

© Copyright 2015

Sahira Khalid

Betel Use in Pregnancy

Sahira Khalid

A thesis

submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2015

Committee:

Peter Milgrom, Chair

Lloyd Mancl

Program Authorized to Offer Degree:

Health Services -Public Health

University of Washington
Abstract

Betel Use in Pregnancy

Sahira Khalid

Chair of the Supervisory Committee:
Peter Milgrom, Professor
Oral Health Sciences

Purpose: The purpose of this study is to pilot test a short questionnaire, which will gain information on pregnant women's views on the risks associated with using betel nut, and to establish the questionnaire's internal consistency and concurrent validity, which will be done by relating it to the developed craving scale.

Study setting: This study was conducted at a Pongee State Hospital, Maternal and Child Department, Federated States of Micronesia. Participants were receiving prenatal care.

Methods: This is a convenience sample. Members of the Dental Department staff confidentially administered the surveys in May and July 2015. Independent samples t-test was used to find difference between the mean number of betel nut users who also used tobacco and those who did not use tobacco with their betel nut use in terms of their responses on the dependence symptom scale (craving scale). Spearman's rank correlation was used to test for a relationship between the dependence symptom scores and health risk beliefs assessment scores for betel nut users who used betel nut at some point in their lives. Chi-square test of association was used to test for association between the level of education of the respondents and their betel nut use (chewers or non-chewers) and to test for association between their betel nut use and whether they smoked or not during pregnancy, alcohol use, and substance abuse.

Results: In this study, 80% of the 55 respondents had ever used betel. More than one sixth of all users (14.7%) used betel in the previous month, and 26 (76.5%) also used tobacco with the betel. Although not statistically significant, the mean (\pm SD) dependence symptom scale score among users who also used tobacco from cigarette was 8.25 ± 0.822 versus 6.00 ± 2.00 among those who used betel nut alone ($t(22) = -0.8, p = 0.432$). The dependency score was positively but not significantly associated with frequency of tobacco use (e.g., mean (SD) = 11 ± 1.761) among most frequent users versus a mean (SD) = 9.14 ± 0.688 among the never users [$F(3,28) = 1.968, p = 0.142$]. 83.3% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that encouragement should be given to pregnant women so that they stop chewing betel nut ($\chi^2 = 13.698, p < 0.05$). 88% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that more help should be given to pregnant women who want stop chewing betel nut ($\chi^2 = 18.429, p < 0.05$). There was no significant relationship found between the craving scale and the health risk belief assessment scale for both, users who had ever used betel ($\rho = -0.240, p = 0.238$) and who used betel within the past 30 days using Spearman's rank correlation ($\rho = -0.394, p = 0.085$).

Conclusion: Dependence was observed in pregnant betel users who also chewed tobacco versus those who used betel nut alone. The beliefs which prompted the pregnant women to chew are: to reduce morning sickness/nausea, for relief and relaxation, to avoid having a smelly mouth, and to prevent them from feeling tired or to work for a longer time. The health belief scale and craving were 80% reliable and had high internal consistency, and the items in the questionnaire are well inter-correlated. There was no significant relationship found between the craving scale and the health risk belief assessment scale for both, users who had ever used betel ($\rho = -0.240, p = 0.238$)

and who used betel within the past 30 days using Spearman's rank correlation ($\rho = -0.394$, $p = 0.085$). Additional studies are required to corroborate the data of this preliminary study and develop effective betel nut cessation intervention program. One possible next step is the collection of samples tied to birth records, examining pregnancy outcomes more thoroughly. Future studies should also involve adolescents or parents who are introducing betel to young children.

TABLE OF CONTENTS

LIST OF FIGURES	iii
LIST OF TABLES	iv
1. BACKGROUND	5
1.1 OVERVIEW OF BETEL NUT	5
1.2 TOBACCO AND BETEL NUT IN THE WESTERN PACIFIC	12
1.3 BETEL NUT DEPENDENCY AND ADDICTION	16
1.4 ORAL HEALTH EFFECT OF BETEL NUT	30
1.5 ADVERSE HEALTH EFFECT OF BETEL NUT ON FETUS	36
1.6 BETEL NUT USE IN PREGNANCY	37
1.7 RISK PERCEPTION OF CHEWING BETEL NUT DURING PREGNANCY	46
1.8 PUBLIC HEALTH SIGNIFICANCE: CHALLENGE TO REGULATE BETEL NUT USE	54
1.9 SUMMARY AND PURPOSE OF THE STUDY	57
2. METHOD	60
2.1 STUDY SETTING	60
2.2 SELECTION OF STUDY SUBJECTS	60
2.3 DATA SOURCE	60
2.3.1 <i>Instrumentation</i>	60
2.3.2 <i>Study participants</i>	62
2.3.3 <i>Criteria for eligibility/exclusion of cases</i>	62
2.4 DATA COLLECTION.....	62
2.4.1 <i>Source</i>	62
2.4.2 <i>Steps taken to assess and assure data quality</i>	63
2.5 ANALYSIS PLAN.....	63
2.5.1 <i>Hypothesis testing/generation</i>	63
2.5.2 <i>Statistical methods</i>	64
3. RESULTS	65
4. DISCUSSION	72
4.1 RESULTS	72

4.2	CONCLUSIONS	74
5.	SYSTEMATIC REVIEW ON PREGNANCY AND BETEL NUT.....	76
6.	GLOSSARY OF TERMS* USED IN THESIS	84
	BIBLIOGRAPHY	86
	APPENDIX	98

LIST OF FIGURES

Figure 1. Reasons to chew outside of vs. during pregnancy	47
Figure 2. Case vs. control group reasons to chew betel nut during pregnancy	49
Figure 3. Reason to chew betel nut outside of vs. during pregnancy (Source: Senn et al.)	52

LIST OF TABLES

(1.1) Table 1. Prevalence of betel nut usage for different Southeast Asian countries [3].....	112
(1.4) Table 2. Periodontal condition* ¹² of non-chewers versus chewers [2]	112
(1.5) Table 3. Studies describing the adverse effects of betel nut on the fetus	113
(1.6) Table 4. Six newborn cases [1]	118
(1.6) Table 5. Univariate analysis of possible factors impacting birth weight [4]	118
(1.6) Table 6. Odds ratios and 95% confidence intervals (CI) for low birth weight (LBW) and preterm birth by maternal betel chewing [5]	119
(3) Table 7. Descriptive analysis of samples	119
(3) Table 8. Rates of use and frequency of use among participants (N = 55).....	123
(3) Table 9. Questionnaire response analysis.....	123
(3) Table 10. Responses to questions in craving scale.....	124
(3) Table 11. Correlation between the craving score and the health risk belief assessment score within the past 30 days.....	126
(3) Table 12. Correlation between the craving score and the health risk belief assessment score for people who ever used betel nut.....	126

1. BACKGROUND

1.1 OVERVIEW OF BETEL NUT

The purpose of this section is to provide broad information on the history, social, cultural, religious, economic aspects and prevalence of betel nut*² use.

Distribution and consumption/chewing patterns of betel nut

Betel nut is consumed in parts of South Asia (e.g., India, Nepal, Pakistan), Southeast Asia (e.g., Cambodia, Indonesia, Malaysia, Papua New Guinea, the Philippines, Taiwan, Vietnam) and Western Pacific islands.¹ The seed of the areca palm (*Areca catechu*) is the areca nut or fruit that grows in most of the tropical Pacific, Asia, and parts of east Africa. *Betel nut* refers to the areca seed wrapped in the leaves of the betel tree (*Piper betle*).²

In the Micronesian Islands, betel nut is traditionally chewed, either alone or with pepper leaf and/or tobacco, which was introduced by the Spaniards. In Yap, betel nut is called *bu*; in Belau (Palau), *bua*; in Pohnpei, *poc*; in Chuuk, *pu*.³ In Micronesia, immature areca nuts are used, with slaked lime derived from cooked coral, and pepper leaf. When chewed, an immature areca nut, which includes the husk, is chewed whole or sliced in half. When the combined betel leaf and lime (or tobacco) is chewed, this forms a “quid” or “betel quid.” The husk forms the structure of the large “quid.” Adding tobacco enhances the central nervous system (CNS) effects, and adding lime increases absorption. The red “*pugua*” betel nut is preferred, but the coarse white “*changnga*” is used when the red nut is not in season. Nuts are sliced with a specialized tool called “*tiheras pugua*.” These customs are shared by the people of Micronesia.²

Betel nut chewing prevalence rates have been recorded in different South East Asian countries and can vary greatly according to the studied populations (Warnakulasuriya and Gupta, 2002).³

Social-cultural-economic-religious aspects of betel nut use

The socio-economic aspect of betel nut use is an important component of a multi-faceted behavior. Most research on betel nut use has been epidemiological so far, focusing on behavioral trends and disease outcomes. By giving the social aspects more attention, discussion move from debate over a disease to discussion of a social model of health, involving recognition that health involves more than individual behaviors. Discussion of prevention should focus not only on messages targeted at individual consumers, but also on policies and initiatives with wider scopes. An alternate method of addressing the issue would involve starting with social and economic policy, which would affect cultivation and marketing, which in turn would affect individual consumption. An effective strategy would also take into consideration the varieties of betel nut use.³ In the United Kingdom, the South Asian model of consumption has been the focus of investigation, and it has been understood as promoting consumption through positive sociocultural messages.⁴ Consumption may differ in other populations due to the associations with abundant availability and tradition in betel nut use.⁵⁻⁶

Betel nut use in the Asian community

A study by Croucher and Islam (2002) focused on South Asian communities' health and behaviors in the United Kingdom. They found that this community was not homogeneous, instead differing in terms of location, education, and wealth, and that their areca nut use could not be assumed to be homogeneous either. Indeed, findings showed a heterogeneous pattern of use, both within and between populations. An emerging outcome was the identification of a heterogeneous method of use, with variation within and between populations. The areca nut could be found wet or dry, in a quid with betel leaf and lime, or in a beverage or in pre-packaged pan masala. The strength and site of chewing also varied. Further research could explore travel to

the country of origin and changes in use over time. Exploration of the socio-economic aspects of areca nut production and consumption may assist in the generation of clear conclusions.³

Betel nut ranks fourth among the most common psychoactive*⁵ drugs worldwide, and it has historically been important socially, culturally, and economically.⁷⁻⁹ According to Auluck et al. (2009), there are four factors that contribute to the popularity of betel nut and betel quid: social acceptability, religious beliefs, perceived health benefits, and addiction*. Because many Indian cultures have strong religious and health beliefs regarding betel nut, it is often offered at important social gatherings and weddings.¹⁰

Social acceptability of betel nut in the Pacific

Betel nut use in the Pacific is more common in rural areas than in urban ones area like Guam. The process of chewing and spitting is much more socially acceptable in sparsely populated rural areas. In Guam and Micronesia, betel nut use is an important part of social life. In Guam in particular, Chamorro offer the nut alone, or sometimes with the leaf, at work, parties, and other social events.¹¹

Bhandry and Bhandry have found that betel nut and chewing tobacco is increasingly being used in the Marshall Islands among the native Marshallese, for whom such use is adopted rather than traditional.¹²⁻¹³ It has also been noted by personal observation that other Micronesian groups (e.g. Chuukese or other Marshallese migrants) have adopted betel nut use in Hawaii. In addition, because a distinct Yapese style of betel nut use has served as a part of ethnic regional identity for Micronesians, this practice may be difficult to reduce, even on the grounds of the potential adverse health effects.¹⁴

Strickland has reviewed historical and contemporary identities of betel nut users, and has explored the reasons provided for such use, as informed by historical, ethnographic, and

experimental evidence for the desired effects of use. In particular, this review has considered the social context and meanings of betel nut use and exchange. Strickland has found that the social pressures that come with migrant status may increase betel nut use. However, this phenomenon has not yet been examined in detail.

In a set of ten focus groups, Chamorros, Palauans, and Yapese all proudly claimed chewing betel nut and betel quid as their custom, and many eagerly wanted to pass it on. The focus groups included adult betel nut users of age 18 and older, and they intended to examine the chewing practices of certain Micronesian populations in Guam. The participants were predominantly Chamorros, Paluans, and Yapese; Chuukese were included as well due to being the most populous non-Chamorro Micronesian group in Guam. In this context, many participants discussed their betel nut use in the context of respecting traditions and social promotion. They made statements about associations between betel nut and wisdom and decision-making in the family, keeping culture alive, and contributing to the cohesion of a small culture.

Chuukese men demonstrated ambivalence about the culture of betel nut use. They discussed social promotion in the context of their family and friends. The Chuukese often began chewing betel quid as part of socializing with groups that they met after migrating to neighboring islands. Many young adults began chewing betel quid after attending school on other islands in Micronesia, as their peers found chewing to be cool and social acceptable. Some considered the chewing to be culturally unacceptable but still acknowledged its role in social adaptation. Many Chuukese men in particular found chewing by women to be unladylike and disrespectful. Many Chuukese women approached chewing from the perspective of social promotion among peers, making statements about the difficulty of not being a part of the experience of chewing among friends. They acknowledged that the community, particularly the elders, view this chewing as

untraditional and unacceptable, but chewed nevertheless. Chewing for them carried a “spirit of brotherhood” and a welcoming atmosphere, even for people socializing for the first time. Betel quid is seen as a peace-maker and a help to critical thinking, particularly when used in group meetings.¹⁵

Religious beliefs about betel nut

Betel nut is viewed as an integral part of many religious and sociocultural activities. Many Indians view areca nut as having a divine origin, as it is considered auspicious within Hinduism, and it is used with betel leaf as a method of communicating honor in religious ceremonies. Areca nut (supari) is considered a central element of food for God (Bhagwan) within Hinduism. The fruit is a component of prayers, and is believed to be blessed before its distribution.¹⁶ Because these religious beliefs are so prevalent in many Indian cultures, it is a common element of social gatherings and weddings.¹⁷

Perceived health benefits

Traditionally, betel nut is perceived in many countries as having many beneficial health effects. It is used as an astringent, a mouth freshener after meals, a taste enhancer, a purgative, an intoxicant, a remedy for impotence and gynecological problems, a remedy for parasitic intestinal infection, and a preventative of pregnancy-related morning sickness.¹⁸ Betel nut is often chewed in betel quid, and it is used as a mildly euphoric stimulant, due to its relatively high level of psychoactive alkaloids. It also results in an increased capacity for work, a hot sensation in the body, heightened alertness, hunger suppression, and even relief from boredom.¹⁹⁻²³

Women claim that when taken in the first trimester, the quid provides relief from pregnancy-related nausea*^{20, 24-28}.

The Palauans and Yapese believe that betel quid works to reduce the appetite by suppressing hunger during the workday or until there is a convenient time to eat.²⁹ The Chamorro and Yapese believe that betel quid works to prevent cavities by providing a coating to the teeth. Anthropological evidence and clinical observation support this belief, as the incidence of dental caries*¹⁰ is low among chewers of betel nut or betel quid. However, further research, controlling for other lifestyle practices, is necessary.³⁰⁻³⁴

Economic significance in Western Pacific region

The nuts of Pwuh are becoming an important cash crop for Pohnpei and are now their most expensive agricultural product. However, theft of the nuts is rising because of their growing popularity, scarcity, and cost.³⁵

Agricultural and economic policymakers of some western Pacific island countries have supported the expansion of betel nut production, believing it to be valuable to both local markets and export markets. It is important that tobacco control and public health advocates communicate to policymakers that expanding betel nut production would negatively impact health and wellbeing, and instead economically viable alternatives to betel nut must be identified.³⁶

Arable land in the Western Pacific is increasingly being used in order to produce betel nut (Vele 1982; Gibson 1998). In Guam, for instance, 16 farms produced 4100 pounds of betel nut (Guam Statistical Yearbook 2008), and large scale areca plantations are growing in visibility overall. Areca palms at times have replaced food in home gardens, which can lead to food insecurity depending on the prices of betel nut and food staples, which can fluctuate due to factors such as market saturation and scarcity. This danger has been seen in Guam, where an areca palm blight took place. Another risk is seen in the fact that areca palms are not productive for at least the first four years, so there is a significant gap between the decision to invest and the

generation of income. In some cases, a switch from traditional crops to areca palms may also lead to long-term problems. For example, in Taiwan, because of the inability of areca palms to retain soil in the rainy season, increasing areca nut cultivation has led to a greater amount of fertile soil loss and land erosion (Ko et al. 1992).³⁶

Highlights

- Betel nut in Micronesia traditionally includes immature nuts, slaked lime from cooked coral, and pepper leaf
- An immature betel nut includes the husk
- Leaf and lime (or tobacco) forms a “quid” or “betel quid”
- Social acceptability, religious beliefs, perceived health benefits, and addiction contribute to popular betel nut use
- Betel nut is socially important in Guam and Micronesia
- The social pressure of migrant status can increase betel nut use
- Betel nut is used as an astringent, a mouth freshener, a taste enhancer, a purgative, an intoxicant, a preventative of morning sickness, and a remedy for impotence, gynecological problems, and parasitic intestinal infection
- Betel nut is a mildly euphoric stimulant due to its psychoactive alkaloids
- Betel quid is believed by the Chamorro and Yapese to prevent cavities by coating the teeth
- The nuts of Pwuh (vernacular name of betel nut in Pohnpei state) are an important cash crop for Pohnpei and their most expensive agricultural product

1.2 TOBACCO AND BETEL NUT IN THE WESTERN PACIFIC

This section describes the risk factors or patterns of risk associated with chewing betel nut*², with or without tobacco.

Research has found an increase in the frequency of betel nut use in the Western Pacific, as well as an increase in the frequency of its use with tobacco. The International Agency for Cancer Research has classified betel nut as a Group 1 carcinogen, meaning that it is carcinogenic to humans. The use of betel nut alone poses a health risk to its user, and the addition of tobacco only further increases the risk of premature illness and death. Such use is a significant health problem.¹

Preparation combining betel and tobacco

Different cultures prepare betel in different ways. The green or dry palm nuts are either crushed and chewed alone, or cut up with slaked lime and tobacco and wrapped in piper betel leaf, a combination which is held like smokeless tobacco in the cheek. Adding tobacco enhances the CNS effects, and adding lime increases absorption. Recently, commercial non-perishable forms of betel quid*³ have been marketed which do not contain betel leaf (e.g. pan masala, betel quid mixtures, gutka). Over the course of only two decades, this industry has grown to be worth several hundred million US dollars (Leech 2003). In Yap and Pohnpei, the tobacco comes from cigarettes, which may be dipped in vodka by children and adults before use, and it is then wrapped in fresh betel leaf.²⁻⁴

Use of betel nut with or without tobacco in Pacific community

In 2005, the Secretariat for the Pacific Community conducted Key Informant interviews in several Pacific island countries, such as the Commonwealth of the Northern Mariana Islands, the Federated States of Micronesia, Guam, Palau, Papua New Guinea, the Marshall Islands, and

Solomon Islands, where betel nut and tobacco use is common. Most participants worked in the health sector, and representation from youth affairs and cultural affairs were also present. Interviews asked about the social importance of betel nut use through questions on the importance of betel nut use to the country and on changes in betel nut use in the past 10 years. Participants noted an increase in the number of betel nut users in the last 10 years (81% agreed or strongly agreed) as well as an increase in the number of young betel nut users (76%). Participants also more commonly observed red saliva patches on the street (95%) and readily available betel nut in markets (100%). In addition, 48% of participants agreed or strongly agreed that people were now more likely to use betel nut with tobacco. It should be noted that these Key Informant interviews do not provide much precise, statistical data for quantification, such as is often expected by decision-makers. As such, survey-based data is crucial as well. It is possible that this information is not an accurate reflection of how betel nut and tobacco are currently used, as smoking is more common while chewing betel nut. Two participants agreed with this statement, and they clarified that they had observed more smoking, but not more use of chewing tobacco with betel quid. Additionally, this data came directly from individuals with prior knowledge about the importance of betel nut to the country and the changes in its use. These participants provided valuable data and insights, offering confidential and specific information. The above information is all that is currently available about this study.^{1,5}

Use of betel nut with or without tobacco in Guam

Betel nut use in Guam is currently in a season of change. According to the Youth Risk Behavioral Surveys from 1999 to 2003, a significant percentage of students used betel nut with tobacco. In 2003, the highest rates of chewing tobacco use were found among Micronesians (21.7% of high school students, 31.7% of middle school students), and rates had increased

among Chamorro high school students since 1999 (3.7% to 6.8%). According to qualitative research, betel use was not traditional for migrants from Chuuk, and rather it was adopted from other Micronesian students at school (Paulino 2009).^{1,6}

Use of betel nut with or without tobacco in Palau

According to a 1996 survey by Ysaol et al. of 1110 Palauans, betel nut was used by 55% of children 5-14 years old and 86% of adults 35-44 years old. Out of the betel nut users, 80% added cigarettes and 24% added another form of tobacco. Higher age and education were associated with chewing. Adding tobacco to the betel quid was slightly more likely among women (84%) than among men (81%). Lime was always added. Age was not significantly associated with tobacco usage, and 87% of children 5-14 years old used tobacco. This study estimated that over 1.21 million packs of cigarettes were used with betel nut each year. Younger users were less likely to use piper leaf, perhaps in order to avoid the associated red discoloration of the saliva. Participants also stated that they did not consider betel nut to be used within a traditional cultural context.^{1,6}

Use of betel nut with or without tobacco in the Federated States of Micronesia Yap

In 2004, the Yap State Department of Health Services and the Ulithian community partnered to create a health survey targeted towards the isolated outer islands of Micronesia. This survey was carried out on two of the four islands of Ulithi Atoll in Yap, FSM. It was found that betel nut was used by 81% of people over the age of 15 (Hancock et al. 2007). This rate of use was similar to that on Mogmog (82%) and Fatharai (81%). Out of those using betel nut, only 24% used the traditional mixture (i.e. betel nut, lime, and pepper leaf), and 76% added tobacco. Out of those adding tobacco, 71% first soaked it in alcohol, and even more on Mogmog (Hancock et al.

2007). Betel nut appeared to be used earlier than cigarettes or alcohol, and 7% of children under the age of 15 had used it.⁷

This study had a number of strengths and limitations. Although the sample size was small, participation included over 90% of the two communities under consideration, and thus the findings are representative. Interviews were carried out face-to-face, which may have influenced data quality due to the high interaction between the interviewer and the respondent, but this decision was made in light of factors such as language, literacy, and cultural preferences, and this style of interviewing was culturally appropriate.⁷

In this study, the research question involved gaining a better understanding of the health issues facing the isolated outer islands of Micronesia. As such, the health survey may have been too broad and multifaceted, and the research may have benefitted from a narrower focus. The authors, Hancock et al., were well-qualified, and they had a suitable amount of knowledge and experience to conduct this study. The literature review was logically organized, and it did not include primary sources or empirical data. Instead, it included background information about the lifestyle and geographical location of Yap state. The aims and objectives of the literature review were not clearly stated, it did not include information about the use of betel nut or tobacco in Yap, and there was no exclusion or inclusion criteria. The target population included the entire population living in Yap, as they were collecting baseline information in order to obtain a picture of basic health statistics (e.g. height, weight, blood pressure) and in order to collect information on health behaviors (e.g. use of alcohol, tobacco, betel nut). Collection techniques were approved by both the Yap State Department of Health Services and local community health leaders, in order to ensure that the survey conduct would be culturally appropriate. However, the research design was not clearly defined. The method section did clearly explain how the survey tool was

initially developed to survey the community of Yap. It also thoroughly described the process of conducting the survey and collecting data. In order to ensure reliability, the survey tool was translated into Ulithian and pre-tested with four Ulithians. The survey included 301 participants from Mogmog and Fatharai. Approximately 20 people on Mogmog were not surveyed. The specifics of the data analysis and the statistical analysis for this study are not available.

Highlights

- Tobacco enhances CNS effects, and lime enhances absorption
- In states of Yap and Pohnpei, added tobacco is from cigarettes, which are sometimes dipped in vodka by children, youth, and adults, and the tobacco is wrapped in fresh betel leaf

1.3 BETEL NUT DEPENDENCY AND ADDICTION

The purpose of this section was to examine dependency among betel nut*² users chewing betel quid*³ without tobacco, and to compare it with the dependency syndrome among betel users chewing betel quid with tobacco.

Chewing betel nut is resulted in sensations of well-being, euphoria, salivation, warmth in the body, sweating, and palpitations, and many of these sensations manifest as dependency symptoms.¹⁻²

Why betel nut causes dependence syndrome

The main alkaloid of betel nut is arecoline, which is a psychoactive*⁵ agent. After thorough study, arecoline has been found to cause a sense of well-being, euphoria, alertness, sweating,

salivation, and a hot sensation in the body.³ The combination of these feelings can lead to tolerance*⁶ building up, which can lead to dependency syndrome.

Evidence suggesting betel nut causes dependence syndrome

Small scale studies supporting dependence syndrome

Pickwell and colleagues in 1994 and Winsock, and colleagues in 2000, in small-scale studies, found that betel use may cause dependence syndrome*¹⁷; however, large-scale studies have not yet been conducted to confirm this finding. Detailed socio-demographic, clinical, laboratory, and psychological studies were carried out with 11 current and former heavy users of betel nut, 9 men and 2 women, who were referred by an Oral Medicine Unit in Northwest London. Winstock reported that 10 out of 11 current and former heavy betel nut users experienced cessation withdrawal effects. A high incidence of cardiovascular disease, truncal obesity, reduced serum B12 levels, and raised urinary cotinine levels were present in the patients. None of the patients currently smoked cigarettes. The betel nut use had been taking place for an average of 35 years, and the patients began using betel nut at a mean age of 13 years. Most patients experienced beneficial psychosocial effects from their use. The mean SDS score was 7.3 (range 1-12, available in 10 patients). A higher score was associated with a greater number of quids used per day, and a score above 1 was present only in those who added tobacco. 10 patients stated that their use was psychologically addictive, 8 that their life would be better if they stopped chewing, and 10 patients that they had experienced cessation withdrawal effects. Combined with the mean SDS score of 7.3, this is consistent with dependency syndrome. The findings of this study are consistent with prior research showing dependency syndrome from the use of areca nut products. Further research is necessary in order to determine the relative contributions of areca nut and tobacco to the findings. It should also be noted that the study was small and not representative of

the community. In addition, because the participants were referred by a hospital, they had already been informed about the harmful effects of their continued use, which may have impacted how they perceived the control they had over their use. A larger community-based study is a necessary next step. As would be expected by the researchers, there was a higher prevalence of dependency among betel users adding tobacco than among those using betel alone. There was also a higher prevalence of dependency among smokers than among betel users adding tobacco. This finding may be explained by the well-documented effect of nicotine in cigarettes in particular.⁴⁻⁵ Nevertheless, this study provides insight into the potential risk of dependency among people using betel alone, and it extends the findings of earlier small-scale studies.

In this study the research question was not clearly specified, and rather was implied. The aims and objectives reflect some of the background information described in the literature. There was not a clear link between the introduction and the research question, but the method section and the results section were written in a logical manner. In the literature review, first the pathogenesis of a number of oral diseases is discussed, then the effect of arecoline on the central nervous system, and then dependency syndrome. Lacking is a balanced critical analysis of the literature. It is worth noting that the oral medicine clinic approached 16 patients about the study, 13 of whom agreed to be seen, and 11 of whom participated in the study. No information was present about the reliability or validity testing, or about the IRB approval. Concepts such as dependency syndrome and other operational terms were not clearly defined. The instrument used in the study was clearly defined. All subjects also completed the Fagerstrom Smoking Questionnaire the five-item version of the Alcohol Use Disorders Inventory Test (AUDIT) (n22), and the Severity of Dependence Scale (SDS) adapted for areca nut users. The details of the data

analysis and the statistical analysis were not included. In the discussion section, the hypothesis was further supported by the study's evidence of dependence syndrome in betel users. However, given that the majority of chewers used the nut in combination with tobacco, it is difficult to differentiate between dependence symptoms associated with tobacco and those associated with the nut itself. Either way, the following patterns of use are certainly compatible with a dependence syndrome. Apart from all users feeling that their use of betel nut was psychologically addictive and the very high (7.3) mean scores on the SDS (for comparison, among amphetamine users, a score of above 4 is indicative of problematic use, the majority of users reported the development of tolerance to the effects of the nut. Support for a dependence syndrome is further provided by a well-defined withdrawal syndrome characterized by mood and cognitive disturbance, which had similarities to a stimulant withdrawal syndrome, and which is seen in withdrawal from nicotine. In the majority who had attempted to stop use, relapse was associated with a desire to alleviate withdrawal symptoms and, in three cases, craving*⁷ for the nut. The study recommends that further research on dependence syndrome be done which will focus on the appropriate health interventions to reduce use and thus the various associated medical conditions, including malignancy.

Whether betel nut or a combination of betel nut and tobacco can lead to dependence and tolerance

Smokeless tobacco is able to deliver levels of nicotine, which are psychoactive and can produce dependence. Tolerance develops with repeated use, and it causes the user to increase the amount of nicotine over time, through increased use and/or use of product with higher amounts of nicotine. Clinical withdrawal signs develop when nicotine use is stopped (Henningfield JE 1995). Limited research suggests that chronic adult users of betel nut alone do develop

dependence. According to Milgrom et al. In Pohnpei, nearly twice as many adolescents use tobacco with betel nut than use betel nut alone (40% vs. 23.8%), and there is clear evidence for tobacco causing dependency. However, there has been little research on whether betel nut use, with or without tobacco, leads to tolerance or a need for more frequent use among youth.⁶⁻⁸

Evidence supporting betel quid dependence

Drug dependence, or addiction^{*4}, is an essential component of behavioral and psychological investigations of addictive substances. However, research about betel quid dependence has been limited (Benegal et al., 2008; Chandra et al., 2003; Lee et al., 2012; Mubeen et al., 2010). These few studies have analyzed betel quid dependence with the approaches of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2000) and the International Classification of Diseases (ICD-10) (WHO, 1992). They consisted of generic assessments of dependence, and did not measure aspects specific to betel quid. Other studies, however, have analyzed betel quid dependence with adapted versions of dependence scales, which were designed for other substances, such as opioids (Winstock, 2002) and tobacco (Bhat et al., 2010).

Guam

In a smaller 2014 study in Guam of adult betel users (mean age: 35.3 years), Herzog and colleagues used different measures and came to the same conclusion of the association between tobacco and betel use dependence.⁹

In Guam, 300 betel quid chewers were administered a survey containing the Betel Quid Dependence Scale (BQDS), which was developed and validated by Lee et al. in 2012. As compensation for their participation, the respondents were given a \$25 gift card. The hypothesized three-factor measurement model was supported by confirmatory factor analysis. According to ANOVAs and structural equations modeling, the findings showed an association

between betel quid dependence and adding tobacco, number of chews per day, years of chewing, and education. The mean age of the participants was 35.3 years old ($SD = 21.7$). 51.7% of participants were male, and 56.7% had a high school level education. 33.1% were Chamorro, 30.1% were Chamorro, 30.1% were Chuukese, 23.8% were Palauan, 6.0% were Yapese, and 7.0% were other ethnicities, including Carolinian, Filipino, and Marshallese. The mean time of use was 14.9 years ($SD = 12.7$) and the mean frequency of use was 12.5 times per day ($SD = 14.5$). Only 10.4% used areca nut alone, and 69.9% added tobacco. Most of those who used areca nut alone were Chamorro, and most non-Chamorro users added tobacco. Three items contributed to assessing betel quid dependence: number of chews per day, number of years chewing, and type of betel quid (i.e. betel nut alone, betel quid without tobacco, or betel quid with tobacco). All chewer categories were found to have significant betel quid dependence. The greatest dependence was found among those who used betel quid with tobacco. Greater dependence was also correlated with greater frequency of chewing. Different ethnic groups had different common types of betel quid. Chamorros used the greatest variation of types; 30% used betel nut alone, 32% used betel quid without tobacco, and 39% used betel quid with tobacco. The other ethnic groups had a strong preference for betel quid with tobacco. Betel quid dependence was more associated with adding tobacco to betel quid, chewing a greater number of times per day, and chewing for a greater number of years. Education was positively correlated and a protective factor against dependence, other than in the case of maladaptive use.⁹

This study was limited by the restriction of the sample to the Micronesian island of Guam. The study used the BQDS in a multivariate analysis of betel quid chewers, revealing good convergent validity and construct validity among English-speaking chewers, both male and

female. The scale had been previously used in Taiwan. Therefore, the BQDS was validated for the second time, in a different culture and language.⁹

The study used a convenience sample, so the results may not be representative of all Guam chewers. Nevertheless, the sample did include a broad range of ethnicities, genders, and ages. Because the study had a cross-sectional design, conclusions regarding causality could not be drawn. Further longitudinal research would be necessary in order to determine the BQDS's predictive validity. This study assessed betel quid dependence as a continuous variable, as is currently done in order to measure dependence for substances such as nicotine and tobacco, and further research would benefit from doing the same. The study has supported the use of BQDS as a valid instrument. The University of Guam institutional review board (IRB) and the University of Hawaii at Manoa IRB approved this study's research protocol. Participants in this study were limited to self-identified chewers of at least three years who currently chewed at least once a week. Participants provided informed written consent to the study. This study was part of a larger examination of the psychological, behavioral, and cultural issues of areca nut use in Guam. The research question was clearly stated, and definitions for the variables, the betel quid dependence scale, and betel nut consumption were clear. The authors were from the Cancer Prevention and Control Program, University of Hawaii Cancer Center, and they had an appropriate amount of knowledge and experience with betel nut for this paper.⁹

Evidence supporting betel quid dependence in Commonwealth of the Northern Mariana Islands

In the Commonwealth of the Northwestern Mariana Islands, areca nut has a soft, non-fibrous coat, which is easier to chew alone than other varieties. Nevertheless, in 1990, Lee found an increase in the addition of tobacco to betel quid, and Joanne Ogo has found the addition of ingredients such as condensed milk in order to improve the taste (pers. comm., 2015). In a recent

unpublished study, 90% of participants added tobacco to their betel nut (Cabrera, in prep). Almost all participants had begun using betel nut at the age of 12 years old, originally without tobacco, but with tobacco after about two years. The mean age for the onset of dependence on betel nut with tobacco was 15.6 years.

Betel quid dependency evidence in Guam

In a paper by Milgrom et al. (2014), two studies found dependence symptoms among young users of betel nut, alone or with tobacco, and tested the hypothesized association between craving and tobacco use.

Evidence of dependence in Micronesia adolescents by Milgrom et al. in Saipan

Pilot study

Milgrom and colleagues (2014) conducted a preliminary study of dependence among adolescents who habitually use betel, alone or with tobacco. This study included 151 9th graders (14.7 ± 1.1 years old) in Saipan. The confirmatory study included 269 9th graders in Pohnpei and Yap. Participants completed a confidential questionnaire on their betel and tobacco use. This questionnaire was adapted from the U.S. National Survey of Drug Use and Health, and it assessed the consequences of substance use and abuse and dependence symptoms. In the preliminary study, over a third (39.1%) had ever used betel. Over two-thirds of betel users (69.5%) had used betel in at least the previous month. Most betel users (87.8%) had also used tobacco with betel. The mean (\pm SD) dependence symptom score among tobacco users was 8.2 ± 4.0 , as compared to 3.4 ± 2.9 among users of betel alone (t-test, $p = .015$). After adjusting for initiation age and gender, dependence was associated with tobacco use among habitual users. In the confirmatory study, 38-85% of participants from Yap had used betel, and most of the current betel users used it habitually. Among habitual users, 90% used it with tobacco in Pohnpei, and

64% did so in Yap. The mean craving score was significantly positively associated with the frequency of tobacco use ($F = 15.4$, $df 3$, $p < .0001$), after adjusting for initiation age, gender, and other tobacco and drug use. Users of betel nut with tobacco may benefit from tobacco cessation strategies. The strength of this study was that for the first time, it collected specific data on betel nut with standardized questions adapted from the U.S. National Survey of Drug Use and Health. One benefit of adaptation from a standardized questionnaire is that the process of psychometric validation has already been completed and the questions have already been narrowed down to those which are most reliable, valid, and sensitive. In order to be able to generalize findings, the sample group must be determined to be representative of the general population, and the sample size must be large enough to allow more extrapolation.¹⁰

However, a weakness was that the study population was a small convenience sample of adolescents surveyed at school, where betel nut use is not allowed, so the findings have a limited generalizability and may have been influenced by underreporting. Social desirability bias may have led respondents to have reported an inaccurate answer, although understanding the question correctly and knowing the accurate answer, in order to look better. Nevertheless, the findings of this survey were consistent with a previous survey in Saipan and other such reports in similar settings.¹⁰⁻¹¹

Second study

In 2014, the Dental Program of the Department of Public Health of the Commonwealth of the Northern Mariana Islands surveyed 151 9th graders in Saipan. The mean age of the participants was 14.7 ± 1.0 years, and 76 of the participants were female. The data was de-identified by university researchers. The study was exempt from IRB review according to the University of Washington IRB. Information on grade, age, and gender was collected. The dependence scale's

internal consistency was Cronbach $\alpha = 0.84$, 95% CI 0.79 to 0.88. The questionnaire included four questions on anxiety and depression (Vani, Seid, & Kurtin, 2001) and six questions on interactions with other children and adaptation to school. The format of the questions was Likert-like: “never a problem” (0), “almost never a problem” (1), “sometimes a problem” (2), “often a problem” (3), and “almost always a problem” (4). Each concept had the items summed for an overall score, in which a higher score was indicative of a greater problem.

Pohnpei State

38% of participants (60/159) had used betel nut before. The average age of first use was 11.8 ± 3.2 years. 67% of betel nut users (40/60) had used it in the past month, and of these, 83% (33/40) had used betel nut with added tobacco, and 3 participants did not provide information on tobacco use. 45% of betel nut users (27/60) had used it in the past day or week.

Yap State

85% of participants (85/100) had used betel nut before. The average age of first use was 11.1 ± 3.3 years. 91% of betel nut users (77/85) had used it in the past month, and of these, 64% (49/77) had used betel nut with added tobacco. 71% of betel nut users (55/77) had used it in the past day or week.

As the frequency of tobacco use increased, the mean dependence symptom score increased as well (mean = 4.8 for never to mean = 11.3 for nearly all the time). After adjusting for many factors (i.e. gender, age of initiation, state, tobacco use, alcohol use, other drug use, anxiety/depression, and coping/adaptation), there was a significant relationship between the dependence symptom score and the use of betel nut with added tobacco. There was an adjusted difference in mean scores of 6.2 between those who never used and those who used nearly all the time.

The average score for the questions on anxiety/depression was 5.2 (SD = 3.7), and the average score for the questions on coping/adaptation was 7.0 (SD = 5.3). 50.4% of the participants (57/113) had smoked tobacco or used smokeless tobacco, 22.1% (25/113) had used alcohol, and 14.1% (16/113) had used other drugs. No relationship was found between the dependence symptom score and the anxiety/depression score or coping/adaptation score. A relationship was found between the dependence symptom score and the state, as Pohnpei had higher scores than Yap.

With the data from two studies, a dose response of dependence symptoms was found with the use of betel nut with added tobacco for most items on the questionnaire. Even for items with differences which were not statistically significant, this finding was consistent overall. It should be noted that the generalizability of the findings is limited by the use of a convenience sample for the study population. Further research may confirm these findings and pursue issues of prevention and treatment. Adolescent betel nut use is strongly influenced by peers and family, particularly because friends and family supply adolescents with betel nut more than personal purchases do (Milgrom et al., 2013). At times, older adults who are missing teeth even ask young children to chew their betel nut for them. Research is needed on the perceptions that older adults have on the use of betel nut by young children.

Craving of betel nut

The definition of craving is a strong desire or sense of compulsion to use.

In Asia

In Asia, previous studies have shown that betel quid containing a nicotine additive is likely to lead to dependence. An investigation was carried out for 12 months on betel quid dependence among six Asian populations, and the impact of dependence on OPMD. This study defined

craving as “a strong desire or sense of compulsion to chew betel-quin.” The findings showed more correlated dependency domains among betel quin users within the six south and southeast Asian populations, within the four east Asian populations, and within the two Nepalese populations. Clustering for these populations were in the first, second, and fourth quadrants. The most important dependency domains were “craving” and “time spent chewing,” respectively, for the populations of Sri Lanka, Malaysia, and Indonesia, and for the populations of Taiwan and mainland China. “Craving” was present in 70.2-89.9%, “time spent chewing” in 43.3-60.7%, and “tolerance*⁶” plus “withdrawal” in 98.9-99.6% of participants. This study found that craving is a critical component of measuring betel-quin dependence in Southeast and South Asian communities.¹²

Multi-item craving questionnaires typically address broader topics than only symptoms of desire, also asking about intentions to use, expectancies of specific outcomes from use (e.g. better mood, lessen withdrawal), or lack of control over use. These topics are included because of the multidimensional nature of craving, extending beyond symptoms of desire. This added complexity and the aspects of craving analysis has been criticized by some as unnecessary, as the additional topics have been argued to be entirely different from desire. However, the analysis of the aspects of multi-category craving termed instruments of analysis is important for basic research on craving response generation and the relationships between traditional expressions of craving and craving-related constructs. In addition, some factors appear to be closely linked to desire. For example, questions on intention to use are almost always linked to desire to use, particularly for those who are not trying to abstain. On the other hand, some instruments of analysis do have more questions than necessary for assessing desire for use. This concern is

particularly important in clinical settings, where instruments or the question detail should be short and focused.¹³

Evidence of craving in Palau

More recent Palau Youth Tobacco Surveys (PYTS) from 2001, 2005 and 2009 measured betel nut and tobacco use in school students. Although less than previous years, very high usage of betel nut was demonstrated in 2009, with 62.9% of middle school students (82% in PYTS 2005) and 74.8% of high school students (78.1% in PYTS 2005) having ever tried betel nut. Use was significantly higher among students of Palauan origin than other students (PYTS, 2009).

The 2009 survey reported 52.2% of high school students usually added tobacco to the chew (down from 61.1% in 2005), with the vast majority of students using cigarettes as the source of tobacco (PYTS, 2009). Over one third of students using tobacco with betel nut had experienced cravings within three hours of their last chew. These studies support the findings of the report questionnaire in which respondents from Palau considered that betel nut was no longer used in the traditional cultural context.¹⁴ In 2012, Tiffany and Wray suggested that addictions therapy could benefit from targeting symptoms (craving). In addition, users of betel nut with added tobacco could benefit from tobacco cessation strategies.¹⁵

Highlights

- Studies have found that arecoline causes a sense of well-being, euphoria, alertness, sweating, salivation, and a hot sensation in the body, which in combination can lead to tolerance and dependency
- Betel nut users who add tobacco have a higher prevalence of dependency than those who do not

- Benegal et al. (2008) found that betel users who add tobacco experienced withdrawal symptoms after abstaining from or decreasing use
- Some studies have used adapted versions of dependence scales for other substances (e.g. opioid) to analyze betel quid dependence
- Education was a protective factor against dependence, except in maladaptive use
- Betel quid dependence was associated with adding tobacco, greater number of uses per day, and greater number of years of use
- Lee et al. found a rate of betel quid dependence within six Asian communities over the course of a year to be less for tobacco free than for tobacco-added chewers.
- The arecoline in betel is a stimulant and an alkaloid, comparable to nicotine as a stimulant and mild intoxicant
- Betel nut, like other addictive substances, increases dopamine availability in the pleasure center of the mesolimbic system
- Rajan et al. found that youth of rural Tamil Nadu indulge in high-risk behavior by chewing betel nut products with tobacco
- Commercial (processed) betel nut is available with tobacco (gutkha) and without tobacco (plain pan masala)
- Increasing use of commercial betel nut by youth increases the risk of oral pre-cancers
- A craving is a strong desire or sense of compulsion to use
- Craving was the most common component of betel quid dependency in Malaysia, Indonesia, and Sri Lanka, so craving is a critical component of measuring betel quid dependency in Southeast and South Asian communities
- Abstinence leads to an increase in tobacco craving, which predicts relapse

- Craving has a positive association with the frequency of tobacco use
- Tobacco cessation strategies may benefit users of betel nut with tobacco

1.4 ORAL HEALTH EFFECT OF BETEL NUT

The purpose of this section is to provide information about the oral health consequences and implications of using betel nut*² with or without tobacco.

Betel nut has a long history of use across various communities in several countries. Over time, several additives have become more common, leading up to the current betel quid*³ and the incorporation of chewing tobacco. Betel nut use has many negative effects on oral soft tissues, including lichenoid lesions, mainly on buccal mucosa. Chronic chewers can develop betel chewer's mucosa at quid retained sites. Betel nut use can lead to oral submucosa fibrosis (OSF) and, when used with tobacco, leukoplakia, both of which can be malignant and can progress from pre-cancer to oral cancer*¹⁵. The effect on dental caries*¹⁰ and periodontal diseases are less documented. It is important that public health measures be taken to prevent conditions such as OSF and oral cancer.¹

Effects of betel nut on periodontal tissues in India

According to *in vitro* studies, conducted in India, betel extract containing arecoline can inhibit the growth and attachment of, and protein synthesis in human cultured periodontal fibroblasts. Some research has found that betel chewers have a greater risk of loss of periodontal attachment and calculus formation. However, several confounding variables complicate these studies, including oral hygiene, diet, general health and dental status, and tobacco smoking.²

A cross-sectional study by Parmar et al. aimed at determining the effects of chewing betel quid and tobacco on periodontal tissue and oral hygiene. The 365 patients who were attending

out patient department of Government Dental College and Hospital and civil hospital Ahmedabad for various dental disease. Written consent was obtained from the patients and the ethics committee approved this cross-sectional study. The participants included 168 chewers and 197 non-chewers, with a mean age of 32.5 ± 0.7 and 30.4 ± 0.8 years, respectively.

Information was collected on periodontal tissues, oral hygiene status, bleeding from gums, ulcers in the oral cavity, and burning sensations in soft tissues, in order to examine the presence and extent of periodontal lesions. Green and Vermillion's Simplified Oral Hygiene Index was used for the oral hygiene status, including the Simplified Debris Index and the Simplified Calculus Index based on 6 tooth surfaces. The extent of gingival recession was determined for each subject. Analyses used a logistic regression analysis, a student test, and a chi square test. No significant differences was found between the oral hygiene of users and non-users according to the oral hygiene measures used. 14.9% of users had a good oral hygiene status, as compared to 49.2% of non-users, and 17.86% of users had a poor oral hygiene status, as compared to 11.6% of non-users. Users had a mean oral hygiene index of 2.12 ± 0.86 , as compared to 1.54 ± 1.12 for non-users. Users had a higher incidence of bleeding gums, and 58.3% had halitosis.

Conditions of the periodontium (e.g. periodontal pockets, gingival lesions, gum recession) were significantly worse among chewers than among non-chewers. After adjusting for age, sex, and smoking, chewers were at a significantly higher risk of various oral complaints and periodontium conditions. These findings indicate that use of betel quid and tobacco negatively impacts periodontal tissues, oral hygiene, and the incidence of oral lesions. However, because this was a cross-sectional study, causal inferences are difficult to make. The data from this study can assess prevalence rather than incidence.²

A statistically significant age sex smoking adjusted odds ratio was found for chewers against non-chewers. This finding indicates that chewing plays a role in periodontal status deterioration. Ling et al. explored the possible association between chewing and periodontal disease, and findings indicated the prevalence of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* among chewers. A comparison was carried out between 34 chewers and 32 non-chewers. Chewers showed a significantly higher prevalence of bleeding on probing (42.6% vs. 34.2%). For those meeting the mean gingival index value, the difference was even greater (50.1% vs. 39.8%).³

Ling et al. previously found that betel quid chewing was associated with a higher prevalence of bleeding when accompanied by another clinical disease, and with a higher likelihood of sub gingival infection. This finding was not corroborated by the study by Parmar et al. However, this study did confirm Waerhaug's finding that more betel users had periodontitis than non-users, even controlling for oral hygiene. This study too found a higher prevalence of deterioration of periodontal condition among chewers than among non-chewers, controlling for oral hygiene. The impact of the factor of age, however, on the prevalence of oral complaints and periodontal conditions may be significant.²

Betel nut and caries

Pakistan, Asia

Tanwir et al. conducted a survey of adults in a deprived district of Karachi concerning perceived oral health. 994 completed questionnaires were returned, out of 1000 questionnaires distributed. All participants were between the ages of 30 and 50 years old, and 49% of the participants were female. It was found that the use of pan and betel nut strongly influenced perceived oral health. Chewers of pan (32%) were at greater risk of oral health problems (odds ratio 3.63), although at

lower risk of dental caries (odds ratio 0.63). Chewers of betel nut (28%) were not at as great a risk of oral health problems. The most significant adverse effects on oral health of betel nut chewing were dental caries (odds ratio 4.51) and gingival bleeding. Almost all participants were aware of the danger to oral health from eating sweets, smoking, and chewing pan and betel nut.⁴ The complete paper was not available through the University of Washington's HSL library, although the request was submitted.

Pacific

According to a study of 301 rural New Guineans from 12-24 years of age, there is a consistent inverse relationship between caries and intensity of betel chewing, thus indicating that betel chewing confers some protection against caries.⁵ The complete paper was not available through the University of Washington's HSL library, although the request was submitted.

Betel quid use may confer this protection against caries due to coating the surface of the teeth with betel stains, thus acting as a physical barrier against tooth demineralization, or due to the tannin in the betel, which may have antimicrobial properties and a cariostatic role.⁶⁻⁷

Betel nut and lichen planus

Cambodia, Asia

In 1991, the epidemiology of oral mucosal lesions was investigated in order to plan an oral health database for Cambodia. The unstable conditions of Cambodia can place the validity of census data into question, so before the study, local health workers worked as registrars in 9 villages for a census registration. From July 4th, 1991 to July 31st, 1991, an oral surgeon examined 1319 people (953 women, 366 men, ages 15-99 years old) in Kok Trop Commune, Kandal Stung District, which is southwest of the capital, Phnom Penh. WHO criteria was used for the clinical diagnoses. In a study of Cambodian natives, 1.8% of participants had lichen

lesions, especially among 60-69 year old participants. There was an age-adjusted relative risk of 3.3 for lichen development among chewers as compared to non-chewers. Notably, these lichen lesions were only present among women. Similarly, an earlier study in India found a higher prevalence of OLP-like lesions among female betel quid users. A study by Stoopler and colleagues (2003) also reported oral lichen planus*¹³ due to betel quid use in a 79-year-old Cambodian woman. It has also been found that discontinuing betel quid use for 2 weeks leads to a significant decrease in staining of the oral mucosa and tongue, and a significant decrease in the size of the lesions. Stoopler and colleagues recommended that patients be encouraged to stop their habitual use of betel quid in order to improve the prognosis of a lesion caused by betel quid, and in order to decrease the risk of malignant transformation. Uniquely, the diagnosis was confirmed by biopsy, strengthening the evidence with its detailed and carefully recorded observations. This study results corroborate with the results of previous studies.⁹⁻¹⁰.

Betel nut and oral cancer

A study of 40 oral cancer patients in Changhua Christian Hospital from 1990 to 1992 compared these patients with 160 population-based controls, matched for sex, age, residence, and education. This study found a positive association between betel quid chewing and the risk of oral cancer, with an adjusted odds ratio of 58.4:1 (95% CI; 7.6-447.6). A greater risk of oral cancer was found with a greater number of years of betel quid use; the adjusted odds ratios were 12.9:1 for < 21 years of age, 93.7:1 for 21-40 years of age, and 397.5:1 for > 40 years of age, as compared with non-users. A greater risk of oral cancer was found with a greater quantity chewed per day; the adjusted odds ratios were 26.4:1 for < 10 quids per day, 51.2:1 for 10-20 quid per day, and 275.6:1 for > 20 quid per day. These odds ratios are all statistically different from the null value of unity.¹¹⁻¹²

The controls were selected from a representative sample in order to minimize bias. However, recall bias may have taken place, as the 160 population controls may remember past exposures less accurately than the cases. Unlike a cohort study, a case-control study is not able to calculate the incidence rates of oral cancer, the relative risks, or the attributable risks. Instead, odds ratios are used to measure the association as a proxy for the true relative risk, especially when the outcome is uncommon, as in the case of most cancers.¹¹⁻¹²

The risk of oral cancer is higher in Micronesia than in the United States. In Guam from 1997-2003, the incidence of mouth cancer, age-adjusted to the 2000 U.S. population, was 17.9 per 100,000 per year for other Micronesians, 8.1 for Chamorros, 5.5 for Whites, 3.6 for Asians, and 2.3 for Filipinos.¹³ This data indicated that smoking and betel nut use were significantly associated with oral disease, each to an equal extent. The study provided descriptive data on patterns of betel nut usage and precancerous lesions, but did not quantify the intensity of the risk factor behaviors (i.e., alcohol use, betel nut use, and smoking).¹⁴⁻¹⁵

Highlights

- Betel nut negatively affects oral soft tissues, and can cause lichenoid lesions on buccal mucosa and at quid retained sites
- Betel nut can cause submucosa fibrosis, and betel nut with tobacco can cause leukoplakia; both can be malignant and can progress to oral cancer
- Betel nut with tobacco negatively affects periodontal tissues, oral hygiene, and oral lesions
- Betel nut use confers some protection against caries, as shown by the consistent inverse relationship between caries and intensity of betel use

- Patients with lichen lesions were encouraged to stop habitually using betel quid in order to improve their prognosis and decrease their risk of a malignant transformation
- A greater number of years using betel quid and a greater quantity chewed per day had a greater risk of oral cancer
- Micronesia has a higher risk of oral cancer than the United States

1.5 ADVERSE HEALTH EFFECT OF BETEL NUT ON FETUS

Betel nut*² causes deleterious effects on fetuses*¹ of betel chewers, and poor knowledge of these harmful effects contributes to the continued use of betel nut in pregnancy. The purpose of this section is to raise awareness about the adverse effects of betel nut on an unborn child.

Studies have documented that betel chewing during pregnancy can lead to adverse effects on a child's neurological status, sex, weight, and newborn ratio, as well as pregnancy outcomes such as anemia and miscarriage.¹

Betel nut also increases the risk of preterm birth and meconium staining of amniotic fluid.² Arecoline the principal alkaloid of the betel nut is associated with placental abnormalities and neonatal withdrawal syndrome*^{16.3} Exposure to hazardous substance such as tobacco or betel nut during pregnancy can affect the development of fetal organ systems and have a teratogenic effect*^{19.4} Because prenatal care is so essential, it is important that people be well informed about the harmful effects of substance use, especially betel quid*³ use, during pregnancy.⁵

The following table lists various studies describing the adverse effects of betel nut on the fetus, listing the region, population, study design, year, sample demographics, and finding

Highlights

- Betel nut use during pregnancy can have adverse effects on the child's neurological status, sex, weight, and newborn ratio
- Betel nut use may result in negative pregnancy outcomes such as anemia and miscarriage
- In low doses, betel nut dilates the umbilical vessels via eNOS
- In high doses, betel nut arrests endothelial cell differentiation, thus causing dysfunction
- Betel quid use may result in a higher concentration of heavy metals (e.g. lead, arsenic, cadmium) which can harm the fetus

1.6 BETEL NUT USE IN PREGNANCY

The purpose of this study is to explain the consequences of betel nut^{*2} use during pregnancy on maternal and fetal health and to describe all the published information on betel nut and pregnancy.

Use of betel nut affects most organs, including the brain, heart, lungs, gastrointestinal tract, and reproductive organs. Use of betel nut during pregnancy puts a fetus^{*1} at risk for harmful effects as well. Some studies have shown that women who chewed betel quid^{*3} during gestation, as compared to those who did not, had a higher prevalence of adverse pregnancy outcomes, such as spontaneous abortion, low birth weight, and preterm birth.¹

Betel nut and blood vessels

Betel nut has a cytotoxic effect on splenocytes and decreases IL-2 and IFN- γ (but not IL-4) production. Betel nut suppresses T-cell activation and cytokine Th-1 production due to the effect of oxidative stress on the immune system.² A clinical observation study was carried out by Garcia et al. (2005) in order to determine whether chronic arecoline exposure may cause adverse

birth outcomes. The participants were six newborns of Asian mothers who had used betel nut while pregnant. The mothers had been recruited by the Meconium Project at the Hospital del Mar in Barcelona, Spain. They received a complete clinical exam and answered questions about their use cigarettes and illicit drugs while pregnant. The newborns' somatometry and clinical signs were recorded at delivery. The concentration of arecoline in the meconium and the placenta was used to determine fetal exposure. The meconium was also analyzed in order to exclude prenatal exposure to other drugs. Two adverse birth outcomes were observed among the newborns, both of whom were not exposed to other risk factors than betel quid and who had an inconclusive neonatal brain ultrasonography. Both placental amniochorical membranes had focal inflammatory changes, and a third case had vessels with a decreased median surface villi diameter in both the mother and the fetus.¹

However, the sample size for this study was only 6 newborns, and this small sample size runs the risk of failing to answer a research question, to detect important effects or associations, or to estimate effects or associations precisely.³

This study determined arecoline in biological matrices which accounted for acute and chronic fetal exposure, associated with established adverse outcomes or those remaining undescribed in the literature. Based on the findings as well as the recognized effects of arecoline on the autonomic nervous system and on embryos, it was hypothesized that adverse birth outcomes would include abnormalities of the fetoplacental circulation, similar to outcomes from nicotine or cocaine.

The procedure for the study was very detailed, and it justified the decision to exclude newborns with prenatal exposure to drugs other than arecoline. Although research has established the effects of betel use among adults, research has only shown the teratogenic

effects*¹⁹ of prenatal betel exposure through animal models, and studies on humans in this respect are limited. The preliminary findings from these studies do not allow for a definitive conclusion on the relationship between fetal exposure to arecoline and clinical health outcomes. The questionnaire did not cover amount, timing, or duration of drug use, and this information could not be extracted from the meconium's arecoline concentration. Because of the lack of information on the meconium concentration, the observations on the meconium were controversial, requiring further investigation with the above issues addressed and an extensive follow-up on prenatally exposed newborns in regions of prevalent betel nut use.¹

Betel nut chewing during pregnancy, Madang province, Papua New Guinea

In Papua New Guinea, betel nut chewing is very common in the general population and in pregnant women. It has similarities in terms of use and complications of use to chewing tobacco (smokeless tobacco), as its active agent, arecoline is similar to nicotine.^{1,3}

Senn and colleagues studied betel chewing habits and pregnancy outcomes through a cross-sectional survey with 310 pregnant women at Alexishafen Health Centre in Madang Province. The participants were interviewed on detailed demographic data, betel nut chewing habits, and other potential addictions* (i.e. smoking, alcohol, and drug use), and a medical examination was performed which recorded information on weight, height, blood pressure, and hemoglobin level. Their babies have been assessed for birth weight and signs of prematurity.

Data analysis was performed using Stata version 10.0. Univariate associations between birth outcomes and maternal use of betel quid as well as socio-economical or obstetrical characteristics were investigated using 2-sided t-tests for continuous variables and χ^2 , and Odds ratios (ORs) were calculated for categorical variables. *p* value and 95% confidence intervals (CI95) have been used to indicate the statistical significance of these analyses.

All significant variables ($OR \neq 1$ or $p < 0.05$) from the univariate analysis have been introduced in a stepwise regression multivariate analysis using an ANOVA regression model controlling for the main factors influencing birth weight: primigravidity, low BMI and use of betel nut during pregnancy to investigate their impact on birth weight, taking into consideration potential interactions between them.

According to a univariate analysis, birth weight was statistically significantly reduced by primigravidity (458 g, $p < 0.001$), betel nut use (221 g, $p = 0.05$), and BMI (162 g, $p = 0.02$). It was not significantly affected by the other factors. According to a multivariate analysis, birth weight was significantly reduced by primigravidity (467 g, $p < 0.001$), betel nut use (238 g, $p = 0.02$), and BMI (175 g, $p = 0.005$). It was not significantly affected by the other factors. 11.1% of non-users had low birth weights, as compared to 18.8% of users, a difference which was not however statistically significant ($OR = 1.9$, $CI_{95}[0.4-17]$, $p = 0.54$). 11.0% of non-users had preterm deliveries, as compared to 6.5% of users ($OR = 0.6$, $CI_{95}[0.1-5.4]$, $p = 0.34$). Out of the full-term deliveries, 6.6% of non-users had low birth weights, as compared to 16.8% of users ($OR = 3.0$, $CI_{95} [0.4-13.0]$, $p = 0.48$).

According to the results for women chewing betel nut during pregnancy, their reasons were: to prevent nausea*²⁰ (28%), to prevent having a smelly mouth (26%), it is my custom (20%), I am addicted to it (10%), to achieve more work when I am tired (7%), and other reasons (after a meal, to relax, to be with others, for its good taste...) (9%). There was a statistically significant effect on birth weight due to primigravidity (467 g ($p < 0.001$)), betel nut chewing (238 g ($p = 0.02$)), and low BMI (175 g ($p = 0.005$)). However, 80% of the participants did not think that betel nut chewing would affect the fetus.⁴

Limited information is present on mothers' chewing habits or perceptions of potential risks to their fetus. Because the PNG population is known to use betel nut without tobacco, it is ideal for an investigation of the sociological behaviors and health effects associated with betel nut use. The information from such an investigation is crucial for improving antenatal public health interventions. Hence this study would provide useful insight, which would be useful.³

The questionnaires were developed and administered with attention to remaining neutral and not influencing the mother's response. In addition, while asking sensitive questions, the researcher worked to help the respondents to feel comfortable with answering truthfully.

The study found an extremely high prevalence of betel nut use during pregnancy, at a rate of 94%. This finding is similar to the rate of 95% previously found in this area (Pindborg and Roed-Petersen B, 1968), and this rate is likely one of the highest worldwide at present. Because this study was cross-sectional, it was not able to measure incidence, and it was more difficult to interpret associations. A higher rate of LBW was found in chewers; however, this was not statistically significant, although perhaps only due to the limited sample size, especially in regard to non-chewers. The findings of this study are consistent with those of other clinical studies which have shown the effect of betel nut use on lower birth weight (de Costa and Griew, 1982; Yang et al., 1999; Yang et al., 2001; Yang et al., 2008; Pinchini et al., 2003; Garcia-Algar et al., 2005; Lopez-Vilchez et al., 2006; Sinha and Rao, 1985). However, the validity of the findings is limited by the small sample size and very high prevalence of betel nut use in the area, so a larger study is recommended.³

Betel quid chewing effect on aborigine pregnant women southern Taiwan

Yang and colleagues conducted a study among on the prevalence of alcohol, cigarette, betel quid, and drug use during pregnancy, and on the adverse effects of betel quid use on pregnancy

outcomes in southern Taiwan. This study included 62 aboriginal women in southern Taiwan with adverse pregnancy outcomes, and 124 age-matched women. The relationship between birth outcome and use of cigarettes and alcohol was examined through crude odds ratios with 95% confidence intervals or Student's t-test. Similarly examined was the relationship between birth outcome and sociodemographic or obstetric characteristics (e.g. age, education, sex of infant, maternal body weight, blood relation, marital status, prenatal care, gravidity*¹⁸). Next, multiple logistic regression was used to assess the odds ratio of significant variables, controlling for the other variables. After univariate analysis, an association was found between adverse pregnancy outcomes and maternal betel quid chewing, maternal illness during pregnancy, and gravidity.

There was a significant relationship between birth outcome (e.g. low birth weight, preterm birth) and maternal betel quid use. Betel quid users had a mean birth weight of 3030 g, as compared to 3200 g for non-users, a significant difference. Those who had used betel quid while pregnant had a significantly higher odds ratio, controlling for age, cigarette use, and alcohol use (AOR = 5.0, 95% CI = 1.1–23.0). Cigarette use and alcohol use had an additive effect, leading to a higher prevalence of adverse birth outcomes (AOR = 5.7, 95% CI = 1.6–20.3).

The effect of betel quid use on birth weight has been studied, but not other adverse pregnancy outcomes such as abortion, premature delivery, still birth, and fetal malformation. Because of the remote and mountainous location of the population studied, and because of the limited time of the study, it was cross-sectional rather than longitudinal, and further research is necessary.⁵

This study included 62 participants with adverse pregnancy outcomes (case group) and 124 age-matched participants with normal pregnancy outcomes (comparison group). One

concern with matching is the toll on study efficiency, due to the effort of finding matched subjects rather than gathering more information on unmatched subjects. One of the strengths of this study was that it had a response rate of 89%. Trained interviewers conducted the interviews in the participants' homes with a questionnaire developed and evaluated by the study's authors. Another strength of the study was that the questionnaire was analyzed by six public health and medical experts on the subject, in order to oversee the coverage and adequacy of the content.⁶⁻⁷

Previous studies found that live mouse fetuses experienced a mean decrease in weight after exposure to betel nuts, according to a dose-response relationship. Similar findings have been found for humans. This study found a significant relationship between maternal betel quid use and adverse pregnancy outcomes; these outcomes have never before included abortion, premature delivery, stillbirth, or fetal malformation. Because of the remote and mountainous location of the population studied, the limited time of the study, and the cross-sectional rather than longitudinal nature of the study, further research is necessary.⁶⁻⁷ Cross-sectional studies span a small length of time, and they are typically used in order to estimate prevalence rather than incidence.⁸

Betel nut effects and pregnant aborigine women in eastern Taiwan

In 2001, Yang MJ studied the use of alcohol, cigarettes, betel quid, and drugs among pregnant aboriginal women in eastern Taiwan, and aimed to determine the risk of adverse effects from betel quid use on birth outcomes. Out of the 229 participants, the case group consisted of 32 women with adverse birth outcomes. The study found that these birth outcomes were associated with maternal age and betel quid use. After adjusting for maternal age, there was a five times higher risk of adverse birth outcomes among users of betel quid as compared to non-users. No significant associations were found with low birth weight and premature delivery, after

examining maternal education, paternal smoking, previous pregnancies, and paternal occupational exposure.

There is not currently a strong understanding of the mechanisms by which exposure to maternal betel quid chewing results in fetal growth retardation and premature delivery. It has been hypothesized through the study of rodents that betel quid may inhibit nucleic acid and protein synthesis in fetuses (Sinha & Rao, 1985a).

Participants in this study gave several reasons for using betel quid while pregnant, including 20.1% to substitute for candy, 17.5% for savor, and 10% for alertness. Only 45% of participants recognized the harmful effects of betel quid use on a fetus. This lack of knowledge may contribute to the high rate of aboriginal women using betel quid while pregnant. Health education concerning the harmful effects of substance abuse, including betel quid use while pregnant, is important to emphasize in the context of routine prenatal care visits. One limitation of this study was its selective set of participants and heterogeneous set of adverse birth outcomes. Further research on this issue is necessary.⁹

Betel nut and neonatal syndrome

A case was present in which a woman who was a chronic betel nut user bore a female infant with neonatal withdrawal syndrome. 48 hours after a eutocic delivery at 38 weeks (Apgar score 9 at 1 minute, 10 at 5 minutes, 10 at 10 minutes), the newborn presented with irritability and hypertonia. The mother was healthy, 38 years old, and an immigrant from Bangladesh, and she had come in to the obstetrics emergency department in order to give birth. The baby weighed 3090 g, was 49 cm long, and had a head circumference of 34 cm. She was at risk for neonatal infection of vertical transmission due to the uncontrolled pregnancy, so she was admitted to neonatology. All routine laboratory testing and drug testing was normal or negative. Every 3

hours, neonatal abstinence syndrome was scored with the system of Kaltenbach and Finnegan. Further information was not provided by ultrasonographic brain study. Phenobarbital (intramuscular bolus of 15 mg/kg, daily 8 mg/kg orally) was started on the third day due to Finnegan scores higher than 8.

Highlights

- Betel nut affects many organs in the body
- Pregnant chewers of betel quid had a higher prevalence of adverse pregnancy outcomes (e.g. spontaneous abortion, low birth weight, preterm birth) than non-chewers
- One study found two adverse birth outcomes among six exposed newborns
- Women chew betel nut during pregnancy to prevent nausea (28%), to prevent having a smelly mouth (26%), because it is their custom (20%), because they are addicted to it (10%), to achieve more work when they are tired (7%), and for other reasons (9%)
- Information on mothers' chewing habits or perceptions of potential risks to their fetus is limited, but crucial for antenatal public health intervention
- On the Thai-Myanmar border, betel nut use and smoking combined reduced the adverse pregnancy effects on birth weight of smoking, and no relationship with anemia was found
- Betel nut users have twice the risk of preterm birth compared to non-users, and an increased risk of meconium staining of amniotic fluid
- Arecoline decreases vascular tone, and higher doses inhibit endothelial cell growth; long-term or high-dose use of betel nut may induce endothelial dysfunction and related diseases

- Arecoline and betel nut extract are cytotoxic, and they inhibit cell growth during pregnancy
- Betel chewers showed higher yields of sister-chromatid exchange (SCE) than normal controls
- Betel quid use is associated with smoking or drinking, and the cumulative effect of such use can lead to adverse birth outcomes; one study had a significantly higher birth weight for the control group, and a lower incidence of neonatal jaundice for the study group
- A chronic betel nut user has borne an infant with neonatal withdrawal syndrome

1.7 RISK PERCEPTION OF CHEWING BETEL NUT DURING PREGNANCY

The purpose of this section is to explore the beliefs, attitudes, behaviors, knowledge, and risk perception of pregnant women towards betel nut^{*2} intake during pregnancy in Asia and Pacific region.

Perceived benefits of betel nut use during pregnancy in Asia

Chewing betel nut during pregnancy is perceived as beneficial in many countries in Asia and in the Pacific.

India

According to a study conducted by Bhat et al. on betel nut users, respondents considered betel use to be safe for post-partum women. Bhat and colleagues used established measurement scales to study evidence of betel dependence with a large, representative sample of betel-only users (i.e. no tobacco use) as well as use patterns. The participants in this study were daily chewers (N = 59) in Karnataka State, India in 2005. Participants were identified and enrolled through purposive sampling such that all used betel-only products. Because of the multilingual region,

the questionnaire was translated into Kannada and Tulu. Participants were informed that the study was examining chewing patterns and perceptions of use. Data analyses were descriptive for the purposes of summarizing user characteristics, chewing patterns, topography, and perceptions of use. The predominant calculations were of frequency and central tendency (mean/SD, mode, median). Summary scores were used for the CDS-5 (5-25) and STDS (0-19), and all other items had individual scores. Relationships between dependence scores and measures of use were examined with Pearson correlation coefficients (r). The questionnaires of this study includes questions on chewing history, patterns of use, and dependence features.

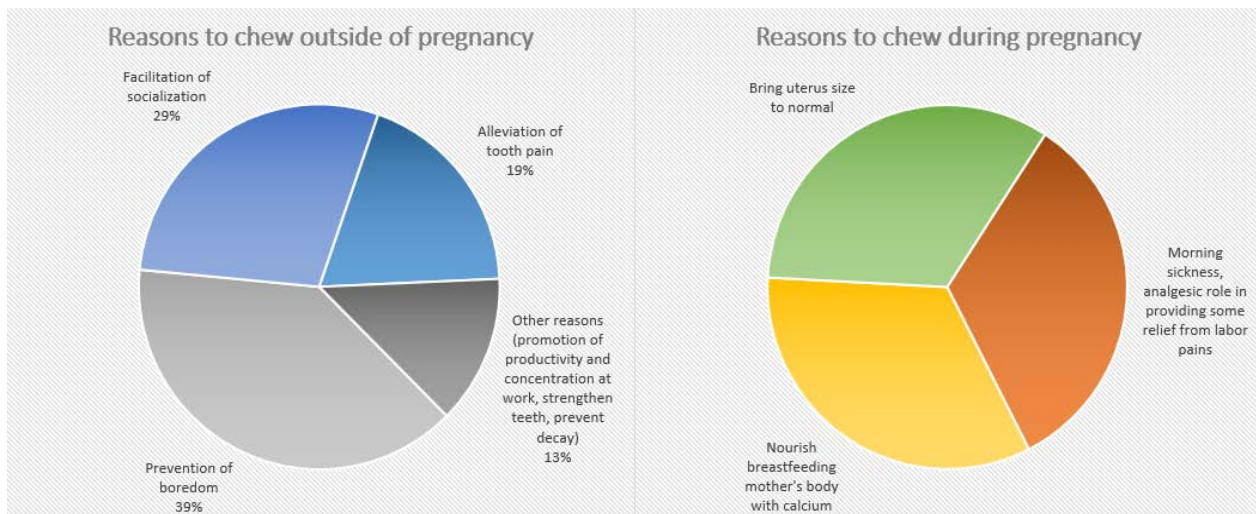


Figure 1. Reasons to chew outside of vs. during pregnancy

The study found that many betel users began their use as adolescents or young adults; 52.5% began before age 30. Elders and Ayurvedic practitioners have given chewers the impression that the slaked lime additive nourishes the breastfeeding mother's body with calcium, and that betel leaf juice returns the mother's uterus to its original size after delivery. Consequently, chewing is perceived as beneficial in moderate amounts, and as having addictive properties similar to caffeine, thus it is viewed as a positive practice. Common reasons for chewing include reduction of boredom and anxiety, increased focus and attention at work, social

facilitation, and digestive and dental health. Informants also explicitly distinguished between betel chewing with tobacco and without tobacco. For example, chewing was considered a “habit,” similar to caffeine consumption, and different from tobacco and alcohol consumption.

A number of studies have found that many chewers endorse these effects of betel nut. However, these data from these studies largely use retrospective reports rather than direct administration of betel nut under controlled laboratory conditions. Further research would require systematic profiling the physiological and subjective effects of areca nut use.⁵

This non-randomized sample may or may not have produced generally applicable findings. Purposive sampling should be used in future research in order to better understand the phenomenon across cultures and user groups. Unique practices are found among some users, such as the chewers in some parts of rural Uttar Pradesh, India who usually place a quid, often with tobacco added, in their cheeks for hours, sometimes overnight.¹

Relieve morning sickness and analgesic effect in Asia

Ethnographic studies and case reports have found the practice of using betel quid*³ for relief from morning sickness in Asian and Asian-Pacific cultures. Singh has found that pregnant women in Andhra Pradesh state in India report that betel quid not only provides relief from morning sickness, but also can have an analgesic role in providing some relief from labor pains during delivery.²

Taiwan

Assessing the risk perceptions of adverse outcome by mothers due to betel chewing in pregnancy

There has been a number of studies on the harmful effects of betel nut on the fetus*¹, including abortion, low birth weight, and other fetal malformations. The study by Yang and colleagues aimed at estimating the prevalence in southern Taiwan of alcohol, cigarette, betel quid, and drug

use among pregnant aboriginal women, and to assess the risk of adverse pregnancy outcomes due to betel quid chewing. This study was carried out from March to October of 1994, and 332 married aboriginal women, chosen by random sampling stratified according to villages, participated with a response rate of 89%. In the DOH-HR study sample, the 186 participants included 62 participants with adverse pregnancy outcomes (case group) and 124 age-matched participants with normal pregnancy outcomes (comparison group).⁸

The risk of adverse pregnancy outcomes were higher among those who used betel quid throughout their pregnancy (OR = 2.2, 95% CI = 1.1 - 4.3). After adjusting for maternal illness, previous pregnancies, and family structure, the risk was still significantly heightened (AOR = 2.8, 95% CI = 1.2 ± 6.8). After logistic regression analysis, it was found that betel quid use was an independent risk factor for an adverse pregnancy outcome.

As was observed in Sothern Taiwan (Yang et al), poor knowledge of the health risks of betel nut chewing may be significant contributor to the high prevalence of betel use among pregnant women. It is important that there be health education on the harmful effects of betel nut use during pregnancy, not only in antenatal care programs, but also in adolescent education.⁸

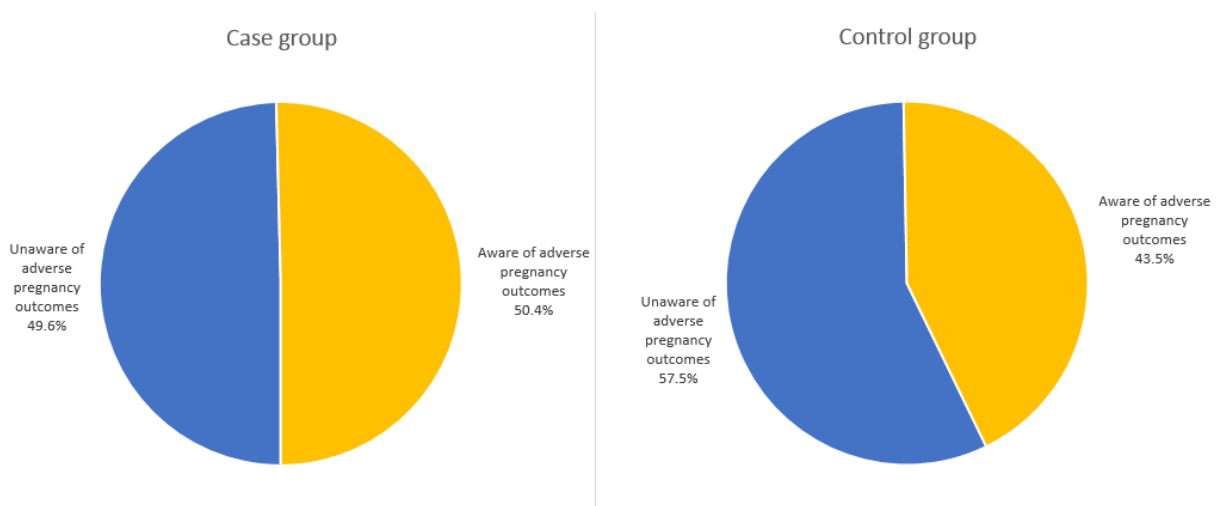


Figure 2. Case vs. control group reasons to chew betel nut during pregnancy

50.4% of the case group and 43.5% of the comparison group recognized the adverse pregnancy outcomes (e.g. retarded fetal growth, abortion) due to betel chewing during pregnancy. Tests on the scores of knowledge on effects of substance use on pregnancy have indicated no significant difference of the scores between the case group and the comparison group. 75-80% of the participants interviewed in both groups recognized the harmful effects of excessive drinking, such as fetal growth malformation, premature labor, abortion, or still birth. On the other hand, 43-50% of the participants recognized that these harmful effects may be brought on by betel nut. The effect of betel quid use on birth weight has been studied, but other adverse pregnancy outcomes such as abortion, premature delivery, still birth, and fetal malformation have not been observed before. Similar findings have been present in studies involving humans. Betel users' babies have a significantly lower birth weight than non-users', controlling for age and province of birth.⁹

Although the association between betel quid chewing Because of the remote and mountainous location of the population studied, and because of the limited time of the study, it was cross-sectional rather than longitudinal, and further research is necessary.⁸

The questionnaire was overseen for content and adequacy by six public health and medical experts in the field. The questionnaire was retested for reliability with 20 people four weeks after the first testing. Reliability coefficients in continuous or ordinary variables were 0.78-0.89, and categorized variables had a consistency of 0.85-0.91, thus there was an acceptable degree of reliability.⁸

Perceived benefits during pregnancy from using betel nut in the Pacific

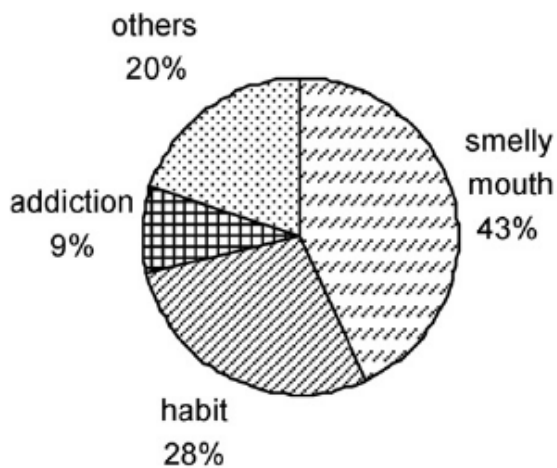
Papua New Guinea

One perceived benefit of betel nut is that it relieves nausea*²⁰ during pregnancy. Nausea is a stomach sickness, particularly in combination with a feeling of loathing food and involuntarily needing to vomit, which is defined as ejecting the contents of the stomach through the mouth (dictionary.com). In the first trimester of pregnancy, about two-thirds of women experience the nausea and vomiting*²¹ of morning sickness.¹⁰

Little is currently known about pregnant women's habits of betel nut use or perceptions of potential risks to the fetus from this use. An ideal candidate for investigating both the sociological behaviors of betel nut use and the effects of this use on pregnancy outcomes is the population of Papua New Guinea due to their use of betel nut without tobacco. The findings from such research will be crucial for effective antenatal public health interventions. In a cross-sectional study, 310 pregnant women at the Alexishafen Health Centre in Madang Province were interviewed with a survey. This survey includes questions on detailed demographic data, habits of betel nut use, and potential addictions* to smoking, alcohol, and other drugs. A medical examination was also carried out, recording weight, height, blood pressure, and hemoglobin level. Unlike many other studies, this study included in the chewing group mothers who had stopped using betel nut during pregnancy. The reported reasons for betel chewing are different during pregnancy as compared to outside of pregnancy, mainly because betel is perceived as reducing morning sickness. In one study, 28% of interviewed mothers perceived that betel nut could control morning sickness, and this therapeutic use may be a major determinant of chewing behavior in this population. In this same study, 80% of pregnant women did not perceive that chewing betel nut would have any negative impact on their fetus. Among those who did perceive

a health risk, their understanding of this risk was poor and vague: “chewing might not be good to my baby but I do not know why,” “the lime I add might burn the unborn baby,” “if I swallow red buai (betel nut) my baby will get cough.” No women indicated knowledge of the risk of lower birth weight or preterm birth.

Reasons to chew outside pregnancy



Reasons to chew during pregnancy

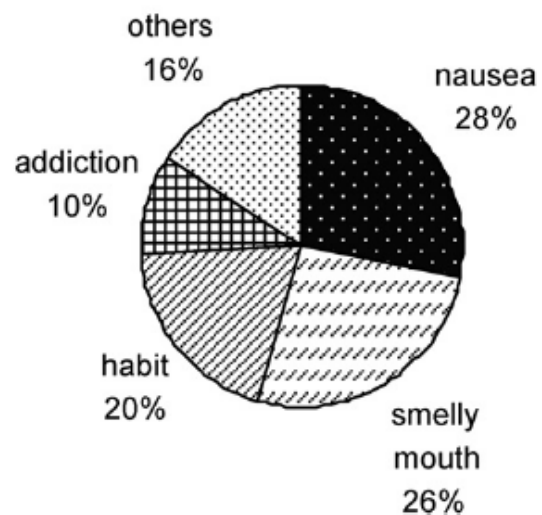


Figure 3. Reason to chew betel nut outside of vs. during pregnancy (Source: Senn et al.)

The validity of the findings of this study are limited by the small sample size and high prevalence of betel nut use in the coastal region, and further research with a larger sample size is necessary.¹¹ In addition, since it was a cross-sectional study, the prevalence of betel chewing can be found, but not the incidence.

This study made a strong choice in deciding to define the chewing group so as to include women who stopped chewing while pregnant, a choice which previous studies had not made. This choice reflected a limitation of the questionnaire to determine with precision when a women had stopped chewing, so it was assumed only that the woman had been chewing for at least some

*See glossary

time while pregnant, likely at least in the first trimester. Pregnant women in PNG infrequently pursue antenatal care before the first trimester, and it was hypothesized that some women may not even have been aware of their pregnancy before this point. This choice also reflected the fact that in the case of smoking, nicotine impacts birth outcomes even when used only in the first trimester, and that its use is discouraged even before conception (Foudas et al., 1997). In addition, this choice reflected that again in the case of smoking, a report of cessation is frequently inaccurate, whereas a report of constant use or no use at all is more trustworthy (George et al., 2006).¹¹

Highlights

- The reported reasons for betel chewing are different during pregnancy as compared to outside of pregnancy, mainly because betel is perceived as reducing morning sickness
- Most pregnant women did not perceive that chewing betel nut would negatively impact their fetus, and those who did had a poor and vague understanding
- In Taiwan, poor knowledge of the health risks of betel nut chewing may have significantly contributed to the high prevalence of betel use among pregnant women
- The majority of women recognized the harmful effects of excessive drinking, but slightly less than half recognized that these harmful effects may be brought on by betel nut
- Women considered betel use to be safe for post-partum women, and the slaked lime additive to nourish the breastfeeding mother's body, and betel leaf juice to return the mother's uterus to its original size
- Common reasons for chewing include reduction of boredom and anxiety, increased focus and attention at work, social facilitation, and digestive and dental health

- Women explicitly distinguished between betel chewing with tobacco and without tobacco
- Although women in the Western Pacific smoke cigarettes at lower rates, a much higher percentage of women of reproductive age use smokeless tobacco, especially in the form of betel quid, in South and Southeast Asia
- Over half of currently pregnant users reported pregnancy-related symptoms as a reason for their tobacco habit
- This use may have an analgesic role in providing some relief from labor pains during delivery
- Pregnant women who did not use tobacco had stronger associations with beliefs about the harmful health effects of tobacco, faith-based reasons against addictive substances, and beliefs that influential community members, health professionals, and children should not use tobacco; these participants were more aware of the harms of tobacco and tended to agree with Buddhist precepts on avoiding addictive substances
- Betel quid may be a traditional medicinal remedy which is encouraged by older female relatives and traditional birth attendants due to arecoline's anthelmintic properties

1.8 PUBLIC HEALTH SIGNIFICANCE: CHALLENGE TO REGULATE BETEL NUT USE

Public health significance

Research has shown a high prevalence of betel quid^{*3} chewing among aborigine women (Yang et al., 1996), and this finding indicates the great public health concern of the negative health effects on pregnant mother and developing children.¹ Betel chewing during pregnancy is prevalent in Micronesia. Pregnant betel users' continued use of betel nut^{*2} in combination with tobacco can lead to dependency syndrome, addiction^{*4}, and neonatal withdrawal syndrome*. A

study led by Chue et al. has shown that betel chewing during pregnancy can lead to adverse effects on a child's neurological status, sex, weight, and newborn ratio, as well as pregnancy outcomes such as anemia and miscarriage.¹⁻²

Low doses of areca nut only causes a dilation of the umbilical vessels via endothelial nitric oxide synthase (eNOS) production of nitric oxide (NO), but by increasing dosage, the endothelial cell differentiation is arrested and reacts accordingly.³ Heavy metals such as cadmium, arsenic, and lead are found in higher concentrations in betel quid users, which can harm the fetus*¹ in a pregnant woman.⁴ As the activity of the -SH enzyme, melandialdehyde level, and cytochrome-450 is adjusted due to effects of carcinogens found in areca nut users, the fetus is also exposed to those damaging effects.⁵

Some pregnant women, especially Asian women, use betel nut during pregnancy in order to prevent morning sickness.⁶ As more Asians immigrate to Europe, European hospitals are faced with newborns who have possibly been prenatally exposed to betel nut.⁴ In Barcelona, Spain, one newborn was diagnosed with neonatal abstinence syndrome, which directly related to the mother's use of areca nut.⁷

Asia and the South

Significance of prenatal visits

Preconception care or prenatal care consists of interventions which make biomedical, behavioral, and social identifications and modifications concerning risks to a woman's health or pregnancy outcomes through prevention and management in order to maximize health outcomes.⁸ During pregnancy, women are highly motivated to stop chewing betel nut with or without tobacco. The biggest incentive is to protect their babies from exposure to the harmful effects of betel quid, especially tobacco and arecoline. Betel nut causes deleterious effects on fetuses of betel chewers,

and poor knowledge of these harmful effects contributes to the continued use of betel nut in pregnancy. Antenatal care visits are an ideal time for targeting this population, learning more about their attitudes and beliefs towards betel nut use in pregnancy, increasing their awareness about the harmful effects on a fetus, giving betel cessation advice, and persuading them to participate in a tobacco cessation intervention. This time is crucial for relevant, effective, and reliable health education.⁶ This study will allow for a better understanding of how pregnant users view their betel nut use and develop culturally appropriate tobacco cessation programs.⁹

Migration

According to several studies, immigration is linked to betel nut use and has a twofold impact on its use (Pinhey et al. 1992). Primarily, immigrants may use betel nut to retain a sense of cultural identity in a new country. Furthermore, immigrants introduce this habit to communities that they join. For example, Micronesian immigrants are responsible for introducing the use of betel nut to the Marshall Islands, Hawaii, and mainland United States.¹⁰⁻¹¹

This study is important as immigration to the U.S. from the Indian subcontinent, Micronesia and other countries continues to expand. Many of these people may bring with them their habit of betel use, so a large portion of this population may be at a significantly higher risk of several oral diseases and other adverse fetal outcomes. By adding items to the routine questionnaire and investigating how pregnant betel users perceive the risk of the use of various substances (e.g. betel nut, tobacco) and exposures, this study will provide important information for formulating behavioral interventions that improve self-management and oral health.¹²⁻¹⁵

Challenge in regulating betel nut use in Micronesia

Production of betel nut is a large source of income for some Pacific Island nations, as well as being used locally, so the control of tobacco chewing with betel nut presents a challenge. In

order to fully address the supply of betel nut, cooperation between departments such as the Ministry of Health in government will be required. An additional issue is the promotion of betel nut as a valuable commodity in some Pacific Island countries by the leaders.¹⁶

However, the greatest challenge to overcome is the social acceptability of betel nut use, so that demand will decrease. In order to implement effective demand-reduction policies, public education about the damaging effects of betel nut use will be necessary. Both governments and the general public have a responsibility to recognize the magnitude of the problems in their country, and to take action in different sectors to reduce betel nut consumption.¹⁷

1.9 SUMMARY AND PURPOSE OF THE STUDY

Use of areca nut is popular among pregnant women in many regions, particularly in southeast Asia. Social acceptability, religious beliefs, perceived health benefits, and addiction*⁴ contribute to popular betel nut*² use.

Arecoline is an alkaloid in areca nut which is genotoxic and cytotoxic through mechanisms which are oxidative stress dependent *in vitro* and *in vivo*.¹ Traditionally in the Pacific Islands, betel nut is chewed either alone or with slaked lime and/or tobacco.²

In Yap and Pohnpei, added tobacco is from cigarettes, which are sometimes dipped in vodka by children, and the tobacco is wrapped in fresh betel leaf. Areca nut use has significant associations with dependency syndrome. One study of dependency syndrome found a particularly high frequency with tobacco addition and cigarette smoking, which may be explained by the addictive potential of nicotine.³ The potential of areca nut as an addictive substance is confounded due to the frequent addition of tobacco.⁴

Craving*⁷ consists of a desire for a substance or activity, with a focus on desiring the effects of the substance and the avoidance of withdrawal symptoms.⁵ An important part of measuring betel quid*³ dependence is craving. Milgrom et al. found a significant positive association between the craving score and the frequency of tobacco use, adjusting for age of initiation, gender, and other substance use.⁶ Studies have found that arecoline causes a sense of well-being, euphoria, alertness, sweating, salivation, and a hot sensation in the body, which in combination can lead to tolerance*⁶ and dependency.

Betel nut negatively affects oral soft tissues, and can cause lichenoid lesions on buccal mucosa and at quid retained sites. Betel nut can cause submucosa fibrosis, and betel nut with tobacco can cause leukoplakia; both can be malignant and can progress to oral cancer*¹⁵. It is possible that areca nut use may protect against dental caries*^{10,7}. However it may also lead to loss of periodontal attachment and greater calculus formation.⁸

The use of betel nut during pregnancy can negatively affect a child, leading to neonatal withdrawal syndrome*¹⁶, preterm labor, low birth weight, meconium staining of amniotic fluid, anemia, miscarriage, and a reduced male newborn rate.⁹

In high doses, betel nut arrests endothelial cell differentiation, thus causing dysfunction. Betel quid use may result in a higher concentration of heavy metals (e.g. lead, arsenic, cadmium) which can harm the fetus.*¹

Betel nut use during pregnancy is perceived as reducing morning sickness improves gum condition and eliminates bad breath. Common reasons for chewing include reduction of boredom and anxiety, increased focus and attention at work, social facilitation, and digestive and dental health. It may be used an analgesic role in providing some relief from labor pains during delivery and relaxing the uterus during labor.

Limited information is present on mothers' chewing habits or perceptions of potential risks to their fetus. The information from such an investigation is crucial for improving antenatal public health interventions. During pregnancy, women are highly motivated to stop chewing betel nut with or without tobacco. The biggest incentive is to protect their babies from exposure to the harmful effects of betel quid, especially tobacco and arecoline. Because prenatal care is so essential, it is important that people be well informed about the harmful effects of betel nut use during pregnancy. Antenatal care visits are an ideal time for targeting this population to learn more about their attitudes, beliefs towards betel nut use in pregnancy, and for giving betel cessation advice and persuading them to participate in a tobacco cessation intervention.

The purpose of this study is to pilot test a short questionnaire, which will gain information on pregnant women's views on the risks associated with using betel nut, and to establish the questionnaire's internal consistency and form of validity, which will be done by relating it to the developed craving scale. A measure of validity comes from analysis of betel chewers vs. those who do not chew betel, and the relationship with the craving scale.

2. METHOD

Preliminary study about betel nut use during pregnancy

2.1 STUDY SETTING

This study was conducted at the Maternal and Child Health clinic of Pohnpei State Hospital in the Federated States of Micronesia (FSM). The Pohnpei State Government operates the hospital and several dispensaries in the outlying areas on Pohnpei proper and in the outer islands.

The study was conducted in English, the official language of Micronesia at the prenatal clinic.

2.2 SELECTION OF STUDY SUBJECTS

Potential subjects were approached by Dental Department staff members in May and July 2015 and asked to participate.

2.3 DATA SOURCE

Questionnaire related betel nut^{*2} use and pregnancy.

2.3.1 *Instrumentation*

- Demographic, smoking, tobacco, drugs and alcohol

The nurses can be asked for information on age, number of previous pregnancies, problems with pregnancies, use of other drugs, and other basic parameters.

- Betel nut use and tobacco use

The questionnaire asked for information on whether the participant had ever used betel, the age of their first use, the frequency of their use, how much/often they use betel nut, and whether they use it with tobacco.

- Pregnancy risk assessment

There were eight questions which assessed issues related to pregnancy: quality of pregnancy, time of first prenatal check-up, total number of pregnancies, total number of pregnancies which did not go to term, diseases during pregnancy, premature births, low birth weight births, and importance of prenatal clinic check-ups.

- Perceived health status

There were four questions which assessed self-perceived health status: quality of personal health, persistent feelings of sadness, worry impacting daily life, and health problems before pregnancy.

- Betel nut use

There were four questions which assessed betel nut use among pregnant women : age of initiation, last use of betel nut, frequency of betel nut use, form of betel nut used, and frequency of betel nut use with tobacco.

- Betel nut craving

The questionnaire included questions on craving*⁷, 15 true or false questions based on the craving scale developed by Milgrom et al.

- Perception of pregnant betel nut users regarding harm to fetus*¹

This questionnaire-adapted question on health beliefs related to smoking during pregnancy from the 2000 Haslam article, modifying them to relate to betel nut use. The

format of these questions was Likert-like, presenting a range of 5 choices, including “Strongly disagree” (1), “Disagree,” “Neither agree nor disagree,” “Agree,” and “Strongly agree” (5).

2.3.2 *Study participants*

The participants in this study were a convenience sample of 55 pregnant women in Pohnpei receiving prenatal care at Pohnpei State Hospital. Dental Department staff members confidentially administered the surveys in May and July 2015. Staff members and the participants speak and write English. Participation in the survey was voluntary.

2.3.3 *Criteria for eligibility/exclusion of cases*

Pregnant and attending the clinic. No exclusions.

2.4 DATA COLLECTION

2.4.1 *Source*

The data source is a survey of 55 in Pohnpei conducted in 2015. The study was conducted in Pohnpei (population 35,981) States, FSM.

Pohnpei is one of four states in the Federated States of Micronesia (FSM), which also includes Kosrae, Chuuk, and Yap. The principal island of Pohnpei state is Pohnpei. The nuts of “Pwuh” (betel nut*² plant/vernacular name of betel nut in Pohnpei state) are becoming an important cash crop in Pohnpei, and they are currently the most expensive agricultural product in Pohnpei’s markets. The use and cultivation of betel nut has begun in the last two decades. Betel nut is being exported from both States [Paulino YC]. Pohnpei has a population of about 34,500 people. According to a 1994 census estimate, each woman of childbearing age in Pohnpei has on average 4.3 children, as compared to 4.7 for all of FSM. The survey is part of an ongoing public

health program by the Dental Program of the Department of Public Health of the Prenatal Clinic and the Dental Services Department of Pohnpei State Hospital. The questionnaire will be completed in English at the prenatal clinic. The instructions read "This survey is about the use of betel nut during pregnancy. Please answer even if you don't use betel. Betel is thought to have both benefits and risks when used, and the Prenatal Clinic and the Dental Services Department of the Hospital are cooperating to learn more about this. Please do not put your name on the survey. All the information you provide is confidential and will not be part of your health records. This survey is voluntary and you do not have to participate if you don't want to. THANK YOU FOR YOUR PARTICIPATION." University researchers analyzed de-identified data. The University of Washington Institutional Review Board determined the study was exempt from IRB review.

2.4.2 Steps taken to assess and assure data quality

These participants will complete the questionnaire in English at the prenatal clinic. In order to ensure that the local staff is following protocol completely so that data is accurate, questionnaire administration will take place under the supervision of trained professionals. Questionnaire checking was done by researchers to ensure that only valid data was included in the study.

2.5 ANALYSIS PLAN

2.5.1 Hypothesis testing/generation

The purpose of this study is to pilot test a short questionnaire, which will gain information on pregnant women's views on the risks associated with using betel nut^{*2}, and to establish the questionnaire's internal consistency and a form of validity, which will be done by relating it to the developed craving^{*7} scale. Second, the study will explore pregnant women's assessment of the health risks associated with maternal betel nut use. This study also explored the relationship

between risk perception and previous adverse pregnancy outcomes, maternal age, previous pregnancies, self-perceived health status, prenatal care, gravidity*¹⁸, and parity*²².

2.5.2 *Statistical methods*

Independent samples t-test was used to find difference between the mean number of betel nut users who also used tobacco and those who did not use tobacco with their betel nut use in terms of their responses on the dependence symptom scale (craving scale). Spearman's rank correlation was used to test for a relationship between the dependence symptom scores and health risk beliefs assessment scores for betel nut users who used betel nut at some point in their lives. Spearman's rank correlation was used to test for a relationship between the dependence symptom scores and health risk beliefs assessment scores for betel nut users who used betel nut within the past 30 days. Chi-square test of association was used to test for association between the level of education of the respondents and their betel nut use (chewers or non-chewers) and to test for association between their betel nut use and whether they smoked or not during pregnancy, alcohol use, and substance abuse. One-Way ANOVA was used to test for a significant difference between mean craving scores of the most frequent users of tobacco with betel nut and those who never used tobacco with betel nut.

Data was collected with Excel spreadsheets, and analysis was completed with SPSS (version 19.0; SPSS Inc.).

3. RESULTS

Demographic characteristics of survey sample (Table 7)

Fifty-five patients in the antenatal care unit during the study period completed the survey. The median age was 22.5 years (interquartile range 20-27.8). The mean age was 23.2 ± 5.6 years. Out of all of the respondents who answered, 26 (48.1%) had received prenatal care before the third month of pregnancy, 14 (26.4%) had 3 or more pregnancies, 5.5% had experienced a miscarriage two or more times, and 9.1% had a baby with a low birth weight. Among women having who had delivered before, 12.7% (7) reported having a child born early, and 9.1% (5) reported having a low birth weight baby.

Some college education had been completed by 41.9% of the participants. High school had been completed by 37.2%, and elementary school had been completed by 20.9%. 80.4% of participants (45) had never smoked, whereas only 3.9% (2) were current smokers and 15.7% (8) had quit smoking. During pregnancy, 9.4% of participants had drunk alcohol, and 44.0% had used drugs (40.0% sakau and 4.0% marijuana).

Frequency distribution table for prevalence among users and non-users (Table 8)

Out of 55 participants, 20 participants (36.4%) had never used betel nut. The average age at which betel nut was first used was 16.18 ± 3.720 years, and the median age was 17 years. 5 (15.2%) had used betel nut by age 16. 5 (14.7%) had used betel at least once in the past month, 3 (8.8%) in the past week, 8.8 (3%) in the past two weeks, 9 (26.5%) longer than a month ago, and 7 (20.0%) had never used betel nut.

A current betel nut user was defined as a person who had last used betel nut within the past day, week, or two weeks. An ex-betel nut user was defined as a person who had last used

betel nut within the past month or over a month ago. A non-user was defined as a person who had never used betel nut.

Out of the 34 users who answered, 20 betel nut users (58.8 %) said they currently used betel nut. 1 (2.9 %) of 35 users who answered used betel nut nearly all of the time, 6 (17.1 %) used betel nut much of the time, 21 (60.0 %) used betel nut not much of the time, 7 (20%) never used betel nut. Four out of thirty four participants who answered (11.8 %) used betel nut alone. Only 4 of 34 (11.8%) current users who answered said that they did not use tobacco with betel nut and lime. Twenty out of thirty four (64.7%) used white unripe betel nut with tobacco from cigarettes, and 4 (11.8%) used white unripe betel with tobacco from cigarettes dipped in alcohol. Participants who added tobacco to their betel nut also added lime.

The perceived benefits, which prompted the pregnant women to chew

Out of the 37 people who chewed betel nut who responded to the question about whether chewing betel nut is able to reduce morning sickness or nausea, 13 people (35.1%) responded true and 24 people (64.9%) responded false. Out of the 38 people who chewed betel nut and responded to the question about whether chewing helps give them relief and relaxation when they are tensed or stressed, 19 people (50.0%) responded true and 19 people (50.0%) responded false. Out of the 38 people who chewed betel nut and responded to the question about whether it is safe for a new mom to chew betel nut after the birth of a child, 7 people (18.4%) responded true and 31 people (81.6%) responded false. Out of the 38 people who chewed betel nut, 16 people (42.1%) believed that chewing betel nut can help to prevent a smelly mouth or bad breath, while 22 people (57.9%) did not believe that chewing betel nut can help to prevent a smelly mouth or bad breath. Out of the 38 people who chewed betel nut, 16 people (42.1%) believed that chewing betel nut right now could help them not feel tired or to work for a longer time, and

19 people (57.9%) did not believe that chewing betel nut right now could help them not feel tired or to work for a longer time.

The relationship between the craving scale and belief about betel nut use

71.4% of the users who did not believe that chewing gives them relief and relaxation when they are tensed or stressed also disagreed or strongly disagreed that betel nut use after pregnancy is safe for the baby ($\chi^2 = 14.355, p < 0.05$). 73.1% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that a baby with a lower birth weight is likely to have health problems ($\chi^2 = 11.992, p < 0.05$). 88.9% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that betel nut use during pregnancy can lead to respiratory infections for the baby ($\chi^2 = 12.007, p < 0.05$). 83.3% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that encouragement should be given to pregnant women so that they stop chewing betel nut ($\chi^2 = 13.698, p < 0.05$). 88% of the users who did not believe that after the birth of a child, it is safe for a new mom to chew betel nut also agreed or strongly agreed that more help should be given to pregnant women who want stop chewing betel nut ($\chi^2 = 18.429, p < 0.05$). 69.23% of users who believed that chewing betel nut can help to prevent a smelly mouth or bad breath also strongly disagreed or disagreed that betel nut use after pregnancy is safe for the baby ($\chi^2 = 8.458, p < 0.05$). 61.5% of users who believed that chewing betel nut right now could help them to not feel tired or to work for a longer time also agreed or strongly agreed that lowering the betel nut use can lead to a lower risk of health problems for the baby ($\chi^2 = 11.287, p < 0.05$). 66.7% of users who did not believe that chewing betel nut right now could help them

to not feel tired or to work for a longer time also strongly disagreed or disagreed that betel nut use after pregnancy is safe for the baby ($\chi^2 = 13.660, p < 0.05$).

The relationship between the craving scale and belief about betel nut use

For these 12 items in health belief scale, in order to dichotomize each item, a positive response (agree or strongly agree, for all items except 2 and 12) was coded as a 1; otherwise, it was coded code as a 0. Therefore, the sum for the coded items resulted in a scale from 0 to 12. The maximum possible score was 12, with higher scores representing better health attitudes towards the health risks of betel nut use during pregnancy. Agreement with these items reflected an acceptance of the known health risks of betel nut use during pregnancy, and a perception that maternal chewing harms the health of the child. The scoring was reversed for 2 items: item 2 (It is easier to deliver smaller babies) and item 12 (Betel nut use after pregnancy is safe for the baby).

Participants' beliefs about using betel nut while pregnant were quantified based on the Haslam and Draper scales, which involve adding up the number of responses indicating agreement/disagreement. This analysis involved adding up the number of responses indicating agreement or strong agreement for statements 1-12. A higher score indicates more accurate health beliefs about using betel nut while pregnant, and the highest possible score was 12. The following table, Table 9, shows the percentage of participants that agreed or strongly agreed with each statement, as well as the score based on the Haslam and Draper scale.

Betel Nut Related Health Belief Scale: description of responses to each question:

Item number 1 revealed a strong bent towards agreement, with 35 of 48 participants who answered (72.9%) agreeing or strongly agreeing and 4 participants (8.3%) indicating strong disagreement. Of the 48 women enrolled in the study who answered, 14.6% (7) agreed to item

number 2 and 16.7% (8) strongly agreed. 22.9% (11) strongly disagreed that it is easier to deliver small babies, 35.4% (17) disagreed, and 10.4% (5) neither agreed nor disagreed. For item number 3, 29.8% (14) reported that they agreed that a baby with a lower birth weight is likely to have health problems, and 42.6% (20) strongly agreed, while 8.5% (4) neither agreed nor disagreed. 8.5% (4) said that they strongly disagreed with this statement, and 10.6% (5) disagreed. Overall, 23.4% of participants (11) who answered reported that they agreed with item number 4, and 48.9% (23) reported that they strongly agreed. 8.5% (4) neither agreed nor disagreed with the statement that betel nut use during pregnancy can lead to a premature birth, 2.1% (1) strongly disagreed, and 17.0% (8) disagreed. Approximately 10.9% (6) of participants indicated that they disagreed or strongly disagreed with the statement that betel nut use during pregnancy can lead to respiratory infections for the baby, whereas 35.4% (17) agreed, 50.0% (24) strongly agreed, and 2.1% (1) neither agreed nor disagreed. More participants strongly agreed 50.0% (24) than agreed 22.9% (11) to the statement that betel nut use during pregnancy can lead to problems with the child's growth and development until the age of ten. For the same question, 10.4% (5) neither agreed nor disagreed, 6.3% (3) strongly disagreed, and 10.4% (5) disagreed. Out the 48 participants who answered, 18.8% (9) strongly agreed, 27.1% (13) disagreed, 14.6% (7) neither agreed nor disagreed, 18.8% (9) agreed, and 20.8% (10) strongly agreed that the betel nut use by other people in the house during pregnancy can lead to health problems for the baby. 29.2% (14) agreed and 45.8% (22) strongly agreed that betel nut use during pregnancy can lead to a change in the child's IQ. 12.5% (6) neither agreed nor disagreed to the statement, while 6.3% (3) disagreed and 6.3% (3) strongly disagreed. Regarding the statement that encouragement should be given to pregnant women so that they stop chewing betel nut, 27.3% (12) agreed, 4.5% (2) strongly agreed, 6.8% (3) were neutral, while 9.1% (4)

disagreed and 4.5% (2) strongly disagreed. 52.3% of participants (23) strongly agreed and 27.3% (12) agreed that more help should be given to pregnant women who want to stop chewing betel nut, 11.4% (5) disagreed, while 9.1% (4) participants neither agreed nor disagreed. Of the 55 women enrolled in the study at Pohnpei State Hospital, 31.8% (14) agreed to item number 11 and 38.6% (17) strongly agreed. 6.8% (3) strongly disagreed that it is easier to deliver small babies, 13.6% (6) disagreed, and 9.1% (4) neither agreed nor disagreed. About 15.6% of participants (7) reported that they agreed and 20.0% (9) reported that they strongly agreed with the statement that betel nut use after pregnancy is safe for the baby. 8.9% (4) neither agreed nor disagreed with the statement that betel nut use during pregnancy can lead to a premature birth, 28.9% (13) strongly disagreed, and 26.7% (12) disagreed.

Reliability of Health Belief Scale

The internal consistency of the health risk belief scale was assessed with a Cronbach Alpha test.

The internal consistency of scale was high (Cronbach $\alpha=0.82$, 95% CI 0.73 to 0.90).

Participants responded to these 12 statements in the questionnaire concerning using betel nut while pregnant. The following table, Table 10, shows the percentage of participants that agreed or strongly agreed with each statement.

Craving scale

The questionnaire included 14 true/false questions and one frequency question based on a craving scale adapted from a study by Milgrom et al. on adolescents. The craving scale includes the assumption that using quid with tobacco from cigarettes, regardless of alcohol content, would result in higher craving. The scale had a range from 0 to 15, based on summing the 15 items, and a higher score indicated higher craving. Out of 31 betel uses, 25 respondents who used betel nut lime and tobacco had higher craving scores than the 2 people who used betel nut alone.

The mean (\pm SD) dependence symptom score among people who used betel nut with lime and tobacco was 8.25 ± 3.854 versus 6 ± 2.828 among those who used betel alone [$t(22)=-0.800$, $p = 0.432$].

Reliability of the craving scale

Out of 55 people, the internal consistency of the craving scale was Cronbach $\alpha=0.84$, 95% CI 0.79 to 0.88. It was high. The mean (\pm SD) dependence symptom score among people who used betel nut with lime and tobacco was 8.25 ± 3.854 versus 6 ± 2.828 among those who used betel alone [$t(22)=-0.800$, $p = 0.432$].

*The relationship between the craving*⁷ score and the health risk beliefs*

The relationship between the craving score and the health risk beliefs was investigated using Spearman rank correlation. Spearman's correlation coefficient was calculated ($\rho S = -0.261$) and it was not significant ($p > 0.05$). No relationship was found between the craving score and the health risk belief assessment score.

Note that there is a stronger relationship between the craving score and the health risk belief assessment score for the people who used betel nut within the past 30 days than between the craving score and the health risk belief assessment score for the people who ever used betel nut at some point in their life.

4. DISCUSSION

4.1 RESULTS

The beliefs which prompted the pregnant women to chew are: to reduce morning sickness/nausea 13(35.1%), for relief and relaxation 19 (50.0%), to avoid having a smelly mouth 16 (42.1%), and to prevent them from feeling tired or to work for a longer time 16(42.1%). About 7 of the people who responded to this question 18.4% felt that it was safe for a new mother to chew betel after the baby's birth.

The reasons for chewing during pregnancy were similar to those found by Senn et al., and the main reason was for the perceived benefits against nausea. As in that study 28% of participants perceived that betel nut could control morning sickness, this therapeutic use, which has been described by Nelson and Heischober in 1999, may be a significant determinant of chewing behavior for this population. Other major reasons in this study for chewing during pregnancy were the habit of chewing(20%) and being addicted (10%).¹

Because smoking can be protective against the morning sickness of pregnancy, the effects attributed to betel in this respect may derive from use with tobacco (Chortatos, Haugen, Iversen, Vikanes, & Velerød, 2013). However, this has not yet been studied with the loose tobacco used in betel quid.

Many studies have discussed the adverse pregnancy outcomes resulting from betel nut use (Chue, Carrara, Paw 2012; Grant, J., & Cardarelli, 2014). Animal data suggests that betel nut is teratogenic.²⁻³ It is urgent that further research be completed in order to develop more effective betel nut intervention programs. For the development of appropriate strategies targeting the Micronesian population, there must be identification and evaluation of the epidemiological evidence regarding the major socio-cultural determinants of betel nut use during pregnancy, as

well as of cessation factors, with or without tobacco and during or after pregnancy. In addition, more data should be collected from other Federated States of Micronesia. For example, there are current plans for the collection of data in Kosrae later in 2015. One possible next step is the collection of samples tied to birth records, examining pregnancy outcomes more thoroughly. Future studies should also involve adolescents or parents who are introducing betel to young children.

Although there was no significant relationship between craving scale and health risk belief assessment score for both, users who used betel nut within the past 30 days and users who had ever used betel nut, a weak negative trend was noticed between the craving scale and the Betel Nut Related Health Risk Belief Assessment Scale. Although caution should be taken due to the non-significant Spearman's correlation coefficient, a negative Spearman's correlation coefficient indicates that people who are more likely crave betel nut tend to be less likely to perceive health risks.

One strength of this survey is that, as suggested by Chue et al., it includes questions on the type of areca nut used (i.e. ripe or unripe), the estimated number of nuts per day, and the contents of the quid (e.g. tobacco, and lime).⁴ Another strength is the use of a craving scale adapted from Milgrom et al. (2014), based on the US National Survey of Drug Use and Health and adapted for the collection of information about betel nut. This standardized questionnaire has gone through psychometric validation.

A limitation of the study is that the dataset was small (55). The greatest problem with a small study is that in the interpretation of results, false-positives may be produced or the magnitude of an association may be overestimated.⁵ Another limitation is that, although this self-reporting questionnaire was well-designed and validated, it is possible that some betel users were

erroneously classified as non-smokers, due to the tendency of pregnant women to underreport their tobacco use.⁶ Similarly, some betel users may have been classified as non-users. This type of misclassification may lead to the results being biased. In addition, because a convenience sample was used, the data may not be representative of the entire pregnant population of Pohnpei. There is a chance that certain types of participants were overrepresented at Pohnpei State Hospital, and other types were underrepresented. Some trends in the sample were identified, but the results of the study could not be generalized.

4.2 CONCLUSIONS

The beliefs which prompted the pregnant women to chew were: to reduce morning sickness/nausea), for relief and relaxation, to avoid having a smelly mouth, and to help prevent them from feeling tired or to work for a longer time. The majority of the users who did not believe in the relaxing effects of betel nut use also did not believe that betel use is safe after pregnancy. The majority of the users who did not believe in the relaxing properties of betel nut also did not believe that its use was safe for the baby after pregnancy. However, this consistency in responses did not hold throughout the questionnaire, as the majority of users who believed that chewing betel nut can help to prevent a smelly mouth or bad breath also did not believe that betel nut use after pregnancy is safe for the baby. On the same note, the majority of users who did not believe that it was safe to use betel nut after pregnancy also strongly agreed that encouragement should be given to pregnant women so that they stop chewing betel nut. Also, the majority of the users who believed that it was harmful to the baby to use betel nut after pregnancy also believed that more help should be given to pregnant women who want to stop chewing betel nut.

Dependence was observed in pregnant betel users who also chewed tobacco versus those who

used betel nut alone. There was no significant relationship found between the craving scale and the health risk belief assessment scale using Spearman's rank correlation, for both users who had ever used betel ($\rho = -0.240$, $p = 0.238$) and for those who had used betel within the past 30 days ($\rho = -0.394$, $p = 0.085$). Betel nut Related Health Belief Scale and craving scale were 80% reliable and had high internal consistency, and the items in the questionnaire were well inter-correlated. There was no significant relationship found between the craving scale and the health risk belief assessment scale for both, users who had ever used betel ($\rho = -0.240$, $p = 0.238$) and who used betel within the past 30 days using Spearman's rank correlation ($\rho = -0.394$, $p = 0.085$).

5. SYSTEMATIC REVIEW ON PREGNANCY AND BETEL NUT

For the systematic review, we searched PubMed for eligible case studies. A systematic review of the literature was completed in order to determine the current findings regarding the maternal risk perception of betel users and in order to highlight gaps in previous research. Relevant publications in the field were also used in order to screen their references for other potential studies. The keywords in the electronic search in PubMed were: “betel nut*²,” “chewing betel nut,” “betel quid*³,” “pan masala,” “pregnancy,” “adverse health effects,” “arecoline,” and “adverse birth outcome.” Electronic and hand searching of relevant journals from 1984 to 2015 was performed in order to identify relevant publications. There were two stages to the review of the articles; the title and abstract were reviewed in the first stage, and an in-depth study of the entire text was conducted in the second stage. Cohort studies, either prospective or retrospective, or case-control, randomized control trial, case reports were included. The systematic review of the literature determined pooled estimates of maternal and fetal risks associated with betel nut. Fetal outcomes included low birth weight, spontaneous abortions, meconium staining of the placenta, inhibited endothelial growth, and fetotoxic effects. The perceived benefits of betel nut by pregnant users included alleviating bad breath, nausea*²⁰, and vomiting*²¹, and aiding in digestion. “Betel nut chewing and pregnancy” by Taufan was excluded from this search, as the paper was not available through the HSL library. In total, 10 studies were chosen to be included. Another study, “Evaluation of the effect of betel nut use during pregnancy in the commonwealth of the Northern Mariana Islands” and “Sister chromatid exchanges in betel and tobacco chewers” had only the abstract included, and the text was not accessible. Because of a dearth of literature specifically on pregnancy and betel nut in Micronesian countries, literature studying pregnancy

and betel nut in different settings was reviewed and the insights gained from them will be transferred to our study.

Authors	Product	Setting	Study design	Sample size	Outcome	Results	Reference
García-Algar et al.	Arecoline (alkaloid in betel nut)	Asian mothers in Meconium Project at the Hospital del Mar in Barcelona Spain	Clinical observational study	6 newborns	Examine fetal exposure to arecoline in the placenta	Two of the six exposed newborns had adverse birth outcomes, both of which had: <ul style="list-style-type: none"> - Risk factors other than betel nut use excluded from material records - Inconclusive neonatal brain ultrasonography - Focal inflammatory changes in the amniochorial membranes In a third case, the fetal surface villi vessels had a decreased median diameter in both mother and fetus* ¹	1
Senn et al.	Betel nut	Alexishafen Health Centre (Madang Province)	Cross-sectional survey	310 pregnant women	Examine betel nut use and possible impact on pregnancy	The most common reasons for betel nut use among pregnant women are: <ul style="list-style-type: none"> - Preventing morning sickness (28%) - Preventing a smelly mouth (26%) - Habit (20%) - Addiction*⁴ (10%) Birth weight reduction was impacted by: <ul style="list-style-type: none"> - Primigravidity (467 g (p < 0.001)) 	2

						<ul style="list-style-type: none"> - Betel nut chewing (238 g (p = 0.02)) - Low BMI (175 g (p = 0.005)) <p>80% of participants did not think betel nut use would affect the fetus</p>	
Chue et al.	Betel nut	Antenatal clinics Thai-Myanmar border	Retrospective cohort analysis	7,685 women	Examine effects of betel nut use among pregnant women	Use of betel nut in a leaf with lime without tobacco was most common among older multigravida women. This study did not find adverse pregnancy effects among betel nut users as compared to non-users. A dose-related effect on miscarriage was found with smoking, but not betel nut use.	3
Grant et al.	Betel quid	Commonwealth of the Northern Mariana Islands	Retrospective chart review	All 2009 deliveries in the Commonwealth of the Northern Mariana Islands	Examine relationship between betel nut use and preterm birth or meconium staining of amniotic fluid	<p>Compared to non-users, betel nut users had:</p> <ul style="list-style-type: none"> - Twice the risk of preterm birth - Increased risk of meconium staining <p>However, these findings were not statistically significant, and the effects of betel nut use during pregnancy were not conclusive.</p>	4
Yang et al.	Betel quid	Aboriginal women in	Crossectional	62 women with adverse	Examine prevalence of	Compared to non-chewers, betel quid chewers had 2.8	5

		southern Taiwan		pregnancy outcomes and 124 age-matched women	substance use among pregnant aborigine women, and examine extent of adverse effects of betel quid chewing on pregnancy outcomes	times the risk of adverse pregnancy outcomes. This finding was adjusted for material illness and number of previous pregnancies.	
Kuo FC et al.	Betel quid	Taiwan	Crossectional	Human umbilical arteries and veins from healthy parturient patients after full-term pregnancy	Examine effects of arecoline on tone of umbilical arteries and veins, eNOS expression, and proliferation of human umbilical vein endothelial cells (HUVECs)	<p>Arecoline:</p> <ul style="list-style-type: none"> - Decreases vascular tone, in part mediated by NO - In higher doses, inhibits endothelial cell growth (thus in the long-term or with high doses inducing endothelial dysfunction and associated diseases) 	6
Ghosh et al.	Betel quid	India	Incidence study	129 pregnant women	Examine effect of betel nut use on sister-chromatid exchange	<p>Among betel users, SCE was higher among pregnant women and women using oral contraceptives than other women</p> <ul style="list-style-type: none"> - Pregnant women: 	7

					(SCE) frequency in lymphocyte chromosomes	11.79 ± 0.38 - Women using oral contraceptives 12.51 ± 0.44 - Other women: 6.28 ± 0.21	
Chou et al.	Betel quid	Aboriginal women in 11 hospitals in Taiwan	Cross-sectional survey	901 aboriginal women	Examine association between betel quid chewing and morning sickness among Taiwanese aboriginal women	Findings showed a significant association between betel quid chewing and morning sickness.	8
De Costa et al.	Betel nut	Papua New Guinean	Case report	400 women antenatal records	Examine pregnant betel users' labor, baby's condition at birth, and baby's condition in the post-natal period	Findings showed significantly: - Higher mean birth-weight for control group - Lower incidence of neonatal jaundice for study group	9
Sinha et al.	Arecoline	New Delhi, India	Randomized controlled trial	6 animal fetuses	Examine effectiveness of inducing fetal mouse blood micronuclei after trans	Different doses of arecoline to fetuses in utero during late pregnancy resulted in a significant increase in micronucleated polychromatic erythrocytes in the blood	10

					placental exposure in late pregnancy		
Sinha et al.	Betel nut powder	New Delhi, India	Control group study	20 animal fetuses (pregnancy outcome and fetus development) 43 animal fetuses (skeletally malformed fetuses)	Examine fetotoxic potential of betel nut on Swiss albino mice	<ul style="list-style-type: none"> - Adverse effect on fetal weight - No major morphological, visceral, and skeletal defects, other than hematomas, curved tails, and rib anomalies - Dose-related decrease in number of fetuses with ossified coccygeal vertebrae, and increase in number of fetuses with unossified 5th metacarpals - Delay in skeletal maturity, especially with prenatal exposure to unprocessed betel nut extract 	11
Yang et al.	Betel quid	Eastern Taiwan	Case control	229 women	Examine betel quid use among pregnant aboriginal	Adjusted for material age, five times higher risk of adverse birth outcome for betel quid chewing women compared to non-users.	12

					women and risk of adverse effects on birth outcomes in eastern Taiwan		
Angeles López-Vilchez et.al	Betel nut	Hospital Universities del Mar, Spain	Case report	1 newborn	Report case of neonatal withdrawal syndrome* ¹⁶ in infant born to chronic betel nut user	<ul style="list-style-type: none"> - Female newborn - Eutocic delivery at 38 weeks of gestation - Irritability and hypertonia 48 hours after delivery - Brownish-red discoloration of mother's oral mucosa and tongue - Mother a chronic betel chewer even during pregnancy - 0.012 µg/g of arecoline placental tissue - Diagnosis of neonatal abstinence syndrome from maternal use of betel nut 	13

Table 1-a Summary of previous studies that assessed the effect of betel nut on maternal and perinatal outcome

*See glossary

6. GLOSSARY OF TERMS* USED IN THESIS

<i>Term*</i>	<i>Definition</i>
1. Fetus	An unborn offspring, from the embryo stage in the end of the eighth week after conception to birth (MedicineNet, 2012)
2. Betel nut	Betel nut is an areca seed wrapped in a leaf of a betel tree
3. Betel quid	Betel quid is composed of the following ingredients: unripe nut (white variety), betel leaf, lime, tobacco from cigarette, and sometimes alcohol
4. Addiction	State of being unable to consistently abstain, being impaired in behavior control, having cravings, being less able to recognize problems in behaviors and relationships, and having a dysfunctional emotional response (ASAM)
5. Psychoactive	Quality of substances which affect mental processes (e.g. cognition, affect) (WHO, 2015)
6. Tolerance	Ability to endure large doses of a poison or toxin (Farlex Medical Dictionary, 2012)
7. Craving	Broadly, the desire to use a substance (e.g. alcohol, drugs, betel nut, nicotine), which increases the likelihood of using that substance (Stalcup SA et al.,2006)
8. Betel quid induced lesion	Localized lesion of oral mucosa at regular site of quid placement (Sylvie Louise Avon Avon SL,2004)
9. Betel quid lichenoid reaction	Lichenoid lesions at site of quid placement, mainly on buccal mucosa or tongue (Daftary DK, Bhonsle,1980)
10. Caries	Tooth decay
11. Gingivitis	Gum disease with inflammation, redness, swelling, and often bleeding during brushing
12. Periodontal condition	Chronic inflammatory disease that destroys bone and gum tissues supporting the teeth (WebMD)
13. Oral lichen planus	Chronic, autoimmune, mucocutaneous (skin and mucous membrane), affects oral mucosa (Ismail, 2007)
14. Oral leukoplakia	Predominantly white patch or plaque on oral mucosa without other clinical or pathological classification and without association with any physical or chemical agent other than tobacco (Axell T, Holmstrup P, 1984)
15. Oral cancer	Formation of malignant cells (cancer) in the lips or mouth (PubMed)
16. Neonatal withdrawal syndrome	Withdrawal symptoms developing shortly after birth due to the mother's dependence on drugs during pregnancy, in which symptoms include loud, high-pitched crying, sweating, yawning, and gastrointestinal disturbance (PubMed)
17. Dependence syndrome	Cluster of physiological, behavioral, and cognitive phenomena involving the prioritization of substance use over other behaviors of previously great value (Chu NS et al., 2002)

18. Gravidity	The number of pregnancies
19. Teratogenic effect	Developmental anomalies or defects because of teratogenic exposure during the time of fetal development (Mosby, 2008)
20. Nausea	Uneasiness of the stomach which often precedes vomiting (WebMD, 2015)
21. Vomiting	Forcible emptying of the stomach through the mouth, whether voluntary or involuntary (WebMD, 2015)
22. Parity	The number of times having given birth to a fetus of age 24 weeks or greater, whether or not the child was born alive

BIBLIOGRAPHY

1.1 Overview of betel nut

1. Gupta, P. C., & Warnakulasuriya, S. (2002). Global epidemiology of areca nut usage. *Addiction biology*, 7(1), 77-83.
2. Paulino, Y. C., Novotny, R., Miller, M. J., & Murphy, S. P. (2011). Areca (betel) nut chewing practices in Micronesian Populations. *Hawaii journal of public health*, 3(1), 19.
3. Croucher, R., & Islam, S. (2002). Socio-economic aspects of betel nut use. *Addiction biology*, 7(1), 139-146.
4. Summers, R. M., Williams, S. A., & Curzon, M. E. (1994). The use of tobacco and betel quid ('pan') among Bangladeshi women in West Yorkshire. *Community dental health*, 11(1), 12-16.
5. Watson, P. (1991). Does abundant supply of drugs lead to heavy consumption? A Papua New Guinea case study. *International Journal on Drug Policy*, 2(4), 11-12.
6. Islam, S., Croucher, R., & O'Farrell, M. (1996). Paan ingredients trade in London boroughs of Tower Hamlets and Newham. *A summary report of an investigation*. London.
7. Winstock, A. R., Trivedy, C. R., Warnakulasuriya, K. A. A. S., & Peters, T. J. (2000). A dependency syndrome related to areca nut use: some medical and psychological aspects among areca nut users in the Gujarat community in the UK. *Addiction Biology*, 5(2), 173-179.
8. Winstock, A. (2002). Areca nut-abuse liability, dependence and public health. *Addiction biology*, 7(1), 133-138.
9. Paulino, Y. C. (2009). *Describing and measuring variability of Areca catechu (betel nut) chewing in Micronesian populations in Guam*. University of Hawaii at Manoa.
10. Brownrigg, H. (1992). Social and Ceremonial use of betel quid. In H. Brownrigg *Betel Cutters* (p. 25). London: Thames and Hudson.
11. Pobutsky, A. M., & Neri, E. I. (2012). Betel Nut Chewing in Hawai 'i: Is it Becoming a Public Health Problem? Historical and Socio-Cultural Considerations. *Hawai'i journal of medicine & public health: a journal of Asia Pacific Medicine & Public Health*, 71(1), 23.
12. Bhandary, S., & Bhandary, P. (2003). Cancer of the oral cavity-a growing concern in the Micronesia: a case report from the Marshall Islands. *Pacific health dialog*, 10, 76-78.
13. Personal communication: John Ishoda, Hawaii State Department of Health, Bi-lingual Health Services, Marshallese translator Personal communication: John Ishoda, Hawaii State Department of Health, Bi-lingual Health Services, Marshallese translator.
14. Pobutsky, A. M., & Neri, E. I. (2012). Betel Nut Chewing in Hawai 'i: Is it Becoming a Public Health Problem? Historical and Socio-Cultural Considerations. *Hawai'i journal of medicine & public health: a journal of Asia Pacific Medicine & Public Health*, 71(1), 23.
15. Strickland, S. S. (2002). Anthropological perspectives on use of the areca nut. *Addiction biology*, 7(1), 85-97.

16. Williams, S., Malik, A., Chowdhury, S., & Chauhan, S. (2002). Sociocultural aspects of areca nut use. *Addiction biology*, 7(1), 147-154.
17. Brownrigg, H. (1992). Social and Ceremonial use of betel quid. In H. Brownrigg *Betel Cutters* (p. 25). London: Thames and Hudson.
18. Villaverde, R. (2011). Betelnut: Mama'on. Retrieved July 31, 2015 from <http://ns.gov.gu/pugua.html>
19. Strickland, S. S. (2002). Anthropological perspectives on use of the areca nut. *Addiction biology*, 7(1), 85-97.
20. Brownrigg, H. (1992). Social and Ceremonial use of betel quid. In H. Brownrigg *Betel Cutters* (p. 25). London: Thames and Hudson
21. Strickland, S. S. (2002). Anthropological perspectives on use of the areca nut. *Addiction biology*, 7(1), 85-97.
22. Williams, S., Malik, A., Chowdhury, S., & Chauhan, S. (2002). Sociocultural aspects of areca nut use. *Addiction biology*, 7(1), 147-154.
23. Croucher, R., & Islam, S. (2002). Socio-economic aspects of areca nut use. *Addiction biology*, 7(1), 139-146.
24. Auluck, A., Hislop, G., Poh, C., Zhang, L., & Rosin, M. P. (2009). Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening. *Rural and remote health*, 9(2), 1118.
25. Williams, S. A. (1995). Betel-quid chewing: a community perspective. *Betel-quid chewing among Bangladeshi community in the United Kingdom*. London: Centre for Transcultural Oral Health, 11-25.
26. Chandra, P. S., Carey, M. P., Carey, K. B., & Jairam, K. R. (2003). Prevalence and correlates of areca nut use among psychiatric patients in India. *Drug and alcohol dependence*, 69(3), 311-316.
27. Núñez-de la Mora, A., Jesmin, F., & Bentley, G. R. (2007). Betel nut use among first and second generation Bangladeshi women in London, UK. *Journal of Immigrant and Minority Health*, 9(4), 299-306.
28. Mehta, F. S., & National Institutes of Health. (1971). *Report on investigations of oral cancer and precancerous conditions in Indian rural populations, 1966-1969*. Munksgaard.
29. Schonland, M. A. R. Y., & Bradshaw, E. V. E. L. Y. N. (1969). Upper alimentary tract cancer in Natal Indians with special reference to the betel-chewing habit. *British journal of cancer*, 23(4), 670.
30. Strickland, S. S., Veena, G. V., Houghton, P. J., Stanford, S. C., & Kurpad, A. V. (2003). Areca nut, energy metabolism and hunger in Asian men. *Annals of human biology*, 30(1), 26-52.
31. Douglas, M. T., Pietrusewsky, M., & Ikehara-Quebral, R. M. (1997). Skeletal biology of Apurguan: A precontact Chamorro site on Guam. *American Journal of Physical Anthropology*, 104(3), 291-313.
32. Pietrusewsky, M., Douglas, M. T., & Ikehara-Quebral, R. M. (1997). An assessment of health and disease in the prehistoric inhabitants of the Mariana Islands. *American Journal of Physical Anthropology*, 104(3), 315-342.
33. Howden, G. F. (1983). The cariostatic effect of betel nut chewing. *Papua and New Guinea medical journal*, 27(3-4), 123-131.

34. Möller, I. J., Pindborg, J. J., & Effendi, I. (1977). The relation between betel chewing and dental caries. *European Journal of Oral Sciences*, 85(1), 64-70.
35. Paulino, Y. C., Novotny, R., Miller, M. J., & Murphy, S. P. (2011). Areca (betel) nut chewing practices in Micronesian Populations. *Hawaii journal of public health*, 3(1), 19.
36. WHO. (2012). Review of Areca (Betel) Nut and Tobacco Use in the Pacific: A Technical Report. Retrieved July 31, 2015 from <http://www.wpro.who.int/tobacco/documents/betelnut.pdf>

Table References

1. Gupta, P. C. (1996). Survey of sociodemographic characteristics of tobacco use among 99,598 individuals in Bombay, India using handheld computers. *Tobacco control*, 5(2), 114-120.
2. NA, J., & SH, Z. (1976). Carcinoma of the oral cavity and oropharynx in Karachi (Pakistan). An appraisal. *Tropical doctor*, 6(2), 63-67.
3. Warnakulasuriya, K. A. A. S. (1992). Smoking and chewing habits in Sri Lanka: implications for oral cancer and precancer. In *International Symposium on Control of Tobacco-Related Cancers and Other Diseases*. Oxford University Press: Bombay (pp. 113-118).
4. Reichart, P. A., Mohr, U., Srisuwan, S., Geerlings, H., Theetranont, C., & Kangwanpong, T. (1987). Precancerous and other oral mucosal lesions related to chewing, smoking and drinking habits in Thailand. *Community dentistry and oral epidemiology*, 15(3), 152-160.
5. Chen, J. W., & Shaw, J. H. (1996). A study on betel quid chewing behavior among Kaohsiung residents aged 15 years and above. *Journal of oral pathology & medicine*, 25(3), 140-143.
6. Strickland, S. S., & Duffield, A. E. (1997). Anthropometric status and resting metabolic rate in users of the areca nut and smokers of tobacco in rural Sarawak. *Annals of human biology*, 24(5), 453-474.
7. Ikeda, N., Handa, Y., Khim, S. P., Durward, C., Axéll, T., Mizuno, T., ... & Kawai, T. (1995). Prevalence study of oral mucosal lesions in a selected Cambodian population. *Community dentistry and oral epidemiology*, 23(1), 49-54.
8. Tang, J. G., Jian, X. F., Gao, M. L., Ling, T. Y., & Zhang, K. H. (1997). Epidemiological survey of oral submucous fibrosis in Xiangtan City, Hunan Province, China. *Community dentistry and oral epidemiology*, 25(2), 177-180.

1.2 Tobacco and betel nut

1. WHO. (2012). *Review of Areca (Betel) Nut and Tobacco Use in the Pacific: A Technical Report*. Retrieved July 31, 2015 from <http://www.wpro.who.int/tobacco/documents/betelnut.pdf>
2. Hatsukami, D. K., & Severson, H. H. (1999). Oral spit tobacco: addiction, prevention and treatment. *Nicotine & Tobacco Research*, 1(1), 21-44.
3. Milgrom, P., Tut, O. K., Gilmatam, J., Gallen, M., & Chi, D. L. (2013). Betel use among adolescents in Yap and Pohnpei, the Federated States of Micronesia. *Harm reduction journal*, 10(1), 26.

4. Henningfield, J. E., Fant, R. V., & Tomar, S. L. (1997). Smokeless tobacco: an addicting drug. *Advances in dental research*, 11(3), 330-335.
5. Kumar, K. (1989). *Conducting key informant interviews in developing countries*. Washington DC: Agency for International Development.
6. Ysaol, J., Chilton, J. I., & Callaghan, P. (1996). A survey of betel nut chewing in Palau. *ISLA: A Journal of Micronesian Studies*, 4(1), 244-255.
7. Hancock, W. T., Durand, A. M., Yolwa, A., Sagury, J., Legthar, C., Ratima, M., ... & Maskarinec, G. G. (2007). Ulithi Atoll health assessment: a peek at the health of rural Micronesia. *Pacific health dialog*, 14, 156-164.

1.3 Betel nut dependency and addiction

1. Benegal, V., Rajkumar, R. P., & Muralidharan, K. (2008). Does areca nut use lead to dependence?. *Drug and alcohol dependence*, 97(1), 114-121.
2. Mirza, S. S., Shafique, K., Vart, P., & Arain, M. I. (2011). Areca nut chewing and dependency syndrome: is the dependence comparable to smoking? a cross sectional study. *Subst Abuse Treat Prev Policy*, 6, 23.
3. Mirza, S. S., Shafique, K., Vart, P., & Arain, M. I. (2011). Areca nut chewing and dependency syndrome: is the dependence comparable to smoking? a cross sectional study. *Subst Abuse Treat Prev Policy*, 6, 23.
4. Sachs-Ericsson, N., Collins, N., Schmidt, B., & Zvolensky, M. (2011). Older adults and smoking: Characteristics, nicotine dependence and prevalence of DSM-IV 12-month disorders. *Aging & mental health*, 15(1), 132-141.
5. McKenzie, M., Olsson, C. A., Jorm, A. F., Romaniuk, H., & Patton, G. C. (2010). Association of adolescent symptoms of depression and anxiety with daily smoking and nicotine dependence in young adulthood: findings from a 10-year longitudinal study. *Addiction*, 105(9), 1652-1659.
6. Hatsukami, D. K., & Severson, H. H. (1999). Oral spit tobacco: addiction, prevention and treatment. *Nicotine & Tobacco Research*, 1(1), 21-44.
7. Milgrom, P., Tut, O. K., Gilmatam, J., Gallen, M., & Chi, D. L. (2013). Betel use among adolescents in Yap and Pohnpei, the Federated States of Micronesia. *Harm reduction journal*, 10(1), 26.
8. Henningfield, J. E., Fant, R. V., & Tomar, S. L. (1997). Smokeless tobacco: an addicting drug. *Advances in dental research*, 11(3), 330-335.
9. Herzog, T. A., Murphy, K. L., Little, M. A., Suguitan, G. S., Pokhrel, P., & Kawamoto, C. T. (2014). The Betel Quid Dependence Scale: replication and extension in a Guamanian sample. *Drug and alcohol dependence*, 138, 154-160.
10. Milgrom, P., Ohnmar, K. T. & Gallen, M. (2015). Dependence Symptoms With Betel Nut And Betel Nut With Tobacco Among Micronesian Youth. *Unpublished manuscript, University of Washington, Seattle, WA*.
11. Chien-Hung Lee, Albert Min-Shan Ko, Cheng-Fang Yen, (2012). Betel-quid dependence and oral potentially malignant disorders in six Asian countries. *The British Journal of Psychiatry*, 201 (5), 383-391.
12. Tiffany, S. T., & Wray, J. M. (2012). The clinical significance of drug craving. *Annals of the New York Academy of Sciences*, 1248(1), 1-17.

13. Heishman, S. J., Singleton, E. G., & Moolchan, E. T. (2003). Tobacco Craving Questionnaire: reliability and validity of a new multifactorial instrument. *Nicotine & Tobacco Research*, 5(5), 645-654.
14. WHO. (2012). *Review of Areca (Betel) Nut and Tobacco Use in the Pacific: A Technical Report*. Retrieved July 31, 2015 from <http://www.wpro.who.int/tobacco/documents/betelnut.pdf>
15. Tiffany, S. T., & Wray, J. M. (2012). The clinical significance of drug craving. *Annals of the New York Academy of Sciences*, 1248(1), 1-17.

1.4 Oral health effect of betel nut

1. Anand, R., Dhingra, C., Prasad, S., & Menon, I. (2014). Betel nut chewing and its deleterious effects on oral cavity. *Journal of cancer research and therapeutics*, 10(3), 499.
2. Parmar, G., Sangwan, P., Vashi, P., Kulkarni, P., & Kumar, S. (2008). Effect of chewing a mixture of areca nut and tobacco on periodontal tissues and oral hygiene status. *Journal of oral science*, 50(1), 57-62.
3. Ling, L. J., Hung, S. L., Tseng, S. C., Chen, Y. T., Chi, L. Y., Wu, K. M., & Lai, Y. L. (2001). Association between betel quid chewing, periodontal status and periodontal pathogens. *Oral microbiology and immunology*, 16(6), 364-369.
4. Tanwir, F., Altamash, M., & Gustafsson, A. (2007). Influence of betel nut chewing, dental care habits and attitudes on perceived oral health among adult Pakistanis. *Oral health & preventive dentistry*, 6(2), 89-94.
5. Schamschula, R. G., Adkins, B. L., Barmes, D. E., & Charlton, G. (1977). Betel chewing and caries experience in New Guinea. *Community dentistry and oral epidemiology*, 5(6), 284-286.
6. Howden, G. F. (1983). The cariostatic effect of betel nut chewing. *Papua and New Guinea medical journal*, 27(3-4), 123-131.
7. De Miranda, C. M., Van Wyk, C. W., Van Der Bijl, P., & Basson, N. J. (1996). The effect of areca nut on salivary and selected oral microorganisms. *International dental journal*, 46(4), 350-356.
8. Daftary, D. K., Bhonsle, R. B., Murti, R. B., Pindborg, J. J., & MEHTA, F. S. (1980). An oral lichen planus-like lesion in Indian betel-tobacco chewers. *European Journal of Oral Sciences*, 88(3), 244-249.
9. Stoopler, E. T., Parisi, E., & Sollecito, T. P. (2003). Betel quid-induced oral lichen planus: a case report. *CUTIS-NEW YORK*, 71(4), 307-311.
10. Ikeda, N., Handa, Y., Khim, S. P., Durward, C., Axéll, T., Mizuno, T., ... & Kawai, T. (1995). Prevalence study of oral mucosal lesions in a selected Cambodian population. *Community dentistry and oral epidemiology*, 23(1), 49-54.
11. Lu, C. T., Yen, Y. Y., Ho, C. S., Ko, Y. C., Tsai, C. C., Hsieh, C. C., & Lan, S. J. (1996). A case-control study of oral cancer in Changhua County, Taiwan. *Journal of oral pathology & medicine*, 25(5), 245-248.
12. Heffernan, C., *Case Control Studies*. Retrieved July 31, 2015 from <http://www.drcath.net/toolkit/casecontrol.html>

13. Haddock, R. L. (2005). Oral cancer incidence disparity among ethnic groups on Guam. *Pacific health dialog*, 12(1), 153-154.
14. Haddock, R. L., Hoffman, J. H., & Williams, W. R. (1981). Betel nut chewing on Guam. *Fiji Medical Journal*, 9, 139-149.
15. Paulino, Y. C., Hurwitz, E. L., Warnakulasuriya, S., Gatewood, R. R., Pierson, K. D., Tenorio, L. F., & Badowski, G. (2014). Screening for oral potentially malignant disorders among areca (betel) nut chewers in Guam and Saipan. *BMC oral health*, 14(1), 151.

1.5 Adverse health effect of betel nut on fetus

1. Chue, A. L., Carrara, V. I., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., van Vugt, M., ... & McGready, R. (2012). Is areca innocent? The effect of areca (betel) nut chewing in a population of pregnant women on the Thai–Myanmar border. *International health*, 4(3), 204-209.
2. Grant, J., & Cardarelli, K. (2014). Evaluation of the effect of areca nut use during pregnancy in the commonwealth of the northern mariana islands. *Obstetrics & Gynecology*, 123, 54S-55S.
3. Garcia-Algar, O., Vall, O., Alameda, F., Puig, C., Pellegrini, M., Pacifici, R., & Pichini, S. (2005). Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 90(3), F276-FF277.
4. Nordeng, H., Ystrøm, E., & Einarson, A. (2010). Perception of risk regarding the use of medications and other exposures during pregnancy. *European journal of clinical pharmacology*, 66(2), 207-214.
5. Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., & Ko, Y. C. (1999). Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in southern Taiwan. *Public Health*, 113(4), 189-192.

Table References

1. Chue, A. L., Carrara, V. I., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., van Vugt, M., ... & McGready, R. (2012). Is areca innocent? The effect of areca (betel) nut chewing in a population of pregnant women on the Thai–Myanmar border. *International health*, 4(3), 204-209.
2. Grant, J., & Cardarelli, K. (2014). Evaluation of the effect of areca nut use during pregnancy in the commonwealth of the northern mariana islands. *Obstetrics & Gynecology*, 123, 54S-55S.
3. Garcia-Algar, O., Vall, O., Alameda, F., Puig, C., Pellegrini, M., Pacifici, R., & Pichini, S. (2005). Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 90(3), F276-FF277.
4. Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., & Ko, Y. C. (1999). Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in southern Taiwan. *Public Health*, 113(4), 189-192.
5. Costa, C., & Griew, A. R. (1982). Effects of betel chewing on pregnancy outcome. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 22(1), 22-24.

6. Senn, M., Baiwog, F., Winmai, J., Mueller, I., Rogerson, S., & Senn, N. (2009). Betel nut chewing during pregnancy, Madang province, Papua New Guinea. *Drug and alcohol dependence, 105*(1), 126-131.
7. Kuo, F. C., Wu, D. C., Yuan, S. S. F., Hsiao, K. M., Wang, Y. Y., Yang, Y. C., & Lo, Y. C. (2005). Effects of arecoline in relaxing human umbilical vessels and inhibiting endothelial cell growth. *Journal of perinatal medicine, 33*(5), 399-405.
8. Kader, M. (2013). Association between betel nut consumption and folate deficiency among pregnant women in rural Bangladesh. *International Journal of Medicine and Public Health, 3*(2), 81.
9. Kile, M., Wright, R., Amarasiriwardena, C., Quamruzzaman, Q., Rahman, M., Mahiuddin, G., & Christiani, D. (2009). Maternal and umbilical cord blood levels of arsenic, cadmium, manganese, and lead in rural Bangladesh. *Epidemiology, 20*(6), S149-S150.

1.6 Betel nut use in pregnancy

1. Garcia-Algar, O., Vall, O., Alameda, F., Puig, C., Pellegrini, M., Pacifici, R., & Pichini, S. (2005). Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes. *Archives of Disease in Childhood-Fetal and Neonatal Edition, 90*(3), F276-FF277.
2. Wang, C. C., Liu, T. Y., Wey, S. P., Wang, F. I., & Jan, T. R. (2007). Areca nut extract suppresses T-cell activation and interferon- γ production via the induction of oxidative stress. *Food and chemical toxicology, 45*(8), 1410-1418.
3. Zodpey, S. P. (2004). Sample size and power analysis in medical research. *Indian Journal of Dermatology, Venereology, and Leprology, 70*(2), 123.
4. Senn, M., Baiwog, F., Winmai, J., Mueller, I., Rogerson, S., & Senn, N. (2009). Betel nut chewing during pregnancy, Madang province, Papua New Guinea. *Drug and alcohol dependence, 105*(1), 126-131.
5. Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., & Ko, Y. C. (1999). Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in southern Taiwan. *Public Health, 113*(4), 189-192.
6. Kuo, F. C., Wu, D. C., Yuan, S. S. F., Hsiao, K. M., Wang, Y. Y., Yang, Y. C., & Lo, Y. C. (2005). Effects of arecoline in relaxing human umbilical vessels and inhibiting endothelial cell growth. *Journal of perinatal medicine, 33*(5), 399-405.
7. Schönfelder, G., Fuhr, N., Hadzidiakos, D., John, M., Hopp, H., & Paul, M. (2004). Preeclampsia is associated with loss of neuronal nitric oxide synthase expression in vascular smooth muscle cells of the human umbilical cord. *Histopathology, 44*(2), 116-128.
8. Levin, K. A. (2006). Study design III: Cross-sectional studies. *Evidence-based dentistry, 7*(1), 24-25.
9. Yang, M. S., Chung, T. C., Yang, M. J., Hsu, T. Y., & Ko, Y. C. (2001). Betel quid chewing and risk of adverse birth outcomes among aborigines in eastern Taiwan. *Journal of toxicology and environmental health Part A, 64*(6), 465-472.
10. Costa, C., & Griew, A. R. (1982). Effects of betel chewing on pregnancy outcome. *Australian and New Zealand Journal of Obstetrics and Gynaecology, 22*(1), 22-24.

11. López-Vilchez, M. A., Seidel, V., Farré, M., García-Algar, O., Pichini, S., & Mur, A. (2006). Areca-nut abuse and neonatal withdrawal syndrome. *Pediatrics*, *117*(1), e129-e131.

1.7 Risk perception of chewing betel nut during pregnancy

1. Bhat, S. J., Blank, M. D., Balster, R. L., Nichter, M., & Nichter, M. (2010). Areca nut dependence among chewers in a South Indian community who do not also use tobacco. *Addiction*, *105*(7), 1303-1310.
2. Nordeng, H., Ystrøm, E., & Einarson, A. (2010). Perception of risk regarding the use of medications and other exposures during pregnancy. *European journal of clinical pharmacology*, *66*(2), 207-214.
3. Kline, J., Stein, Z., Shrout, P., Susser, M., & Warburton, D. (1980). Drinking during pregnancy and spontaneous abortion. *The Lancet*, *316*(8187), 176-180.
4. Little, R. E., ASKER, R. L., Sampson, P. D., & Renwick, J. H. (1986). Fetal growth and moderate drinking in early pregnancy. *American Journal of Epidemiology*, *123*(2), 270-278.
5. Armstrong, B. G., McDonald, A. D., & Sloan, M. (1992). Cigarette, alcohol, and coffee consumption and spontaneous abortion. *American Journal of Public Health*, *82*(1), 85-87.
6. Clarren, S. K., Alvord, E. C., Sumi, S. M., Streissguth, A. P., & Smith, D. W. (1978). Brain malformations related to prenatal exposure to ethanol. *The Journal of pediatrics*, *92*(1), 64-67.
7. Ahlborg, G., & Bodin, L. (1991). Tobacco smoke exposure and pregnancy outcome among working women a prospective study at prenatal care centers in Örebro County, Sweden. *American journal of epidemiology*, *133*(4), 338-347.
8. Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., & Ko, Y. C. (1999). Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in southern Taiwan. *Public Health*, *113*(4), 189-192.
9. Costa, C., & Griew, A. R. (1982). Effects of betel chewing on pregnancy outcome. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *22*(1), 22-24.
10. Flaxman, S. M., & Sherman, P. W. (2000). Morning sickness: a mechanism for protecting mother and embryo. *Quarterly Review of Biology*, 113-148.
11. Senn, M., Baiwog, F., Winmai, J., Mueller, I., Rogerson, S., & Senn, N. (2009). Betel nut chewing during pregnancy, Madang province, Papua New Guinea. *Drug and alcohol dependence*, *105*(1), 126-131.
12. Singh, P. N., Lopez, J., Job, J. S., & Yel, D. (2013). Patterns of Maternal Tobacco Use Among Cambodian Women Findings From a Nationwide Sample. *Asia-Pacific Journal of Public Health*, *25*(5 suppl), 54S-63S.

1.8 Public health significance: challenge to regulate betel nut use

1. Yang, M. S., Chung, T. C., Yang, M. J., Hsu, T. Y., & Ko, Y. C. (2001). Betel quid chewing and risk of adverse birth outcomes among aborigines in eastern Taiwan. *Journal of toxicology and environmental health Part A*, *64*(6), 465-472.

2. Chue, A. L., Carrara, V. I., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., van Vugt, M., ... & McGready, R. (2012). Is areca innocent? The effect of areca (betel) nut chewing in a population of pregnant women on the Thai–Myanmar border. *International health*, 4(3), 204-209.
3. Kuo, F. C., Wu, D. C., Yuan, S. S. F., Hsiao, K. M., Wang, Y. Y., Yang, Y. C., & Lo, Y. C. (2005). Effects of arecoline in relaxing human umbilical vessels and inhibiting endothelial cell growth. *Journal of perinatal medicine*, 33(5), 399-405.
4. Al-Rmalli, S. W., Jenkins, R. O., & Haris, P. I. (2011). Betel quid chewing elevates human exposure to arsenic, cadmium and lead. *Journal of hazardous materials*, 190(1), 69-74.
5. Singh, A., & Rao, A. R. (1995). Effect of arecanut, a masticatory, on hepatic drug metabolizing enzymes suckling neonates. *Cancer letters*, 92(2), 175-180.
6. Nelson, B. S., & Heischouer, B. (1999). Betel nut: a common drug used by naturalized citizens from India, Far East Asia, and the South Pacific Islands. *Annals of emergency medicine*, 34(2), 238-243.
7. López-Vilchez, M. A., Seidel, V., Farré, M., García-Algar, O., Pichini, S., & Mur, A. (2006). Areca-nut abuse and neonatal withdrawal syndrome. *Pediatrics*, 117(1), e129-e131.
8. CDC. (2006). Recommendations to Improving Preconception Health and Health Care. *Morbidity and Mortality Weekly Report*, 55 (No RR-06), 1-23.
9. Internet pages (2012). Smokeless Tobacco and Public Health: A Global Perspective: Smokeless Tobacco Use in the Western Pacific Region. Retrieved April 11, 2015 from <http://cancercontrol.cancer.gov/brp/tcrb/global-Migration>
10. Pinhey, T. K. (1997). Employment Status, Ethnicity, and Alcohol Use in Guam. *Pacific Studies*, 20(1), 101-110.
11. WHO. (2012). Review of Areca (Betel) Nut and Tobacco Use in the Pacific: A Technical Report. Retrieved July 31, 2015 from <http://www.wpro.who.int/tobacco/documents/betelnut.pdf>.
12. Milgrom, P., Ohnmar, K. T. & Gallen, M. (2015). Dependence Symptoms With Betel Nut And Betel Nut With Tobacco Among Micronesian Youth. Unpublished manuscript, University of Washington, Seattle, WA.
13. Little, S. J., Hollis, J. F., Stevens, V. J., Mount, K., Mullooly, J. P., & Johnson, B. D. (1997). Effective group behavioral intervention for older periodontal patients. *Journal of periodontal research*, 32(3), 315-325.
14. Persson, R. E., Persson, G. R., Powell, L., & Klyak, H. A. (1998). Periodontal effects of a biobehavioral prevention program. *Journal of clinical periodontology*, 25(4), 322-329.
15. Powell, L. V., Persson, R. E., Kiyak, H. A., & Hujoel, P. P. (1999). Caries Prevention in a Community–Dwelling Older Population. *Caries research*, 33(5), 333-339.
16. Lee, S., Ghandi, F. & Elliptico (2007). Internet pages (2013). *Federated States of Micronesia, Business Opportunities Report, Island Business Opportunities* . Retrieved August 16, 2015 from http://www.islandbusinessopportunities.com/links_resources/islands/FSM.pdf
17. Pinhey, T. K. (1997). Employment Status, Ethnicity, and Alcohol Use in Guam. *Pacific Studies*, 20(1), 101-110.

□SH content ar

18. WHO. (2012). Review of Areca (Betel) Nut and Tobacco Use in the Pacific: A Technical Report. Retrieved July 31, 2015 from <http://www.wpro.who.int/tobacco/documents/betelnut.pdf>.

1.9 Summary and purpose of the study

1. Shih, Y. T., Chen, P. S., Wu, C. H., Tseng, Y. T., Wu, Y. C., & Lo, Y. C. (2010). Arecoline, a major alkaloid of the areca nut, causes neurotoxicity through enhancement of oxidative stress and suppression of the antioxidant protective system. *Free Radical Biology and Medicine*, 49(10), 1471-1479.
2. Pobutsky, A. M., & Neri, E. I. (2012). Betel Nut Chewing in Hawai 'i: Is it Becoming a Public Health Problem? Historical and Socio-Cultural Considerations. *Hawai'i journal of medicine & public health: a journal of Asia Pacific Medicine & Public Health*, 71(1), 23.
3. Mirza, S. S., Shafique, K., Vart, P., & Arain, M. I. (2011). Areca nut chewing and dependency syndrome: is the dependence comparable to smoking? a cross sectional study. *Subst Abuse Treat Prev Policy*, 6, 23.
4. Milgrom, P., Ohnmar, K. T. & Gallen, M. (2015). Dependence Symptoms With Betel Nut And Betel Nut With Tobacco Among Micronesian Youth. Unpublished manuscript, University of Washington, Seattle, WA.
5. Trivedy, C. R., Craig, G. & Warnakulasuriya, S. (2002). The oral health consequences of chewing areca nut. In *Addiction Biology*, 7. Retrieved July 31, 2015 from <http://www.medilexicon.com/medicaldictionary.php?t=21139>
6. Milgrom, P., Ohnmar, K. T. & Gallen, M. (2015). Dependence Symptoms With Betel Nut And Betel Nut With Tobacco Among Micronesian Youth. Unpublished manuscript, University of Washington, Seattle, WA.
7. Trivedy, C. R., Craig, G., & Warnakulasuriya, S. (2002). The oral health consequences of chewing areca nut. *Addiction biology*, 7(1), 115-125.
8. ÁRnerud, Á. R., Löe, H., & Boysen, H. (1991). The natural history and clinical course of calculus formation in man. *Journal of Clinical Periodontology*, 18(3), 160-170.
9. Yang, M. S., Lee, C. H., Chang, S. J., Chung, T. C., Tsai, E. M., Ko, A. M. J., & Ko, Y. C. (2008). The effect of maternal betel quid exposure during pregnancy on adverse birth outcomes among aborigines in Taiwan. *Drug and alcohol dependence*, 95(1), 134-139.

4.1 Results

1. Senn, M., Baiwog, F., Winmai, J., Mueller, I., Rogerson, S., & Senn, N. (2009). Betel nut chewing during pregnancy, Madang province, Papua New Guinea. *Drug and alcohol dependence*, 105(1), 126-131.
2. Paul, K., Moitra, P. K., Maity, C. R., & Ghosal, S. K. (1996). Teratogenicity of crude areca nut extract in chick embryos. *Indian Journal of Physiology and Allied Sciences*, 50, 182-187.
3. Sinha, A., & Rao, A. R. (1985). Embryotoxicity of betel nuts in mice. *Toxicology*, 37(3), 315-326.
4. Chue, A. L., Carrara, V. I., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., van Vugt, M., ... & McGready, R. (2012). Is areca innocent? The effect of areca (betel) nut chewing

- in a population of pregnant women on the Thai–Myanmar border. *International health*, 4(3), 204-209.
5. Hackshaw, A. (2008). Small studies: strengths and limitations. *European Respiratory Journal*, 32(5), 1141-1143.
 6. Chaaya, M., Awwad, J., Campbell, O. M., Sibai, A., & Kaddour, A. (2003). Demographic and psychosocial profile of smoking among pregnant women in Lebanon: public health implications. *Maternal and child health journal*, 7(3), 179-186.
6. *Systematic review on pregnancy and betel nut*
1. Garcia-Algar, O., Vall, O., Alameda, F., Puig, C., Pellegrini, M., Pacifici, R., & Pichini, S. (2005). Prenatal exposure to arecoline (areca nut alkaloid) and birth outcomes. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 90(3), F276-FF277.
 2. Senn, M., Baiwog, F., Winmai, J., Mueller, I., Rogerson, S., & Senn, N. (2009). Betel nut chewing during pregnancy, Madang province, Papua New Guinea. *Drug and alcohol dependence*, 105(1), 126-131.
 3. Chue, A. L., Carrara, V. I., Paw, M. K., Pimanpanarak, M., Wiladphaingern, J., van Vugt, M., ... & McGready, R. (2012). Is areca innocent? The effect of areca (betel) nut chewing in a population of pregnant women on the Thai–Myanmar border. *International health*, 4(3), 204-209.
 4. Grant, J., & Cardarelli, K. (2014). Evaluation of the effect of areca nut use during pregnancy in the commonwealth of the northern mariana islands. *Obstetrics & Gynecology*, 123, 54S-55S.
 5. Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., & Ko, Y. C. (1999). Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in southern Taiwan. *Public Health*, 113(4), 189-192.
 6. Kuo, F. C., Wu, D. C., Yuan, S. S. F., Hsiao, K. M., Wang, Y. Y., Yang, Y. C., & Lo, Y. C. (2005). Effects of arecoline in relaxing human umbilical vessels and inhibiting endothelial cell growth. *Journal of perinatal medicine*, 33(5), 399-405.
 7. Ghosh, R., & Ghosh, P. K. (1984). Sister chromatid exchanges in betel and tobacco chewers. *Mutation Research Letters*, 139(2), 79-81.
 8. Chou, F. H., Yang, Y. H., Kuo, S. H., Chan, T. F., & Yang, M. S. (2009). Relationships among smoking, drinking, betel quid chewing and pregnancy-related nausea and vomiting in Taiwanese aboriginal women. *The Kaohsiung journal of medical sciences*, 25(2), 62-69.
 9. Costa, C., & Griew, A. R. (1982). Effects of betel chewing on pregnancy outcome. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 22(1), 22-24.
 10. Sinha, A., & Rao, A. R. (1985). Transplacental micronucleus inducing ability of arecoline, a betel nut alkaloid, in mice. *Mutation Research/Genetic Toxicology*, 158(3), 193-194.
 11. Sinha, A., & Rao, A. R. (1985). Embryotoxicity of betel nuts in mice. *Toxicology*, 37(3), 315-326.
 12. Yang, M. S., Chung, T. C., Yang, M. J., Hsu, T. Y., & Ko, Y. C. (2001). Betel quid chewing and risk of adverse birth outcomes among aborigines in eastern Taiwan. *Journal of toxicology and environmental health Part A*, 64(6), 465-472.

13. López-Vilchez, M. A., Seidel, V., Farré, M., García-Algar, O., Pichini, S., & Mur, A. (2006). Areca-nut abuse and neonatal withdrawal syndrome. *Pediatrics*, *117*(1), e129-e131.

APPENDIX

**POHNPEI STATE HOSPITAL
ORAL HEALTH PROGRAM
BETEL NUT SURVEY**

This survey is about the use of betel nut during pregnancy. Please answer even if you don't use betel. Betel is thought to have both benefits and risks when used, and the Prenatal Clinic and the Dental Services Department of the Hospital are cooperating to learn more about this. Please do not put your name on the survey. All the information you provide is confidential and will not be part of your health records. This survey is voluntary and you do not have to participate if you don't want to. **THANK YOU FOR YOUR PARTICIPATION.**

SECTION 1: ABOUT YOUR PREGNANCY

1. How well has your pregnancy gone? (Check the box)
 - VERY WELL
 - WELL
 - NOT SO WELL

2. At about how many months did you have your first prenatal check-up?
 - BEFORE 3 MONTHS
 - 3-6 MONTHS
 - AFTER 6 MONTHS

Next Page 

3. How many pregnancies have you had, including this time, even if the pregnancy did not go to term?

- 1
- 2
- 3 OR MORE TIMES

4. How many pregnancies have you had where there was a miscarriage or where the pregnancy did not go to term?

- NONE
- 1
- 2 OR MORE TIMES

5. Have you had any of these diseases while pregnant?

- GESTATIONAL DIABETES
- HIGH BLOOD PRESSURE
- ASTHMA
- NO

6. Were any of your babies born early?

- YES
- NO
- THIS IS MY FIRST PREGNANCY

7. Were any of your babies born with low birth weight?

- YES
- NO
- THIS IS MY FIRST PREGNANCY

8. How important are your prenatal clinic check-ups for the health of you and

Next Page 

- EXTREMELY IMPORTANT
- VERY IMPORTANT
- IMPORTANT
- NOT VERY IMPORTANT
- NOT AT ALL IMPORTANT

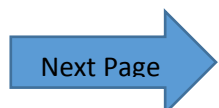
SECTION 2: ABOUT YOUR HEALTH

1. How is your personal health?
 - POOR
 - FAIR
 - GOOD
 - EXCELLENT

2. Have you had times when you felt especially low or down for 2 weeks or more?
 - NEVER
 - A FEW TIMES
 - SOMETIMES
 - A LOT OF TIMES

3. Do you sometimes worry so much that it affects your daily life?
 - NO, NOT AT ALL
 - A LITTLE
 - SOMEWHAT
 - YES, TO A GREAT EXTENT

4. Did you have any health problems before you became pregnant?
 - YES



NO

IF YES, PLEASE DESCRIBE _____

SECTION 3: ABOUT BETEL NUT

If you have never used betel nut, check the box below and skip to question number 31. OTHERWISE, please answer all the questions in this section.

I HAVE NEVER USED BETEL NUT → GO TO QUESTION 31

1. How old were you when you started chewing betel nut?

_____ YEARS OLD.

2. When was the last time that you used betel nut?

TODAY

IN THE PAST WEEK

IN THE PAST TWO WEEKS

IN THE PAST MONTH

LONGER THAN ONE MONTH AGO

I HAVE NEVER USED BETEL NUT

3. About how often do you use betel nut now?

NEARLY ALL OF THE TIME

MUCH OF THE TIME

NOT MUCH OF THE TIME

I NEVER USE BETEL NUT

Betel quid is composed of the following ingredients: unripe nut (white variety), betel leaf, lime, tobacco from cigarette, and sometimes alcohol.

4. What form of betel nut do you use?

Next Page 

- BETEL NUT ALONE
- BETEL NUT (WHITE SOFT), LIME, WITHOUT TOBACCO FROM CIGARETTE
- BETEL NUT (WHITE UNRIPE), LIME, AND TOBACCO FROM CIGARETTE
- BETEL NUT (WHITE UNRIPE), LIME, AND TOBACCO FROM CIGARETTE WITH ALCOHOL

5. How often do you use betel nut with tobacco?

- NEARLY ALL OF THE TIME
- MOST OF THE TIME
- NOT VERY OFTEN
- I NEVER USE BETEL NUT WITH TOBACCO

6. You use betel nut during the course of the day on most days.

- TRUE
- FALSE

7. You use betel nut around the same number of times each day.

- TRUE
- FALSE

8. You use the same amount of betel nut on weekends and on weekdays.

- TRUE
- FALSE

9. It is difficult to say how many times each day you use betel nut, because the number of times changes often.

- TRUE
- FALSE

Next Page

10. It is normal for you to use betel nut several times in a short period, then not use it for many hours.
- TRUE
- FALSE

In this section, please tell us how you feel about betel nut and tobacco. Please answer even if you chew betel nut without tobacco.

11. Chewing betel nut can help to reduce morning sickness or nausea.
- TRUE
- FALSE
12. Chewing helps to give me relief and relaxation when I am tense or stressed.
- TRUE
- FALSE
13. After the birth of a child, it is safe for a new mom to chew betel nut.
- TRUE
- FALSE
14. Chewing betel nut can help to prevent a smelly mouth or bad breath.
- TRUE
- FALSE
15. Chewing betel nut right now could help me to not feel tired or to work for a longer time.
- TRUE
- FALSE
16. I think we get addicted when we start chewing betel nut with cigarette tobacco

Next Page

- TRUE
- FALSE

17. I think adding tobacco to betel quid makes it difficult to quit.

- TRUE
- FALSE

18. It is difficult for me to see my friends chewing, because I want to be able to join them and enjoy chewing together.

- TRUE
- FALSE

19. Since you began using betel nut, the amount that you use has increased.

- TRUE
- FALSE

20. In comparison to when you began using betel nut, the amount that you need to use in order to be satisfied has increased.

- TRUE
- FALSE

21. In comparison to when you began using betel nut, the amount that you can use before you start feeling anything has increased.

- TRUE
- FALSE

22. When you use betel nut, how soon after waking up do you use betel nut for the first time?

Next Page

- VERY SOON AFTER WAKING UP
- LATER IN THE DAY

23. After you have not used betel nut for some time, you need to use it in order to feel less restless and irritable.

- TRUE
- FALSE

24. After you have not used betel nut for a few hours, you start to crave betel nut.

- TRUE
- FALSE

25. You sometimes crave betel nut strongly, and it feels like you are in the grip of a force that you cannot control.

- TRUE
- FALSE

26. You feel in control over your use of betel nut, and you can “take it or leave it” at any time.

- TRUE
- FALSE

27. You usually avoid places that do not allow betel nut use, even if you would enjoy them otherwise.

- TRUE
- FALSE

28. Sometimes you choose to not be around your friends who do not chew betel nut, because they do not like it if you use betel nut.

- TRUE
- FALSE

Next Page

29. Sometimes you are worried that you will run out of betel nut.

TRUE

FALSE

30. Other things do not affect your betel nut use very much. For example, you use it around the same number of times each day whether you are relaxed or stressed by school, happy or sad, alone or with other people.

TRUE

FALSE

Please answer question 31 even if you do not chew betel nut.

Respond to each statement by marking the box that indicates how much you disagree or agree with the statement. Please only mark one box for each statement.

31.

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
	1	2	3	4	5

Next Page

1. Betel nut use during pregnancy can lead to a lower birth weight for the baby.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. It is easier to deliver smaller babies.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. A baby with a lower birth weight is likely to have health problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Betel nut use during pregnancy can lead to a premature birth.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Betel nut use during pregnancy can lead to respiratory infections for the baby.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Betel nut use during pregnancy can lead to problems with the child's growth and development until the age of ten.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<p>7. Betel nut use by other people in the house during pregnancy can lead to health problems for the baby.</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>8. Betel nut use during pregnancy can lead to a change in the child's IQ.</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>9. Encouragement should be given to pregnant women so that they stop chewing betel nut.</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<div style="background-color: #ADD8E6; padding: 5px; text-align: center;">Next Page</div>
<p>10. More help should be given to pregnant women who want to stop chewing betel nut.</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<p>11. Lowering the amount of betel nut use can lead to a lower risk of health problems for the</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

baby.					
12. Betel nut use after pregnancy is safe for the baby.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SECTION 4: OTHER QUESTIONS ABOUT YOU

1. What is the highest grade in school that you have completed? (Check one box)

- ELEMENTARY SCHOOL
- HIGH SCHOOL
- SOME COLLEGE

2. What is your age?

_____ YEARS OLD.

3. Have you ever smoked?

- CURRENT SMOKER
- I HAVE QUIT SMOKING
- NEVER SMOKED

4. When you found out you were pregnant, how many cigarettes did you usually smoke each day?

_____ CIGARETTES EACH DAY

(Write 0 if you did not smoke before you became pregnant.)

Next Page

*See glossary

5. Did you drink alcohol during your pregnancy?

YES

NO

6. Have you used any of the following during your pregnancy?

SAKAU (KAVA)

POT OR MARIJUANA

NO

THANK YOU FOR YOUR PARTICIPATION IN THIS SURVEY

(1.1) Table 1. Prevalence of betel nut usage for different Southeast Asian countries [3]

Country	Men		Women		ALL		Chewing practice		Reference
	n	%	n	%	n	%	Nut only	Quid	
India, Bombay	40071	34.5	50527	27.2	99598	32.1		X	1
Pakistan, Karachi	2661	3.2	2093	8.2	4754	5.4		X	2
Sri Lanka	316	54	817	42	1133	45.2		X	3
Thailand	986	16	880	19	1816	17		X	4
Taiwan, Kaohsiung	511	28.3	651	1.4	1162	13.3	X		5
Sarawak	195	30	263	63	458	49.3	X		6
Cambodia	366	6.8	953	40.6	1319	31.2			7
China, Xiangtang City	6057	39.3	4989	30.5	11406	35.3	X		8

(1.4) Table 2. Periodontal condition*¹² of non-chewers versus chewers [2]

Periodontal condition	Non-chewers (%)	Chewers (%)	Odds ratio	95% CI
Periodontal pocket	61 (30.96)	92 (54.76)	*1.643	(1.26, 2.14)
Gingival lesion	2 (1.02)	10 (5.95)	*2.868	(1.24, 6.65)
Gingival recession	52 (26.40)	85 (50.60)	*1.729	(1.32, 2.32)

(1.5) Table 3. Studies describing the adverse effects of betel nut on the fetus

Region	Population	Study design	Year	Age of participants	Reference	Gender	Sample	Findings
Southeast Asia	Thai–Myanmar border	Retrospective cohort analysis	July 1997 to November 2006	Not given	1	Female	7685 women	<ul style="list-style-type: none"> • 29.7% never used areca or smoked cheroots; 32.3% only used areca; 5.7% only smoked cheroots; 32.3% used areca and smoked cheroots • No dose-response relationship for miscarriage for heavy use, as compared to occasional use • Adverse pregnancy outcomes related to smoking, but not to areca use • Mean difference in birthweight between babies of users and non-users was 51 g; no significant difference between babies of heavy areca users and those of occasional areca users
Pacific	Commonwealth of the Northern Mariana Islands	Retrospective chart review	2009	Not given	2	Female	All single child deliveries in 2009	Twice the odds of preterm birth for areca nut users than for non-users, and increased odds of meconium

*See glossary

								staining for users than for non-users, but neither statistically significant
Europe	Barcelona Spain	Clinical observational	2009	Not given	3	Not given	6 newborns	Two of the six exposed newborns had adverse birth outcomes, both of which had: <ul style="list-style-type: none"> • Risk factors other than betel nut use excluded from material records • Inconclusive neonatal brain ultrasonography • Focal inflammatory changes in the amniochorial membranes <p>In a third case, the fetal surface villi vessels had a decreased median diameter in both mother and fetus</p>
East Asia	Southern Taiwan	Cross-sectional	1999	Not given	4	Female	62 women with adverse pregnancy outcomes and 124 age-matched women	Compared to non-chewers, betel quid chewers had 2.8 times the risk of adverse pregnancy outcomes. This finding was adjusted for material illness and number of previous pregnancies

*See glossary

Pacific	Papua New Guinean	Medical review	Around 1980	Not given	5	Female	400	Significantly higher mean birth weight and higher incidence of neonatal jaundice for control group than for study group
Pacific	Papua New Guinean	Cross-sectional	Between September 2007 and June 2008	Not given	6	Female	310	<ul style="list-style-type: none"> • Birth weight was significantly reduced by primigravidity, betel nut use, and low BMI • 80% of the participants did not think that their betel nut use would impact their fetus • The largest contributor to birth weight was related to gravidity rather than betel nut • PNG has a well-known effect of gravidity on birth weight • Although low birthweight was more prevalent among betel nut users, this effect was not statistically significant
Asia	Taiwan	Cross-sectional	2004	Not given	7	Female	Human umbilical	<ul style="list-style-type: none"> • Decreases vascular tone, in part

*See glossary

							arteries and veins from healthy parturient patients after full-term pregnancies	mediated by NO <ul style="list-style-type: none"> • In higher doses, inhibits endothelial cell growth (thus in the long-term or with high doses inducing endothelial dysfunction and associated diseases)
Asia	Bangladesh	Cross-sectional	2011-2012	14-50 years of age	8	Female	730	<ul style="list-style-type: none"> • 63% of the participants used betel nut, and 17% of them had folate deficiency, at rates 2.57 times higher for those who used betel nut and tobacco and 2.51 times higher for those who used betel nut 2-3 times per day • Non-users had significantly higher mean serum folate levels than betel nut users • It is concerning that folate deficiency in early pregnancy is so prevalent, as this deficiency could lead to adverse pregnancy outcomes and general health risks

*See glossary

Asia	Bangladesh	Experimental	September 2008	Not given	9	Female	12	<ul style="list-style-type: none"> • Average concentration of 0.04 µg of As, 1.86 µg of Mn, 0.07 µg of Cd, and 13.0 µg of Pb in maternal samples from pregnant women in the first trimester • Average concentration of 0.34 µg of As, 6.88 µg of Mn, 0.04 µg of Cd, and 8.64 µg of Pb in umbilical cord blood • Umbilical cord blood showed regional differences in Pb concentrations
------	------------	--------------	----------------	-----------	---	--------	----	--

*See glossary

(1.6) Table 4. Six newborn cases [1]

Case number	Somatometry		Clinical signs	Placental morphology	Arecoline in biological matrices ($\mu\text{g/g}$) Meconium
	Birthweight (grams)	Gestation			
1	3450	41 weeks	None	577 g; macro and micro normal	ND
2	3090	38 weeks	Neonatal withdrawal syndrome* ¹⁶ treated with 5 mg/kg phenobarbital for 3 subsequent days	655 g; macro normal; micro acute focal chorioamnionitis	0.012
3	2430	41 weeks	Low birth weight, low intrauterine growth, small for gestational age, hyporeflexia, hypotonia	435 g; macro normal; micro acute focal chorioamnionitis, reduced vascular diameter	0.009
4	3260	39.6 weeks	None	548 g; macro and micro normal	0.013
5	2865	38 weeks	None	498 g; macro and micro normal	0.015
6	3575	40.4 weeks	None	468 g; macro and micro normal	0.014

(1.6) Table 5. Univariate analysis of possible factors impacting birth weight [4]

Factor	Respective mean birth weights	Δ	P
Primigravidae (n = 103)/multigravidae (n = 207)	2607 g vs. 3065 g	458 g	$p < 0.001$
Betel nut (n = 292)/no betel nut (n = 18)	2901 g vs. 3122 g	221 g	$p = 0.05$
Body mass index < 20 (n = 55)/BMI > 20 (n = 252)	2781 g vs. 2943 g	162 g	$p = 0.02$

*See glossary

(1.6) Table 6. Odds ratios and 95% confidence intervals (CI) for low birth weight (LBW) and preterm birth by maternal betel chewing [5]

Maternal betel chewing	LBW with full terms (n=10)		Preterms (n=20)	
	Yes/No CI)	OR (95% CI)	Yes/No CI)	OR (95% CI)
Yes	110/1	1.0	79/3	1
No	109/9	9.1 (1.6–51.8) ^a	130/17	3.4 (1.1–11.4) ^a

(3) Table 7. Descriptive analysis of samples

		Total N (%)	Chewer N (%)	Non- chewer N (%)	X2-Value (p-Value)
Education level	Elementary school	9 (20.9%)	6 (13.9%)	3 (7.0%)	3.42 (0.843) No sig. Assoc.
	High school	16 (37.2%)	9 (37.2%)	7 (16.3%)	3.42 (0.843) No sig. Assoc.
	Some college	18 (41.9%)	10 (23.2%)	8 (18.6%)	3.42 (0.843) No sig. Assoc.
Age mean ± SD (range)	23.19 ± 5.994				
During your pregnancy					
Smoking status	Current smoker	2 (3.9%)	2 (3.9%)	0 (0.0%)	4.559 (.102) No sig. Assoc.
	I have quit smoking	8 (15.7%)	7 (13.7%)	1 (2.0%)	4.559 (.102) No sig. Assoc.
	Never smoked	41 (80.4%)	22 (43.1%)	19 (3.7%)	4.559 (.102) No sig. Assoc.
# of cigarettes		.62			
Alcohol use	Yes	5 (9.4%)	4	1	0.739 (0.390) Nos sig. Assoc.

*See glossary

	No	48 (90.6%)	29	19	0.739 (0.390) No sig. Assoc.
Substance abuse	Sakau (Kava)	20 (40%)	15	5	4.372 (0.112) No sig. Assoc.
	Pot or Marijuana	2 (4.0%)	2	0	4.372 (0.112) No sig. Assoc.
	No	34 (61.8%)	14	14	4.372 (0.112) No sig. Assoc.
How well the pregnancy has gone	Very well	34 (61.8%)	21	13	1.143 (0.565) No sig. Assoc.
	Well	15 (27.3%)	9	6	1.143 (0.565) No sig. Assoc.
	Not so well	6 (10.9%)	5	1	1.143 (0.565) No sig. Assoc.
At how many months the first prenatal check- up took place	Before 3 months	26 (48.1%)	16	10	0.248 (0.883) No sig. Assoc.
	3-6 months	21 (38.9%)	13	8	0.248 (0.883) No sig. Assoc.
	After 6 months	7 (13%)	5	2	0.248 (0.883) No sig. Assoc.
Number of pregnancies	1	24 (45.3%)	14	10	.306 (.858) No sig. Assoc.
	2	15	10	5	.306 (.858)

*See glossary

		(28.3%)			No sig. Assoc.
	3 or more	14 (26.4%)	9	5	.306 (.858) No sig. Assoc.
Miscarriage or preterm delivery	0	6 (10.9%)	5	1	4.098 (.251) No sig. Assoc.
	None	43 (78.2%)	26	17	4.098 (.251) No sig. Assoc.
	1	3 (5.5%)	1	2	4.098 (.251) No sig. Assoc.
	2 or more	3 (5.5%)	3	0	4.098 (.251) No sig. Assoc.
Disease while pregnant	Gestational Diabetes	1 (2.1%)	1	0	1.892 (.595) No sig. Assoc.
	High Blood Pressure	2 (4.2%)	2	0	1.892 (.595) No sig. Assoc.
	Asthma	2 (4.2%)	1	1	1.892 (.595) No sig. Assoc.
	No	43 (78.2%)	27	16	1.892 (.595) No sig. Assoc.
Babies born early previously	Yes	7 (12.7%)	5	2	1.534 (.464) No sig. Assoc.
	No	29 (52.7%)	20	9	1.534 (.464) No sig.

					Assoc.
	This is my First Pregnancy	19 (34.5%)	10	9	1.534 (.464) No sig. Assoc.
Babies born low weight previously	Yes	5 (9.1%)	5	0	3.503 (.174) No sig. Assoc.
	No	30 (54.5%)	19	11	3.503 (.174) No sig. Assoc.
	This is my First pregnancy	20 (36.4%)	11	9	3.503 (.174) No sig. Assoc.
Importance of prenatal care	Extremely Important	22 (40.7%)	10	12	6.284 (0.099) No sig. Assoc.
	Very Important	24 (44.4%)	19	5	6.284 (0.099) No sig. Assoc.
	Important	7 (13.0%)	4	3	6.284 (0.099) No sig. Assoc.
	Not very important	1(1.8%)	1	0	6.284 (0.099) No sig. Assoc.

(3) Table 8. Rates of use and frequency of use among participants (N = 55)

Question	Pohnpei State hospital n%
1. Have you ever used betel?	
Yes	35 (63.6%)
2. When was the last time that you used betel nut?	
Today	14 (41.2%)
In the past week	3 (8.8%)
In the past two weeks	3 (8.8%)
In the past month	5 (14.7%)
Longer than one month	9 (26.5%)
3. About how often do you use betel nut now?	
Current use	
Nearly all the time	1 (2.9%)
Much of the time	6 (17.1%)
Not much of the time	21 (60.0%)
I never use betel nut	7 (20.0%)

(3) Table 9. Questionnaire response analysis

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree	N
	1 N= n (%)	2 N= n (%)	3 N= n (%)	4 N= n (%)	5 N= n (%)	
1. Betel nut use during pregnancy can lead to a lower birth weight for the baby.	4 (8.3%)	5 (10.4%)	4 (8.3%)	12 (25%)	23 (47.9%)	48
2. It is easier to deliver smaller babies.	11 (22.9%)	17 (35.4%)	5 (10.4%)	7 (14.6%)	8 (16.7%)	48
3. A baby with a lower birth weight is likely to have health problems.	4 (8.5%)	5 (10.6%)	4 (8.5%)	14 (29.8%)	20 (42.6%)	47
4. Betel nut use during pregnancy can lead to a premature birth.	1 (2.1%)	8 (17.0%)	4 (8.5%)	11 (23.6%)	23 (48.9%)	47
5. Betel nut use during pregnancy can lead to respiratory infections for the baby.	1 (2.1%)	5 (10.4%)	1 (2.5%)	17 (35.4%)	24 (50.0%)	48

*See glossary

6. Betel nut use during pregnancy can lead to problems with the child's growth and development until the age of ten.	3 (6.3%)	5 (10.4%)	5 (10.4%)	11 (22.9%)	24 (50.0%)	48
7. Betel nut use by other people in the house during pregnancy can lead to health problems for the baby.	9 (18.8%)	13 (27.1%)	7 (14.6%)	9 (18.8%)	10 (20.8%)	48
8. Betel nut use during pregnancy can lead to a change in the child's IQ.	3 (6.3%)	3 (6.3%)	6 (12.5%)	14 (29.2%)	22 (45.8%)	48
9. Encouragement should be given to pregnant women so that they stop chewing betel nut.	2 (4.5%)	4 (9.1%)	3 (6.8%)	12 (27.3%)	23 (52.3%)	44
10. More help should be given to pregnant women who want to stop chewing betel nut.		5 (11.4%)	5 (9.1%)	12 (27.3%)	23 (52.3%)	45
11. Lowering the amount of betel nut use can lead to a lower risk of health problems for the baby.	3 (6.8%)	6 (13.6%)	4 (9.1%)	14 (31.8%)	17 (38.6%)	44
12. Betel nut use after pregnancy is safe for the baby.	13 (28.9%)	12 (26.9%)	4 (8.9%)	7 (15.6%)	9 (20.0%)	44
Total	54	88	52	140	226	560

(3) Table 10. Responses to questions in craving scale

Item	Response	All betel users (n=X) N (%)	Betel nut only (n=X) N (%)	Habitual tobacco users from cigarettes with/without alcohol (n=X) N (%)
6. You use betel nut during the course of the day on most days.	True = 1 20	35	3	17
19. Since you begin using betel nut, the amount that you use has increased.	True =1 19	33	5	14
20. In comparison to when you began using betel nut, the amount that you need to use in order to be satisfied has increased.	True =1 21	33	6	15
21. In comparison to when you began	True = 1		3	15

*See glossary

using betel nut, the amount that you can use before you start feeling anything has increased.	18			
22. When you use betel nut, how soon after waking up do you use betel nut for the first time?	True =1 16	33	4	12
23. After you have not used betel nut for some time, you need to use it in order to feel less restless and irritable	True = 1 19	32	6	13
24. After you have not used betel nut for a few hours, you start to crave betel nut.	True =1 15	32	4	11
25. You sometimes crave betel nut strongly, and it feels like you are in the grip of a force that you cannot control.	True = 1 17	32	4	13
26. You feel in control over your use of betel nut and you can take it or leave it at any time	True =1 13	32	5	8
27. You usually avoid places that do not allow betel nut use even if you would enjoy them otherwise.	True = 1 18	32	3	15
28. Sometimes you choose to be not be around your friends who do not chew betel nut because they do not like it if you use betel nut.	True =1 21	34	6	15
29. Sometimes you are worried that you will run out of betel nut.	True = 1 19	34	4	15
30. Other things do not affect your betel nut use	True = 1 21	34	5	16
7. You use betel nut around the same number of times each day.	True =1 19	35	4	15
8. You use the same amount of betel nut on weekends and weekdays.	True =1 21	35	4	17

(3) Table 11. Correlation between the craving score and the health risk belief assessment score within the past 30 days

			Craving Scale (0 to 15)	Health Beliefs Scale (0 to 12)
Spearman's rho	Craving Scale (0 to 15)	Correlation Coefficient	1.000	-.394
		Sig. (2-tailed)	.	.085
		N	24	20
	Health Beliefs Scale (0 to 12)	Correlation Coefficient	-.394	1.000
		Sig. (2-tailed)	.085	.
		N	20	20

(3) Table 12. Correlation between the craving score and the health risk belief assessment score for people who ever used betel nut

			Craving Scale (0 to 15)	Health Beliefs Scale (0 to 12)
Spearman's rho	Craving Scale (0 to 15)	Correlation Coefficient	1.000	-.240
		Sig. (2-tailed)	.	.238
		N	32	26
	Health Beliefs Scale (0 to 12)	Correlation Coefficient	-.240	1.000
		Sig. (2-tailed)	.238	.
		N	26	44

*See glossary

**ELSEVIER LICENSE
TERMS AND CONDITIONS**

Aug 17, 2015

This is a License Agreement between Sahira Khalid ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard, Langford Lane Kidlington, Oxford, OX5 1GB, UK
Registered Company Number	1982084
Customer name	Sahira Khalid
Customer address	
License number	3686910060596
License date	Aug 13, 2015
Licensed content publisher	Elsevier
Licensed content publication	Drug and Alcohol Dependence
Licensed content title	Betel nut chewing during pregnancy, Madang province, Papua New Guinea
Licensed content author	M. Senn, F. Baiwog, J. Winmai, I. Mueller, S. Rogerson, N. Senn
Licensed content date	1 November 2009
Licensed content volume number	105
Licensed content issue number	1-2
Number of pages	6
Start Page	126
End Page	131
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Original figure numbers	Figure1

<https://s100.copyright.com/CustomAdmin/PLF.jsp?ref=c0b25082-98b1-42af-b25c-3cfaf...> 8/17/2015

Title of your thesis/dissertation	Betel Use in Pregnancy
Expected completion date	Aug 2015
Estimated size (number of pages)	100
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	0.00 USD
Terms and Conditions	

INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at <http://myaccount.copyright.com>).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.

3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

"Reprinted from Publication title, Vol /edition number, Author(s), Title of article / title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]." Also Lancet special credit - "Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier."

4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.

5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com)

6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.

<https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=c0b25082-98b1-42af-b25c-3cfaf...> 8/17/2015

7. **Reservation of Rights:** Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

8. **License Contingent Upon Payment:** While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. **Warranties:** Publisher makes no representations or warranties with respect to the licensed material.

10. **Indemnity:** You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. **No Transfer of License:** This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. **No Amendment Except in Writing:** This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. **Objection to Contrary Terms:** Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. **Revocation:** Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the

amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. Translation: This permission is granted for non-exclusive world **English** rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator must perform all translations and reproduce the content word for word preserving the integrity of the article. If this license is to re-use 1 or 2 figures then permission is granted for non-exclusive world rights in all languages.

16. Posting licensed content on any Website: The following terms and conditions apply as follows: Licensing material from an Elsevier journal: All content posted to the web site must maintain the copyright information line on the bottom of each image; A hyper-text must be included to the Homepage of the journal from which you are licensing at <http://www.sciencedirect.com/science/journal/xxxxx> or the Elsevier homepage for books at <http://www.elsevier.com>; Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

Licensing material from an Elsevier book: A hyper-text link must be included to the Elsevier homepage at <http://www.elsevier.com>. All content posted to the web site must maintain the copyright information line on the bottom of each image.

Posting licensed content on Electronic reserve: In addition to the above the following clauses are applicable: The web site must be password-protected and made available only to bona fide students registered on a relevant course. This permission is granted for 1 year only. You may obtain a new license for future website posting.

17. For journal authors: the following clauses are applicable in addition to the above:

Preprints:

A preprint is an author's own write-up of research results and analysis, it has not been peer-reviewed, nor has it had any other value added to it by a publisher (such as formatting, copyright, technical enhancement etc.).

Authors can share their preprints anywhere at any time. Preprints should not be added to or enhanced in any way in order to appear more like, or to substitute for, the final versions of articles however authors can update their preprints on arXiv or RePEc with their Accepted Author Manuscript (see below).

If accepted for publication, we encourage authors to link from the preprint to their formal publication via its DOI. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help users to find, access, cite and use the best available version. Please note that Cell Press, The Lancet and some society-owned have different preprint policies. Information on these policies is available on the journal homepage.

<https://s100.copyright.com/CustomAdmin/PLF.jsp?ref=c0b25082-98b1-42af-b25c-3cfaf...> 8/17/2015

Accepted Author Manuscripts: An accepted author manuscript is the manuscript of an article that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and editor-author communications.

Authors can share their accepted author manuscript:

- immediately
 - via their non-commercial person homepage or blog
 - by updating a preprint in arXiv or RePEc with the accepted manuscript
 - via their research institute or institutional repository for internal institutional uses or as part of an invitation-only research collaboration work-group
 - directly by providing copies to their students or to research collaborators for their personal use
 - for private scholarly sharing as part of an invitation-only work group on commercial sites with which Elsevier has an agreement
- after the embargo period
 - via non-commercial hosting platforms such as their institutional repository
 - via commercial sites with which Elsevier has an agreement

In all cases accepted manuscripts should:

- link to the formal publication via its DOI
- bear a CC-BY-NC-ND license - this is easy to do
- if aggregated with other manuscripts, for example in a repository or other site, be shared in alignment with our hosting policy not be added to or enhanced in any way to appear more like, or to substitute for, the published journal article.

Published journal article (JPA): A published journal article (PJA) is the definitive final record of published research that appears or will appear in the journal and embodies all value-adding publishing activities including peer review co-ordination, copy-editing, formatting, (if relevant) pagination and online enrichment.

Policies for sharing publishing journal articles differ for subscription and gold open access articles:

Subscription Articles: If you are an author, please share a link to your article rather than the full-text. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help your users to find, access, cite, and use the best available version.

Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

If you are affiliated with a library that subscribes to ScienceDirect you have additional private sharing rights for others' research accessed under that agreement. This includes use for classroom teaching and internal training at the institution (including use in course packs and courseware programs), and inclusion of the article for grant funding purposes.

Gold Open Access Articles: May be shared according to the author-selected end-user license and should contain a [CrossMark logo](#), the end user license, and a DOI link to the formal publication on ScienceDirect.

Please refer to Elsevier's [posting policy](#) for further information.

18. **For book authors** the following clauses are applicable in addition to the above: Authors are permitted to place a brief summary of their work online only. You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version. **Posting to a repository:** Authors are permitted to post a summary of their chapter only in their institution's repository.

19. **Thesis/Dissertation:** If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be published commercially, please reapply for permission. These requirements include permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for Proquest/UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission. Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

Elsevier Open Access Terms and Conditions

You can publish open access with Elsevier in hundreds of open access journals or in nearly 2000 established subscription journals that support open access publishing. Permitted third party re-use of these open access articles is defined by the author's choice of Creative Commons user license. See our [open access license policy](#) for more information.

Terms & Conditions applicable to all Open Access articles published with Elsevier:

Any reuse of the article must not represent the author as endorsing the adaptation of the article nor should the article be modified in such a way as to damage the author's honour or reputation. If any changes have been made, such changes must be clearly indicated.

The author(s) must be appropriately credited and we ask that you include the end user license and a DOI link to the formal publication on ScienceDirect.

If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder.

Additional Terms & Conditions applicable to each Creative Commons user license:

CC BY: The CC-BY license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article and to make commercial use of the Article (including reuse and/or resale of the Article by commercial entities), provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. The full details of the license are available at <http://creativecommons.org/licenses/by/4.0>.

CC BY NC SA: The CC BY-NC-SA license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article, provided this is not done for commercial purposes, and that the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. Further, any new works must be made available on the same conditions. The full details of the license are available at <http://creativecommons.org/licenses/by-nc-sa/4.0>.

CC BY NC ND: The CC BY-NC-ND license allows users to copy and distribute the Article, provided this is not done for commercial purposes and further does not permit distribution of the Article if it is changed or edited in any way, and provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, and that the licensor is not represented as endorsing the use made of the work. The full details of the license are available at <http://creativecommons.org/licenses/by-nc-nd/4.0>. Any commercial reuse of Open Access articles published with a CC BY NC SA or CC BY NC ND license requires permission from Elsevier and will be subject to a fee.

Commercial reuse includes:

- Associating advertising with the full text of the Article
- Charging fees for document delivery or access
- Article aggregation
- Systematic distribution via e-mail lists or share buttons

Posting or linking by commercial companies for use by customers of those companies.

20. Other Conditions:

v1.7

<https://s100.copyright.com/CustomerAdmin/PLF.jsp?ref=c0b25082-98b1-42af-b25c-3cfaf...> 8/17/2015

Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.

*See glossary