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Substance misuse in pregnancy

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Summary Most studies suggest that licit and illicit substance misuse has an adverse effect on pregnancy outcome. However, interpretation of many studies is complicated by the failure to control for important co-morbid reproductive risk factors and a publication bias towards positive findings. This article analyses research into the substances most commonly misused in pregnancy to determine the degree to which they directly affect obstetric outcome. Although substance misuse is a clear marker for 'high risk' pregnancy, it remains unclear whether many of these substances are directly responsible for the adverse consequences associated with them.

INTRODUCTION

Regina McKnight, a 23-year-old woman from South Carolina in the USA, was sentenced to 12 years imprisonment in May 2001. She was prosecuted for 'killing her unborn child' following a stillbirth in a pregnancy during which she had misused cocaine. Prosecution rested on the belief that, beyond all reasonable doubt, substance misuse had a direct effect on the obstetric outcome.

This paper examines the scientific literature in this area to determine the degree to which substance misuse adversely affects pregnancy.

LICIT SUBSTANCE MISUSE

Cigarette smoking

Cigarette smoking in pregnancy has been consistently associated with a wide variety of adverse pregnancy outcomes in large numbers of well-designed studies. A summary of these effects is given in Table 1.

After controlling for confounding factors, such as socio-economic status (SES), ethnicity and other substance misuse, retrospective and prospective studies have found smoking to be associated with miscarriage with a relative risk of between 1.2 and 1.8. In addition, most studies have noted a dose-dependent relationship.

A meta-analysis of 10 published studies by the United States Department of Health and Human Services found a mean reduction in birthweight of almost 200 g amongst smokers. Meta-analysis of 10 further studies suggests a dose–response relationship with recent estimates suggesting a 100 g reduction with each 1 g/l increment in serum cotine concentration. Studies of neonatal outcome following smoking cessation during pregnancy have yielded encouraging results with recovery of birthweight to levels similar to non-smokers and low birthweight may be prevented in women who stop smoking by as late as the third trimester. This suggests that the window of opportunity for pregnant women to benefit from cessation of smoking may be wider than frequently appreciated.

The risk of placenta praevia increases from 5/1000 pregnancies in non-smokers to 20/1000 in smokers (> 10 cigarettes/d). This has been supported by data from the Swedish Medical Birth Registry of 2345 cases of placenta praevia, which also found a dose–response relationship. A study of 12 825 women interviewed immediately after childbirth at the Boston Hospital for Women found a 90% increase in risk of placenta praevia in women who smoked in the first two trimesters but did not find a dose–response relationship. The incidence approximates that of non-smokers in women who stop smoking during pregnancy.

In a recent meta-analysis of 13 published studies smoking was associated with a 90% increase in the incidence of

Table 1 Perinatal complications following cigarette smoking in pregnancy

Miscarriage
Intrauterine growth restriction (IUGR)
Placenta praevia
Abrupti placenta
Preterm delivery
Premature rupture of membranes (PROM)
Preterm premature rupture of membranes (PPROM)
Sudden infant death syndrome (SIDS)
Neurobehavioural abnormalities

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placental abruption. The incidence of abruption in those women who stop smoking in pregnancy has been found to be similar to those women who have never smoked.

The first report of an association between smoking and preterm delivery by Simpson in 1957 has been supported by subsequent studies. The largest and most recent study of this relationship analysed 300 000 live births in Sweden from 1991 to 1993 and reported a dose-dependent relationship. This study also revealed a dose-dependent relationship between smoking and PPROM (which accounts for ~30% of all preterm deliveries). In a separate study smoking cessation in the first trimester has been found to significantly reduce the rate of preterm delivery.

Maternal smoking antenatally has been associated with SIDS in a number of epidemiological studies. A recent case-control study in New Zealand estimates this risk to be 4-fold higher than the background risk. A separate case-control study in the USA supports the strength of this association for Caucasians, Asians and Hispanics but not for Native Americans. The reasons for this are not clear but it has been suggested that other factors (e.g. diet) may be contributing to the effect of cigarette smoking.

Maternal smoking has been reported to have a persistent effect on the cognitive and behavioural skills of children studied up to 6-years old using a variety of tests. Although these studies have controlled for many important confounding factors, extrapolating from batteries of tests to the 'real world' requires caution.

Alcohol

Surveys of alcohol consumption generally find that women consume less alcohol than men. However, data from the 1996 British Household Survey suggest that this gap is closing with a 4% rise in women drinking over 14 units per week compared to 1986 (14% vs 10%, respectively).

The primary concern of alcohol misuse in pregnancy is its teratogenic potential. High levels of alcohol consumption have been associated with a specific fetal alcohol syndrome (FAS). This includes (i) growth restriction, (ii) central nervous system damage and (iii) facial dysmorphology. The worldwide incidence of FAS has been estimated to be 0.97 cases per 1000 live births. However, a recent analysis of all the published prospective studies of FAS worldwide revealed that 91 of the 95 cases observed were diagnosed in the USA despite less children being examined in the USA compared to other countries (46 497 and 51 079, respectively). Since alcohol consumption is not believed to be markedly different in the USA compared to the other countries studied, this has been recently termed the 'American Paradox'.

One explanation for this paradox may be attributable to the socio-economic status (SES) of the populations studied within each country. This is supported by the finding that the incidence of FAS was 2.29/1000 live births in populations of lower SES in the USA compared to 0.26/1000 in populations of higher SES. This latter figure is closer to the incidence of FAS in Europe. If further studies support the role of poverty in the aetiology of FAS the next task will be to isolate the mechanism(s) through which poverty exerts this effect. Inadequate nutrition may play a key role in this process offering a variety of options for prevention.

A similar paradox exists when analysing the literature on alcohol consumption during pregnancy and miscarriage. Although it is widely believed that alcohol consumption is associated with an increase in miscarriage rate, these data come mostly from studies done in the USA. Studies from other countries repeatedly fail to find a significant relationship. However, most studies from the USA are biased in their sampling of pregnant women with a disproportionate number being of very low SES. Studies in Europe or Australia, however, include a much more homogenous group. When SES is controlled for, the abortifacient potential of alcohol disappears.

Although animal studies support the proposition that alcohol is capable of causing miscarriage, the threshold blood levels of alcohol required in these studies is at least 200 mg/dl. This level leads to coma in laboratory animals and is analogous to a 55 kg woman drinking about eight drinks over a 3-h period. This is an unlikely scenario in the majority of pregnant women and extrapolation to humans is tenuous. However, this pattern of drinking raises the important question of the effects of 'binge drinking'. This drinking pattern has been defined as 'the consumption of five or more standard drinks per occasion' and has become increasingly popular in countries in northern Europe and the USA. There is, however, a lack of prospective human studies aimed at assessing the outcome of binge drinking. The most comprehensive study of neurodevelopment assessed 486 children between 7- and 8-years old after questioning mothers about their drinking habits during pregnancy. The study suggests a correlation between binge drinking behaviour and neurobehavioural deficits. However, in addition to the potential recall bias at this time, the study failed to define a threshold for binge drinking making it difficult to draw any firm conclusions. A more recent retrospective study measuring developmental outcome 18 and 42 months after delivery has failed to find a correlation between binge drinking and development. A large multi-centre prospective trial is clearly needed to determine whether a relationship exists.

ILLICIT SUBSTANCE MISUSE

Cocaine

The primary mechanism through which cocaine is believed to exert its toxic effects on the foetus is via

inhibition of the re-uptake of noradrenaline, leading to constriction of blood vessels. This has an *indirect* effect of reducing uterine artery blood flow causing fetal hypoxia in addition to a *direct* effect on the fetus resulting in fetal vasoconstriction, hypertension and tachycardia. If alcohol and cocaine are taken simultaneously the metabolite cocaethylene is formed which is a more potent vasoconstrictor than cocaine alone.

Initial studies on the effects of maternal cocaine use on the fetus and neonate revealed alarming results. A number of associations were documented which are summarized in Table 2.

The number of MEDLINE citations on cocaine and pregnancy increased from 23 to 663 (i.e. ~30-fold) between the periods 1970–1981 and 1982–1993. The majority of these studies, however, are limited by both sample size and a failure to control for other co-morbid risk factors that have an adverse effect on pregnancy outcome. These are summarized in Table 3.

Despite these limitations earlier studies were generally, and, to a large extent, uncritically accepted by the scientific community. This has been partly explained by the social and political climate during the 1980s, especially in the USA. The availability of a new, cheaper and more addictive form of cocaine, commonly known as 'crack', led to a shift in the population misusing it from a wealthy minority to a large, poor and disadvantaged population. The 'crack epidemic' that followed was made worse by rising unemployment and homelessness. In response to the crisis, government agencies launched an 'anti-crack campaign' and the 'crack baby' became a powerful symbol, quickly and relentlessly promoted by the media. In this context, it has been suggested that negative results were not acceptable to journals and other agencies. This suggestion is backed up by the observation that among abstracts submitted to the Society for Pediatric Research between 1980 and 1989, 57% of those describing positive results were accepted compared to only 11% suggesting no effect of cocaine on fetal outcome.

Table 2 Perinatal complications following maternal misuse of cocaine during pregnancy

Ectopic pregnancy
Miscarriage
Perinatal cerebral infarction
Placental abruption
Premature rupture of membranes/labour and delivery
Intrauterine growth restriction (IUGR)
Reduced head circumference
Sudden infant death syndrome (SIDS)
Congenital malformations
Necrotizing enterocolitis (NEC)
Neurobehavioural abnormalities

Table 3 Comorbid reproductive risk factors in women misusing coc-aine

Alcohol misuse
Tobacco misuse
Other substance misuse (e.g. opiates, amphetamines)
Mental illness
Low socio-economic status (SES)
Teenage pregnancy
Single parent
Sexually transmitted infections (e.g. HIV)

More recent studies, however, suggest that the magnitude of harm following fetal exposure to cocaine is significantly less than previously portrayed by the 'crack baby'. Frank and colleagues (2001), for example, have carried out the most comprehensive meta-analysis of studies assessing the relationship between maternal cocaine misuse during pregnancy and several childhood outcomes. After excluding abstracts or non-reviewed proceedings of scientific meetings they identified 74 human studies published in English and listed on MEDLINE or *Psychological Abstracts* between 1984 and October 2000. Meta-analysis was then restricted to 36 studies in which the cocaine-exposed cohort (1) was prospectively recruited, (2) did not include a substantial proportion of women who were HIV positive or abusing multiple agents and (3) where examiners of offspring were blinded to their exposure status. This study did *not* find a significant association between cocaine misuse during pregnancy and (i) cognitive or psychomotor development, (ii) receptive or expressive language scores, (iii) motor development after age 7 months or (iv) physical growth.

The animal model has also been used to avoid confounding variables that effect many human studies. Cocaine has been found to exert a number of neurobiological effects on the fetus including a reduction in REM sleep, transient reduction in noradrenaline and dopamine turnover. However, whether cocaine leads to long-term neurobehavioural changes remains controversial. Animal studies also suggest that cocaine may lead to significant decreases in fetal weight. There are, however, conflicting results with regard to its teratogenic potential which has been partly explained by inter-species differences. This highlights the need for caution when extrapolating to humans.

Opiates

The lack of research into opiate misuse in pregnancy over the past 15 years has been attributed to the shift in interest towards cocaine. However, attention is gradually

returning to the perinatal consequences of opiate misuse following a recent increase in the prevalence of heroin addiction amongst the female reproductive population. This has been associated with the introduction of a new, cheaper and smokeable form of heroin that is devoid of much of the stigma associated with intravenous misuse.

A number of obstetric complications have been associated with opiate use in pregnancy which are summarized in Table 4.

Many studies have, however, failed to control for the confounding effect of co-morbid reproductive risk factors associated with this patient population. These include factors already summarized in Table 3, in addition to those given in Table 5.

A recent study found that many opiate misusers fail to attend for *any* antenatal care. However, studies into the consequences of opiate misuse consistently fail to assess antenatal attendance despite it being independently associated with many of the above obstetric complications. An equally serious confounding factor is cigarette smoking, which is more common amongst opiate misusers. A recent meta-analysis of all published studies between 1966 and 1996, assessing the relationship between opiate misuse in pregnancy and neonatal mortality, notes that none had controlled for smoking. Similarly, studies assessing the association of opiate misuse and other obstetrics complications (listed in Table 3) repeatedly fail to control for this variable.

Although opiate misuse remains an important marker for 'high-risk' pregnancy, the failure to control for the above factors makes interpretation of studies very difficult. However, it is widely accepted that opiate misuse has a *direct* adverse effect on obstetric outcome and that intravenous misuse is especially detrimental as it exposes the developing fetus to repeated episodes of opiate intoxication and withdrawal. Consequently, women misusing opiates in pregnancy are offered an orally administered alternative, methadone, which is considered to be safer. Although neonatal outcome is more favourable in cases where methadone is commenced earlier in pregnancy this may, however, be attributable to the increased antenatal care taken up by this group and the move away from high-risk 'life-styles'.

Although other maintenance treatments have been developed more recently (e.g. buprenorphine) insufficient data exist with regard to their use in pregnancy or lactation and they are therefore not recommended.

Total withdrawal of opiates in the antenatal period is rarely undertaken, as it is widely believed that withdrawal in the first trimester may increase risk of miscarriage and third trimester withdrawal may cause preterm labour. Consequently, if opiate withdrawal is attempted in pregnancy it is generally undertaken in the second trimester. However, anecdotal reports suggest that withdrawal may be undertaken during any trimester without adverse consequences. Larger studies are required to determine whether there is an optimum time to withdraw opiates in those women wishing to.

Table 4 Perinatal complications following opiate misuse in pregnancy

Miscarriage
Placental abruption
Premature rupture of membranes/labour and delivery
Chorioamnionitis
Intrauterine growth restriction (IUGR)
Low birthweight
Pre-eclampsia (PET)
Intrauterine death (IUD)
Postpartum haemorrhage (PPH)
Respiratory distress syndrome (RDS)
Neonatal abstinence syndrome (NAS)
Neonatal mortality
Neurocognitive abnormalities

Table 5 Co-morbid reproductive risk factors in women misusing opiates

Absence of antenatal care
Anaemia
Cardiac disease (e.g. endocarditis)
Diabetes mellitus
Hypertension
Infections (e.g. urinary and respiratory tract infections)
Poor dental hygiene

4-Methylenedioxymethamphetamine (MDMA/ Ecstasy)

There are only a few studies on the effects of MDMA on human pregnancy. The UK National Teratology and Information Service (NTIS) collected prospective follow-up data from 1989 to 1998 on 136 pregnancies following primarily first trimester exposure to MDMA. 35% of these women had elective terminations (one after prenatal diagnosis of malformations) and ~10% had miscarriages. Of the remaining 78 liveborn infants over 15% had congenital malformations, which is 5–7-fold higher than the expected incidence of 2–3%. Extrapolation from this study is, however, difficult in view of (i) the small sample size, (ii) evidence of polysubstance misuse in 5 (of the 12) women and (iii) absence of control for any other confounding factors.

There have been equally few animal studies published on the teratogenic potential of MDMA. The results have been mixed. The offspring of rats fed with 2.5 or 10 mg/kg

of MDMA between gestation days 6 and 18 showed neither malformations nor any effect on litter size or birthweight. In contrast, others have noted decreased brain and body weight and reduced motility in chicks following injection of MDMA, and other MDMA analogues, into day 14 chick embryos. In a study of the effect of MDMA on learning and memory development, neonatal rats were exposed to MDMA on postnatal days 1–10 or on days 11–20 (analogous to early and late third trimester fetal exposure in humans). Rats in the late exposure group showed dose-related impairments of sequential and spatial learning and memory, while rats in the early exposure group showed no significant impairment. This might suggest vulnerability of the brain to MDMA later in its development but drawing any further conclusions from a single study is clearly tenuous.

Marijuana

It has been estimated that up to 10–20% of women misuse marijuana during pregnancy leading some researchers to comment on the 'surprising paucity' of data on the perinatal consequences of marijuana misuse. However, marijuana is usually smoked with tobacco, making it difficult to identify complications attributable to marijuana as opposed to the multiple perinatal complications associated with tobacco. Additional confounding factors are similar to those found in women who misuse other illicit substances and include lower SES and a high incidence of polysubstance misuse. Studies that attempt to control for these variables, however, are generally composed of small or skewed populations making extrapolation difficult. Furthermore, perinatal outcome data following marijuana misuse are conflicting. Despite these shortcomings, a summary of the main perinatal complications suggested by some of these studies is illustrated in Table 6.

Fried and colleagues have carried out one of the longest and most frequently quoted longitudinal studies on marijuana misuse in pregnancy, testing children up to 6 years after prenatal exposure. This study is, however, limited to a predominantly white, middle class population in Canada and confounded by a higher prevalence of other drug misuse (especially cigarettes and alcohol) in those women misusing cannabis. In addition, there are only 25 women in the regular marijuana usage category. Fried (1993) acknowledges these limitations when accounting for negative findings in the study (e.g. a lack of association between antenatal marijuana misuse and preterm delivery or congenital anomalies) but is less critical when discussing positive associations (e.g. neurobehavioural development including poorer habituation to light, higher levels of irritability and increased startle response). Furthermore, Fried does not criticize the instruments used following detection of inferior vocabulary and motor test scores at 4 years of age in those exposed to marijuana *in utero*. However, when this relationship is not found to persist at 5–6 years of age he suggests the instruments may not be 'subtle' enough to detect the 'nuances' in these children. These inconsistencies highlight an interpretation bias found throughout much of the substance misuse literature.

Table 6 Perinatal complications following marijuana misuse in pregnancy

Miscarriage
Intrauterine growth restriction (IUGR)
Abruptio placentae
Preterm delivery
Neurobehavioural abnormalities

More recently, Dreher and colleagues have found that neonates exposed to marijuana *in utero* had *better* scores on autonomic stability, quality of alertness, irritability and self-regulation compared to non-exposed neonates. An important difference in this study, compared to virtually all others, was that it was carried out in Jamaica in a population where the use of marijuana is 'culturally integrated' into society. In addition, the study was carried out in a rural parish where there is less variation with other confounding factors (e.g. SES or antenatal care). The use of alcohol and tobacco was minimal in both groups and 'did not exceed three beers or 15 tobacco cigarettes per week for any woman in the study'. The study also noted the absence of an association between antenatal marijuana exposure and birthweight or length of gestation. Although this prospective study is limited by a number of factors, including sample size of the exposed group (n=24) and higher levels of education noted amongst the heaviest users of marijuana, it supports the hypothesis that the association between marijuana and perinatal complications may not be straightforward.

One explanation for these contradictory findings may be due to an interaction between marijuana and 'poor diet'. Animal studies have demonstrated worse perinatal outcome in pregnant rats exposed to marijuana smoke and fed on a low-protein diet compared to those fed on a high-protein diet. Although this has not been assessed directly in human studies, most data on the perinatal consequences of marijuana have been obtained in the USA where women who smoke marijuana are more likely to be black, younger, of lower SES and engage in polysubstance misuse, which are all risk factors for 'poor diet'.

Well-designed multicentre studies are still required to determine whether marijuana exerts a detrimental effect on perinatal outcome in human pregnancy and the degree to which diet may modify this risk.

CONCLUSION

Research into the effects of substance misuse on pregnancy has yielded complex and contradictory findings. Although all of the licit and illicit substances discussed have been associated with adverse obstetric outcome, the mechanism(s) by which they operate remains highly speculative. This is primarily attributable to the failure of most studies to control for factors known to have a negative impact on obstetric outcome.

The role of low SES in the aetiology of adverse obstetric outcome in women misusing substances is a recurring theme. 'Poor diet' has been suggested as one of the possible mechanisms through which women of lower SES are rendered more susceptible to the toxic effects of these drugs. Further human studies are required to determine additional factors associated with low SES that contribute to poor outcome in this patient population. However, in order for pregnant women to be appropriately educated with regard to diet and other modifiable risk factors it is vital that they attend antenatal clinics. A punitive attitude to substance misuse in pregnant women may deter those most in need of antenatal care from attending clinics.

It is ironic that substances deemed licit, by the majority of governments, also appear responsible for some of the more adverse pregnancy outcomes. Cigarette smoking has been most consistently associated with obstetric complications. However, it still remains the most widely utilized substance of misuse in pregnancy. Furthermore, despite studies suggesting that many adverse obstetric outcomes can be prevented by cessation of smoking *during* the antenatal period, only 20% of women give up smoking in pregnancy.

The degree to which substances of misuse are *directly* detrimental to obstetric outcome remains unclear. However, it is clear that pregnant women who misuse licit or illicit substances are at higher risk of obstetric complications and frequently require 'high risk' antenatal care. Further studies are required to determine the degree to which individual substances contribute to the associated obstetric complication and elucidation of those factors that may reduce this risk.

PRACTICE POINTS

- Screen all women for substance misuse in the perinatal period
- Counsel women who are engaging in substance misuse of the associated obstetric complications
- The current literature does not support a *direct* link between the misuse of most substances in pregnancy and obstetric complications, highlighting the importance of exploring associated risk factors
- Educate women about the potential for additional risk following polysubstance misuse (e.g. cocaine and alcohol)
- Continue to encourage women to reduce or stop misusing substances at *each* antenatal visit
- Refer to specialist teams for help with cessation of substance misuse or implementation of a maintenance regime
- Educate women about the importance of a healthy diet/lifestyle
- Consider establishing locally agreed multi-disciplinary practice guidelines

RESEARCH AGENDA

- Large multi-centre prospective studies are required to determine the risk of substance misuse in pregnancy. It is vital that these studies control for the additional obstetric risk factors associated with this patient population
- Studies are required to assess the consequences of different *patterns* of substance misuse (e.g. 'binge' drinking) in addition to the *quantity* of the substance misused
- Research is needed to assess the *interaction* between substance misuse and other variables (e.g. diet)

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