

12 Tobacco use in pregnancy: health risks and intervention for smoking cessation

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The risk factor responsible for the greatest disease burden in Australia is tobacco smoking, which accounts for about 12% of the total burden of disease in men and 7% in women (Mathers et al 1999). Tobacco smoking contributes to higher drug-related morbidity and mortality than both alcohol and illicit drug use combined (Australian Institute of Health and Welfare 2002). It is the leading preventable cause of morbidity and mortality, particularly from: cardiovascular disease; cancers of the lung, larynx and mouth; and chronic obstructive pulmonary disease. It is estimated that about half of all long-term smokers will die from smoking-related causes (Lopez et al 1994). Nicotine has been described as being as addictive as heroin and cocaine (Royal College of Physicians 2000). Tobacco dependence is recognised as a condition in the World Health Organization's International Classification of Diseases (ICD-10) (World Health Organization 2003) and the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV) (American Psychiatric Association 1994).

Reproductive health is harmed by smoking tobacco in both men and women. There is conclusive evidence that smoking causes compromised fertility, and that parental smoking potentially has long-term and serious consequences for child health. Smoking while pregnant contributes to an increased risk of a broad range of obstetric complications, including ectopic pregnancy, spontaneous abortion, pregnancy and labour complications, stillbirth, low birth weight and sudden infant death syndrome (SIDS) (British Medical Association 2004). Exposure to environmental tobacco smoke (ETS), otherwise known as "secondhand smoke", is a risk factor for lung cancer and cardiovascular disease in adults, and for SIDS, asthma, and lower respiratory disease in children (Ridolfo and Stevenson 2001). Exposure to environmental tobacco smoke is a risk during pregnancy, and harms both the mother and fetus.

This paper summarises and quotes expert scientific reports that have reviewed the large body of available evidence for the harmful effects of smoking during pregnancy on maternal and infant health and evidence-based best practice for smoking cessation interventions.

Prevalence

Since the early 1970s, smoking rates in Australia have fallen steadily. Smoking prevalence in Australia is now among the

lowest of all countries participating in the Organisation for Economic Cooperation and Development (OECD). According to the 2004 National Drug Strategy Household Survey, 17.4% of Australians older than 14 years were daily smokers (18.6% of males and 16.3% of females). A further 3.2% smoked weekly or less than weekly. Around 25% were ex-smokers and slightly more than half (52.9%) of the population had never smoked (Australian Institute of Health and Welfare 2005). The highest smoking rates were recorded among those aged 20–29 years, with around 30% of this age group reporting current smoking (including those who smoke daily plus weekly and less than weekly). Overall, males were more likely than females to report being a smoker.

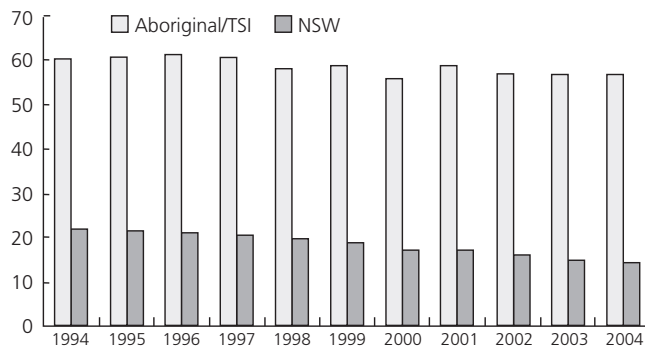
There is significant socio-economic variation in smoking prevalence. Respondents to the 2004 NSW Health Survey from the least disadvantaged socioeconomic quintile reported significantly lower rates of current smoking (16.9%) compared with the overall population of NSW (20.9%). People in the most disadvantaged quintile reported higher rates of smoking (25.6%). The term 'current smokers' in the NSW Health Survey includes both those who smoke daily and those who smoke occasionally (NSW Health 2005).

By contrast, 51% of Aboriginal and Torres Strait Islander people aged 18 years and over in Australia were current smokers in 2001 (Australian Bureau of Statistics 2003), compared with 24% of non-Indigenous people. Smoking was more commonly reported in 2001 among Aboriginal and Torres Strait Islander males and females in every age group compared with the non-Indigenous population (Australian Bureau of Statistics 2003). The prevalence of daily smoking among Aboriginal and Torres Strait Islander women (47%) was more than two and-a-half times the rate for non-Indigenous women (18%). For Aboriginal and Torres Strait Islander men the daily smoking rate was 43%, double that of non-Indigenous men (21%). Aboriginal and Torres Strait Islander peoples are at greater risk than non-Indigenous Australians of hospitalisation and death from tobacco-related health problems. Smoking during pregnancy is also a risk factor for low birth weight, which is about twice as common among babies born to Indigenous mothers as it is among non-Indigenous babies (Australian Bureau of Statistics 2003).

The proportion of NSW mothers reporting that they smoked during their pregnancy declined from 22.1% in 1994 to 14.8% in 2004 (Figure 1). For the same period, the rate of smoking during pregnancy among NSW Aboriginal and

Torres Strait Islander women was consistently three times that of all pregnant women in NSW and demonstrated a slower rate of decline, from 60.3% in 1994 to 56.6% in 2004 (NSW Health 1999–2004).

Figure 1: Comparison of the prevalence of smoking in Aboriginal and Torres Strait Islander and all NSW pregnant women by year, NSW, 1994–2004



Source: NSW Midwives Data Collection (HOIST). Centre for Epidemiology and Research, NSW Department of Health.

Most women who smoke before pregnancy either quit or reduce their levels of smoking during pregnancy. However, most information on prevalence of smoking during pregnancy, including that obtained for studies on reproductive effects, comes from self-reports by pregnant women. Under-reporting of smoking during pregnancy is a common practice, as smoking during pregnancy is now widely viewed as unacceptable. High rates of underreporting have been reported in intervention trials. Underreporting may be a result of the social stigma associated with smoking or the typical change in patterns of smoking during pregnancy. Windsor et al (1998) found an error or “deception” rate of 28% for self-reports at the end of pregnancy compared with an objective biological validation (salivary cotinine testing).

Mechanisms for harm caused by smoking in pregnancy

The precise mechanisms underlying the various effects of smoking on pregnancy are not completely understood; however, various components of tobacco smoke have been implicated in processes that reduce fetal growth and birth weight. Within minutes of inhalation of tobacco smoke, wherever the blood flows, many of the more than 4000 chemicals from tobacco smoke also rapidly flow (US Department of Health and Human Services 2004). Nicotine induces vasoconstriction, or narrowing of the blood vessels. This affects the function of the placenta, restricting blood flow and reducing the supply of nutrients and oxygen to the fetus.

The increased risk of stillbirth related to maternal smoking may be accounted for by growth restriction and placental complications. Vascularisation, the growth and proliferation of blood vessels, plays an important part in the establishment

and maintenance of the placenta, as well as in growth and development of the embryo itself. Tobacco smoking disrupts the process of vascularisation (British Medical Association 2004).

The physiological effects of tobacco on fetal growth result primarily from the combined vasoconstrictive effects of nicotine on the uterine and umbilical arteries and an increase in carboxyhaemoglobin, leading to reduced oxygenation of the fetus (US Department of Health and Human Services 2004).

Carbon monoxide in tobacco smoke inhaled by the mother displaces oxygen in the circulation, reducing the amount available to the fetus (British Medical Association 2004). A maternal 10% blood carboxyhaemoglobin level, which can be observed in a two-pack-per-day cigarette smoker, can be associated with a 10% to 15% higher carboxyhaemoglobin level in the fetus than in the mother. This has been equated to a 60% reduction in fetal blood flow (Benowitz 1991). Abstaining from smoking for 48 hours during the third trimester has been demonstrated to increase the available oxygen to the fetus by 8% (US Department of Health and Human Services 2004).

There is growing evidence that smoking during pregnancy affects the normal development of the brain systems that regulate oxygen uptake and heart function, increasing the risk of stillbirth, neonatal death and sudden infant death syndrome (SIDS) (British Medical Association, 2004). Blood vessel constriction and high levels of carbon monoxide in the blood caused by smoking may induce hypoxia, which has been implicated in placental abruption. Hypoxia can also result in the enlargement of the placenta, causing it to extend over the cervix, as seen in placenta praevia. Vasoconstriction may also explain the increased risk of premature rupture of the membranes and premature birth associated with smoking (British Medical Association 2004).

Cessation of smoking can reduce or eliminate many of the risks to reproductive life and health (US Department of Health and Human Services 1990). As smoking prevalence is highest among younger age groups who are in their best reproductive years, to reduce rates of smoking in pregnancy strategies and services to reduce uptake and support cessation must target the larger population of younger adults (British Medical Association 2004).

Health effects

There are more than 4000 chemicals in tobacco smoke, at least 50 of which are known carcinogens; others are toxic and mutagenic. When tobacco is smoked, these chemicals are quickly delivered throughout the body wherever the blood flows and every organ is affected (US Department of Health and Human Services 2004). There is conclusive evidence that there is a very strong causal association between smoking during pregnancy and placental complications, premature rupture of the membranes, premature birth, low

birth weight babies and perinatal death (British Medical Association 2004).

The United States Surgeon General's reports on tobacco smoking have reviewed the evidence regarding smoking as a cause of harmful reproductive effects since the first report in 1964, which stated: "Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight." Subsequent reports have continued to confirm, review and update the literature, adding substantially to the overwhelming volume of evidence for the harm caused by smoking in pregnancy. Smoking causes an acute reduction in intervillous blood flow of the human placenta in near-term pregnancy. Repeated decreases in intervillous blood flow may explain growth restriction of the fetus and other pregnancy-related complications in women who smoke (US Department of Health and Human Services 2004). A selection of evidence for a range of health effects associated with smoking in pregnancy is outlined below.

Ectopic pregnancy

Ectopic pregnancy is a rare but serious complication that can be fatal for the mother. It occurs when the fertilised ovum is implanted outside the uterus, usually in the fallopian tubes. Surgical intervention is required to remove the embryo, which can result in reduced fertility due to tubal damage or removal. The aetiology is not fully understood; however, reduced motility of the fallopian tubes is a factor. Animals exposed to tobacco smoke have reduced tubal motility, with suppressed rhythmic movement of the cilia, the small hairs that line the fallopian tubes and waft the ovum toward the uterus. Reduced motility may result in the ovum remaining in the fallopian tube longer, increasing the chance of tubal implantation and an ectopic pregnancy (British Medical Association, 2004; US Department of Health and Human Services 2004).

The British Medical Association (2004) reviewed the evidence for the effects of smoking on reproductive life and states that there is *substantial* evidence that smoking causes ectopic pregnancy, quoting studies that estimate an increased risk of 1.5-2.5 times in women who smoke. The risk may be significant even when relatively few cigarettes are smoked, with one study reporting that among women who smoke 1-5 cigarettes a day, the risk of ectopic pregnancy may be 60% higher than in non-smokers (British Medical Association, 2004).

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of ectopic pregnancy. The report concludes:

The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

Findings of the review include:

- Several studies report an increased risk of ectopic pregnancy among active smokers. Odds ratios (ORs) for active smokers compared with non-smokers in these studies ranged from 1.3 to 2.5.
- Dose-response relationships have been reported in some studies, with an estimated RR from 1.4 (95% CI 0.8–2.5) for a woman smoking fewer than 10 cigarettes per day to 5.0 (95% CI 2.9–8.7) at 30 or more cigarettes per day.
- Smoking cessation before the month of conception may reduce the risk of ectopic pregnancy.

Level of evidence: III-2

Placental complications

Smoking during pregnancy increases the risk of complications affecting the placenta, which supplies oxygen and nutrients to the developing fetus (British Medical Association 2004). Increasing levels of maternal smoking result in a highly significant increase in the risk of abruptio placentae, placenta praevia, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery, all of which carry high risks of perinatal loss (US Department of Health and Human Services 1980).

Placental complications are an important cause of morbidity and mortality in mother and baby, and contribute to perinatal mortality. Premature separation of the placenta from the wall of the uterus (placental abruption) is one of the main causes of perinatal death. Smoking increases the risk of placental abruption 1.4 to 2.4 fold, and there is a dose-response relationship, with the risk increasing with cigarette consumption. Another placental complication associated with maternal smoking is placenta praevia, which occurs when the placenta obstructs the opening at the neck of the uterus. There is an increased risk of maternal bleeding and of premature birth, both of which can be extremely hazardous for both mother and fetus. Women who stop smoking during pregnancy have a lower risk of placental complications than those who continue to smoke (British Medical Association 2004).

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of placental complications. The report concludes:

The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta praevia, and placental abruption.

Findings of the review include:

- Current cigarette smoking is associated with a 1.3 to 4.4 fold increased risk of placenta praevia, with most estimates around 2.3.
- Some studies examined dose response associations based on the number of cigarettes smoked per day. One

study reported a significant dose response relationship, while others were only suggestive.

- Smoking during pregnancy is associated with a 1.4 to 2.4 fold increased risk of placental abruption.
- Some studies report a dose-response relationship, with risks increasing for heavy smokers compared with light smokers.

Level of evidence: III-2

Spontaneous abortion

Spontaneous abortion or miscarriage is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation. The aetiology of spontaneous abortions is multifactorial and not fully understood. The study of spontaneous abortions is difficult, as most early fetal losses are unrecognised. As many as 50% of all pregnancies end in miscarriage, and 20% to 40% of all pregnancy losses may occur too early to be recognised or confirmed. There is evidence that smoking plays a role in promoting spontaneous abortions, as several components of tobacco smoke and its metabolites are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, carbon monoxide, and polycyclic aromatic hydrocarbons (US Department of Health and Human Services 2004). The UK Royal College of Physicians (in British Medical Association 2004) suggests that there is *substantial* evidence that smoking increases the risk of miscarriage by 25%.

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of spontaneous abortion. The report concludes:

The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

Findings of the review include:

- Several studies have reported an increased risk of spontaneous abortion among smokers compared with non-smokers, ORs range from 1.2 to 3.4.
- Combining alcohol and smoking increases the risk. The OR of spontaneous abortion for a woman who smoked one pack per day and drank alcohol daily was 4.08 times more than for an abstinent non-smoker.
- Some studies examined dose response associations based on the number of cigarettes smoked per day:
 - One study reported that as the number of cigarettes smoked increased from 1-9 cigarettes per day to 10-19 and 20 or more, ORs for spontaneous abortion increased from 1.07 to 1.22 and 1.68 respectively
 - Another study reported that the OR of spontaneous abortion increased by 46% for the first 10 cigarettes smoked and 61% for the first 20 cigarettes smoked

- Another reported that the adjusted OR for 11 or more cigarettes per day was 3.35 (95% CI 1.65–6.92).

Level of evidence: III-2

Perinatal death

The term "perinatal death" includes both stillbirth, loss of the fetus after the 24th week of pregnancy and neonatal death (death of the newborn during the first 4 weeks of life).

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of perinatal death. The report makes no summary statement about the level of evidence in relation to smoking and perinatal deaths but contains the following statement:

Numerous studies have demonstrated increased risks for neonatal mortality, with reported ORs for infants of smokers approximately 1.2 compared with infants of non-smokers.

The report 'Smoking and reproductive life: The impact of smoking on sexual, reproductive and child health,' prepared by the British Medical Association (British Medical Association 2004) also contains the BMA consensus view on the effect of maternal smoking on perinatal death. The main findings include:

- Smokers are more likely to lose their baby through stillbirth;
- It is estimated that one third of all perinatal deaths in the UK are caused by smoking;
- A large Swedish study of more than 600 000 pregnancies found that the risk of stillbirth increased by 40% in smokers compared with non-smokers;
- Babies born to mothers who smoke are around 40% more likely to die within the first 4 weeks of life than babies born to non-smokers

Level of evidence: Consensus

Sudden infant death syndrome (SIDS)

SIDS is defined as the sudden, unexplained, unexpected death of an infant before 12 months of age. Research into smoking-related increases in the risk of SIDS relates both to fetal exposure from maternal smoking and exposure of the infant to smoking by the mother and others during the postpartum period. Although social and behavioural risk factors for SIDS have been identified, the biological mechanism is still not completely understood. Proposed mechanisms include chronic hypoxia, elevated levels of carbon monoxide and/or reduced placental perfusion affecting factors such as the normal development of the central nervous system. Animal studies investigating neurotoxic effects suggest that nic-

otine targets neurotransmitter receptors in the fetal brain, reducing cell proliferation and altering synaptic activity (US Department of Health and Human Services 2004). The effects of smoking during pregnancy include premature birth and retardation of fetal development, both of which increase the risk of the baby being born before the development of brain systems that regulate the uptake of oxygen and heart function. There is evidence that exposure of the fetus to nicotine may also interfere with the normal development of these systems (British Medical Association 2004).

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of sudden infant death syndrome. The report concludes:

The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.

Findings of the review include:

- Maternal smoking is strongly related to SIDS even after controlling for other risk factors, including sleeping position and low birth weight. Adjusted ORs for mothers who smoked compared with non-smokers ranged from 1.4 to 3.0
- Some studies examined dose response associations based on the number of cigarettes smoked per day.
 - One large US study (1 million infants) suggested a strong dose-response association between maternal smoking and SIDS for mothers who smoked 1-9 cigarettes a day during pregnancy, compared to non-smokers (adjusted OR=1.6-2.5), and for mothers who smoked ≥ 10 cigarettes a day during pregnancy (adjusted OR=2.3-3.8)
 - Another study observed a dose-response relationship, indicating an increase in the risk of SIDS associated with an increase in the child's exposure to tobacco smoke in the first year of life
- However, as few women smoke only during pregnancy it has been difficult to separate the risks associated with antenatal and postnatal exposure to cigarette smoke, although the available studies suggest that both prenatal and postpartum exposures to tobacco smoke increase the risk of SIDS.
- One study reported that breastfeeding was protective against SIDS among non-smokers (OR=0.37) but not smokers (OR=1.38).
- In one study, infants who died from SIDS were found to be significantly more likely to have been exposed to environmental tobacco smoke from the mother (OR 2.28), father (OR 3.46), or other live-in adults (OR 2.18) than control infants.

Level of evidence: III-2

Premature birth

Premature babies (those born before 37 weeks of pregnancy) are at greater risk of illness and death. Women who smoke are at increased risk of having a premature baby. The risk is 1.5–2.0 times higher than that of non-smokers. One trigger for labour is rupture of the membranes that surround the fetus in the womb. Smokers have a two to threefold increased risk of the membranes breaking prematurely before 37 weeks of pregnancy (British Medical Association 2004). Smoking cessation by pregnant women may reduce the risk of premature rupture of the membranes (PROM) (US Department of Health and Human Services 2004).

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of shortened gestation. The report concludes:

The evidence is sufficient to infer a causal relationship between active smoking and pre-term delivery and shortened gestation.

Findings of the review include:

- A shortened gestation attributable to smoking, measured by a preterm delivery, has been reported in numerous studies. In a meta-analysis of 20 prospective studies, Shah and Bracken (2000) reported an overall adjusted OR for a preterm delivery of 1.27 (95 percent CI, 1.21–1.33) for smokers compared with nonsmokers.
- Prenatal smoking may act to increase rates of preterm deliveries by causing complications and also by a more direct pathway.

Level of evidence: III-2

Low birth weight

Low birth weight (LBW) is defined by the WHO as a birth weight below 2500g. LBW can result from the fetus failing to grow as normal (intrauterine growth restriction) or from premature birth (British Medical Association 2004). The primary mechanism by which birth weights are reduced among infants of smokers compared with those of non-smokers is through fetal growth restriction (US Department of Health and Human Services 2004). The evidence is conclusive that smoking during pregnancy is a cause of LBW, the effect increases with the number of cigarettes smoked, and stopping smoking reduces the risk (British Medical Association 2004). Low birth-weight babies are at increased risk of illness and there is a close association between low birth-weight and death in infancy (British Medical Association 2004). Numerous US Surgeon General's reports have confirmed the evidence for the causal association between smoking in pregnancy and having a LBW baby.

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on the risk of low

birth weight and intrauterine growth retardation. The report concludes:

The evidence is sufficient to infer a causal relationship between active smoking and fetal growth restriction and low birth weight.

Findings of the review include:

- Many studies have consistently demonstrated a positive association between maternal smoking during pregnancy and reduced birth weight
- Numerous studies have demonstrated a dose-response relationship between the number of cigarettes smoked and the degree of reduction in birth weights, with studies reporting biochemically-measured smoking exposures (e.g., cotinine levels) demonstrating an even stronger dose-response pattern than that seen from self-reported data.
- For smoking throughout pregnancy the effect is large, and successful cessation of smoking before the third trimester eliminates much of the reduction caused by maternal smoking.
- Some mechanisms by which smoking reduces birth weight have been established. They act in large part through reduced fetal growth, but the association between smoking and birth weight also results from early delivery, often from pregnancy complications.
- The biologic evidence supporting this causal effect is strong and includes fetal hypoxia from increased carboxyhemoglobin; reduced blood flow to the uterus, placenta, and fetus; and direct effects of nicotine and other compounds in tobacco smoke on the placenta and fetus.

Level of evidence: III-2

Longer term effects on child development

An overview of the impact of smoking on reproductive life and health in the United Kingdom (British Medical Association 2004) suggests that smoking during pregnancy may increase the risk of a range of longer term effects on child development, including lung function; respiratory illnesses; middle-ear disease, cancer; impaired growth and development and behavioural problems. Reduced growth of the fetus can have long-term consequences in impaired growth and development, with babies born to mothers who smoke during pregnancy being smaller during childhood. Low birth weight has been associated with an increased risk of diabetes, cardiovascular disease and obesity in adulthood. A dose-dependent association between maternal smoking during pregnancy and childhood obesity has also been reported (British Medical Association 2004).

Maternal smoking during pregnancy adversely affects lung function in newborn babies and can result in impaired lung

development that may persist into adult life. Infants born to mothers who smoke have poorer lung function than those born to non-smoking women, with the reduction persisting into childhood. Impaired development and growth of the lungs has been implicated as a risk factor for chronic obstructive pulmonary disease (COPD) in adult life (British Medical Association 2004).

Exposure to ETS during infancy and childhood has also been associated with slower rates of growth in lung function and increased risk of asthma, middle ear disease and respiratory disease (British Medical Association 2004). Some studies have found that compared to children of non-smokers, the children of smokers have a poorer performance at school, with lower scores in cognitive tests and greater likelihood of having behavioural problems, including hyperactivity and shorter attention spans (British Medical Association 2004).

There is a large body of epidemiological data to support the evidence for profound negative effects of maternal smoking during pregnancy on fetal health; many of which may potentially have longer-term consequences for the child. It must be acknowledged that much of the data reviewed was from studies with retrospective self-reporting of smoking. This method of data collection in the presence of an adverse outcome leads to under-reporting of smoking during pregnancy, which in turn may lead to an under-estimation of the strength of association between maternal smoking during pregnancy and the outcome under investigation, therefore the effects reported above may be conservative.

The 2004 US Surgeon General's Report (US Department of Health and Human Services 2004) contains a review of the evidence on the effect of tobacco smoking on child physical and cognitive development. The report concludes:

The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children.

Level of evidence: III-2

Care of the pregnant smoker

Smoking cessation is an effective intervention in antenatal care, with many of the risks to mother and fetus reduced or eliminated on cessation. Pregnancy and the pre-conception and postpartum periods present a unique opportunity or teachable moment to intervene to encourage and assist women to quit smoking. Women are more motivated to stop smoking during this time, when the salience of not only their own health, but also that of their infant is more relevant to them. They are also more likely to experience increased social support for quitting smoking during pregnancy.

Opportunities for the delivery of cessation support are increased, as pregnant women have greater contact with the health care system. Health care providers are well placed to provide quit smoking interventions to smokers and antenatal

staff are more likely to provide cessation counselling than other health care providers. Many women who may not usually seek or receive primary care are able to be reached through prenatal care visits, with later follow-up opportunities in hospital, paediatric offices, health clinics, day care programs or home nursing visits. Health care providers and health systems have compelling reasons to intervene, given the dramatic and immediate health benefits of quitting for the pregnant woman and her baby, and the significant cost savings associated with averting pregnancy complications and low birth weight deliveries. Health professionals should take advantage of a woman's unique quitting motivation by reinforcing knowledge that quitting smoking will reduce health risks to the fetus, and reviewing the important post-partum benefits for both the mother and child (Orleans et al 2000).

Smoking cessation

Around two-thirds of smokers are interested in quitting, about half try to quit each year and less than a quarter of smokers who try to quit remain non-smokers for 6 months or more (Miller and Wood 2002). Most cessation attempts are unaided and the success rate of unaided attempts is low. Smoking is a chronically relapsing condition, and even in the general population of smokers trying to stop, the relapse rate is high. The natural population cessation rate is low, estimated to be about 2% each year (Raw 2001).

The effectiveness and potential public health benefit of intervention by health care professionals is well documented. The evidence supports the development of three main types of smoking cessation intervention for health care systems (Raw 2001):

- Brief opportunistic interventions delivered by health professionals in the course of their routine work';
- More intensive support delivered by treatment specialists, often in what have been called 'smokers clinics';
- Pharmacological aids, which approximately double cessation in minimal or more intensive settings.

The pharmacological aids currently available in Australia are nicotine replacement therapy (NRT) and bupropion. NRT is available over the counter on general sale from pharmacies. Three forms of NRT, patches, lozenges and gum, are unscheduled and can be provided by non-pharmacists. Two other formulations, the sublingual tablet and the inhaler, are available from pharmacies. Bupropion is a prescription-only medicine. Bupropion and most forms of NRT are contraindicated (not recommended) during pregnancy and lactation.

The World Health Organization recommends that all health professionals coming into contact with a smoker should opportunistically provide an evidence-based smoking cessation intervention (Raw, 2001). It states: "Although the evidence base is stronger for some health professionals than others, the involvement of health professionals in offering smokers help should be based on factors such as their access to smokers and level of training and skill, rather than profes-

sional discipline." The recommendations are relevant for all health professionals, not just those based in primary care. The WHO also recommends that smoking cessation should be part of the core curriculum of the basic training of all health professionals (Raw 2001).

The "5As" are an evidence-based framework for structuring smoking cessation in health care. As part of their normal clinical work, health professionals should provide brief interventions including the following essential features:

- **Ask*** about and record smoking status, keep record up to date;
- **Advise** ALL smokers of the benefit of stopping in a personalised and appropriate manner (this may include linking the advice to their clinical condition);
- **Assess** their motivation to stop and their level of nicotine dependence;
- **Assist** smokers in their quit attempt if possible; this might include the offer of support; the provision of accurate information and advice; referral to a GP or to a specialist cessation service for consideration of the use of NRT if necessary (see below) or to the Quitline 13 7848 for ongoing support;
- **Arrange** follow up if possible. The Quitline 13 7848 can provide follow-up support.

* It is important to remember that high levels of deception about smoking cessation (up to half) have been reported during pregnancy as women may feel guilty or stigmatised if they admit to smoking. For this reason accurate information on smoking status in pregnancy may be better collected using a written questionnaire rather than verbal questioning.

If help can be offered a few key points can be covered in a few minutes:

- Set a quit day and stop smoking completely on that day;
- Review past experience and learn from it (when you last quit how bad were withdrawal symptoms? what helped? what hindered?);
- Make a personalised action plan;
- Identify likely problems and triggers and plan how to cope with them;
- Ask family and friends for support (Raw 2001).

Although abstinence early in pregnancy will produce the greatest benefits, smoking cessation at any point during the pregnancy will be beneficial to both the mother and fetus. Smoking cessation programs are effective at achieving smoking cessation in pregnant women. Minimal intervention (recommendation to stop smoking, supplemented by self help material or referral to a quit smoking program) achieves estimated abstinence rates of 6.6% in pregnant women (Fiore et al 2000). Participation in smoking cessation programs compared with usual care during pregnancy improves birth outcome, including rate of low birth weight (OR 0.80, 95% CI 0.67–0.95), rate of preterm birth (OR 0.83, 95% CI 0.69–

0.99) and mean birth weight (average increase 28 g, 95% CI 9–49 g) (Miller and Wood 2002). In the first instance, pregnant women who smoke should be advised of the adverse outcomes associated with smoking during pregnancy and offered counselling and supportive behavioural therapies to help them to stop.

The Cochrane Collaboration review of smoking cessation interventions in pregnancy (Lumley et al 2000) recommends that, as interventions have been shown to increase smoking cessation, reduce preterm birth and low birth weight, and increase mean birth weight, smoking cessation programs need to be implemented in all maternity care settings. Lumley et al also recommend that attention to smoking behaviour together with support for smoking cessation and relapse prevention should be “as routine a part of antenatal care as the measurement of blood pressure” (Lumley et al 2000).

Use of NRT in pregnancy

The safety of use in pregnancy of effective pharmacotherapies such as NRT and bupropion is still debated. Nicotine itself has potential teratogenic effects and there is no known safe level of nicotine that can be administered during pregnancy. It may cause fetal harm by multiple mechanisms. Nicotine can inhibit the production of prostacyclin, an inhibitor of platelet aggregation and a potent vasodilator of the umbilical arteries, with deleterious effects on fetoplacental blood flow. Reductions in uterine blood flow occur during peak nicotine concentration, resulting from catecholamine release. It is plausible that the pharmacodynamic effects of the nicotine bolus from smoking have a more deleterious effect on uteroplacental blood flow than nicotine delivered by a more sustained, non-reinforcing delivery method, such as gum (Oncken et al 1998).

Dose-related effects of nicotine gum on maternal heart rate and blood pressure with attenuated effects on fetal heart rate and breathing have been demonstrated. However, these effects are less pronounced than the effects of cigarette smoking. Overall, nicotine patches and gum do have some measurable cardiovascular effects during pregnancy, but the effects are small and do not appear to compromise the mother and baby (Dempsey and Benowitz 2001).

There are no prohibitions in Australia on pregnant women using NRT; however, it is classified as a category D product and it is recommended that medical advice be sought before use. In Australia, NRT packages carry warnings about use in pregnancy, however, the Therapeutic Goods Administration notes that “Short term use during the first trimester is unlikely to cause a hazard to the fetus” (Therapeutic Goods Administration 1999). The advised use of NRT by pregnant smokers seems to be more accepted in some countries than it has been in Australia (Miller and Wood 2002). The United States (Fiore et al 2000), United Kingdom (West et al 2000) and Scotland (Health Education Board for Scotland and ASH Scotland 2000) evidence-based guidelines for best practice in smoking cessation all cautiously recommend NRT “when a pregnant woman is otherwise unable to quit and when the

likelihood of quitting, with its potential benefits, outweighs the risk of NRT use or continued smoking”.

The recently released Smoking Cessation Guidelines for Australian General Practice (Zwar et al 2004) state that: “there is currently a lack of evidence on the safety of pharmacotherapy in pregnancy but reports of expert committees have recommended use in certain circumstances” and recommend that “pharmacotherapy should be considered when a pregnant woman is otherwise unable to quit, and when the likelihood and benefits of cessation outweigh the risks of pharmacotherapy and potential continued smoking.”

Women who are unable to quit smoking during pregnancy with behavioural intervention alone should be considered for NRT. The continuing smoker receives not only much higher levels of nicotine compared with that delivered by NRT, approximately double, but also bears the additional risks described above for the fetus and the mother, related to high blood levels of carbon monoxide and many of the other 4000 chemicals in tobacco smoke.

NRT is clearly beneficial in smoking cessation for more highly dependent or heavier smokers, and it is these who are more at risk for adverse reproductive outcomes and who are less likely to stop smoking when becoming pregnant (Benowitz 1991). The ratio of potential benefit to harm is not conclusive; therefore, most recommendations are to consider pharmacotherapy only after psychosocial intervention has failed (Fiore et al 2000; Melvin et al 2000).

There is evidence that nicotine is a neuroteratogen and can cause significant damage to the fetus by itself, through multiple mechanisms, including defects in the adrenomedullary, cardiac and respiratory centres of the brain. The physiological defects associated with sudden infant death syndrome (SIDS) can be reproduced in animals exposed to nicotine prenatally, possibly explaining the epidemiological association of tobacco smoking and SIDS (Slotkin 1998). Slotkin (1998) warned that standard developmental indices of safety, such as fetal or neonatal weight, are inappropriate because the threshold of impaired nervous system development lies below that for growth suppression and states that the only safe course is to discontinue nicotine exposure in pregnancy.

During pregnancy, the goal should be to be both smoke-free and nicotine-free and the evidence supports better pregnancy outcomes with earlier smoking cessation. When smoking is discontinued before 16 weeks gestation, much of the risk for fetal growth restriction can be avoided. Mid to late gestation appears to be the period most vulnerable to the effects of nicotine for the developing fetal brain. The mature fetus responds more adversely to nicotine administration than the immature fetus. Therefore if, after consideration and discussion of the risk/benefit ratio, the pregnant woman and her doctor decide it is necessary to begin NRT, the sooner it is used and discontinued the better, if the result is cessation of smoking (Oncken et al 1998). Nicotine exposure may be harmful in pregnancy, and while NRT is probably less harmful than smoking, there is no known safe dose of nicotine in pregnancy (Oncken et al 1998).

The World Health Organization expert consensus (McNeill and Hendrie 2001) recommends that regulators should license NRT products available for use under medical supervision by pregnant women who have been unable to quit with non-pharmaceutical interventions, and this assessment should be made in the early stages of pregnancy or, if possible, before. It is also recommended that doctors should assess pregnant smokers early in pregnancy or before, to assess whether they will be able to quit using non-pharmaceutical interventions and prescribe or supply NRT if appropriate. For women who continue to smoke in pregnancy, using NRT is likely to be less hazardous than smoking. The decision about appropriate use of NRT by pregnant women is a trade-off between the benefits to women who use NRT and stop smoking as a result, compared with the risks to women who use NRT but would have been able to stop without NRT (McNeill and Hendrie 2001).

The safety of the transdermal patch during pregnancy has not been established. If the clinician or the pregnant or lactating patient decides to use NRT to quit smoking, delivery systems should be considered that yield intermittent, rather than continuous nicotine exposure (i.e. inhaler, gum, lozenge or sublingual tablet, rather than transdermal patch) because of potential neurotoxicity in the fetus of continuous exposure to nicotine (Benowitz 1991; Fiore et al 2000; Dempsey and Benowitz 2001).

As many of the effects of smoking in pregnancy are dose-related, Oncken et al (1998) recommended that NRT should only be offered if it delivers equivalent or lower concentrations of nicotine than are usually achieved with smoking. In a prospective human study of the use of NRT during pregnancy compared with continued smoking, plasma cotinine levels were lower among those chewing nicotine gum ad libitum, compared with those who continued smoking, indicating that short-term nicotine use is likely to be safer than smoking in pregnant smokers unable to quit without such measures. "NRT can be considered reasonably safe only to the extent that it does not exceed the physiological perturbations or foeto-placental nicotine exposure of the pre-existing smoking behaviour it treats" (Oncken et al 1998).

To sum up, nicotine is toxic to the developing fetus; however, tobacco smoke also contains thousands of other chemicals, including reproductive toxins. One of the most potent toxins in tobacco smoke for the fetus is carbon monoxide. The use of nicotine replacement products in pregnancy is not completely without risk; however, the risk is much lower than that of smoking. The selection of delivery method and dose of NRT rests on its ability to achieve abstinence in an individual woman (Dempsey and Benowitz 2001).

Bupropion (Zyban)

Bupropion SR (slow release) is an effective non-nicotine medication for smoking cessation that approximately doubles cessation rates compared to placebo (Miller and Wood 2002). It was originally developed and marketed as an antidepressant. Its presumed mechanism is mediated through its capacity to block the re-uptake of dopamine and norepi-

nephrine centrally (Miller and Wood 2002). Bupropion can be combined with NRT to help with quitting and there is good evidence that this combination is more effective than nicotine patch alone (Miller and Wood 2002). At the time of publication Zyban is the only form of bupropion available in Australia and it is available only on prescription. It is included on the Pharmaceutical Benefits Scheme, therefore may be more affordable than other smoking cessation pharmacotherapies, particularly for people with a health care card. However, the use of bupropion during pregnancy or lactation is listed as a precaution in MIMS (2005) and is not recommended. In addition, it may not be appropriate for all smokers, as there are several contraindications to its use, including a history of seizure disorders, current or recent use of certain medications for depression, a current or prior diagnosis of anorexia nervosa or bulimia or those with a history of bi-polar disorder. The medication is commenced approximately one week prior to quitting and reduces the urge to smoke, but should be combined with counselling.

Neonatal withdrawal syndrome

There is some evidence emerging for neonatal effects from nicotine withdrawal. A prospective study of the effects of maternal smoking during pregnancy on newborn neurobehaviour, found that tobacco-exposed babies were more excitable and hypertonic, required more handling and showed more stress or abstinence signs, specifically in the central nervous system (brain and spinal cord), gastrointestinal and visual areas (Law et al 2003). Dose-response relationships existed, between higher maternal salivary cotinine values and stress or abstinence signs in the baby, including central nervous system (CNS) ($r = 0.53$), visual stress ($r = 0.69$), and higher excitability scores ($r = 0.62$). Number of cigarettes per day during pregnancy was related to more stress or abstinence signs ($r = 0.58$), including CNS ($r = 0.56$) and visual stress ($r = 0.64$). These findings may indicate neonatal withdrawal from nicotine. Another prospective study (Godding et al 2004) concluded that withdrawal symptoms occur in newborns exposed to heavy maternal smoking during pregnancy. These studies suggest neurotoxic effects of maternal smoking in pregnancy on newborn neurobehaviour.

Breastfeeding

Nicotine is both water and lipid soluble, and distributes rapidly to and from breast milk. As maternal plasma nicotine concentration rises and falls, breast milk concentration rises and falls. The mean elimination half-life of nicotine in breast milk is 95 minutes (Dempsey and Benowitz 2001).

Smoking and breastfeeding

Breastfeeding has important health benefits for both infant and mother. Mothers who smoke are less likely to start breastfeeding their babies than non-smoking mothers, and tend to breastfeed for a shorter time. Breast milk production is lower in smokers than in non-smokers. In breastfeeding mothers who smoke, milk output is reduced by more than

250 mL/day compared with non-smoking mothers. The effect of smoking on breastfeeding may be mediated by nicotine regulation of the hormone prolactin. Prolactin is essential for the initiation and maintenance of milk production by the mother. Breastfeeding women who smoke have lower levels of prolactin than those who do not smoke. Exposure to environmental tobacco smoke (ETS) or passive smoking may also influence breastfeeding, with non-smoking women who are exposed to ETS stopping breastfeeding sooner than those who are not exposed (British Medical Association 2004).

NRT and breastfeeding

Even with maternal exposure consistent with a high level of NRT, the daily exposure normalised for the weight of the infant has been estimated to be more than 50 times lower than the exposure of the mother (Dempsey and Benowitz 2001). It is unlikely that such low levels of exposure are harmful to the infant. In contrast, there is good evidence that exposure to environmental tobacco smoke is harmful to the infant. Therefore, the provision of NRT to the mother, if this results in her not smoking, would be of great potential benefit to the baby.

The formulation of NRT used may affect the level of nicotine in breast milk. The nicotine transdermal patch provides a steady level of nicotine in plasma, and therefore in breast milk, and the mother has no control over the level of nicotine in the milk. Mothers who use intermittent delivery systems of NRT (inhaler, gum, lozenge or sublingual tablet) may be able to minimise the nicotine in their milk by prolonging the duration between nicotine administration and breastfeeding (Dempsey and Benowitz 2001).

Bupropion and breastfeeding

Bupropion is contraindicated (not recommended for use) during lactation. However, a recent study on the use of bupropion during lactation (Haas, Kaplan et al 2004) indicated that the daily dose of bupropion and its metabolites that would be delivered to the infant of a mother taking a therapeutic dose of bupropion is small. The authors conclude that the effectiveness of bupropion to prevent post-partum relapse to tobacco use should be evaluated without excluding women who plan to breast-feed.

Postnatal relapse

Women who quit smoking during pregnancy should not be considered to have quit permanently. About 20% to 30% of women quit when they become pregnant, but about 70% of these women relapse either during pregnancy or after the baby is born. Pregnancy is a strong motivation to quit, but some women do not intend to maintain cessation after pregnancy and lactation. Those who quit during pregnancy and do intend to remain abstinent are just as vulnerable to relapse as other women (Miller and Wood 2002).

Relapse in the postpartum period is high; however, there is evidence that this can be reduced by smoking cessation interventions in the postpartum period, preventing 25% of

relapse for various periods less than 6 months (OR 0.74, 95% CI 0.53–1.04) (Lumley et al 2000). It is important to use antenatal visits as opportunities for discussing behavioural risk factors such as smoking. Effective smoking cessation interventions should be offered to pregnant smokers at the first antenatal visit and throughout pregnancy and after delivery (Lumley et al 2000).

Emphasis on the health risks of exposure to environmental tobacco smoke for the baby and other children in the family may help to maintain the motivation experienced in pregnancy. Clinicians should ascertain postpartum cessation intentions and advise, assist and arrange follow-up as appropriate (Miller and Wood 2002).

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13 Cannabis

Reviewer:

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The most abundant active agent in the marijuana plant (*cannabis sativa*) is Δ^9 -tetrahydrocannabinol (THC). This agent is one of a family of about 60 bi- and tricyclic compounds, formally derived from geranyl-pyrophosphate and olivetol, and these are known as cannabinoids (Zimmer and Morgan 1997). Marijuana, hashish and hash oil are the three main forms of cannabis. Marijuana is the most common form used in Australia and it is smoked. It consists of the dried leaves and flowers ("heads") of the *cannabis sativa* plant. The heads are preferred as they are the most potent part (Makkai and McAllister 1997). The preferred mode of administration among younger users is a water pipe ("bong") or pipe; older users are more likely to smoke hand-rolled cigarettes ("joints") (Hall and Swift 2000). Hashish ("hash") is small blocks of dried cannabis resin. The concentration of THC is higher in hash than in marijuana. Hashish is added to tobacco and smoked, or baked and eaten in foods such as "hash cookies". Hash oil is extracted from hashish. It is usually spread on the tip or paper of cigarettes and then smoked. Hash oil has the highest concentration of THC, but is rarely used in Australia.

Prevalence

Cannabis is the most widely used illicit drug in Australia and its use since the 1980s has continued to increase. In 1998, the National Drug Strategy Household Survey reported 39% of the Australian population (44% of men and 35% of women) had ever used cannabis, with 18% using cannabis in the previous 12 months. More recent surveys have found similar results (Degenhardt et al 2001; Australian Institute of Health and Welfare 2002). Cannabis use is more common in younger age groups. The average age of first using cannabis was 18.7 years (Reid et al 2000), but there is evidence that this is decreasing (Degenhardt et al 2000). People with higher education levels are more likely to have tried cannabis at some time in their lives, but regular users tend to have lower levels of education (Makkai and McAllister 1997). Those aged 18–24 years are the most likely to report use and meet criteria for abuse and dependence on cannabis within the past year (Degenhardt et al 2001). There is considerable variation in the estimates of women who use cannabis during pregnancy.

Effects of cannabis

Cannabinoids (e.g. THC) and endogenous cannabinoid ligands (e.g. anandamide) act on endogenous cannabinoid

receptors. The highest density of these receptors are found in the hippocampus, cerebral cortex, outflow nuclei of the basal ganglia and the cerebellum. Consequently, acute intoxication with cannabis ("stoned" or "high") results in mild euphoria, relaxation, drowsiness, the intensification of experiences including altered perception of colour, sound, time, spatial dimensions and other sensations, and disturbance of memory, cognitive and motor performance. Physical effects include an increase in appetite ("munchies"), increased heart rate, lowering of blood pressure, reddening of eyes (conjunctival injection) and dry mouth. When used in a social setting, the high often lasts 2 to 3 hours and is accompanied by infectious laughter, talkativeness, disinhibition and increased sociability. Acute intoxication with high quantities may cause restlessness, anxiety, confusion, hallucinations and paranoia. Cannabis and alcohol intoxication is more dangerous than intoxication by cannabis alone because of the cumulative impairments on cognition, coordination and judgement (Hall et al 1994).

A minority of users develop cannabis dependence, including tolerance and withdrawal phenomena. THC is highly fat-soluble, so withdrawal is usually mild and gradual. Withdrawal symptoms may last from days to several weeks and include insomnia, mood disturbance, vivid dreams, night sweats, headache, loss of appetite, abdominal cramping, fatigue and cough. Withdrawal severity is greater with heavier cannabis use and in those with psychiatric symptoms (Budney et al 1999). Psychological dependence is common, as cannabis is often used to reduce stress and provide structure, including replacing other activities. Cessation is often difficult and associated with cravings. Many regular users find it difficult to stop or reduce using cannabis despite wanting to and acknowledging the adverse effects that cannabis has on their lives (Hall et al 1994).

There are numerous physical health complications that may occur from cannabis use, but it is difficult to differentiate the effects of comorbid tobacco use (e.g. on carcinomas of the respiratory system or ischaemic heart disease). In animals, cannabinoids acutely activate the hypothalamic–pituitary–gonadal axis and suppress gonadal steroids, growth hormone, prolactin and thyroid hormone. The effects in humans have not been demonstrated on a consistent basis because of the development of tolerance and problems with research design (Brown and Dobs 2002). Chronic cannabis use is associated with delayed ovulation (Murphy 1999).

There are complex associations between cannabis use and a wide range of mental health problems, including psychosis (Andreasson et al 1987; Thornicroft 1990; Mathers and Ghodse 1992; Linszen et al 1994), cognitive impairment (Hall

and Solowiji 1997), depression and anxiety (Paton et al 2002; Rey and Tennant 2002).

Diagnosis and assessment

A complete drug and alcohol history is required. Physical examination is usually within normal limits. Cannabinoids can be detected in blood and urine for many weeks after cannabis use has ceased, especially in dependent users.

Care of the pregnant cannabis user

There have been at least four randomised controlled trials examining the effectiveness of psychologically based treatment for cannabis dependency. In Sydney, Copeland et al (2001) followed up 229 patients allocated to either a six-session cognitive-behavioural therapy (CBT) program, a single session brief intervention (SSBI) or a delayed-treatment control (DTC) group. The six-session intervention consisted of motivational interviewing, cognitive restructuring, coping skills training, relapse prevention, lifestyle modification, and learning management of withdrawal symptoms, urges and triggers. The single-session brief intervention consisted of feedback from the initial assessment, education on addictive behaviour, planning strategies for quitting, goal setting, coping with craving and withdrawal, and behavioural self-management. Subjects were followed up for a median of 8 months after their last attendance. Compared with the DTC group, those in the treatment groups reported better outcomes, including being more likely to report abstinence, less concerned about their use and less cannabis-related problems. The CBT group reported significantly lower levels of cannabis use compared with the DTC group. Comparison of the CBT and SSBI groups showed that treatment compliance was significantly associated with decreased dependence and fewer cannabis-related problems (Copeland et al 2001). (Evidence level: II.)

From the United States, Stephens et al (2000) followed up 291 patients allocated to either a 14-session cognitive-behavioural treatment program, a two-session treatment program using motivational interviewing or a 4-month delayed treatment control group. Compared with pretreatment levels, both treatment groups had significantly improved outcomes for cannabis use, dependence symptoms and negative consequences of use at follow-up assessments over 14 months. There were no significant differences between the two types of therapy (Stephens et al 2000). Similar results have been found in other randomised controlled trials of brief cognitive-behavioural (McLellan 2001) and relapse prevention interventions (Stephens et al 1994). (Evidence level: II for all.) Other psychologically based interventions include CBT Internet resources (Grenyer et al) and Marijuana Anonymous groups, adapted from Alcoholics Anonymous (Marijuana Anonymous Australia).

Pharmacological therapies, including herbal remedies, are often used to treat cannabis withdrawal symptoms despite no double-blind, randomised controlled trials demonstrating their effectiveness. Benzodiazepines may reduce insomnia and anxiety, but there is the risk of dependence in the substance-using population. Antidepressants may be effective in treating comorbid affective or anxiety disorders, but their use is often limited by adverse effects, for example, serotonin specific reuptake inhibitors (SSRIs) exacerbate insomnia (O'Brien 1996). (Evidence level: I.)

Fetal effects

Cannabinoids cross the placenta in animals and humans (Harbison and Mantilla-Plata 1972; Tennes et al 1985). In animal models, high doses of cannabinoids in pregnancy produce resorption, growth retardation and malformations (Bloch 1983). In human studies, epidemiological studies have not demonstrated a consistent relationship between cannabis use in pregnancy and birth abnormalities. One of the earliest of these studies reported an increase in birth abnormalities with features similar to fetal alcohol syndrome (Milman 1982), but subsequent studies have not (Hingson et al 1982; Gibson et al 1983; Linn et al 1983; Tennes et al 1985; Zuckerman et al 1989). The most rigorous of these studies involved a large sample of women among whom there was a substantial rate of cannabis use that was verified by urinalysis. The low rate of birth abnormalities among the cannabis users was no different to the control group (Zuckerman et al 1989). (Evidence level: III-2.)

Epidemiological studies may have failed to demonstrate birth abnormalities from cannabis use in pregnancy for several reasons. Pregnant women may not admit to substance use because of stigma, or forget about drug use during early pregnancy when asked later in pregnancy or after the birth (Day and Richardson 1991). Also, as adverse reproductive outcomes and heavy cannabis use during pregnancy are relatively rare, cannabis use would have to greatly increase in the risk of abnormalities or very large sample sizes are necessary to detect adverse effects of cannabis use on fetal development (Fried and Smith 2001). Finally, even with large sample sizes, there are numerous confounding variables (Day and Richardson 1991). Cannabis users have higher rates of other substance use during pregnancy (Eyler and Behnke 1999), are less likely to seek antenatal care, and have poorer nutrition (Tennes et al 1985).

There is no evidence that cannabis use in pregnancy is associated with an increased risk of infant mortality after adjusting for confounding variables especially other substance use. Two recent studies, involving 12 000 women in Britain and 2964 women in Michigan, failed to demonstrate an increase in prenatal mortality or morbidity (Ostrea et al 1997; Fergusson et al 2002). (Evidence level: IV and III-2, respectively.) Another recent study in New Zealand failed to demonstrate a link between sudden infant death syndrome (SIDS) and cannabis use in pregnancy (Scragg et al 2001). (Evidence level: III-2.)

Obstetric effects

Several studies from the 1980s reported an association between cannabis use in pregnancy and reduced birth weight (Gibson et al 1983; Hatch and Bracken 1986; Zuckerman et al 1989). A study of 7301 pregnant women in South Australia found cannabis use was not significantly associated with intrauterine growth retardation, congenital anomalies, perinatal death or respiratory status at birth. After controlling for confounding variables, cannabis use was associated with prematurity and low birth weight. However, once premature births were excluded, the association was not significant (Gibson et al 1983). (Evidence level: III-2.)

More recently, in a prospective study, Fried et al (1999) observed a smaller head circumference at all ages, which reached statistical significance in the 9–12-year-old children and remained significant after adjusting for maternal cigarette and alcohol use. Fergusson et al (2002) found that frequent and regular use of cannabis throughout pregnancy may be associated with small but statistically detectable decrements in birth weight. (Evidence level: III-2.)

A meta-analysis of 10 studies that controlled for nicotine use from 1966 to 1995 found no consistent evidence of cannabis use during pregnancy and reduced mean birth weight or low birth weight. Methodological problems with the various studies included reliance on self-reported consumption, difficulties in estimating quantity and frequency of use and the confounding variable of using cannabis and nicotine together (English et al 1997). (Evidence level: III-2.) After adjusting for confounding variables, including nicotine and other substance use, more recent studies have failed to demonstrate an association between cannabis use and low birth weight, birth defects or obstetric complications (Shiono et al 1995; Sherwood et al 1999; Fergusson et al 2002). (Evidence level: III-2 for all.)

Neonatal withdrawal syndrome

There is no evidence of a neonatal withdrawal syndrome solely from cannabis use. A study by Fried and Makin (1987) found that neonates exposed to cannabis antenatally had increased tremors and startles, which were not accompanied by other typical neonatal withdrawal symptoms. Poorer habituation to visual stimuli was also observed in these neonates. Although the authors acknowledged the uncertain predictive validity of the Brazelton scale, they suggested the altered behaviour of the neonate could have consequences on parent–infant interaction. (Evidence level: IV.)

Breastfeeding

Little is known about the effects of using cannabis and breastfeeding (Hall et al 1994). A study by Astley and Little (1990) reported that neonates exposed to marijuana via breast milk during the first month postpartum had a decrease in infant motor development at 1 year of age.

While suggesting these results be interpreted cautiously, the authors noted that postnatal exposure could play a critical role on infant development. (Evidence level: III-3.)

Postnatal effects

There is conflicting evidence whether in utero exposure to cannabinoids affects postnatal development. Most of the research into developmental abnormalities in children born to mothers that used cannabis during pregnancy comes from the Ontario Prospective Prenatal Study (OPPS). Just after birth, neonates of mothers who had used cannabis during pregnancy had impaired development of their visual system, increased rate of tremors and increased startle reflex. These differences were no longer detectable 1 month later (Fried and Makin 1987; Fried and Smith 2001). However, these results have not been replicated by another research group using the same measurement instruments (Tennes et al 1985). Another cohort from the OPSS had subtle developmental impairment attributed to cannabis and nicotine use in pregnancy at 36 and 48 months (Fried and Watkinson 1990), but only for nicotine use in pregnancy at 60 and 72 months (Fried and Watkinson 1990; Fried et al 1992). This cohort has been followed up to 9 to 12 years old. Those exposed to cannabinoids in utero have no differences in IQ score, but have subtle differences in higher cognitive processes and perceptual organisation (Fried et al 1998; Fried and Smith 2001; Fried 2002). (Evidence level: III-2 for all.) These effects are less than those due to the use of nicotine or other substances during pregnancy (Lee 1998).

Another cohort study from Pittsburgh, US, has followed up 665 children born to teenage women. At 3 years old, those exposed to cannabinoids in utero had reduced memory and verbal scales of the Stanford–Binet Intelligence Scale (Day et al 1994). At 6 years old, this group had reduced height, even after controlling for other predictors of impaired growth, including alcohol and tobacco use (Cornelius et al 2002). At 10 years old, cannabis use in pregnancy was significantly related to mother and teacher reports of increased child hyperactivity, impulsivity and inattention. First trimester use of cannabis also seems to be indirectly related to delinquency and externalising problems, owing to the effect on inattention (Goldschmidt et al 2000). From the OPPS, in utero exposure to cannabinoids was not significantly related to any growth measures in all age groups examined up to early adolescence (Fried et al 1999). (Evidence level: III-2 for all.)

Polysomnographic recordings of 3-year-olds showed that those exposed to cannabinoids in utero have significantly more nocturnal arousals, more awake time after sleep onset and lower sleep efficiency than matched controls (Dahl et al 1995). (Evidence level: III-2.)

Three case–control studies have suggested that cannabis use in pregnancy is associated with an increased risk of childhood cancers, including acute nonlymphoblastic leukaemia, rhabdomyosarcoma and astrocytoma. These findings emerged from large exploratory analyses with numerous confounding variables and the results need to be replicated.

The incidence of these cancers had not increased during the period of these studies. (Evidence level: III-2 for all.)

Conclusions

Cannabis is the most commonly used illicit substance in the Australian community and in women of childbearing age. Cannabis use in pregnancy has been associated with lower birth weight, but this association is no longer significant after adjusting for confounding variables, including nicotine and other substance use. Cannabis is unlikely to be a major cause of birth defects. There is conflicting evidence regarding post-natal development to those exposed to cannabinoids in utero. There is some evidence that behavioural and developmental effects occur in the first few months after birth, and subtle cognitive and developmental problems occur in early childhood. Despite widespread cannabis use, there is a paucity of research on its effects during pregnancy and breastfeeding, or on the description of a neonatal withdrawal syndrome.

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14 Amphetamine-type substances

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Amphetamine-type substances include a range of drugs that have similar properties. The ones that cause most concern are amphetamines, methylamphetamine and amphetamine methylenedioxyamphetamine (MDMA, Ecstasy). They are similar in structure to dopamine and noradrenaline, and methamphetamine differs from amphetamine only in the addition of a methyl group on the chain.¹

Prevalence

The results of the 2004 National Drug Strategy Household Survey indicate that amphetamines were used by more than 1.4 million Australians aged 14 years and over at least once in their lifetime.² An estimated 532 100 had used in the year before the survey. The mean age of initiation to use of amphetamines was 20.8 years.

Those aged 20–29 years are most likely to be recent users, followed by those in the 14–19 year age group.² More than a third (37.7%) of recent users used crystal amphetamines, and the concomitant use of drugs such as alcohol, cannabis, benzodiazepines and opiates is common. Amphetamines may be administered orally, intranasally, intravenously, or (in the case of methamphetamine) may be smoked. The drug is vaporised and the fumes are inhaled. Methamphetamines were reported as the most common first drug injected by injecting drug users. In 2002–2003, amphetamines were the main drug of 10.7% of those who sought treatment at alcohol and other drug services.³

In 2004, about 1.2 million Australians aged 14 years and over had used MDMA (ecstasy). Of these, 6% were women.² Estimates of the number of women using amphetamines during pregnancy vary. In a retrospective audit of 96 infants born in a chemical dependence unit, 6% of mothers used only amphetamines.⁴ In another retrospective study of 141 illicit drug using mothers, the main drug of 28% ($n = 50$) was amphetamines. The proportion of women using MDMA during pregnancy is unknown.

Effects of amphetamines

Amphetamines are psychostimulants. They produce feelings of euphoria, provide relief from fatigue, increase activity levels and may induce anorexia. The adverse effects are dose related and range from mild to severe.⁵ They include effects on neurological and physiological functioning (excitation syndrome, hyperthermia, tachycardia, circulatory collapse with

possible fatal outcome), mental health, risks associated with drug content and purity and risks of blood-borne virus infection associated with injecting practices. The most common psychiatric disorders are depression, anxiety and drug induced psychosis.⁶ In a study of regular amphetamine users, 49% had ever been diagnosed with a mental health problem. Of these, 63% were diagnosed after commencing regular use.⁷ Users of amphetamines have been reported to have a greater hazard of a psychiatric admission than heroin dependents (hazard ratio [HR] 1.27; $P < 0.001$).⁸ The social consequences include violence, crime and accidents.

In regard to MDMA, there have been a number of case studies of acute toxicity and death following use, and concerns have been expressed that it may produce long-term damage to serotonin nerve terminals.⁹

Fetal effects

Several studies done on animals have reported that amphetamine use is associated with cardiac malformations¹⁰ and other malformations, including clefting¹¹ and neurotoxicity.¹² For a review of studies done on mice, rats, chicks, rabbits and sheep see Plessinger.¹³

The results of studies done on humans are contradictory. Fetal dexamphetamine exposure has been associated with cardiac abnormalities.¹⁴ Clefting has been associated with exposure to amphetamines before 7 weeks gestation.¹⁵ Amphetamines and methamphetamine have been implicated in impaired placental function by targeting the norepinephrine and serotonin transporters.¹⁶ Other studies have failed to demonstrate a relationship between amphetamines and malformations.¹⁷ More recently, in a retrospective uncontrolled study, it has been reported that 16% of infants of mothers who had used methamphetamine concomitantly with other drugs had major congenital abnormalities, including cardiac defects, gastroschisis and hydronephrosis. In addition, 5% of infants had thrombocytopenia.¹⁸ Smith and colleagues, in a controlled study of 134 neonates, found no malformations or anomalies.¹⁹ In a study of 228 women who used amphetamines during pregnancy compared with a control group of 337 who did not use amphetamines, the proportion of live born infants with structural defects did not differ significantly between the groups (5% vs 3.4%).²⁰

The defects reported in the exposed group included tracheal–esophageal fistula, pyloric stenosis, transposition of great vessels, cystic adenomatoid malformation, tracheal stricture, inguinal hernia, and chromosomal anomaly. In

regard to minor abnormalities there was a significantly proportion in the exposed group.

Other studies have reported an association between amphetamine exposure and outcomes such as reduced body weight, reduced length and head circumference at birth.^{17,19} Others have reported stillbirths and intracranial haemorrhage.^{21,22}

Obstetric effects

Cocaine and amphetamines are both central nervous system stimulants and have similar effects and mode of action. Hence, the adverse effects of amphetamines during pregnancy are similar. Methamphetamine use during pregnancy is associated with an increased incidence of intrauterine growth retardation (IUGR), premature delivery and placental abruption. The extent and effect of psychiatric morbidity associated with amphetamine use during pregnancy is not known, but is well documented in the wider population.

Diagnosis and assessment

Dependence on amphetamine can be assessed by the Severity of Dependence Scale (SDS).²³ This is a short, five-item questionnaire that provides a subjective measure of dependence. A much longer one is the Severity of Amphetamine Dependence Questionnaire (SamDQ).²⁴ Quantity and frequency of drug use can be assessed by the Opiate Treatment Index (OTI).²⁵ Patterns of drug use by amphetamine users vary, but bingeing is common.

Amphetamines can be detected in toxicology screens, but these are expensive. The best method is a comprehensive maternal drug history done by an experienced interviewer who has developed a good therapeutic relationship with the patient.

Care of the pregnant amphetamine user

There is no evidence for best practice in the treatment of pregnant or nonpregnant amphetamine dependents or users. Srisurapanont and colleagues found that evidence for specific treatment is very limited.²⁶ They examined the usefulness of four drugs (fluoxetine, amiodipine, imipramine and desipramine) in four studies with small sample sizes and reported that these had limited value in treatment. There is no evidence for replacement or maintenance pharmacotherapy for amphetamine users.

There have been few studies of nonpharmacological interventions for treatment of amphetamine use. Baker and colleagues conducted a randomised controlled trial of a brief cognitive-behavioural intervention of either two or four sessions versus a self-help booklet ($n = 214$).²⁷ More people in

the intervention group than the control group abstained from amphetamine use at 6 months follow-up. Whether such an approach would be effective for pregnant women is unknown.

Care of pregnant amphetamine users should be provided within a multidisciplinary framework with referrals to drug and alcohol services, social work, and psychiatric medicine where necessary. Screening for blood-borne viruses such as hepatitis C virus (HCV) and HIV should be done, with monitoring of liver function tests and referral to appropriate specialist clinics in the event that test results are positive. Blood-borne virus tests in the first trimester should be repeated in the third trimester in the event of continuing intravenous drug use.

Because of the association with IUGR, a growth and wellbeing scan at 32–34 weeks should be considered, with regular fetal monitoring where indicated. Weight problems associated with the appetite suppressant effect of amphetamines, sleep patterns, anaemia and diet should be monitored throughout pregnancy, with referral to a dietician and supplementation where necessary. Amphetamine use is associated with a range of mental health problems. Hence, mental health status should be monitored. Education regarding harm minimisation for breastfeeding should be provided.

Some patients may present in a state of amphetamine-type stimulant intoxication, which can range from mild to severe. The symptoms of this are dilated pupils, increased pulse, blood pressure and core body temperature, hallucinations, paranoia, delusions, possible cardiac and serotonin toxicity and psychosis. Behavioural disturbances include agitation and aggressive outbursts. Mild symptoms may require no more than supportive care in a quiet environment. In the event of moderate or severe intoxication, sedation is necessary until symptoms subside.

Should a woman undergo withdrawal during pregnancy?

The withdrawal symptoms from any drug are the opposite to the effects of the particular drug. For amphetamines they include irritability, aches and pains, depressed mood and impaired social functioning. Symptoms vary in severity and may persist for up to 3 weeks. There is no evidence-based strategy for management and patients are treated symptomatically. The effect of amphetamine withdrawal during pregnancy is unknown. If withdrawal is deemed necessary, then it is best done under medical supervision.

Neonatal withdrawal syndrome

The risk of neonatal withdrawal is greatest with exposure to opiates, but has been found to occur in neonates following exposure to amphetamines. The symptoms described include poor feeding, abnormal sleep patterns, tremors and

increased muscle tone.²⁸ In a retrospective, controlled study of at-term infants exposed to methamphetamine (134 exposed infants versus 160 unexposed), 49% of the exposed group exhibited withdrawal symptoms, but only 4% required pharmacological treatment.¹⁹ It was noted that a withdrawal syndrome for methamphetamine exposed infants has not been well defined. The type of pharmacotherapy used for the withdrawal symptoms was not noted.

There are no set criteria for pharmacological treatment of amphetamine-related withdrawal symptoms. Phenobarbitone or other sedatives may be helpful in reducing severity of symptoms. D'Apolito has described a number of supportive therapies, such as placing the infant in a quiet environment and giving frequent small feedings, which may be of benefit.²⁹ In some cases, it may be necessary to use supportive strategies plus a sedative. Mothers should be encouraged to remain in hospital for at least 5 days to monitor the infant's weight gain and feeding patterns.

Neonatal withdrawal instrument

There is no specific withdrawal instrument designed to monitor neonatal amphetamine-related abstinence symptoms. The tool most commonly used to assess drug withdrawal is that developed by Finnegan.³⁰ This was specifically designed to measure opiate-related withdrawal symptoms and its utility for use with amphetamines has not been demonstrated.

Breastfeeding

Amphetamines are excreted into breast milk and measurable amounts have been reported in infants' urine.³¹ Amphetamines have been ascribed a lactation risk category L4 (hazardous). In one study of 103 breastfed infants of mothers who were taking amphetamines, no neonatal insomnia or stimulation was observed over a 24-hour period.³² In the event of continued amphetamine use, breastfeeding should be suspended for 24 hours following the last dose of the drug. During this period, breast milk should be expressed and discarded to prevent breast engorgement.

The American Academy of Pediatrics considers amphetamines to be contraindicated during breastfeeding.³³ Although their recommendation is in part based on the notion that the administration of psychoactive drugs to developing infants has a high risk of causing adverse effects, others have made amphetamines contraindicated more on the basis that the maternal dose injected by a drug user is uncontrolled and unknown and may therefore cause unwanted adverse effects in the breastfed infant.³⁴

Neurobehavioural development

Prospective studies of 65 children at 8 years and 14 years who were prenatally exposed to amphetamines have

reported they lagged in growth, language, mathematics, and physical training compared with unexposed controls.³⁵ Despite this, the exposed group were within normal limits for their ages. The findings were confounded by not controlling for polydrug use of the mothers concerned.

MDMA

There are few data on the effects of MDMA on animal or human pregnancies. In one human study of 136 infants exposed to MDMA in utero, there was an increased risk of congenital defects, mainly cardiovascular and musculoskeletal anomalies.³⁶ However, most women in the study were polydrug users and the adverse effects could not be solely attributed to MDMA. In a review of the few animal and human studies done on MDMA, it was concluded that there is insufficient evidence to attribute teratogenicity or obstetric complications to use of MDMA.³⁷

No studies were located that have examined neonatal withdrawal symptoms or risks of breastfeeding associated with use of MDMA. However, because the structures are similar to methamphetamine, it is likely that it is transferred in breast milk. Breastfeeding should be interrupted for 24 hours following last dose.

Conclusion

Animal and human studies indicate that exposure to amphetamines during pregnancy increases the risk of adverse outcomes. The abnormalities reported in animal studies have been reproduced in some human studies. However, the animal studies have been in situations where the dose of the drug is controlled. In human studies, the dose of the drugs is not able to be controlled, and many of the results are confounded by not taking into account the extent of polydrug use, including tobacco, and environmental factors. Hence, there is little firm evidence to support causal links between use of amphetamines and the adverse effects reported in some studies.

Most of the studies are retrospective, have small sample sizes, and, because of the similarities between amphetamine and cocaine, exposure data to these drugs are often combined. Moreover, little attempt has been made to examine the effects of what form of amphetamines have been used or to detail exposure of these drugs throughout pregnancy. This should include patterns as well as quantity of drug use, as binge use may be more harmful to the fetus than regular use, particularly in the teratogenic period.

Knowledge of the maternal and fetal outcomes of exposure to MDMA is also lacking. The available data raise concerns about use of amphetamines during pregnancy and underscore the need for better research in this area. The fact that a woman takes these drugs during pregnancy does not mean that she will deliver a malformed infant. It can be con-

cluded on the limited evidence available, however, that use of these drugs will increase risk of adverse outcomes.

Given the prevalence of use of amphetamine type substances large prospective studies incorporating good data on prenatal exposure, extent of polydrug use, and relationship with psychosocial and environmental factors are urgently needed.

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15 Cocaine

Cocaine is a central nervous system (CNS) stimulant derived from the leaves of the shrub, *Erythroxylon coca*. It is a local anaesthetic that exerts its effect by binding specifically to presynaptic monoamine transporters, inhibiting reuptake of amines following synaptic release. As a result, extracellular concentrations of dopamine, 5-hydroxytryptamine and norepinephrine are increased, resulting in vasoconstriction, tachycardia and hypertension (Resnick et al 1977; Beuchimol et al 1978). The euphoric and the reinforcing properties of cocaine are exerted through its effects on the dopamine receptor (Nestler and Aghajanian 1997).

Cocaine is highly lipid-soluble and crosses biological membranes easily. It has been found in amniotic fluid (Garcia et al 1996), the placenta and fetal tissues (Srinivasan et al 2000). Fetal and maternal concentrations rapidly equilibrate, exposing the fetus to high concentrations of cocaine (Chasnoff and Lewis 1988). The parent drug and its metabolites are readily detectable in many infant tissues, including nails (Skopp and Potsch 1997), hair, meconium and urine (Vinner et al 2003). Cocaine is metabolised into ecgonine and benzoylecgonine by plasma cholinesterase. The activity of plasma cholinesterase is reduced in pregnant women, fetuses and neonates, increasing the susceptibility of this patient group to the toxic effects of cocaine (Fajemirokun-Odudeyi and Lindow 2004).

The specific perinatal complications due to cocaine are hard to isolate because cocaine users are also more likely to use other drugs, such as heroin, tobacco, alcohol and marijuana (Leri et al 2003). Cocaine-using women have less antenatal care than non-cocaine-using women (Chasnoff et al 1990), although comparison between Australian women who use cocaine and other illicit drugs has not been made.

Risk of pregnancy complications and fetal effects

Is there evidence of pregnancy complications (antepartum haemorrhage, perinatal mortality)?

The incidence and severity of adverse cocaine-associated perinatal effects is dependent on the dose of cocaine ingested and the stage of gestation at which cocaine was ingested (Fajemirokun-Odudeyi and Lindow 2004). Cocaine-induced vasoconstriction, sudden hypertension or cardiac

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arrhythmias may interrupt blood supply to the placenta and fetal tissues (Bingol et al 1987), resulting in an increased chance for intrauterine hypoxia, preterm labour and placental abruption (Tarr and Macklin 1987). Cocaine causes hypertension and increased uterine contractility, leading to an increased incidence of placental abruption, estimated to occur in 2% to 15% of cocaine-affected pregnancies (MacGregor et al 1987; Chasnoff et al 1989; Handler et al 1991), compared with 0.3% of the general population (Sheiner et al 2003). The incidence of placental abruption is increased with bingeing, but the risk of abruption persists even if cocaine ingestion is limited to the first trimester (Chasnoff et al 1989). First trimester cocaine use also increases the risk of spontaneous abortion (Chasnoff et al 1985) compared with drug-free controls matched for socioeconomic status, smoking and ethnicity (Chasnoff et al 1989).

Preterm labour (after 20 weeks and before 37 weeks gestation) and delivery occurs in 17% to 29% of cocaine-affected pregnancies (MacGregor et al 1987; Dombrowski et al 1991; Handler et al 1991; Snodgrass 1994), compared with about 5% of the general population (Roberts et al 2003). Cocaine increases spontaneous myometrial contractility more than threefold via both α -adrenergic and non-adrenergic mechanisms (Hurd et al 1998), and an intravenous dose (1 mg/kg) of cocaine significantly increases plasma oxytocin levels in gravid baboons (Morgan et al 1996).

Is there evidence of teratogenicity?

Congenital anomalies occur in 7% to 17% of infants exposed to cocaine in utero (Fajemirokun-Odudeyi and Lindow 2004), but there is no firm evidence for a type-specific cocaine-induced teratogenicity. Case reports have noted an increased incidence of abnormalities postulated to be caused by vascular disruption, such as complex choroid plexus cysts, gastroschisis, meconium peritonitis, urethral stenosis, and radial hypoplasia (Hume et al 1994). However, most studies do not acknowledge the confounding presence of other illicit drugs, especially of alcohol, which 60% to 90% of cocaine-users consume concomitantly and which is probably a more potent teratogen than cocaine (Frank et al 1990). Recreational drugs such as alcohol, tobacco and marijuana are independent predictors of altered fetal growth (Singer et al 2002). A meta-analysis of 33 studies comparing 4184 cocaine-exposed women with 31 544 drug-free controls found no significantly increased risk for congenital malformations after exclusion of poly-drug use (Addis et al 2001).

Is there evidence of fetal growth restriction?

Small but statistically significant growth restriction is one of the most consistent findings of studies into prenatal cocaine use. Umbilical vessels are sensitive to catecholamines (Lester et al 1996), and cocaine may constrict uterine arteries and impede oxygen supply to the fetus. This, coupled with the anorexic effects of cocaine, places the developing fetus at increased risk of somatic and cephalic growth retardation (Fulroth et al 1989; Hadeed and Siegel 1989; Yoon et al 1989). Unlike the other problems, growth restriction is significantly increased even after exclusion of polydrug use (Addis et al 2001).

Newborn and infant outcomes

Neonatal abstinence syndrome (NAS): Is the drug associated with an identifiable NAS?

Incidence and risk factors

Neonatal cocaine withdrawal does not appear to be as severe as opiate withdrawal. The incidence and severity of withdrawal is complicated as always, by difficulty in obtaining an accurate picture of maternal drug use. Polydrug use is frequent and dosage information is often not available. However, in a small study, about a third of cocaine-exposed infants, as determined by maternal history and toxicology screen, demonstrated signs of withdrawal on routine assessment and only 6% required pharmacological treatment (Fulroth et al 1989). In comparison, more than half of all opiate-exposed infants withdraw in the neonatal period and up to 75% of these infants require medical treatment (Oei et al 2001).

Diagnosis and assessment

Is there a screening tool?

A detailed maternal drug and alcohol history is the most frequently used screening tool, as self-reports have been generally considered a reliable indicator of drug use in a non-punitive environment (Solbergdottir et al 2004). Toxicology may be a useful adjunct, and cocaine has been detected in a variety of neonatal products, including meconium, urine, hair (Vinner et al 2003) and nails (Skopp and Potsch 1997). However, the accuracy of toxicological testing for cocaine in biological specimens is highly dependent on the types of specimens tested, the types of drugs tested for, and the availability of expertise to perform the tests. For example, elimination half-lives depend on the route of administration and are rarely longer than 4 hours (Cone et al 2003), so tests on newborn products such as urine that are constantly eliminated may be negative if the mother abstained a day or so

before delivery. The probability of detecting maternal cocaine is decreased if the collection of such specimens as meconium and urine is delayed (Wingert et al 1994), but large-scale screening may be practically achieved by mass meconium analysis. Ostrea et al (1992) collected meconium from 3010 discarded nappies from a major hospital in Detroit, US, and found that 44% tested positive for cocaine, morphine or cannabinoids, 31% for cocaine, 21% for morphine, and 12% for cannabinoids. In contrast, only 335 (11%) mothers admitted to illicit drug use, whereas 52% of newborns had a positive urine drug screen and 88% had a positive meconium drug screen.

Is there an assessment tool?

The usual methods of assessing neonatal drug withdrawal (e.g. Finnegan's scoring) have only been validated for opiate exposure (Finnegan et al 1975), but have been used in most institutions as the most comprehensive assessment tool for neonatal drug withdrawal. Infants with cocaine-positive urine have lower scores (increased startle, tremulousness) on the Neonatal Behavioural Assessment Scale, and this effect lasts through the first week of life (Eyler et al 2001), but this scale has not been validated for treatment purposes.

Other infant and childhood outcomes

Neurodevelopmental problems

The ultimate effect of cocaine on the developing central nervous system (CNS) is difficult to ascertain because the severity of cocaine-related effects may be dose-dependent and effects may be blurred by concomitant polydrug use. Nevertheless, there is no evidence, after correction for socioeconomic confounders, of a statistically increased risk of gross neurodevelopmental abnormalities at school age (Frank et al 2001). Differences are more subtle, with cocaine-exposed children showing difficulties in initiating inhibition. Functional magnetic resonance imaging (MRI) studies demonstrate greater overall activation, which is particularly evident in the right frontal, anterior cingulate, and striatal regions (Sheinkopf et al 2004). Cocaine-exposed infants also have considerably less frontal lobe white matter (Belcher et al 2004), which has been postulated as being secondary to ischaemia during fetal neurodevelopment.

Treatment

Pharmacological treatment

There are no set criteria for medicating an infant withdrawing from maternal cocaine. Most physicians medicate an infant when supportive measures (see below) prove ineffective and when the infant is adversely affected by poor feeding, poor sleeping or failure to thrive. Opiates are not beneficial in cocaine-withdrawal and, as withdrawal is mostly a consequence of a sympathetic withdrawal, sedation with an appropriate agent such as phenobarbitone has been found to be highly effective in most instances.

Supportive therapies

A quiet environment is vital for drug-exposed infants, and non-pharmacological measures such as nursing in a dim environment, swaddling and frequent small feedings or easy access to non-nutritive sucking are conducive in the treatment of neonatal withdrawal. Overstimulation may be harmful. In one study, polydrug-exposed infants who were nursed on rocking beds had worse withdrawal than infants nursed on standard beds (D'Apolito 1999), whereas waterbeds lessened the severity of neonatal methadone withdrawal (Oro and Dixon 1988). Similar research has not been performed on cocaine-exposed infants.

Breastfeeding

What are the levels of the substance in breast milk?

Cocaine is lipophilic and is excreted in breast milk. For example, cocaine was detected in 6 of 11 mothers who admitted to using cocaine during pregnancy. The highest cocaine concentration found was over 12 µg/mL, with levels of the parent compound being higher than any of the other metabolites (Winecker et al 2001). Therefore, the infant can ingest significant quantities of cocaine via breast milk. However, a dose-dependent transmission gradient for maternal cocaine into breast milk has not been established.

What are the levels of the substance in the infant and the effect of the substance on the infant?

Levels in fetal rhesus monkeys are about one-fifth of maternal plasma levels after both single intravenous and oral administration of cocaine (Zhou et al 2001). There are no similar human studies. The extent of cocaine-deposition in fetal tissue depends on the route of cocaine administration to the mother. For example, in fetal rats, intravenous administration results in a cocaine concentration that is three to four times higher in the brain and three to five times higher in the liver than in serum. Using the oral route, the concentration in brain was two to three times higher and 10 to 20 times higher in liver than in blood. Cocaine appears to be concentrated in milk: after administering radioactive cocaine to lactating dams, the average milk : blood ratio for cocaine was 7.8 (Wiggins et al 1989).

The effects of breast milk transmission of cocaine have been documented only as an isolated case report. A 2-week-old girl demonstrated evidence of cocaine intoxication after breastfeeding from a mother who had used about 0.5 g of cocaine intranasally before feeding. The mother's milk and the infant's urine both contained cocaine and benzoylecgonine. The infant's urine cleared by 60 hours and the breast milk cleared by 36 hours, with rapid resolution of the symptoms of cocaine intoxication (Chasnoff et al 1987).

Conclusions

Cocaine use in pregnancy has well-established effects on fetal and placental development. However, the effects of cocaine on childhood neurodevelopment and congenital malformation appear to be less problematic than previously thought, especially when the influences of other neuroteratogens are taken into account. The long-term effects of a drug-using household on the social behaviour of an affected child remain to be seen. Cocaine may pass through breast milk in sufficient quantities to intoxicate an infant, but definitive studies of a dose-response relationship are lacking. In conclusion, cocaine has the potential to cause significant long-term and short-term hazards for both the mother and infant, and moderation or complete abstinence is recommended for pregnant women. Further definitive studies are urgently required, especially pertaining to the fields of breastfeeding and treatment of neonatal abstinence secondary to cocaine.

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16 Cocaine

Discussant:

Anne Bartu

1. Identification of crucial issues

- Prevalence
- Assessment
- Screening
- Type of drug use (dependent, regular, recreational including partner's drug use)
- Quantity and frequency of all drug use, including tobacco
- Management of cocaine withdrawal during pregnancy
- Fetal effects
- Management of neonatal abstinence syndrome

- Breastfeeding
- Postnatal effects, possibly depression
- Environmental issues.

Additional crucial issues identified

- Models of care
- SIDS
- Developmental outcomes.

2. Guidelines emerging

Guideline	Level of evidence (NHMRC)
Assessment and screening (including type of drug user, quantity and frequency)	No evidence
Model of care	No evidence
Pregnancy complications and fetal effects	III–IV
If withdrawal required during pregnancy, when should this be done	No evidence
What pharmacotherapies should be used for detoxification	No evidence
Assessment of neonatal abstinence syndrome (what tool to use)	No evidence
Breastfeeding	Insufficient evidence
Postnatal care	No evidence

3. Recommendations or “good practice points” identified (where insufficient evidence for making a guideline, and consensus may be expected)

- Assessment, including a comprehensive drug use history of the woman and her partner.
- Assessment of dependence on main drug.
- Model of care.
- Drug use monitoring during the antenatal period (what measures, how often).
- Mental health issues.
- Management of withdrawal during pregnancy.
- Collaboration with alcohol and drug treatment services.

4. Areas lacking consensus

- Breastfeeding advice to women (Should they breast-feed? What to do if they use cocaine prior to feeding? What is a safe withholding period?)
- SIDS.
- Drug use monitoring (mother and fetus).
- Postnatal follow-up (for how long?).
- Mental health issues.
- Neurodevelopmental outcomes.

5. Gaps in available evidence, and recommendations for further research

- Further studies are required on breastfeeding, measurement of neonatal abstinence syndrome, mental health issues during pregnancy and in the postnatal period, influence of polydrug use outcomes and neurodevelopmental outcomes.

17 Benzodiazepines

Benzodiazepines are one of the most commonly used drugs in the world. The exact consequences of maternal benzodiazepine use on the newborn infant are difficult to ascertain because their use is often undisclosed and, as with all drugs of dependency, they are often used in combination with other drugs, so that it becomes difficult to separate their effects from those of other substances such as alcohol, cigarette smoking or narcotics.

Benzodiazepines exert their effects by increasing the concentration of the inhibitory neurotransmitter, γ -aminobutyric acid (GABA) (Hafely 1982) in the limbic, thalamic and hypothalamic levels of the central nervous system, causing activation of the GABA receptor, opening of chloride channels and hyperpolarisation of the cellular membrane (Olsen et al 1984). Benzodiazepines cause sedation, hypnosis, anxiolysis and skeletal muscle relaxation and are also antiepileptic (Iqbal et al 2002).

There are three major categories of benzodiazepines: long acting (e.g. diazepam, chlordiazepoxide, chlorazepate, flurazepam, halazepam, prazepam), intermediate acting (e.g. clonazepam, lorazepam, quazepam, estazolam), and short acting (e.g. alprazolam, oxazepam, temazepam, midazolam and triazolam). Transplacental transfer of benzodiazepines is well established: maternal benzodiazepines have been found in amniotic fluid, umbilical cord blood, milk and neonatal blood (Rey et al 1979), with the amount of drug transferred depending on individual drug lipophilicity and pharmacokinetics.

Risk of pregnancy complications and fetal effects

Is there evidence of pregnancy complications (antepartum haemorrhage, perinatal mortality)?

Few studies have examined the relation between perinatal complications and benzodiazepine use. It is also difficult to isolate the effects of benzodiazepines from other contributions to pregnancy-related complications. Laegreid et al (1992a) screened first trimester maternal serum for benzodiazepines in 48 cases of perinatal death in Denmark. They found a significant association between benzodiazepine use and perinatal death, but numbers were small (nine target cases). Three of these infants had major congenital malfor-

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mations (one cyclopia and polytactyly, one renal dysplasia and pulmonary hypoplasia, one polycystic kidneys and pulmonary hypoplasia), three died from anoxia, and the cause of death in the remaining three was undetermined (Laegreid et al 1992a). Pastuszak et al (1994) found almost double the rate of miscarriages in 137 cases of first-trimester benzodiazepine exposure, and three of 80 infants of women who were given more than 10 benzodiazepine prescriptions during pregnancy died in utero (Bergman et al 1992). However, there are no studies examining other prenatal complications related to benzodiazepines.

Is there evidence of teratogenicity?

The evidence for teratogenicity is inconclusive, as most of the studies are case reports, are of a small study population, and examine multiple classes of benzodiazepines. Benzodiazepine receptors are present in human fetuses by 12 to 15 weeks gestation (Aaltonen et al 1983). GABA has been shown to regulate neuronal proliferation and migration in the developing cortex (Owens and Kriegstein 2002) and, although not directly neurotoxic (Saito et al 1986), benzodiazepines were embryocidal to 50% of exposed rat fetuses (Saito et al 1984). Women who overdose on benzodiazepines do not have an increase risk of teratogenicity (Czeizel et al 1984). Seventy-five normal infants exposed to one of either nitrazepam, medazepam, tofisopam, alprazolam or clonazepam during pregnancy were matched to 57 infants with congenital abnormalities who had been exposed to one of these benzodiazepines (Eros et al 2002), and no appreciable teratogenic risk to fetuses exposed to those particular benzodiazepines was found. The incidence of congenital abnormalities (3.1%) was not different in 460 benzodiazepine-exposed pregnancies compared with 2.6% of control pregnancies in a recent study (Ornoy et al 1998).

Oral clefts

GABA inhibits the developmental orientation of the palate, but vulnerability to oral clefts is thought to be influenced by individual genetic susceptibility to the effects of GABA (Zimmerman 1985). The first reports of an association between benzodiazepines and oral clefts occurred in 1975 in Finland (Saxen 1975; Saxen and Saxen 1975), but in these studies, the use of other drugs such as analgesic, chemotherapeutic and antipsychotic agents could not be excluded.

First trimester benzodiazepines, in a meta-analysis by Dolovich et al (1998), were not associated with an increased risk of oral clefts or major malformations in cohort studies. In case-

control studies, however, there was an association between major malformations (OR 3.01, 95% CI 1.32–6.84) and oral clefts (OR 1.79, 95% CI 1.13–2.82) (Dolovich et al 1998). However, the need for benzodiazepines as a psychotropic medication is sometimes vital for the health of the mother, and the authors recommend ultrasonography to rule out visible forms of oral clefts in utero.

Benzodiazepine dysmorphism

An embryopathy has been described in relation to maternal benzodiazepine use, but causation has not been established with pooled studies. Laegreid et al described eight infants in whom characteristic craniofacial abnormalities were noticed. These included a low nasal bridge with a short upturned nose, short palpebral fissures, epicanthic folds, slightly malformed or low-set ears, hypoplastic mandible and full, flat lips (Laegreid et al 1987; Laegreid et al 1989). Bergman described six infants in whom nonspecific neurological problems, atrial and ventricular septal defects and minor abnormalities (undescended testes, talipes, syndactyly) were noted, but the mothers of these infants were taking various other medications as well as diazepam during pregnancy (Bergman et al 1992).

Associated problems

The preservative component of intravenous diazepam, sodium benzoate, may compete with bilirubin binding to albumin and may lead to prolonged severe jaundice and potentially to kernicterus (Schiff et al 1971).

Is there evidence of fetal growth restriction?

Seventeen infants exposed to prenatal benzodiazepines had lower birth weight to length ratios than control infants (Laegreid et al 1992a). On follow-up to 18 months, compared with 29 control infants, the benzodiazepine-exposed infants caught up early in growth, but motor development, especially that of the fine pincer grasp, remained delayed until 18 months (Laegreid et al 1992b).

Newborn and infant outcomes

Neonatal abstinence syndrome (NAS): Is the drug associated with an identifiable NAS?

Incidence and risk factors

The incidence of neonatal withdrawal secondary to maternal benzodiazepines is not clear. Benzodiazepine use is not kept under the same degree of surveillance as regulated drugs

such as methadone, and the exact number of women taking some form of benzodiazepines during pregnancy is unknown. Nevertheless, the risk of withdrawal is increased with high maternal drug doses (e.g. diazepam > 30 mg/day) and may appear from as soon as a few days after birth, lasting for several months (Iqbal et al 2002).

Consequences and symptomology

Intramuscular or intravenous diazepam before delivery may cause the “floppy infant syndrome” (Gillberg 1977; Haram 1977; Rementeria and Bhatt 1977; Speight 1977). The infants are lethargic, hypothermic, feed poorly and may have respiratory problems, but seem to recover without sequelae. Chronic prenatal benzodiazepine exposure may cause neurological dysfunction (hypertonicity, hyperreflexia, tremors), settling problems (restlessness, irritability, inconsolable crying, abnormal sleep behaviour), feeding issues (sucking difficulties, diarrhoea, vomiting, failure to thrive) and cardiorespiratory instability (heart rhythm abnormalities, apnoea) after an infant is born.

Inappropriate secretion of antidiuretic hormone (with oliguria and hyponatremia) has been noticed in four cases (Rementeria and Bhatt 1977; Nako et al 2000) and has been postulated to be due to GABA-associated inhibition of arginine vasopressin (Wible et al 1985).

Diagnosis and assessment

Is there an assessment tool?

There are no validated screening or assessment tools particularly devised or validated for neonatal benzodiazepine abstinence. The Finnegan’s scoring system (Finnegan et al 1975), initially formulated for newborn opiate withdrawal, is most frequently used to monitor benzodiazepine-exposed newborns in addition to clinical assessment (e.g. feeding, weight gain, sleeping patterns, behaviour and irritability).

Treatment

Pharmacological treatment

Pharmacological treatment for neonatal benzodiazepine withdrawal has not been systematically examined. Replacement therapy with other benzodiazepines is not advised because of the long half-life of most forms. There are also reports of adverse effects in infants exposed to benzodiazepines after birth. In a chart review of 63 infants who received benzodiazepines as a sedative or anticonvulsant, side effects attributable to treatment were documented in 10 (15%), including seizures, hypotension and respiratory depression (Ng et al 2002).

Phenobarbitone is the most frequently used medication for non-opiate withdrawal. As benzodiazepine withdrawal is often masked by opiate withdrawal, treatment for the former may not be required until opiate withdrawal is controlled.

Supportive therapies

Supportive measures include swaddling, nursing in a quiet environment and small frequent feeds for feed intolerance, but there are no studies assessing their effectiveness in neonatal benzodiazepine withdrawal.

Infant outcomes

Neonatal growth and development and child developmental outcomes

There have been reports of neurodevelopmental concerns associated with fetal benzodiazepine exposure. In one case series, only one of eight exposed infants were of normal intelligence. Two were microcephalic, two had severe mental retardation and five had mild mental retardation (Laegreid 1990). Seventeen infants were assessed on the Griffith's Developmental Scale by Viggedal et al (1993) from the age of 5 months and were found to fall short on all subscales, with personal-social behaviour and hearing and speech deficits being most marked at 18 months of age. The mothers of these infants were long-term users of benzodiazepines, mainly for psychiatric disorders such as anxiety and panic disorders. Fifteen used combinations of oxazepam (15–60 mg/day) and diazepam (5–30 mg) and one used lorazepam (5–15 mg/day) (Viggedal et al 1993). However, the contribution of parenting ability to infant development could not be excluded, and it has been suggested that the premorbid psychological condition of the mother is more important to the child's neurological development than prenatal exposure to benzodiazepines (Misri et al 2004).

Breastfeeding

What are the levels of the substance in breast milk?

The amount of benzodiazepines crossing into the infant from breast milk depends on individual drug bioavailability. Benzodiazepine and metabolite concentrations in breast milk are unlikely to be high if the drug is only taken once. The breast milk of women who received diazepam general anaesthesia induction had undetectable levels of diazepam or its metabolite, nordiazepam (Borgatta et al 1997).

Maternal plasma and breast milk benzodiazepine ratios have not been correlated. However, there are case reports of sedation after breastfeeding, especially if the last dose was less than 8 hours before a feed (Wesson et al 1985) and if more than 30 mg of diazepam was taken (Patrick et al 1972).

Estimated milk : plasma ratios for various benzodiazepines range from 0.1 to 0.5 (Pons et al 1994). In a patient on high doses of oxazepam and diazepam, diazepam, N-desmethyldiazepam, temazepam and oxazepam were found in the maternal plasma and milk with mean milk : plasma ratios of 0.2, 0.13, 0.14 and 0.10, respectively. Diazepam could not be detected in the infant's plasma, but low levels of *N*-desm-

ethyl diazepam (20 and 21 µg/L), temazepam (7 µg/L) and oxazepam (7.5 and 9.6 µg/L) were present in the 1-year-old asymptomatic infant (Dusci et al 1990). Cord blood clonazepam level in the infant of a mother treated with clonazepam for sleep myoclonus was 19 ng/mL, compared with 32 ng/mL in maternal serum and 11–13 ng/mL in breast milk. The infant was apnoeic, lethargic and hypotonic after birth, but normalised by 10 days of age (Fisher et al 1985).

Alprazolam is the most widely prescribed benzodiazepine for anxiety. It has a shorter half-life than other benzodiazepines (10–24 hours) and both it and its metabolites cross the placenta (St Clair and Shirmer 1992). Alprazolam has been found in low concentrations in breast milk (Oo et al 1995), with clinical signs of neonatal withdrawal occurring after cessation of breastfeeding (Anderson and McGuire 1989).

What are the levels of the substance in the infant?

There are no studies assessing the effects of chronic maternal benzodiazepine intake on newborn blood or tissue levels. Studies have been confined to acute administration of one or several doses of various benzodiazepines, which have confirmed that newborn levels are similar or considerably lower than maternal plasma levels. Diazepam was detected in cord blood 0.5 minutes after its administration to the mother just before delivery (McAllister 1980). Cord blood levels of diazepam and its metabolite, *N*-demethyldiazepam, were similar to maternal levels shortly after administration, but diazepam has been found to accumulate in the heart and lungs of deceased infants. The mean half-life of diazepam in newborn infants in this study was 31 ± 2 hours, considerably longer than the half-life in adults, probably because of reduced urinary excretion of metabolites (Mandelli et al 1975).

Lorazepam levels are considerably lower in the newborn than in mothers (McBride et al 1979), but levels higher than 35 µg/L in the cord blood were associated with an increased need for temporary artificial ventilation (Whitelaw et al 1981).

What is the effect of the substance on the infant?

Benzodiazepines may cross into the infants from the mother during the post-neonatal period if the infant is breastfed. Breastfeeding a short time after acute maternal ingestion may cause infant sedation and respiratory depression, although no studies have assessed the effects of breastfeeding in infants *chronically* exposed to benzodiazepines in utero.

Conclusion

There are few rigorous studies examining the effects of benzodiazepines in pregnancy or on the developing fetus. There is a syndrome of neonatal abstinence associated with chronic use, but its exact nature is unpredictable. Further studies, especially of the most commonly used benzodiazepines such

as diazepam and temazepam, are needed to examine these effects.

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18 Benzodiazepines

Discussant:

David Jackson

1. Identification of crucial issues

- One of the most commonly used group of drugs in the world.
- A group of drugs with widely differing pharmacokinetics despite essentially identical pharmacological actions.
- Effect on infants difficult to ascertain due to tendency toward nondisclosure of use; lack of monitoring; frequency of intake as part of polydrug use; and lack of research.
- Transplacental transfer occurrence is well established.
- Some evidence of increased frequency of perinatal death and miscarriage.
- Inconclusive whether they are teratogenic, but may cause oral clefts and craniofacial abnormalities.
- Neonatal abstinence syndrome (NAS) occurs, particularly with higher doses.
- No NAS assessment tool, but Finnegan’s scale used.

- NAS treatment unsubstantiated, possibly phenobarbitone, but certainly benzodiazepines contraindicated.
- Reports of neurodevelopmental concerns, but just as likely to be due to impaired maternal psychological status.
- Breastfeeding: wide variation in breast milk depending on particular drug. Uncertain consequences, but probable sedation and even withdrawal on cessation of breastfeeding.

Additional crucial issues

- The approach to pregnant benzodiazepine users. Should withdrawal be considered or maintenance therapy, and if the latter, which benzodiazepine?
- Selective withdrawal of the other drugs used in combination with benzodiazepines—particularly alcohol and nicotine—needs addressing.

2. Guidelines emerging

There are few explicit guidelines for practice in the paper, given the paucity of evidence available in the scientific literature.

Guideline	Level of evidence (NHMRC)
Antenatal care	
Ultrasonography to screen for oral clefts	IV
Neonatal abstinence syndrome	
Monitoring: Finnegan scale in the interim	IV
Treatment: Supportive only, and no administration of benzodiazepines	IV

3. Recommendations or “good practice points” identified (where insufficient evidence for making a guideline, and consensus may be expected)

- Selective withdrawal.
- Avoidance of breastfeeding in high-dose users.
- Avoidance of breastfeeding at peak plasma periods.

4. Areas lacking consensus

Lack of consensus is unlikely. Because of the insufficiency of good quality research findings, clinicians are likely to take a cautious approach to all aspects of pregnancy and benzodiazepines and this conservatism will probably produce a consensus of approach. Exceptions might be debate about the interim use of Finnegan’s scale and the use of phenobarbitone in managing NAS.

5. Gaps in available evidence, and recommendations for further research

All areas of benzodiazepines and pregnancy urgently require basic research with particular emphasis on:

- The best approach to withdrawing (or maintaining) benzodiazepines from the pregnant woman
- Whether the different pharmacokinetics have major clinical implications for pregnancy and the neonate
- Elucidating the exact nature of NAS
- Researching the possibility of developing a measuring scale for NAS
- Research into the best treatment approach to NAS
- How best to approach breastfeeding
- What to watch for, and how to deal with, developmental problems.