WORKSHOP SUMMARY

The use of pharmacotherapies for smoking cessation during pregnancy

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A workshop entitled “The use of pharmacotherapies for smoking cessation during pregnancy”, sponsored by the National Institute of Child Health and Human Development (NICHD) and the Robert Wood Johnson Foundation (RWJF), was held in Rockville, Maryland, on 19 May 1999. The goals of the workshop were: (1) to determine the current state of knowledge related to the use of pharmacotherapies for smoking cessation during pregnancy; and (2) to outline a research agenda to determine the effectiveness and safety of these pharmacotherapies. Attending the workshop were many of the academic experts working in this area in the USA and representatives from NICHD, RWJF, the National Cancer Institute (NCI), the National Institute of Drug Abuse (NIDA), the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), the Society for Research on Nicotine and Tobacco (SRNT), and several pharmaceutical companies.

Background

In the USA, of the four million women who deliver babies each year, approximately 0.8–1 million smoke during their pregnancies. Smoking has a substantial adverse impact on pregnancy outcomes including growth retardation, preterm birth, perinatal mortality, sudden infant death syndrome (SIDS), and childhood behavioural problems. In developed countries, more than a third of all cases of growth retardation is caused by maternal smoking, and the more a woman smokes, the larger the effect on fetal growth. Stopping smoking is one of the more a woman smokes, the larger the effect of smoking—binds to haemoglobin, resulting in a substantial adverse impact on improving pregnancy outcomes. While most of the studies of the fetal effects of smoking have focused on nicotine, it is unclear which components of cigarette smoke actually do the damage. In addition to nicotine, cigarette smoke contains carbon monoxide, cyanide, cadmium, lead, methanol, and many others; and (5) smoking may also alter the maternal/fetal nutritional status.

Behavioural interventions are effective in reducing smoking during pregnancy. A meta-analysis of 16 randomised controlled smoking cessation trials during pregnancy with validated outcomes confirms that a single 5–15 minute counselling session by a trained provider with appropriate printed materials approximately doubles the typical cessation rates of 5–10% achieved without counselling to about 20%. This increased level in cessation is associated with a reduction in low birth weight and is estimated to save $3 in medical costs for every $1 spent on the intervention. Unfortunately, brief counselling does not achieve cessation in the remaining 80% of pregnant smokers, is least effective in the most dependent smokers, and may not be acceptable to some pregnant women. Studies testing more intensive counselling—more time and more occasions—have not generally achieved larger effects. Thus, it is unlikely that additional behavioural interventions used alone will achieve a substantial increase in cessation in pregnant smokers.

Components of cigarette smoke

Cigarette smoking during pregnancy is associated with a number of adverse outcomes; however, it is unclear which components of cigarette smoke actually do the damage. In addition to nicotine, cigarette smoke contains carbon monoxide, cyanide, aniline, methanol, hydrogen sulfide, arsenic, lead, cadmium, and 3000 other potential toxins or carcinogens. While most of the studies of the fetal effects of smoking have focused on nicotine, it is unknown which other components of smoke actually lead to some or all of the known adverse outcomes.

Nicotine activates the sympathetic nervous system and evokes the release of catecholamines and other neurotransmitters. In animal fetuses, nicotine administered by osmotic minipump to simulate transdermal patch application can reduce overall fetal growth and produce some neurologic abnormalities secondary to perturbation of neuronal maturation and neuronal cell death. In the first trimester, even short term...
nicotine exposure can elicit neuronal cell death. Also in study animals, the impact of nicotine is related to the time in pregnancy when it is administered, the dosage level, and whether it is given intermittently or by continuous infusion. The adverse effects of nicotine were worse in the presence of even mild hypoxia. In animals, nicotine—used alone in doses similar to nicotine blood concentra-

cations associated with smoking or nicotine replacement therapy (NRT)—can cause abortion and fetal death, growth retardation, and a decrease in fetal brain growth. In humans, nicotine is associated with increased heart rate and vasoconstriction. There is no evidence that in the usual dosage range, nicotine, even when used early in pregnancy, is dysmorphic.

Aside from nicotine, carbon monoxide has been the most studied component of cigarette smoke. In animals, chronic carbon monoxide exposure resulting in carboxyhaemoglobin concentrations in the range found in human smokers is associated with fetal growth retardation. Postnatal effects in animals associated with prenatal carbon monoxide exposure are similar to the spectrum of effects seen with nicotine (alterations in behaviour and cognition, neurotransmitter changes in the central nervous system, decreased cerebellar weight, etc). One likely benefit of NRT as an alternative to smoking is to spare the fetus exposure to carbon monoxide.

Possible effects of pharmacotherapies

In non-pregnant smokers, NRT, whether administered by gum, patch, inhaler or nasal spray, and antidepressant drugs, such as bupropion and nortriptyline, have all achieved a twofold increase in cessation rates compared to placebo medications. In non-pregnant smokers, when used according to instructions, NRT in any form and bupropion are generally safe. Therefore, pharmacologic treatments have the potential for achieving an important reduction in smoking during pregnancy. However, the use of pharmacologic agents in pregnancy raises at least two concerns. First, the developing fetus is at risk for teratogenic, asphyxic, and neurodevelopmental damage. Second, pregnancy itself is a powerful motivator for cessation, with a substantial number of women quitting spontaneously or with behavioural therapy. Whether pharmacologic treatments are safe for the fetus, and whether pharmacologic treatment will be as effective in achieving cessation in pregnant smokers compared to non-pregnant smokers, is unknown. Another significant gap in our knowledge concerns the optimal dose of nicotine and the response to the drug in pregnant women.

Currently in the USA, nicotine gum and patch are available over-the-counter with a warning not to use during pregnancy without consulting a physician. Nicotine inhaler and nasal spray are available by prescription and have a category D pregnancy warning (that is, “There is positive evidence of human fetal risk, but benefits from the use during pregnancy may be acceptable despite the risk . . .”). The package inserts on these products state that “. . . pregnant smokers should be encouraged to attempt cessation using educational and behavioural interventions before using pharmaco-

logical approaches” and these therapies “ . . . should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it by the pregnant patient, who might continue to smoke.”

There are several unanswered questions about nicotine safety in pregnancy: (1) whether there is a critical period of exposure to nicotine that increases the risk of fetal or obstetrical toxicity; (2) whether there is a dose threshold of toxicity; (3) whether a better pharmacokinetic model of fetal exposure to nicotine from smoking can be developed; and (4) whether a biomarker of nicotine effect on neural development in neonates could be discovered to assess some of the potential toxic effects of nicotine in vivo.

Bupropion and nortriptyline—anti-depressant medicines—increase dopamine and noradrenaline activity. However, the mechanisms by which these medications aid in smoking cessation are unknown. Since these medications achieve similar levels of cessation in depressed and non-depressed smokers, the mechanism of action is not completely related to their action as antidepressants. There are no data on the safety of bupropion or nortriptyline for smoking cessation during pregnancy. Bupropion is classified as a pregnancy category B medication (that is, animal studies have shown no risk without confirmation in human studies, or animal studies have shown risk but controlled studies in humans showed no risk), and nortriptyline is listed as a category D medication.

Almost no efficacy research related to the use of NRT in pregnant human subjects has been conducted. One large efficacy study of NRT (nicotine patch) use by pregnant women was carried out in Scandinavia; however, to date, the results have not been published and only an abstract—without outcome data—is available. An oral presentation of this study suggested that NRT (nicotine patch) was not effective. There are no other randomised studies; thus, no decision on the efficacy of NRT in pregnancy can be made at this time. Two small clinical trials in pregnant women suggest short term use of NRT administered by commercially available patches or gum achieved serum nicotine concentrations comparable or less than those obtained while smoking 10–20 cigarettes per day. Among these few pregnant women, there were no adverse outcomes to the mother or fetus, although nicotine apparently has effects on fetal breathing movements and on fetal heart rate variability. Because of the small number of pregnant smokers studied to date, rare or subtle adverse fetal outcomes would not likely have been detected.

No conclusion could be reached as to whether the effects of intermittent dosing of nicotine—such as achieved by smoking—were different than steady state delivery such as...
achieved with the nicotine patch. Some discus-
sants expressed concern about potential harm
to a fetus continually exposed to nicotine with
no rest period as would occur with a 24 hour
patch. Some discussants believed that it was
unlikely that delivering concentrations of nic-
toine by NRT that are similar to those seen in
smokers would increase the risk of adverse
outcomes over those seen in women who
smoke, given that pregnant smokers are
exposed not only to nicotine but also to the
many other toxins in tobacco smoke. Others
emphasised that high dose patches might
deliver higher doses of nicotine and at a higher
constant concentration than that seen in
smokers—many—and especially light—smokers.
The major adverse effects of smoking, especially
those related to birth weight, appear to occur
late in pregnancy. It was hypothesised that with
NRT, the potential adverse side effects in terms
of fetal growth would also occur late in
pregnancy. Several participants therefore
suggested that if NRT were used, it should be
started earlier rather than later in pregnancy.

Research needed
Both basic research and clinical outcomes
research are necessary to determine whether
pharmacologic treatment of pregnant smokers
is safe and effective. Further work in
experimental animals is necessary to answer
questions related to the influence of dose, time,
pattern of administration on the adverse effects
of nicotine, carbon monoxide, and other com-
ponents of tobacco smoke. It is also important
to determine the specific effects of the tobacco
smoke components (for example, nicotine ver-
sus carbon monoxide versus others) on mater-
nal blood flow, placental development and
function, and on fetal somatic cell growth and
brain development.

Equally important is the study of the efficacy
of various NRT strategies and antidepressants
in pregnant smokers. Effectiveness studies that
deal with acceptability in actual use are also
important. Since reduction in the absence of
cessation is common in pregnancy, further
investigation of both smoking cessation and
reduction are indicated, as well as measures of
fetal growth such as mean birth weight, the per
cent small-for-gestational-age infants (< 10th
centile), and preterm birth. The impact of pharmaconterapies on rarer outcomes such as
abruption and fetal death would require a very
large sample size. Outcomes, such as infant
neurodevelopmental status at ages 2 to 5 years,
as well as growth status at the same ages, are
important but difficult to study.

The interaction between pharmacological
agents and various behavioural interventions
also needs further study. A randomised
torial design contrasting a behavioural
method versus brief advice and a pharma-
ologic intervention versus placebo is needed.
A related issue is that if the prenatal care provider
waits for a woman to fail a behavioural therapy
before presenting pharmacotherapy, this may
result in medication being used later rather
than early in pregnancy. As stated earlier, there
is reason to prefer the opposite. Other

important questions to explore include when
during pregnancy to initiate pharmacologic
treatment and for how long to maintain its use.

NRT efficacy and safety should be evaluated in
a standardised manner, known adverse preg-
nancy outcomes associated with smoking dur-
ing pregnancy. Although large sample sizes
would be needed to detect differences in risk
for any one outcome, by combining
standardised outcomes (that is, low birth
weight, premature delivery, abruptio placenta,
placenta previa, SIDS, etc) across studies, it
may be possible to estimate the safety of NRT
compared to placebo for smoking cessation
during pregnancy. This type of safety study has
been done to determine the safety of NRT in
cardiac patients.

Conclusions
Despite the absence of data on safety, efficacy,
and effectiveness, the use of pharmacologic
agents in pregnancy is becoming increasingly
considered, given the increased awareness of
the harm from smoking in pregnancy and the
benefits of pharmacotherapy. Given the large
attributable risk of adverse outcomes in
pregnancy associated with cigarette smoking,
the current over-the-counter status of NRT,
and the potential for substantial benefit in
reducing adverse pregnancy outcomes using
pharmacologic agents, clinical studies in this
area should be undertaken immediately.

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