



Consumption of Areca Nut During Pregnancy and its Effects on Newborns

KEYWORDS

Areca nut; Pregnancy; Adverse outcome; Newborn

Mercadal M

Paediatric Unit, Hospital del Mar, Barcelona, Spain

Álvarez AT

Paediatric Unit, Hospital del Mar, Barcelona, Spain

Manzano C

Paediatric Unit, Hospital del Mar, Barcelona, Spain

Torres F

Paediatric Unit, Hospital del Mar, Barcelona, Spain

Garcia-Algar O

Unitat de Recerca Infància i Entorn (URIE), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain

ABSTRACT

Betel nut is commonly used in a "social" manner in Asian countries, including pregnant women, because of its antiemetic effects. The adverse outcomes in newborns such as neonatal withdrawal syndrome and low birth weight and length have been described in various reports.

The aim of our review was to gather the information that has been described until now on behalf of betel nut use during pregnancy and possible deleterious effects on newborns. A research on PubMed was carried out searching "arecoline and newborn" and "areca nut and newborn". The main results of our revision were that along with adverse outcomes, the presence of arecoline has been studied not only in pregnant women but also in neonatal biological matrices as meconium, cord blood and urine. Therefore it would be important to advise pregnant women against the consumption of areca nut in any of its forms.

Introduction

Betel nut is known to be the fourth most widely used addictive product in the world, after tobacco, alcohol and caffeine-containing beverages (1,2). Betel can be consumed smoked or chewed being mixed with different substances. It is commonly used in Asian countries, including pregnant women. Although its side effects as oral cancer are known, women use betel because of it is perceived to confer reproductive benefits (1,3).

Usually, the nut is sliced into thin shards, combined with a variety of other ingredients (including tobacco), and rolled in a betel pepper (*Piper betle*) leaf. This preparation, usually referred to as 'quid' or 'pan', is held in the mouth and episodically chewed to extract the juice.

Arecoline is the main alkaloid in areca nut. Arecoline has a muscarinic cholinergic effect that can provoke bronchial constriction and a sympathetic activation, which can lead to arrhythmias. It also explains a lower diastolic pressure which would relate with a lower blood flow in the placenta and could lead to lower birth weight (4). The claimed effects of betel nut chewing are euphoria, a sense of well-being, palpitations, increased alertness and resistance to anger. Pregnant women use it because it eases nausea and vomiting during the first months of pregnancy (1,3).

It has been demonstrated that it is possible to find arecoline in meconium, cord blood and neonatal urine (2). Some authors have found that the prevalence of adverse pregnancy outcomes, including spontaneous abortion, was significantly higher among women who chew betel quid (3,4); others have demonstrated that the birth weight of babies born from pregnant betel nut chewers was significantly lower than that of infants born from women of similar age who never chewed betel quid (2). However, none hypothesized chronic exposure of the foetus to arecoline as a possible mechanism.

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 from humans are few (6).

Even though there is scarce literature on behalf of possible deleterious effects on newborns due to betel nut use during pregnancy, our objective was to gather the information on this subject included in the literature until now.

Methodology

We searched the Medline (Pubmed) database. As keywords we used "arecoline and newborn" at first. For this search 17 publications were brought up, from which we included in the analysis 6 as all others weren't addressed neither to arecoline or its effects on humans. We carried out second search using as keywords "areca nut and newborn". For this search 19 articles we up to revise but only 3 were included (5 had already been included in the previous search, other 2 papers from the early 90's were not accessible). We did not place any limit of year (the oldest article reviewed is from 1999). We extended our research though the bibliography included in these articles since some of the authors had other articles related and also to effects of arecoline in adults (cancer or reproductive impairment) and other species (mice).

Results

A study carried out in Papua New Guinea with 310 pregnant women revealed 94% chewed betel nut during pregnancy and 80% of these women did not perceive any risk for their babies. In agreement with other studies, they showed the effect of areca nut consumption on the reduction of birth weight (1). Another study carried out in Taiwan with 1264 pregnant women from whom 40% consumed betel quid, concluded that these ones were more likely to deliver an infant with lower birth weight and length (3,7). Anyhow, some studies have not proved this effect. Chue AL et al studied 4963 pregnant women in Myanmar who reported areca nut use during pregnancy, with any adverse effect on maternal or neonatal outcomes. They also studied the effects of tobacco smoking in these women, which was a significant risk factor for adverse neonatal outcomes. Furthermore, smoking and areca nut use in this population did not result in worse outcome than smoking alone (8). As seen in a study carried out in Taiwan about the relationship between smoking, alcohol consumption, chewing betel and nausea or vomiting related

to pregnancy, an increased risk of nausea and vomiting in women who consumed more than 10 cigarettes a day was showed. However when considering other variables, such as alcohol and betel, no significant associations were found. Alcohol and betel consumption was associated with tobacco consumption, so there could be a cumulative effect, as well as interactions between different substances that could cause adverse effects during pregnancy (9).

In order to correlate these adverse outcomes to actual betel consumption, questionnaires has showed no to be reliable in pregnant women and some authors have used different techniques to determine arecoline in several alternative biological matrices. A high-performance liquid chromatography (HPLC) method with mass spectrometric detection has been described to determine arecoline in neonatal meconium, urine and cord serum (2) and hair (10) and a liquid chromatography/tandem mass spectrometry (LC/MS/MS) test has been used to determine arecoline in breast milk (11).

The effects of arecoline not only have been studied in human but also in mice. Arecoline is related to cytotoxic and genotoxic effects in several cell lines. Shao L et al studied the *in vitro* effects of arecoline in the early weeks of gestation, showing that in mice it produces decrease in the number of viable embryos and blastocyst growth inhibition. Therefore, it seems that arecoline has a foetal toxic effect, although the cytotoxic mechanisms are still unclear (5).

Not only arecoline may be harmful for the newborn of women who chew betel during pregnancy, but also the exposure to other elements such as arsenic, cadmium and lead found in betel quid in Bangladesh and India can have deleterious effects (12).

Discussion

In some societies, women chew areca nut more frequently than men, due to its feminine connotation mostly during courtship and marriage signalling female sexual availability through attractive red lips. This contrasts with its real effects over reproduction. It has been proved that tobacco and areca nut chewing has deleterious effects over sperm (reduction of number and motility as well as frequency of abnormal sperm) (13). A study from Yang et al showed that only 45% of their participants recognized the harmful effects, considering the contribution of lack of knowledge to the significant higher rate of betel use during pregnancy in aborigines of Taiwan (14). This highlights the need to implement awareness campaigns for pregnant women about the risks of betel consumption.

Arecoline can be detected in different alternative biological matrices during the pregnancy. Meconium analysis allows the detection of maternal substances consumption or exposure during the last 20 weeks of gestation, and therefore provides information on foetal chronic exposure. In the foetus, hair starts growing during the last 3 to 4 months of pregnancy and therefore accounts for exposure occurring in the last trimester. Maternal hair testing has been considered the "gold standard" to assess chronic maternal substances of abuse consumption during pregnancy, but it only permits an indirect estimation of those reaching the fetus. Placenta may reveal the passage of a substance from the mother to the foetus. Maternal blood and cord blood account only for foetal substances exposure during the previous hours or days before collection, and that represents a limitation as a matrix predictive of prenatal exposure, and neonatal urine and maternal urine are useful for determining acute exposure to substances of abuse in the period immediately previous to delivery (15).

Arecoline found in meconium, cord serum, neonatal urine (2) and the placenta of infants of chewing mothers and has been related to placental damage (6). The relationship between pregnant women consumption and the effects on their new-

borns is due to the arecoline crossing of the barrier between them, as seen in different studies where arecoline was found in placenta and meconium (6). In this study, Garcia-Algar O et al found focal inflammatory changes in the amniochorial membranes in the placenta along with decreased median diameter of the vessels in both maternal and foetal surface villi (6). In addition, arecoline detected in the placenta of betel nut chewing mother has shown to lead in some cases to neonatal withdrawal syndrome requiring treatment with phenobarbital (16), which demonstrates that arecoline can cross de maternal-foetal barrier.

The determination of arecoline in hair can be used as a non-invasive method to assess chronic use of areca nut preparations (10) by pregnant women whose newborns have the suspicion of a withdrawal syndrome. Moreover, studies that have determined arecoline in breast milk, point to possible effects during also during breastfeeding (11). The measurements of biomarkers in these biological matrices could be very important since it provides the basis for appropriate treatment and adequate follow up of newborns presenting symptoms of drug withdrawal (2).

Various studies highlighted that the differences in outcomes after using areca nut during pregnancy might be related not only to small samples but also to the different ways the nut is prepared across Asia (8). For example, tobacco is an important additive in areca nut products in India and Southeast Asia in general but it is not an ingredient added to betel quid in Taiwan (3).

Due to the migratory flow of Asian people to industrialized countries, European health systems face to pregnant Asian women who consume betel nut during pregnancy and possibly to newborns prenatally exposed to this substance (2,16). Also, it is important that neonatal healthcare professionals could be recognize the effects of arecoline not only in newborns but also in adults.

Conclusions

Tobacco (nicotine), caffeine containing beverages and areca nut (arecoline) are three of the four most widely consumed substances worldwide. These are often consumed in poor countries where breastfeeding interruption may cause serious health risk for the infant. Breastfeeding mothers often do not want to admit consumption of these substances or even worse, they are not aware of the risk of consuming them (11).

Betel nut in Asian countries is widely used as stimulant or relaxant. The recognized biochemical effects of arecoline on the autonomic nervous system and the identified embryotoxicity in animals, together with finding of arecoline in meconium (6), allow to hypothesize a number of effects on the foetus related to abnormalities of the foetoplacental circulation, similar to those observed with nicotine or cocaine.

The passage of arecoline through the placenta would explain adverse outcomes as low birth weight and prematurity (3), and even withdrawal. For this reason, it is essential that pregnant women are aware of the implications of the consumption of products that contain areca nut.

The accurate assessment of both acute and chronic foetal exposure to drugs of abuse, through the objective measurement of biomarkers in matrices such as cord blood, meconium or hair, could be of most importance since it provides the basis for appropriate treatment and an adequate follow-up of exposed newborns, which can present the symptoms of a neonatal withdrawal syndrome (2).

In addition, further investigations are needed in order to extend the follow up of prenatally exposed newborns in areas with a high prevalence of betel nut consumption.

Because of growing migratory flows, arecoline use should be investigated in pregnant woman from Asian countries, not

only by asking about toxic habits (their awareness of toxicity is very low), but also by checking for red stains on teeth, gingival and oral mucosa (16) and sometimes by studying arecoline in alternative maternal and neonatal matrices. Furthermore, areca nut consumption should be recorded by the GP before getting pregnant and during pregnancy and breastfeeding follow up.

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