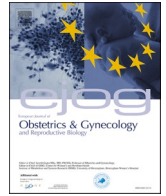


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Review article

Harmful effects of opioid use in pregnancy: A scientific review commissioned by the European Board and College of obstetrics and gynaecology (EBCOG)

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ABSTRACT

Caring for pregnant women who have a recreational opioid use disorder is a common clinical challenge in modern obstetric care. These are an elusive population who often have multiple social issues that complicate their pregnancy management. Comprehensive and supportive maternal care can motivate these mothers to change her lifestyle. Multidisciplinary non-judgemental approach with appropriate medication and management, can result in good pregnancy outcomes for mother and her baby.

Introduction

The use of illicit substances such as cocaine, heroin and cannabis has become an increasingly common occurrence, especially in the young adult population [1]. An estimated 30,000 pregnant women are said to use illicit opioids each year in the European Union [2]. In Ireland's capital, opiate use disorder has been shown to account for about 1 every 160 women booking for pregnancy care [3]. There has been reported a high availability and greater diversity in patterns of drug consumption during the past years. From the last EMCDDA report it was stated that almost any substance with psychoactive potential is now at risk of appearing on the market, often poorly labelled, meaning that those consuming these substances may be unaware of what they are using. It is very hard therefore to quantify how many women use recreational drugs, but it is even more difficult to quantify how many are using solely opioids. Many women use opioids together with nicotine, alcohol, and other psychoactive substances. Opioid use by women, especially during pregnancy and while breastfeeding, presents a unique set of complex issues that necessitate specific expertise and counselling for the management of clinical issues including abnormal fetal growth, methadone treatment, premature birth, pain management during labour, neonatal

abstinence syndrome (NAS), nutritional issues and maternal withdrawal. [4–5]Table 1.Table 2..

Effects of opioids on the mother and new-born

Maternal heroin use during pregnancy is associated with low birth weight, ante-partum haemorrhage and increased neonatal mortality even after adjusting for smoking cigarettes antenatal care and prior preterm births [6–13]. Other pregnancy complications, like the premature rupture of membranes, meconium-stained liquor, and foetal distress, have also been noted to occur more frequently in mothers using opioids [14]. It is not possible to confirm a direct relationship between antenatal opioid use and foetal adverse effects outcomes since other confounding maternal biological and social factors, commonly found in these women, could also contribute to similar adverse effects [15–17]. The specific effects of opioids on the neonate are often confounded by the mother's lifestyle, which may include drug intoxication/withdrawal cycles, polydrug use, infections, poor diet, cigarette smoking and poverty [16,18–19]. This implies that the increased morbidity and mortality associated with infants born to mothers using opioids is a multi-faceted problem needing a multidisciplinary approach to

Abbreviations: MMT, Methadone maintenance treatment; NAS, Neonatal abstinence syndrome.

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Table 1

The booking session.

Ask specifically if she drinks alcohol occasionally or regularly	
Ask about the use of specific substances:	During history taking while booking a pregnancy the mother must be helped to feel at ease. The aim of the questioning is not to punish or judge the mother but to help her if she has issues with psychoactive substances. She must feel that she can trust the interviewer who is showing concern and is ready to offer help
Opioids, Cocaine, Cannabis	
Ask specifically about:	
Regular or Occasional Use	
Ask about Medication: Psychiatric/Opioid Substitution	
Ask for a urine sample and for consent to test for psychoactive substances	Refer to Addiction specialists or to Psychiatrists as needed. Refer to Social worker. Refer to the Specialised Multi-Disciplinary team if available

Table 2

Mother with an opioid use disorder.

The Multidisciplinary Team	
Gynaecologist with an interest in Addiction	Follow pregnancy carefully especially: Mother's weight, Cigarette smoking, Foetus's growth, and progress, STI screening.
Addiction Specialist	Opioid substitute treatment: Methadone or Buprenorphine; Counselling;
Psychiatrist	Assessment of other use of substances Treat any mental disorder with medication that is safe during pregnancy. Psychological support through therapy.
Counsellor specialised in Addiction	Offer sessions to advise about cravings, harm reduction and related issues
Social worker	Assessment and help with regard to social needs: Housing, Food, Benefits, Work, Domestic Violence, legal/court problems etc.
Social worker from Child Protection	Assessment to be done to see that new-born will be safe. Once baby is born frequent supervision, and provision of all needs especially food and education. Best option for mother and baby to stay together. Fostering and adoption should be the last resort.
Midwife	A specialised midwife who will accompany the mother through her pregnancy supporting her when in fear or doubt. To explain the whole process of pregnancy and procedures after baby is born. To be with mother during the assessment of NAS. To encourage non-medical forms of soothing new-born with NAS
Parental Craft Coach	Mother to be encouraged to attend classes with other mothers. Special session re NAS and management
Paediatrician	Paediatrician to explain the signs and symptoms of NAS and the treatment given. Assessment of Hepatitis C and any malformations

management [20]. It is furthermore difficult to specify and quantify drug use throughout the pregnancy because the population of mothers using opioids tends to be elusive and, unless urine tests are done regularly throughout pregnancy, continuing drug use is difficult to confirm [21]. It is even more difficult to associate definite signs and symptoms in the new-born to specific drugs when so many factors are involved [20]. Additionally the mother should be screened for blood born viruses during pregnancy including hepatitis B and C, HIV and sexually transmitted diseases including chlamydia.

Treatment for mothers using opioids.

The medical treatment of choice for the opioid-dependent pregnant mother is opioid substitution therapy using Methadone or

Buprenorphine [7]. While heroin has been associated with restricted foetal growth [15,23–26], the use of methadone has been shown to be associated with higher birth weights when compared to women who continued to use heroin [9,27–29]. It has been further shown that methadone tended to reduce the risk of premature labour so that foetuses exposed to methadone had a higher birth weight and less morbidity than heroin-exposed babies [30]. This was attributed to the fact that mothers on methadone maintenance had better antenatal care and possibly were better motivated to care for themselves and their pregnancy. Yet Mactier et al. (2013) have shown that even after adjusting for cigarette smoking, low socio-economic background, parity, and maternal age, methadone-maintained new-borns still exhibited better birth weights and head circumferences [15].

Methadone maintenance treatment (MMT)

The pharmacological characteristics of Methadone contribute towards helping to prevent the opioid-withdrawal syndrome in opioid-dependent patients Wolff et al. 1997; Hutchings et al. 1991 and 1993, Saia et al. 2016; Ferrari et al. 2004; Faggiano et al. 2003; D'Aunno et al. 2002; Ward et al. 1999; Drummond et al. 1989) [22,31–39] MMT is a harm minimisation approach which results in reduction of illicit substance misuse, crime, morbidity, and mortality (Van den Brink et al. 2006; Warner-Smith et al. 2001; Ward et al. 1994 and 1996; Kreek 1992) [40–44]. MMT during pregnancy has been extensively studied and is still considered to be the gold standard treatment (Shanker et al. 2012; Jones et al. 2010; Centre of Substance Abuse Treatment 2009; Farid et al. 2008; Rostami-Hodjegan et al. 1999; Kaltenbach et al. 1998) [45–50].

Methadone metabolism in pregnancy is different from that of the non-pregnant patient and is influenced by the normal physiological changes mediated by the pregnancy hormones. The changes influencing methadone requirements include the relative increase in body fluid volume associated with pregnancy, especially during the third trimester and the increase in protein-binding capacity [7,51]. Because of the increased metabolism by the liver and the increased renal clearance associated with pregnancy, the half-life of methadone is shorter in pregnant women (Wolff 2005; Swift et al. 1989; Gabrielsson et al. 1985; Pond et al. 1985) [51–54]. Furthermore, gastrointestinal absorption of the drug is reduced (Jarvis et al. 1999; DePetrillo et al. 1995) [55–56]. The physiological changes of pregnancy affecting methadone pharmacokinetics require changes in dosage to achieve the optimal dose of methadone required during pregnancy. During pregnancy, some women may require increases in methadone dose and upward adjustments may be needed in opioid medications with advancing gestation [7,52,57]. The methadone dose during pregnancy should be dispensed to a level that not only blocks withdrawal symptoms but also suppresses heroin use [7]. Given the shorter half-life and faster clearance during pregnancy, many pregnant women may benefit from dividing the daily methadone dose to achieve a steady state plasma concentration over the 24-hour dosing period [51,58–61].

Buprenorphine maintenance treatment

An alternative treatment management to methadone is buprenorphine, a long-acting opioid that has both agonist and antagonist properties, which is increasingly being used in obstetric care [48,62]. Its use during pregnancy has been associated with improved maternal and foetal outcomes and reduced NAS severity in exposed neonates. Methadone maintenance was however deemed better with regards to patient compliance [46,63–65]. Studies have further shown that buprenorphine resulted in better fetal biophysical profile scores with less fetal movement suppression than methadone [66–68]. In addition, Welle-Strand et al. (2012) demonstrated more favourable neonatal growth parameters with buprenorphine with neonates being heavier, longer and had larger head circumferences when compared to methadone-exposed

newborns [69]. Although both methadone and buprenorphine accumulate in breast milk, both are compatible with breastfeeding unless the mother is using other illicit substances [66–67]. Though this accumulation might be a potential threat to the new-born, breastfeeding is not discouraged in opioid-dependent mothers since the benefits of breastfeeding largely outweigh any theoretical minimal risks [45,70–71].

Medication choices for opioid dependent women during pregnancy need to be made on an individual basis, after considering the patient's history, previous and current experiences, medical circumstances, and treatment preferences [66–67]. A woman who initiates her pregnancy on methadone or buprenorphine treatment is advised to continue her pregnancy on the same treatment, since transitioning from methadone to buprenorphine may cause destabilization and relapse [72]. Starting buprenorphine treatment on a pregnant woman may prove critical since present methods of induction dictate that the patient must be in withdrawal status to start buprenorphine [66–67]. This may cause the pregnant woman to miscarry if still in her first trimester. It appears that second trimester pregnant patients can be transferred from immediate release morphine onto methadone or buprenorphine with equal ease (Jones et al. 2004) [73].

Neonatal abstinence syndrome (NAS)

Several studies have been undertaken in relation to the NAS [50,74–75]. Opioids, in the form alcohol-free oral morphine sulphate (0.4 mg/mL) preparation or morphine hydrochloride (0.2 mg/mL), have been suggested as the treatment of choice for NAS [76]. Empirical literature exists regarding the non-pharmacological care that NAS babies need. These include swaddling, the provision of a quiet environment, small frequent feeds and the use of a pacifier and waterbeds [77–80]. Maguire [80] suggested that the basic standards of care, such as decreasing environmental stimuli, holding the infant, providing non-nutritive sucking, swaddling, containment to gently restrain flailing limbs or head, and rubbing rather than patting, should always be provided to infants suffering from NAS [81]. Other interventions, such as vertical rocking and demand feeding, need to be empirically tested. Artigas [81] highlighted the importance of complementary therapies and the identification of an appropriate environment for new-born babies with NAS [82]. Aroma, music, and massage therapy, as well as skin-to-skin contact have been reported to be successful in the pre-term newborns suffering from NAS [83–85].

Breast-feeding has been recommended by paediatricians for women both on methadone and buprenorphine, unless the mother is HIV positive or is taking on other illicit substances [86–87]. Brandt et al. [87] highlighted the role that breastfeeding has in reducing the need for and the duration of care for NAS treatment [88]. Breastfeeding has been proved to decrease the severity of NAS [24,89]. Methadone concentrations in breast milk have been found to be low with no correlation to maternal dose [90]. However, the concentration of buprenorphine in breast milk varies markedly due to the variations of milk protein and fat content [91]. Nevertheless, concentrations are low, and neonates did not suffer NAS once weaned off breast milk at age 8 weeks [66–67].

Long term effects of opioids on newborns

Long-term effects of exposure to opioids in utero on infant development have been difficult to assess primarily due to many other confounding factors especially nicotine, alcohol, and other illicit drug use in pregnancy. Besides, there are environmental and medical factors like low socio-economic status, poor prenatal care severity and treatment for NAS that may act as influencers of infant development [92]. A completely new area of debate has been developing about the effects of opioids on these neonates especially in the developmental period following birth. Coyle et al. [92], investigating neuro-behaviour in opioid-exposed neonates in utero, concluded that while the neuro-behavioural effects improved during the first month of postnatal life,

buprenorphine exposure resulted in better neuro-behavioural scores [93]. There were statistically fewer stress-abstinence signs, neonates were less excitable, less over-aroused, exhibited less hypertonia, had better self-regulation, and required less handling to maintain a quiet alert state relative to in utero methadone-exposed infants [93].

Conclusions from different studies differ considerably depending on what factors were considered important and studied and what were in turn ignored. More research considering all confounding factors needs to be done so as to determine the real causes of the severity of NAS. The Cochrane Central Register of Controlled Trials reported the safety of opioid use to combat NAS as opposed to a lack of treatment or to the use of sedatives such as phenobarbitone and diazepam [74]. A recently updated Cochrane review in 645 infants confirmed that opiate (morphine) treatment was superior to supportive care only in the case of NAS [94]. There is however a need for further research regarding the pathophysiology and treatment of NAS [63].

MMT and buprenorphine in pregnancy have been shown to achieve harm reduction and reduce the mortality of the child, while improving the quality of life for the mother [40–44,95–96]. However, some neuropsychological studies on adults exposed to longterm prescribed opioids have identified deficits in executive function measures including cognitive flexibility [97–98], strategic planning [99–100] and decision-making [101]. A review of the literature dealing with the neurodevelopmental outcome as reflected by childhood learning abilities in infants with NAS suggest that small neurodevelopmental deficiencies were already evident at all ages irrespective of the tool used to examine the children. Infants exposed to opiate in utero were significantly more likely to have neurodevelopmental impairment compared to healthy control infants, when assessed at 18 months and 3 years of age [102].

Reviewing the American National Survey on Drug Use and Health, Behnke et al. [102] concluded that short-term effects of opioids included delayed foetal growth and neurobehavioral differences [103]. The data also suggested long-term effects of opioids on behaviour, though there was no consensus concerning cognition, and limited data on language and achievement. No analysis of potential confounding factors was carried out and neither was nature or nurture influences on effects noted.

Visual function is one of the most important perceptions for development since it leads to the development of functions such as eye-hand coordination, object recognition and visual-spatial recognition and learning, etc. There are various studies that have suggested an association between opioid misuse in pregnancy and impaired visual development in children, especially those suffering from NAS [104–107]. The rate of strabismus in infants of opioid-dependent mothers was reported to be about 10 times more than in the general population [108]. However, many studies assessing VEP's in this population had not considered and corrected for important confounding factors such as intrauterine growth restriction, gestation, and ongoing drug misuse [109].

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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