hours during pregnancy. The difference should be taken into account in population studies in which cotinine levels in blood or urine are measured, and cutoff points should be adjusted downwards in studies of pregnant women.[28]

Safety of NRT During Pregnancy

To date, only very few studies have analyzed the development of adverse effects in pregnant smokers using NRT as a tobacco cessation aid. Some of these effects are discussed below.

Oncken et al,[29] in a study of 19 pregnant smokers who used 2 mg nicotine gum for 5 days at a dose of 5 to 8 pieces of gum a day, found that the hemodynamic effects (increase in maternal and fetal heart rate and decrease in the variability of the fetal heart rate) produced by NRT were significantly less pronounced than those caused by smoking.

The use of nicotine patches in pregnant smokers has also been studied. A study of 15 pregnant smokers who used 21 mg patches for 8 hours found that both cigarette smoking and the use of patches during this

short period was accompanied by an increase in maternal heart rate, a slight increase in uterine artery resistance, and a small decrease in the middle cerebral artery resistance index. No differences were found in the short term between NRT and smoking.[30] However, in a study of 6 women who wore 21 mg patches for 6 hours, Wright et al[31] did not observe any such alterations. In a more controlled study in which 21 pregnant smokers used 22 mg nicotine patches for 4 days (during which period they abstained from smoking), the authors found that the mean nicotine concentration in plasma associated with patch use was appreciably lower (11.8 ng/mL) than that produced by smoking cigarettes (14.4 ng/mL). Fetal heart rate was also significantly lower with NRT than with tobacco consumption, although no differences were found in the velocity of umbilical artery blood flow or fetal reactivity.[31] In a later analysis of the same 21 patients, Schroeder et al[32] studied the 8 women who stopped smoking and continued to use 22 mg patches for 8 weeks and found no abnormalities in fetal growth or fetal stress tests.

A recent analysis of the records of 76 768 pregnant women found that women who abstained from smoking during pregnancy but used NRT had a slightly higher relative risk of bearing children with congenital malformations (odds ratio, 1.61; 95% confidence interval, 1.01-2.58). However, given the wide confidence interval, the authors concluded that further studies are necessary before their results can be attributed greater validity.[33]

Effectiveness of NRT During Pregnancy

To date, only 2 studies have analyzed the effectiveness of transdermal nicotine patches in the treatment of smoking addiction in pregnant women,[27,34] and this form of NRT was not shown to be effective by either one. Wisborg et al[27] studied 250 pregnant smokers after their first term of pregnancy. The participants were assigned to 2 treatment groups. In the first group, the treatment program comprised moderate psychological intervention and 3 weeks of 16-hour transdermal patches releasing 15 mg of nicotine. The second group received the same psychological intervention and placebo patches. There were no significant differences in abstinence between the two groups: 28% and 25%, respectively, on follow-up at 4 months; and 15% and 14% one year after childbirth. However, marked differences were observed between the 2 groups in the weight of the newborn infants. The offspring of the mothers who wore the active patches had significantly higher birth weights than the infants whose mothers had used the placebo patches (3539 g compared to 3381 g).

There are at least 2 reasons why transdermal nicotine patches were not effective in this group of pregnant smokers: firstly, the changes in the metabolic clearance of nicotine associated with pregnancy described above; and secondly, the low dose of nicotine used, especially in light of the fact that it is probable that these women were highly nicotine dependent. All of these findings highlight the need for controlled studies in pregnant smokers using appropriate doses of NRT in order to determine the precise effectiveness of this type of therapy in this special subgroup of smokers.

Recommendations for the Use of NRT During Pregnancy

Two important conclusions can be drawn from a review of the literature: *a)* the risks associated with smoking during pregnancy are significantly higher than those associated with the use of pure nicotine,[9,35] and *b)* the use of NRT during pregnancy has not been shown to be completely harmless to the fetus and the mother. However, a proper analysis of the risks and benefits of NRT reveals that the use of such treatment as an aid to tobacco cessation in pregnant women is appropriate. In a recent study carried out in the United Kingdom, it was found that only about 27% of general practitioners prescribe NRT to pregnant smokers although up to 62% of them considered that NRT could be effective in this group of smokers and, of course, believed it to be safer than smoking. Notwithstanding, they tended not to prescribe NRT because of a lack of knowledge about how it should be used during pregnancy.[36]

Guidelines on how NRT should be used during pregnancy would, therefore, appear to be necessary. The review articles that have been published propose the following recommendations[9,35-42]:

1. All pregnant women should be informed of the need to stop smoking immediately. If a mother abstains from smoking during the first 3 months of her pregnancy the fetus is exposed only to the same risks as the fetus of a nonsmoking mother.

2. All pregnant smokers should receive behavioral therapy and appropriate social and family support aimed at helping them to quit permanently.

3. Pharmacological treatment should be considered when the pregnant woman is moderately or highly dependent on nicotine, when psychological treatment has failed, or if she smokes 20 or more cigarettes a day.

4. Before pharmacological treatment is prescribed to aid tobacco cessation in pregnant women, the physician and the patient should evaluate together whether the benefit obtained—given the higher probability of quitting associated with treatment and all the consequent benefits of stopping smoking—is greater than the risk to the mother and fetus posed by the use of pharmacological tobacco cessation therapy.

5. Pharmacological tobacco cessation therapy should be started as early as possible in the pregnancy. The sooner the pregnant woman stops smoking, the greater are the benefits for both the fetus and the prospective mother. Once it is clear that psychological treatment alone has failed, pharmacological treatment should be prescribed immediately.

6. Once it has been established that pharmacological tobacco cessation therapy is needed, such therapy should always be prescribed in addition to psychotherapy.

7. Of the 2 first-line pharmacotherapies in current use, NRT is the preferred option. Bupropion should only be used in controlled clinical trials.

8. The appropriate dose of NRT should be carefully evaluated. Cotinine values should be measured before treatment is started, and the NRT dose prescribed should be adjusted to achieve cotinine levels similar to baseline values. Measurement of cotinine values before and after treatment not only ensures the prescription of more effective doses of nicotine, but also helps to ensure a safer dosage.

9. The most appropriate type of NRT to be used in each case should also be evaluated. In general, ad libitum forms are preferred, that is, nicotine gum and oral inhalers rather than transdermal patches. However, the type of NRT should be decided on a case-by-case basis. In women who suffer from frequent vomiting and nausea during pregnancy, nicotine patches are preferable to gum.

10. If it is decided that patches are the appropriate choice, 16-hour patches are preferred over 24-hour patches. The use of 16-hour patches reduces daily exposure to nicotine and, at least theoretically, minimizes the risk of fetal toxicity.

11. Once it has been established that the appropriate treatment is nicotine gum or another ad libitum form of NRT, the prescription should be for use on demand when required to deal with cravings.

12. National registries of pregnant smokers who have used pharmacological tobacco cessation therapies should be established.

Conclusions

We have reviewed studies that analyze the safety and effectiveness of NRT in pregnant women. Although the effectiveness of NRT in this subgroup of patients has not yet been demonstrated and it has not been possible to demonstrate that this type of treatment is absolutely harmless in pregnancy, the recommendations of experts in the treatment of smoking addiction in pregnant women consider NRT to be the treatment of choice when psychotherapy alone is not successful.

A national register of pregnant women who have received pharmacological therapy should be set up in Spain. This record would contribute significantly to the understanding of the risks and benefits associated with the use of such treatment in pregnant smokers.

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