Abuse of antiretroviral drugs combined with addictive drugs by pregnant women is associated with adverse effects in infants and risk of resistance

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Reports of the use of antiretroviral drugs (ARVs) to produce a highly addictive drug called nyaope or whoonga are of major concern as ARVs are easily accessible in sub-Saharan Africa, including to pregnant women. Use of illicit drugs by pregnant women may result in serious adverse effects in their infants. We have noticed a sudden increase in the number of infants presenting with signs suggestive of neonatal abstinence in Chris Hani Baragwanath Academic Hospital. Here we report two neonates who were born to mothers addicted to nyaope. Both infants were growth restricted and presented with signs of neonatal abstinence syndrome that are likely due to nyaope or whoonga. We suggest that in growth-restricted infants born to mothers who are at high risk of substance abuse and/or are receiving ARVs, screening for substance abuse should be considered.

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The illicit use of substances, especially during pregnancy, remains a worldwide problem. Data on substance abuse in South African (SA) pregnant women are scanty. The substances abused by SA women include: alcohol (51%), cannabis (21%), cocaine (9.6%), heroin/opiates (7.9%), methamphetamine (4.5%) and over-the-counter drugs (2%).[1] Recently there have been reports of the abuse of a highly addictive drug cocktail called nyaope, also known as whoonga, in many SA urban townships. Nyaope, which is smoked, is reported to contain a combination of heroin, morphine, methamphetamine, marijuana, rat poison and the antiretroviral (ARV) medications efavirenz (EFV) or ritonavir.[2,3]

Use of illicit drugs during pregnancy is associated with abnormal outcomes in neonates, which include abnormal intrauterine growth, neonatal abstinence syndrome (NAS) and abnormal behaviour.[4,5] NAS is a combination of signs and symptoms of withdrawal in a newborn as a result of abrupt discontinuation of one or more illicit substances abused by the mother during her pregnancy. In this report we present two patients born to women addicted to nyaope during their pregnancies.

Case 1

Baby A was a term female infant with a birth weight of 2 165 g and Apgar scores of 9 and 10 at 1 and 5 min, respectively. She was born to a 26-year-old primigravida woman receiving ARV treatment and who was a known addict to nyaope. She refused treatment for her addiction despite knowing that she was pregnant. Post delivery, she was started on clonazepam and methadone for her addiction because of withdrawal symptoms.

The baby was symmetrically growth restricted. She was alert and responsive, but was noted to be jittery with excessive sucking movements. Her tone was normal. The remaining systemic examination was unremarkable. She was being exclusively breastfed and was tolerating her feeds well with normal stools. Hypoglycaemia, hypocalcaemia and electrolyte abnormalities were excluded. A diagnosis of NAS was made. Her Finnegan NAS (FNAS)[6] was 3. She did not require any pharmacological intervention. The mother was assessed by the social worker and subsequently referred to a rehabilitation centre. The baby was discharged on day 6 of life, to be followed up at the neonatal clinic.

Case 2

Baby B was a 1 300 g male infant born at 34 weeks' gestation to an HIV-negative 29-year-old woman. His Apgar scores at 1 and 5 min were 9 and 10, respectively. The mother was a known tobacco smoker. She had not attended an antenatal clinic during her pregnancy. The baby was symmetrically growth restricted. He required endotracheal intubation and mechanical ventilation, most likely due to respiratory distress secondary to pneumonia. He was started on intravenous (IV) ampicillin and gentamicin. He was extubated by 48 hours of life and the IV antibiotics were discontinued by 72 hours of life. Expressed breastmilk feeds were commenced on day 2 of life.

At about 72 hours of life the baby was noted to be very jittery. He had a hyperactive moro reflex. His tone was normal. Infection, hypoglycaemia, hypocalcaemia and electrolyte abnormalities were excluded. The cranial ultrasound was normal. He was tolerating feeds well with normal stools. On further history taken from the mother, she confessed to taking nyaope throughout her pregnancy. A diagnosis of NAS was made in the infant. The FNAS was 10. Urine and meconium were sent for toxic screen; however, the results could not be traced.

Methadone was started at a dose of 0.3 mg orally, 12-hourly. Feeds were changed from breastmilk to formula milk, as the mother admitted to the ongoing abuse of nyaope. The mother was referred to the social worker and was admitted for rehabilitation. The infant's FNAS improved gradually to 2 and methadone was weaned and discontinued by day 9 of life. On the 11th day of life, he was again noted to have marked tremors and his FNAS had increased to 8. Methadone was reinstated at 0.3 mg 12-hourly. By day 26 the FNAS score had improved to 1 and methadone was weaned and discontinued.

Four days later he developed a generalised tonic-clonic seizure, which was aborted with IV phenobarbital. Serum glucose, electrolytes and lumbar puncture results were within normal limits. The cranial

ultrasound remained normal. The FNAS was 15 and methadone was reinstated at 0.15 mg 12-hourly. The FNAS improved to 1 and the methadone was weaned and subsequently discontinued. The baby remained asymptomatic thereafter, with normal neurological examinations. Audiology and retinopathy of prematurity (ROP) screening were normal. At 18 g/kg/day, his weight gain was appropriate and he was discharged at 40 days of life with a weight of 1 890 g, to be followed up at the neonatal clinic.

Discussion

The use of illicit drugs during pregnancy may be on the rise in SA. The potential use of ARV medication for recreational purposes is of major concern. Nyaope has been reported to contain ARVs, notably EFV, in addition to other illicit substances.[2,3] EFV has been reported to have psychoactive effects, such as hallucinations, dizziness and night terrors, which can be aggravated by the concomitant use of other psychoactive drugs. Studies have shown that EFV has lysergic acid diethylamine (LSD)-like activity, mediated via the 5-HT(2A) receptor, which is responsible for many of its behavioural effects.[7]

One of the major implications of recreational use of ARVs is the development of ARV pretreatment resistance. A recent meta-analysis indicated a 14% annual increase in HIV-1 pretreatment resistance in southern Africa since the ARV rollout.[8] Other implications of recreational ARV use include poor adherence to ARV treatment, limited access to treatment, criminal behaviour towards patients and healthcare providers and further stigmatisation of HIV.[3,9] In Case 1, the mother, who was HIV-positive and receiving ARV treatment, could have been non-adherent to treatment and at risk of treatment resistance.

Risk factors for substance abuse during pregnancy include addiction to other drugs such as alcohol or tobacco, comorbid psychiatric conditions, previous history of sexual or physical abuse, and environmental pressures and easy access to substances of abuse. Demographic factors such as socioeconomic status and race also play a role. A detailed history from the mother regarding these risk factors and the use of illicit drugs during her pregnancy is crucial. In Case 1, the mother was a known addict but defaulted management during her pregnancy, and in Case 2, the mother, a known tobacco smoker, only admitted to her addiction after delivery. Therefore, neither mother received adequate antenatal management.

Fetal exposure to illicit drugs during pregnancy can result in adverse manifestations. Acute exposure just prior to delivery results in intoxication, and chronic *in utero* exposure results in prematurity, intrauterine growth restriction and low birth weight (LBW).[4,5] There are also reports of sudden infant death syndrome and congenital abnormalities such as spina bifida, gastroschisis and congenital heart disease.[10,11] Approximately 50 - 90% of exposed infants will develop NAS,[4] with 50 - 70% of cases requiring treatment. Long-term adverse neuro-developmental outcomes have been reported. Both patients in this report were growth restricted and had LBW. The second patient developed NAS requiring pharmacological treatment. Both neonates will be followed up and monitored for adverse neuro-developmental outcomes at our neonatal clinic.

Conclusion

The use of illicit drugs and ARV medication for recreational purposes during pregnancy appears to be on the rise. Identification and management of drug-abusing mothers is crucial as it affects both maternal and fetal/neonatal outcomes. Clinicians need to screen for possible substance abuse in babies who are born growth restricted with/without signs of NAS. These infants will need continued follow-up for possible long-term adverse outcomes. The psychosocial aspects of the mother-baby pair should also be managed carefully. Steps to reduce the recreational use of ARV medication should be considered.

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