

SHORT REPORT

Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes

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The betel nut is commonly used as a drug by Asian populations. A high prevalence of adverse pregnancy outcomes has been reported in women who chewed betel quid during gestation. The hypothesis that chronic exposure of the fetus to arecoline (the principal alkaloid of the areca nut) is the cause was investigated in a clinical observational study on six newborns from Asian mothers who chewed betel nut during pregnancy.

The betel nut, composed of the sliced nut of the areca palm (areca nut), the leaf of the betel pepper (*Piper betle*), and lime, is a drug commonly consumed by Asian populations and Asian communities living in Europe and North America.¹

Some authors have reported a significantly higher prevalence of adverse pregnancy outcomes, including spontaneous abortion, low birth weight, and preterm birth,² among women who chewed betel quid during gestation than in non-consumers. However, none hypothesised chronic exposure of the fetus to arecoline (the principal alkaloid of the areca nut) as a possible mechanism.

To investigate if chronic exposure to arecoline can lead to adverse birth outcomes, some not yet recognised, we set up a clinical observational study on six newborns from Asian mothers who admitted to betel nut consumption during pregnancy.

Pregnant women, recruited within the framework of the Meconium Project at the Hospital del Mar in Barcelona Spain, had a complete clinical examination and were interviewed about their use of cigarettes and illicit drugs during pregnancy. At the time of delivery, newborn somatometry and clinical signs were recorded.

Arecoline concentration was determined in meconium to assess fetal exposure to this alkaloid and in the placenta, to be associated with studies on the morphology of placental tissue from consumer mothers.^{3–4} Meconium samples were also analysed for the principal drugs of abuse and cotinine to exclude prenatal exposure to drugs other than arecoline.

Two adverse birth outcomes were observed in the six exposed newborns (table 1). In both cases, risk factors other than chronic betel quid consumption could be excluded from maternal records, and neonatal brain ultrasonography was inconclusive. Focal inflammatory changes in the amniochorial membranes were observed in the placentas in both cases (table 1), and in case 3 a decreased median diameter of the vessels in both maternal and fetal surface villi was also observed.

Although the effects of betel chewing are well established in adults, teratogenic effects of prenatal betel exposure have only been shown in animal models,⁵ and data for humans are scant.²

In our study, arecoline was determined in biological matrices accounting for acute and chronic fetal exposure to this substance, exposure associated with placental abnormalities, and neonatal outcomes, including neonatal withdrawal syndrome, as an exceptional adverse birth outcome not yet described in the literature. The recognised biochemical effects of arecoline on the autonomic nervous system and the recognised embryotoxicity in animals, together with our findings, allowed us to hypothesise a number of effects on the fetus related to abnormalities of the fetoplacental circulation, similar to those observed with nicotine or cocaine.

These preliminary findings did not allow any definitive conclusion on the correlation between fetal exposure to arecoline and clinical outcomes. Information on differences in patterns of drug use (amount, timing, and duration of drug exposure), related to clinical outcomes, was not

Table 1 Results of the clinical observational study on six newborns from mothers who chewed betel nut during pregnancy

Case No	Somatometry				Clinical signs	Placental morphology	Arecoline in biological matrices (µg/g)	
	Birth weight (g)	Crown-heel height (cm)	Cranial perimeter (cm)	Gestation (weeks)			Meconium	Placenta
1	3450	51	34	41	None	577 g; macro and micro normal	0.008	ND
2	3090	49	34	38	Neonatal withdrawal syndrome treated with 5 mg/kg phenobarbital for 3 subsequent days	655 g; macro normal; micro acute focal chorioamnionitis	NA	0.012
3	2430	47	33	41	Low birth weight, low intrauterine growth, small for gestational age, hyporeflexia, hypotonia	435 g; macro normal; micro acute focal chorioamnionitis, reduced vascular diameter	0.006	0.009
4	3260	49	34	39.6	None	548 g; macro and micro normal	0.022	0.013
5	2865	48	32	38.3	None	498 g; macro and micro normal	NA	0.015
6	3575	52	35	40.4	None	468 g; macro and micro normal	0.017	0.014

NA, Not available; ND, not detected.

available from the study questionnaire, nor could it be deduced from the arecoline concentration in the meconium, as is the case for other illicit drugs. Furthermore, as this was the first time that arecoline had been detected in meconium and placenta, no concentration ranges were available, which may have allowed speculations on amounts.

Our observations require support from further investigations, addressing the above issues and including an extended follow up of prenatally exposed newborns in areas with a high prevalence of betel nut consumption.

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