Management of drug misuse in pregnancy

Ed Day & Sanju George

Abstract

Use of both licit and illicit drugs can lead to a range of medical, psychiatric and social problems, and the situation becomes further complicated if the user is pregnant. Prescribed and non-prescribed substances can affect a pregnancy, and substances are seldom used in isolation. In this review we focus on users of illicit drugs (including prescribed drugs used illicitly) during pregnancy and describe some of the issues in managing such cases. We consider the impact of substance use on the foetus, the mother and the newborn child, and highlight the importance of multidisciplinary working in this area. Space precludes a detailed account of the issues surrounding the use of legal substances such as alcohol and tobacco during pregnancy, but we note their significant impact in this group.

Effects of drug use on the mother

Dependence on heroin or other drugs can lead to neglect in many areas of the user’s life. The need to obtain a steady supply of the drug is both time-consuming and expensive, and so neglect of medical, nutritional and social well-being is common. Injected drug use leads to an increased risk of acquiring blood-borne viruses such as HIV and hepatitis, as well as abscesses and endocarditis. Maternal infection, neglect and malnourishment are partly responsible for the observed low birth weights, high incidence of preterm birth and poor nutritional status of neonates born to drug users (Fischer, 2000). Women may become involved in crime such as prostitution, robbery and burglary in an attempt to finance their drug habit.

Parenting issues

Parental drug use during and after pregnancy can have a serious impact on the emotional, cognitive and behavioural development of children. It has been estimated that 20 000–50 000 children in England and Wales have one or both parents with a serious drug problem (Advisory Council on the Misuse of Drugs, 2003). After the birth, parental drug use may present the child with a range of difficulties that can
affect emotional, behavioural, cognitive and psychological development (Box 1).

Drug use does not necessarily lead to problems in child care or the neglect or abuse of children, and substance misuse treatment services have long had an important role in supporting the mother in such cases. However, it is important to consider the impact of parents’ substance misuse on the welfare of children in their care: some of the risks posed are shown in Box 2.

### Effects of drug use on the child

As a general principle, exposure to substances in the first trimester of pregnancy affects foetal organogenesis, whereas use in the second and third trimesters mainly results in growth and functional abnormalities or impairments in the newborn. Persistent drug use close to term can result in preterm labour, sudden infant death syndrome (SIDS) and neonatal abstinence syndromes.

### Shorter-term effects

It is often difficult to establish direct causal effects of substances. The foetus is potentially at risk of harm from the direct effects of drugs, infection and poor maternal health and nutrition. These effects may be compounded by lack of adequate antenatal care.

#### Opioids

Dependent heroin use during pregnancy is associated with a reduction of foetal growth, resulting in low birth weight, prematurity, and foetal and neonatal death (Hulse et al., 1997, 1998; Dunlop et al., 2003). The specific effects of opioids on the neonate are confounded by harm associated with the mother’s lifestyle (intoxication–withdrawal cycle, drug contaminants, infections, poverty), the difficulty specifying and quantifying drugs taken and the influence of other factors, for example the almost universal incidence of cigarette-smoking among opioid users (Ward et al., 1998).

The clinical signs of opioid neonatal abstinence syndrome (Box 3) occur in 48–94% of infants exposed to opioids in utero, with signs of withdrawal from methadone being more common than from heroin (Osborn et al., 2004). The onset, duration and severity vary and are mainly influenced by the type of drug used, the severity of maternal drug dependence, the timing of the last drug intake and foetal metabolic factors. Onset usually occurs within 24–72 h of birth, but it can be delayed by up to 7–10 days. Methadone tends to produce withdrawal symptoms with a later onset, longer duration and greater severity (Coghlan et al., 1999). Neonatal opioid withdrawal may result in sleep–wake abnormalities, feeding difficulties and weight loss, which can disrupt the mother–infant relationship (Osborn et al., 2004).

### Box 1 Potential difficulties faced by the children of drug users

- Physical and emotional abuse or neglect
- Inadequate parenting or supervision
- Separation
- Poverty
- Poor education
- Exposure to criminal behaviour
- Social isolation

### Box 2 Potential impact of parental drug use on children’s welfare

- Impaired judgement, coordination and consciousness can affect a parent’s ability to care for and supervise young children
- Drug-induced disinhibition can lead to aggressive behaviour, including domestic violence
- Withdrawal from certain drugs can cause irritability and mood disturbance
- Unemployment, poverty and criminality may impair family functioning
- Drug use can become a higher priority for the parent than buying basic essentials for the family
- Reduced parental vigilance may leave children vulnerable to abuse by visitors to the home
- The presence in the home of drugs and/or injecting equipment puts children at risk

(National Treatment Agency for Substance Misuse, 2002; Advisory Council on the Misuse of Drugs, 2003; Department for Education and Skills, 2003)

### Box 3 Characteristics of opioid neonatal abstinence syndrome

- Gastrointestinal disturbances
- Irritability
- Hyperactivity
- Feeding and sleeping disturbances
- Autonomic hyperactivity
- Seizures (these are rare, occurring in less than 5%)

(Osborn et al., 2004)
Cocaine and amphetamines

Cocaine is available as a powder that can be snorted or injected and as ‘crack’, a ‘free base’ form which is suitable for smoking and has a more immediate and intense high. However it is used, cocaine is a potent vasoconstrictor and can reduce blood flow and oxygen supply to the foetus. Maternal cocaine use during pregnancy has been associated with numerous foetal and neonatal problems (Box 4). However, cocaine and amphetamine appear to have low specific teratogenicity, and as yet a ‘foetal cocaine syndrome’ has not been conclusively demonstrated (Plessinger & Woods, 1993).

Benzodiazepines

Benzodiazepines also have low teratogenic potential, although high-dosage use during pregnancy has been associated with abnormalities such as cleft lip and cleft palate. Continued maternal use near term can result in ‘floppy baby syndrome’, characterised by lethargy, irritability, reduced muscle tone and respiratory depression in the newborn, and a neonatal abstinence syndrome (Sanchis et al, 1991).

Blood-borne viral infections

Intravenous drug users who share needles or injecting paraphernalia are at particular risk of contracting blood-borne viral infections such as HIV, hepatitis B and hepatitis C. Pregnant women who are infected can transmit the infection to their babies (vertical transmission) during pregnancy, during the process of birth or through breast-feeding. Early detection and prompt initiation of treatment and other protective interventions can reduce the risk of mother-to-baby transmission.

Many HIV-infected children die in the first few years of life, whereas hepatitis B or C infection can result in babies becoming chronic ‘carriers’ or can lead to chronic liver disease, cirrhosis and death. Therefore routine antenatal screening for such infections is recommended, provided that informed consent is obtained and adequate pre- and post-test counselling is provided. If the mother is infected, all possible measures should be taken to prevent mother-to-baby transmission, and appropriate immunisation and treatment should be instituted at the earliest opportunity to prevent long-term sequelae for the mother and the child.

Longer-term effects

Knowledge about longer-term effects of drugs on children is limited and contradictory. Some studies report a range of behavioural and learning difficulties, whereas others show few or none, especially if the research has controls for other life conditions and health problems. Children of opioid-dependent mothers show high levels of irritability, hyperactivity, and feeding and sleep disturbances in the first few weeks of life that may render them liable to difficulties with attachment behaviour (Householder et al, 1982). Furthermore, these behavioural and psychological problems appear to continue throughout early and middle childhood. However, it is difficult to draw firm conclusions because huge methodological difficulties affect research in this area and longitudinal studies are needed (Householder et al, 1982; Johnson & Leff, 1999). It is also important to remember that developmental problems may result primarily from severe environmental deprivation and the fact that one or both parents are using drugs: in utero heroin exposure, for example, may be less important than the home environment (Örnöy et al, 1996).

Maternal drug use may continue to have an impact on the child’s cognitive, educational, emotional and behavioural development throughout early life. Studies of pre-school children with drug-using parents have noted high rates of inattention, hyperactivity and aggression (Örnöy et al, 1996), as well as lower school attendance and reduced concentration when compared with controls (Hogan & Higgins, 2001). Kandel’s research on parents of primary school children noted an association between parental drug use in the past year and more punitive forms of parental disciplining and less supervision of the child (Kandel, 1990). In early adolescence, having drug-using parents is associated with increased risk of offending and...
bullying behaviour, and adolescent children of drug-using parents are also more likely to play truant from school, repeat a year or even be suspended from school (Kolar et al., 1994). There is also a strong correlation between parents’ and adolescents’ use of illicit substances: adolescents who use drugs are likely to have one or more parents who are users (Fergusson & Lynskey, 1998; Johnson & Leff, 1999).

**Formulating a management plan**

The medical and social problems associated with drug use make it especially important that drug-using women do not become pregnant unless they want to. Treatment services should aim to help users to maximise their health before becoming pregnant, and attempts to improve lifestyle and diet are helpful (Hepburn, 2002). When heroin-using women do become pregnant it is often unexpected, as menstrual problems such as amenorrhoea are common in this population. Early signs and symptoms of pregnancy such as nausea, headaches and fatigue may become lost among withdrawal-related effects. This may lead drug-using women to present late for treatment, and many factors can dissuade them from seeking professional help. One such factor is the fear of being seen as irresponsible or inadequate carers, which often results in poor self-esteem, guilt, depression and denial of drug use (Klee et al., 2002).

The basic principles underlying good treatment of substance misuse problems in general (Luty, 2003) apply to pregnant women, with special emphasis on the health of the unborn child. Drug use is only one of a number of interacting physical, psychological, social and environmental factors that influence the course and outcome of any pregnancy. It is wrong to assume that drug use by itself makes a woman incapable of caring for a baby in a healthy, supportive environment. Unfortunately, practice varies widely in different locations, and approaches to antenatal care and addiction treatment often conflict.

**Assessment**

A comprehensive assessment forms the cornerstone of a good care plan. It is often best provided as the first step in a well-integrated care package by a multi-disciplinary team in a shared specialised clinic. The specialist drug service needs to work in conjunction with the general practitioner, midwife, obstetrician, paediatrician and social worker in organising and providing care for drug-dependent women throughout the antenatal, intranatal and postnatal periods. The pregnant drug user (and possibly her partner) needs to be actively involved in all phases of planning and decision-making. Assessment of drug use should include the type and quantity of drug used, route of administration, injecting behaviour, degree of dependence, previous treatment history and motivation to change. Good practice guidelines for assessment of drug use are outlined elsewhere (Department of Health, 1999), and these should be supplemented by a more detailed history of factors relevant to the pregnancy (Box 5). The assessment process must consider the risk to the physical and mental health of the mother during pregnancy, the risk of teratogenicity or the development of a neonatal abstinence syndrome, and ongoing child care and parenting issues. It should ultimately lead to a plan involving well-coordinated, multidisciplinary care with realistic and practical treatment goals.

**Neonatal abstinence syndromes**

Drug-using women should be prepared for the possibility that their newborn child will experience withdrawal symptoms (neonatal abstinence syndrome). Such preparation may help to allay their fears and engage them in treatment. They may be advised to stay in hospital for at least 3 days after delivery, to allow monitoring of the child for a neonatal abstinence syndrome. Mild-to-moderate symptoms can be managed by purely supportive measures (Box 6) and no specific pharmacological intervention is required. After discharge from hospital, the midwife should provide support at

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**Box 5 Assessment factors specific to pregnant women**

- Past obstetric and gynaecological history
- Screening for sexually transmitted diseases and blood-borne viral infections such as HIV and hepatitis B and C
- Feelings about the pregnancy and the baby
- Plans for the baby’s future
- Feelings of guilt or self-blame
- Fears about the baby being taken into care
- Existing needs and available resources

**Box 6 Supportive measures for a neonate with a neonatal abstinence syndrome**

- Keep the baby in a quiet, dimly lit room
- Ensure close, gentle interaction with the mother
- Provide small, frequent feeds
- Ensure close monitoring by nursing and medical staff
There is a significant body of evidence to suggest that methadone maintenance treatment during pregnancy, when combined with a comprehensive psychosocial treatment programme, can reduce the incidence of obstetric and foetal complications as well as neonatal morbidity and mortality (Finnegan, 1991; Ward et al, 1998). Methadone maintenance enables stabilisation of the mother’s drug use and lifestyle, and can also facilitate access to comprehensive antenatal and postnatal care. Furthermore, by reducing or eliminating illicit drug use it can help to stabilise the in utero environment, while not increasing the risk of congenital abnormalities in the foetus. Research evidence has consistently shown that methadone maintenance during pregnancy produces superior outcomes compared with not being in treatment (Ward et al, 1998). Opioid-dependent women who receive methadone maintenance therapy during their pregnancy are more stable both physically and psychologically, and receive more prenatal care than women who are not in treatment (Fischer et al, 2000). Obstetric complications may be seen in any woman not receiving prenatal care, but the incidence of such problems in pregnant heroin users maintained on methadone is lower than that in those who continue to use heroin during pregnancy (Kaltenbach et al, 1998).

Use of street heroin presents the foetus with problems created by the cycle of withdrawal and intoxication produced by using a relatively short-acting drug. Both intoxication and withdrawal place stress on the foetus, and withdrawal in particular has been associated with foetal death (Ward et al, 1998). A further problem is the teratogenic nature of many of the adulterants added to illicit drugs to increase their bulk.

Many of the difficulties experienced by infants born to opioid-dependent mothers are due to premature birth and being small for gestational age (Finnegan, 1991). Infants born to methadone-maintained mothers are born later and are larger for gestational age than those born to opioid-dependent women who are not in treatment (Householder et al, 1982). In addition, pregnant women in methadone maintenance therapy attend for more antenatal care, and this can be an important predictor of outcome for both mother and foetus.

Most clinicians recommend that methadone maintenance therapy should be started as soon as possible after confirmation of pregnancy. If the woman is already on a methadone programme, maintenance should be continued. Detoxification from all drugs is unrealistic for most of this population, and often results in the mother experiencing an abstinence syndrome leading to foetal distress (Ward et al, 1998). The overall aim should therefore be to maintain the woman on methadone for the entire pregnancy, as withdrawal may lead to a risk of miscarriage in the first trimester or premature labour and foetal death in utero in the third trimester (Finnegan, 1991). However, many women express a strong desire to undertake a detoxification process, and there is some dispute as to how many are able to

**Pharmacological management**

**Opioid dependence**

**Methadone**

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**Box 7 Indications for drug therapy in neonates with confirmed in utero exposure to opioids**

- Seizures
- Poor feeding
- Diarrhoea and vomiting resulting in excessive weight loss and dehydration
- Inability to sleep
- Fever unrelated to infection

(American Academy of Pediatrics, 1998)
achieve this goal (Day *et al*., 2003; Luty *et al*., 2003). The metabolism of methadone is increased by pregnancy, and this may cause previously stable women to experience withdrawal symptoms in the final trimester. If not carefully managed this can lead to an increased risk of relapse. An alternative to increasing the daily methadone dose is to use a split dose in order to maintain steadier plasma levels (Wittman & Segal, 1991).

Buprenorphine

Buprenorphine shows considerable potential as a treatment for opioid-dependent pregnant women, and may be associated with a low incidence of neonatal abstinence syndrome (Fischer *et al*., 2000). However, as yet there is insufficient controlled research with adequate follow-up periods to demonstrate its safety during pregnancy and breastfeeding (Dunlop *et al*., 2003). Buprenorphine does not have a specific licence to be used in pregnancy, and methadone maintenance remains the treatment of choice for pregnant and breast-feeding women.

Cocaine dependence

Despite the wide range of pharmacological treatments for cocaine dependence (antipsychotics, antidepressants, dopamine agonists, anti-epileptics), no one drug has been found to be unequivocally effective. Furthermore, many of these treatments are not recommended in pregnancy, and should be initiated and monitored only by a specialist in a hospital setting. Withdrawal symptoms that emerge on abrupt cessation of cocaine during pregnancy may be reduced with short-term use of benzodiazepines or antipsychotics, but the use of dopaminergic drugs or desipramine in the longer term for managing craving and depressive symptoms is not recommended. Unlike the situation with opioids, there is no safe drug for substitute prescribing during pregnancy (Kaltenbach & Finnegan, 1998). Treatment is often a combination of symptomatic interventions during the withdrawal phase and psychosocial interventions, and there has been very little systematic research into the effectiveness of this approach in pregnant women. A similar approach should be adopted in managing the use of other psychostimulant drugs such as amphetamines and methylenedioxymethamphetamine (MDMA, ecstasy), where the evidence base is also limited.

Benzodiazepine dependence

Sudden cessation of benzodiazepine use can lead to maternal convulsions and so should be avoided (Hepburn, 2002). The primary aim in treating benzodiazepine dependence in pregnant women is usually to identify a mutually agreeable and realistic goal, be it low-dose ‘maintenance’, gradual reduction or detoxification. For women using high doses of benzodiazepine alone, without any significant psychosocial or medical complications, gradual reduction and detoxification in the community are recommended. Women who are taking short- or medium-acting benzodiazepines (e.g. lorazepam, oxazepam) should be transferred to an equivalent dose of diazepam and the dose gradually reduced to zero. Women who are using high doses of benzodiazepine in combination with other drugs, or those who have complicating medical, psychiatric or psychosocial problems, are best managed in hospital. Once admitted for detoxification, the level of withdrawal symptoms and other problems should be objectively assessed. With long-acting benzodiazepines, symptoms of withdrawal may not be manifest for the first 5–7 days, and post-withdrawal problems such as sleep disturbance may take several weeks to resolve. Pharmacological treatment is best supplemented with individual supportive psychotherapy, anxiety management and other supportive measures.

Alcohol

It is worth noting that many drug-dependent pregnant women also misuse alcohol, and this should be assessed and managed appropriately (Mayo-Smith, 1997). Alcohol is an established human teratogen and there is no clear safe level of consumption during pregnancy. Consumption of less than 7 units per week is thought to cause no significant harm to the baby, but more regular use can adversely affect the developing foetal brain and result in a series of physical, neurological and behavioural abnormalities known as the foetal alcohol syndrome (Jones & Smith, 1973). It is therefore recommended that pregnant women abstain from drinking alcohol.

Drug use and breast-feeding

Most substances of misuse are lipid soluble and hence are excreted in significant amounts in breast milk and easily cross the blood–brain barrier of the infant (O’Mara & Nahata, 2002). This exposes the newborn child to a range of adverse effects, including intoxication and withdrawal. Guidelines are slowly being developed about breast-feeding by women dependent on either legal or illegal drugs (Drug Misuse in Pregnancy Breastfeeding Project, 2003). Contraindications for breast-feeding are listed in Box 8. It is generally accepted that women who are well stabilised on reasonably low doses of
prescribed drugs may breast-feed their babies, as the potential benefits far outweigh the risks. Breastfeeding is not thought to be a significant route of transmission of hepatitis B or C.

It is preferable to avoid breast-feeding a baby for 1–2 h after taking any street drug or medication, as this is the time of highest plasma drug concentration.

Mothers should be taught about signs and symptoms of intoxication and withdrawal in the baby and should seek medical advice if any doubts arise. Breast-feeding should not be abruptly discontinued, as this can precipitate withdrawal symptoms, and gradual weaning with slow introduction of alternative semi-solid foods should be instituted (Drug Misuse in Pregnancy Breastfeeding Project, 2003).

Psychosocial issues

There is a wide range of psychosocial approaches available for the treatment of drug dependence, but no single approach has been found to be better than the others for use with pregnant drug users. Therefore the principles used to guide addiction treatment in general apply to this subgroup (Ghodse, 2002: pp. 211–241). However, the impact of drug use on parenting capacity and any risks to the children must also be assessed in order to guide the most appropriate intervention. Questions about child care and parenting issues are sensitive and can have important implications for drug-using parents. Although parents have the right to confidentiality in most circumstances, society has a duty to protect children, particularly as they often cannot advocate for themselves. The emphasis should be on working collaboratively with parents to maximise the care of children and protect them from harm (Department of Health et al, 1999). There is some evidence to suggest that deficiencies in parenting attitudes and skills may be prevalent among drug misusers, but that parenting training can lead to dramatic improvements in self-esteem, parenting knowledge and attitudes (Camp & Finkelstein, 1995).

In many cases, children’s welfare can be safeguarded by appropriate health and social care without recourse to formal child protection measures (Department of Health et al, 1999), but more formal steps sometimes need to be taken. Section 17 of the Children Act 1989 obliges local authorities to make appropriate enquiries and take action to protect children if there is reasonable cause to suspect that they are likely to suffer ‘significant harm’. A child protection case conference may be convened to determine the facts and decide on further action. The child’s name may be placed on the child protection register or proceedings may be instituted for a care or supervision order if the case warrants such intervention. Each local authority has an area child protection committee (ACPC) responsible for developing and promoting local child protection arrangements and effective multiagency working and information-sharing.

Outcome of treatment

Pregnancy is a temporary phase in a woman’s life and her patterns of drug use, engagement with treatment services and eventual outcome will be only partially determined by what happens during this period. It is often hoped that pregnancy will act as a catalyst for change in a drug-using woman, although there is little evidence that this is true. The outcome of drug treatment in pregnancy can be viewed from both the woman’s and the child’s perspective. The successful delivery of a healthy baby is in itself a good outcome in the short term. However, few studies have focused on the long-term outcome of children born to drug-dependent women and the effectiveness of various maternal treatment interventions in preventing adverse consequences. A further problem is the lack of consensus about which outcome measures should be used in this subgroup of patients. Abstinence rates during pregnancy or soon after birth are commonly used, but this approach neglects long-term relapse rates and the impact on the child’s development.

Most research on drug use during pregnancy has focused on opioid users in methadone treatment programmes, and overall it shows better birth outcomes and more regular antenatal care visits for women maintained on methadone than for those not in treatment (Edelin et al, 1988). Methadone maintenance has been shown to retain a higher proportion of pregnant women in treatment than brief abstinence-focused interventions (Anderson et al, 1996). Furthermore, enhancing methadone maintenance therapy with more frequent antenatal care and relapse prevention groups can lead to further improvements in treatment engagement, fewer positive urine screen results and higher birth weights (Chang et al, 1992).
The treatment setting

Treatment may take place in residential or outpatient settings, although the capacity of the former is limited in the UK. There is some evidence that residential treatment programmes that include facilities to admit children alongside their parents have improved rates of retention in treatment and higher abstinence rates (Hughes et al., 1995), and that the more comprehensive a residential programme is, the better the outcome (Stevens & Arber, 1995). However, other work has found out-patient programmes to be as effective as residential ones for this group (Strantz & Welch, 1995). There is evidence that significant improvement in the health of pregnant opioid-dependent women and their babies occurs if they are monitored as out-patients by specialist obstetric units with expertise in managing substance use (Ward et al., 1998; Dunlop et al., 2003).

A range of service models have been developed in the UK in response to specific local needs, and many report positive results (Dawe et al., 1992; Morrison et al., 1995; Hepburn, 2002; Day et al., 2003).

Conclusions

Drug use in pregnancy is a potentially complex biopsychosocial problem and is best managed through careful assessment leading to a care plan that is implemented by a multidisciplinary team. The predominantly negative attitudes towards drug-using pregnant women must be taken into consideration, as these will have an impact on whether an individual seeks help and subsequently enters a treatment programme. Medical management through maintenance prescribing can have a significant effect on both health and social outcomes, but the best results are obtained when working in conjunction with obstetric, neonatal and social services. Taking illicit drugs certainly does not preclude a woman from providing adequate child care, but there is a need to provide support in more than just the high-risk cases if poor long-term outcomes for the child are to be avoided (Advisory Council on the Misuse of Drugs, 2003).

References


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MCQs

1 As regards breast-feeding by women who use illicit substances:
   a most substances of misuse are not found in significant concentrations in breast milk
   b most psychoactive substances readily cross the foetal blood–brain barrier
   c breast-feeding is not recommended in anyone currently using opioid drugs
   d HIV can be transmitted via breast milk from mother to baby
   e the timing of breast-feeding can influence drug concentrations in the baby.

2 As regards neonatal opioid abstinence syndrome:
   a the onset may be delayed until 7–10 days after birth
   b foetal metabolism can determine the severity of symptoms
   c heroin-induced symptoms last longer than symptoms induced by methadone
   d opioids are a recommended treatment for the neonate
   e mild symptoms can be managed without medication.

3 The following occur more frequently in children born to opioid-dependent mothers:
   a a characteristic facial abnormality
   b Ebstein’s anomaly
   c low birth weight
   d a characteristic opioid neonatal abstinence syndrome
   e neonatal death.

4 As regards methadone maintenance treatment of pregnant opioid users:
   a detoxification and abstinence is the usual goal
   b mothers on this treatment have babies with higher birth weights than those who are not
   c it should be started soon after confirmation of pregnancy
   d it is more effective than no treatment
   e a split dose of methadone should never be used.

5 Which of the following statements is true?
   a women that use heroin rarely get pregnant
   b exposure to drugs in the third trimester primarily affects foetal organogenesis
   c methadone maintenance therapy should not be started during pregnancy
   d buprenorphine leads to increased rates of opioid neonatal abstinence syndrome
   e opioid withdrawal in the mother has been associated with foetal death.

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