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BETEL QUID CHEWING AND RISK OF ADVERSE BIRTH OUTCOMES AMONG ABORIGINES IN EASTERN TAIWAN

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It is known that substance abuse during pregnancy is associated with increased risk of adverse birth outcomes. The aim of this study was to determine the use of alcohol, cigarettes, betel quid, and drugs among pregnant aboriginal women and to assess the risk of adverse effects of betel quid use on birth outcomes in eastern Taiwan. Of a total of 229 women recruited into this study, 32 women with adverse birth outcomes constituted the case group. Analyses revealed that adverse birth outcomes were associated with maternal betel quid chewing and maternal age. After adjusting for maternal age, the risk of adverse birth outcome was five times higher among betel quid chewing women as compared to substance nonusers. Based on this finding, it is suggested health education, especially when concerned with the harmful effects of substance abuse, which includes betel quid use during pregnancy, should be stressed in concert with routine prenatal care.

In the general population in Taiwan, the prevalence rate of betel quid chewing is approximately 10% irrespective of gender or age; however, in the aborigine population the rate of betel quid chewing is as high as 42% (Ko et al., 1995). Further, chewing betel quid is associated with alcohol drinking or cigarette smoking. The association between adverse birth out-

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comes and cigarette smoking or alcohol use has been widely studied (Larroque et al., 1993; Brown et al., 1996; Hulse et al., 1997; Bennett, 1999). However, few studies have examined the relationship between betel quid chewing and adverse effects on reproduction. Previously, Yang et al. (1999) found adverse pregnancy outcomes, including spontaneous abortion, premature labor, and stillbirth, in women who had chewed betel quid during their pregnancy.

Betel quid is a known cocarcinogen implicated in oral cancer (Ko et al., 1995; Lu et al., 1996). Betel quid consists of three ingredients: betel nut, slaked lime, and a piece of unripe fruit from piper betel. Consumption of betel nut is known to produce various autonomic nervous system effects including feeling warm, sweating, cardioacceleration, salivation, and enhanced alertness. The cytotoxicity and carcinogenic effects of betel nuts are well known (Dave et al., 1992; Jeng et al., 1999). The unripe piper betel fruit contains safrole, which is suspected to be a possible human carcinogen (Vainio & Wilbourn, 1992). In Taiwan, it has been found that 23.7% of aboriginal women chewed betel quid during their pregnancy, as compared to 0.78% of nonaboriginal women in eastern Taiwan (Lua et al., 1995). Due to the high prevalence of betel quid chewing in female aborigines (Yang et al., 1996), the negative health effects on pregnant mothers and developing children are of the greatest public health concern. However, little is known of the relationship between betel quid chewing and adverse birth outcomes. The purpose of this study was (1) to estimate the exposure rate of psychoactive substance use among aboriginal pregnant women, especially betel quid chewing, and (2) to assess the extent of adverse effects of betel quid chewing on birth outcomes.

METHODS

Study Population

From February to September 1998, 229 aboriginal women who gave birth during that period were recruited from a regional hospital in eastern Taiwan for this case-control study. The response rate was 70.1%. Among the participants, those had given birth to a child with (1) low birth weight at full term (birth weight less than 2500 g and with gestation of more than 37 wk), (2) preterm delivery (delivery before 37 wk), or (3) any malformation were considered as the case group. Thirty-two participants were recruited as the case group, which included 10 of low birth weight with full term, 20 preterm, and 2 with malformation. Participants whose babies were without any of these conditions constituted the control group (n = 197). The average age of the mother in the case group was 29.1 yr (SD = 7.0 yr), average body weight before pregnancy was 57.0 kg (SD = 9.0 kg), weight after pregnancy was 70.0 kg (SD = 11.5 kg), average body height was 155.0 cm (SD = 4.8 cm), average husband body height was 168.1 cm (SD = 5.3 cm), and average husband body weight was 70.1 kg (SD = 9.2 kg). In the control group the average maternal age was 25.8 yr (SD = 5.6

yr), average body weight before pregnancy was 57.0 kg (SD = 10.5 kg) weight after pregnancy was 71.3 kg (SD = 11.4 kg), average body height was 157.1 cm (SD = 5.2 cm), average husband body height was 169.4 cm (SD = 5.6 cm), and average husband body weight was 71.9 kg (SD = 9.1 kg). There were no significant differences between the case and control mothers with the exception of average age, which was significantly higher in betel quid chewers.

Data Collection

The participants, who were admitted into the hospital (length of stay approximately 3–5 d) for delivery, were interviewed by trained interviewers using a questionnaire developed and evaluated by the authors. The questionnaire was designed to collect information about (1) sociodemographic background, (2) substance use (betel quid chewing, alcohol consumption, smoking, drug use) during pregnancy, and (3) obstetric data such as past obstetric history, parity, and birth outcomes including birth weight, body length, APGAR score, and malformation of newborn. Part 3 was completed according to the hospital's chart records. The majority of the participants completed the questionnaire within 72 h after their delivery.

Validity and Reliability

Five public health and two obstetric experts were called on to analyze the items of this questionnaire and oversee content coverage and adequacy. Reliability coefficients for the continuous or ordinary variables were reported in the range of 0.78 to 0.89 within the aboriginal women sample; the internal consistency in categorized variables was in the range of 0.85 to 0.91, respectively.

Statistical Analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) or Student's *t*-test was used to examine the relationship between the birth outcome and the variables such as usage of betel quid, cigarettes, and alcohol. Similar procedures were applied to examine the relationship between adverse birth outcome and the sociodemographic or obstetric characteristics (age, education, sex of the infant, maternal body weight, blood relation, martial status, prenatal care, gravidity), and then subsequently examined using multiple logistic regression to assess the odds ratio (OR) of the significant variables in relation to the adverse birth outcome while at the same time controlling for other variables.

RESULTS

The rate of substance use during pregnancy in the case group was found to be as follows: 65.6% for alcohol drinking (more than 3 drinks per occasion: 34.4%), 37.5% cigarette smoking, 68.8% for betel chewing, 75% cigarette smoking by husband. In the control group there were 48.73% alcohol drinking (more than 3 drinks per occasion: 23.4%), 22.3%

cigarette smoking, 48.7% betel chewing, and 75.6% cigarette smoking by husband. Bivariate analyses between case and control by maternal age, level of education, occupation, marital status, number of prenatal care (prenatal OPD visit: number of visits), gravidity, blood relations, maternal body weight and body height, husband's body weight and body height, husband's smoking habit, and husband's occupational exposure were performed. The partial results are shown in Table 1. There were no significant differences between the adverse birth outcome and maternal parameters except for age. The correlation between adverse birth outcome such as low birth weight or preterm birth and substance abuse is shown in Table 2. A significant association was found between low birth weight, preterm birth, and maternal betel quid chewing. The mean birth weight for the infants of betel quid chewers and those of betel nonchewers was 3030 and 3200 g, respectively, which was significant. Comparisons of the demographic variables, maternal alcohol drinking, cigarette smoking, and betel quid chewing during pregnancy between the case group and control group are shown in Table 3. The estimated odds ratio of adverse birth outcome was significantly higher in women who were betel quid chewers during their pregnancy. After controlling for maternal age, cigarette smoking, and alcohol consumption, a significantly higher rate of adverse birth outcome occurred in women who chewed betel quid during pregnancy (adjusted odds ratio, AOR = 5.0, 95% CI = 1.1–23.0). There also appeared to be an additive effect of cigarette smoking and alcohol consumption, as betel quid chewers who were exposed to these other known teratogens had a higher prevalence of adverse birth outcome than betel quid chewers who did not drink or smoke (AOR = 5.7, 95% CI = 1.6–20.3) (Table 4).

DISCUSSION

The genotoxicity and carcinogenicity of tobacco and alcohol are well established. There is abundant evidence to indicate that there are adverse effects of alcohol drinking and cigarette smoking on birth outcome, in-

TABLE 1. Demographic and Selected Obstetric Features of Aborigines With and Without Adverse Birth Outcome

Maternal parameter	Aborigines without adverse birth outcomes, mean (SD)	Aborigines with adverse birth outcomes, mean (SD)
Age (yr)	25.8 (5.6)	29.1 (6.9)[a]
Body weight after pregnancy (kg)	71.3 (11.4)	69.9 (11.5)
Body weight before pregnancy (kg)	56.9 (10.5)	57.0 (9.0)
Height (cm)	157.1 (5.2)	155.0 (4.8)
Body weight increase during pregnancy (kg)	10.9 (17.1)	7.9 (21.8)

[a]Significant versus no adverse birth outcome ($p < .05$).

TABLE 2. Odds Ratios and 95% Confidence Intervals (CI) for Low Birth Weight (LBW) and Preterm Birth by Maternal Betel Chewing, Drinking, and Smoking Among Aboriginal Women

	LBW with full terms (n = 10)		Preterm (n = 20)	
	No/yes	OR (95% CI)	No/yes	OR (95% CI)
Maternal betel chewing				
No	110/1	1.0	79/3	1.0
Yes	109/9	9.1 (1.6–51.8)[a]	130/17	3.4 (1.1–11.4)[a]
Maternal drinking				
No	108/4	1.0	160/13	1.0
Yes	111/6	1.5 (0.4–5.3)	49/7	1.8 (0.7–4.6)
Maternal smoking				
No	167/6	1.0	105/7	1.0
Yes	52/4	2.1 (0.6–7.7)	104/13	1.9 (0.7–4.8)

[a]Significant.

cluding low birth weight, preterm delivery, and malformations (Little et al., 1986; Ahlborg & Bodin, 1991; Larroque et al., 1993; Brown et al., 1996; Hulse et al., 1997; Bennett, 1999). A similar trend was found in this study, but due to the limited number of cases statistical significance was not reached. The habit of betel quid chewing, together with tobacco chewing or smoking, has been associated with an increased risk of oral cancers (IARC, 1985). Data in this study also demonstrated an additive adverse effect of betel quid chewing and smoking or alcohol on adverse birth outcome.

The fetotoxic potential of betel nuts has been investigated in rodents. It was found that arecoline, a component of betel nuts, is mutagenic (Shirname et al., 1983) and carcinogenic to rats (Nishikawa et al., 1992). Betel nuts also inhibit the synthesis of nucleic acids and protein in mouse fetuses (Sinha & Rao, 1985a). The mean weight of live mouse fetuses was found to be reduced by exposure to betel nuts in a dose-response manner (Sinha & Rao, 1985b). In humans a similar result was found in that the birth weight of babies born to pregnant betel nut chewers was significantly lower than that of infants born to women of similar age and province of birth but who had never chewed betel quid (De & Griew, 1982). Chewing betel quid was found to significantly reduce infant birth weight, confirming previous findings. It is of interest that maternal cigarette smoking also lowered infant birth weight.

In Taiwan, most betel quids are prepared with a piece of unripe piper betel fruit, which contains about 1% safrole, which is both genotoxic and mutagenic (Darroudi & Natarajan, 1993; Diamon et al., 1998). Our previous study found that the prevalence of adverse pregnancy outcome (such as abortion) was significantly higher among betel quid chewing women (Yang et al., 1999). Similar results were found in this study (data

not shown). The variables that were probably associated with low birth weight and premature delivery were examined, but no significant differences were found in maternal education, paternal smoking, previous pregnancies number, or paternal occupational exposure in this study. The mechanisms underlying fetal growth retardation and premature delivery due to exposure from maternal betel quid chewing remain poorly understood. As shown in rodents, betel quid components may inhibit the synthesis of nucleic acids and protein in fetuses (Sinha & Rao, 1985a).

There are a number of reasons cited for betel quid chewing during pregnancy: 20.1% for candy substitute, 17.5% as a savor, and 10% for an alertness effect. In tests to find out how betel quid chewing affects the

TABLE 3. Demographic Features and Substance Use During Pregnancy of Aborigines With and Without Adverse Birth Outcomes

	Control group, *n* (%)	Case group, *n* (%)	OR
Educational level			
> 9 yr	110 (55.8)	13 (40.6)	1.0
≤9 yr	87 (44.2)	19 (59.4)	1.9
Marital status			
Married	173 (87.8)	29 (90.6)	1.0
Others	24 (12.2)	3 (9.4)	0.8
Employment status			
Employed	36 (18.3)	8 (25)	1.0
Unemployed	161 (81.7)	24 (75)	0.7
Maternal betel chewing			
No	101 (51.1)	10 (31.3)	1.0
Yes	96 (48.9)	22 (68.7)	2.3[a]
Maternal smoking			
No	153 (77.7)	20 (62.5)	1.0
Yes	44 (22.3)	12 (37.5)	2.1
Maternal drinking			
No	101 (51.3)	11 (34.4)	1.0
Yes	96 (48.7)	21 (65.6)	2.0
Paternal smoking			
No	48 (24.4)	8 (25.0)	1.0
Yes	149 (75.6)	24 (75.0)	0.9
Paternal occupational exposure			
No	145 (73.6)	21 (65.6)	1.0
Yes	52 (26.4)	11 (34.4)	1.5
Maternal drug use			
No	194 (98.5)	32 (100)	—
Yes	3 (1.5)	0 (0)	

[a]Significant versus respective control.

TABLE 4. Adjusted Odds Ratios (AOR) and 95% Confidence Intervals (CIs) of Substance Use During Pregnancy in Aborigines With and Without Adverse Birth Outcomes

	Alcohol drinking					
	User			Nonuser		
Substance use	Cases/ controls	AOR[a]	(95% CI)	Cases/ controls	AOR[a]	(95% CI)
Betel chewing users						
User of cigarettes	9/33	5.7	1.6–20.3[b]	1/6	3.2	0.3–33.4
Nonuser of cigarettes	7/42	3.1	0.8–11.3	5/15	5.0	1.1–23.0[a]
Betel chewing nonusers						
User of cigarettes	1/3	4.5	0.3–69.5	1/2	10.7	0.8–152.5
Nonuser of cigarettes	4/18	4.3	0.98–19.0	4/78	1.0	—

[a]AOR: odds ratios adjusted for the maternal age covariate.
[b]Significant.

fetus, only 45% of the participants recognized the harmful effects. It is considered that a lack of knowledge may contribute to the significant higher rate of betel use during pregnancy in aborigines. Strategies of prevention or control of betel quid chewing among aboriginal women should include (1) cessation of substance use habits, (2) removal of carcinogenic components (piper betel fruit) and/or change to a safe substitute, and (3) emphasis on the undesirable effects of substance use on reproduction in the health-promotion side of prenatal care. This study is limited by the selected nature of the population examined and the heterogeneous population of adverse birth outcomes. Clearly, further research is needed.

REFERENCES

Ahlborg, G., and Bodin, L. 1991. Tobacco smoke exposure and pregnancy outcome among working women: A prospective study at prenatal care centers in Orebro County, Sweden. *Am. J. Epidemiol.* 133:338–347.

Bennett, A. D. 1999. Perinatal substance abuse and the drug-exposed neonate. *Adv. Nurse Pract.* 7:32–36.

Brown, H. L., Watkins, K., and Hiett, A. K. 1996. The impact of the women, infants and children food supplement program on birth outcome. *Am. J. Obstet. Gynecol.* 174:1279–1283.

Dave, B. J., Trivedi, A. H., and Adhvaryu, S. G. 1992. In vitro genotoxic effects of areca nut extract and arecoline. *J. Cancer Res. Clin. Oncol.* 118:283–288.

Darroudi, F., and Natarajan, A. T. 1993. Metabolic activation if chemicals to mutagenic carcinogens by human hepatoma microsomal extracts in Chinese hamster ovary cells. *Mutagenesis* 8:11–15.

De, C. C., and Griew, A. R. 1982. Effects of betel chewing on pregnancy outcome. *Aust. N. Z. J. Obstet. Gynaecol.* 22:22–24.

Diamon, H., Sawada, S., Asakura, S., and Sagami, F. 1998. In vivo genotoxicity and DNA adduct levels in the liver of rat treated with safrole. *Carcinogenesis* 19:141–146.

Hulse, G. K., English, D. R., Milne, E., Holman, C. D., and Bower, C. I. 1997. Maternal cocaine use and low birth weight newborns: A meta-analysis. *Addiction* 92:1561–1570.

IARC. 1985. Betel-quid and areca-nut chewing. *IARC Monogr.* 37:141–291.

Jeng, J. H., Tsai, C. L., Hahn, L. J., Yang, P. J., Kuo, Y. S., and Kuo, M. Y. P. 1999. Arecoline cytotoxicity on human oral mucosal fibroblasts related to cellular thiol and esterase activities. *Food Chem. Toxicol.* 37:751–756.

Ko, Y. C., Huang, Y. L., Lee, C. H., Chen, M. J., Lin, L. M., and Tsai, C. C. 1995. Betel quid chewing, cigarette smoking and alcohol consumption related to oral cancer in Taiwan. *J. Oral Pathol. Med.* 24:450–453.

Larroque, B., Kaminski, M., Lelong, N., Subtil, D., and Dehaene, P. 1993. Effect on birth weight of alcohol and caffeine consumption during pregnancy. *Am. J. Epidemiol.* 137:941–950.

Little, R. E., Asker, R. L., Sampson, P. D., and Renwick, J. H. 1986. Fetal growth and moderate drinking in early pregnancy. *Am. J. Epidemiol.* 123:270–278.

Lu, C. T., Lan, S. J., Yen, Y. Y., Ho, C. S., Hsieh, C. C., and Ko, Y. C. 1996. A case-control study of oral cancer in Changhua County, Taiwan. *J. Oral Pathol. Med.* 25:245–248.

Lua, A., Wei, T. C., Liao, C. Y., Chen, C. Y., and Lin, D. Y. 1995. Ethanol and methamphetamine abuse in obstetric population in the Hualien Area. *Tzu Chi Med. J.* 7:111–118.

Nishikawa, A., Prokopczky, B., Rivenson, A., Zang, E., and Hoffmann, D. 1992. A study of betel quid carcinogenicity of 3-(methylnitrosoamino) propionaldehyde in F344 rats. *Carcinogenesis* 13: 369–372.

Shirname, L. P., Menon, M. M., Nair, J., and Bhide, S. V. 1983. Correlation of mutagenicity and tumorigenicity of betel quid and its ingredients. *Nutr. Cancer* 5:87–91.

Sinha, A., and Rao, A. R. 1985a. Transplacental micronucleus inducing ability of arecoline, a betel nut alkaloid in mice. *Mutat. Res.* 158:193–194.

Sinha, A., and Rao, A. R. 1985b. Embryotoxicity of betel nuts in mice. *Toxicology* 37:315–326.

Vainio, H., and Wilbourn, J. 1992. Identification of carcinogens within the IARC monograph program. *Scand. J. Work Environ. Health* 18:64–73.

Yang, M. S., Ko, Y. C., and Wen, J. K. 1996. Prevalences and related factors of substances use in female aborigines in southern Taiwan. *Kaohsiung J. Med. Sci.* 11:634–640.

Yang, M. S., Chang, F. T., Chen, S. S., Lee, C. H., and Ko, Y. C. 1999. Betel quid chewing and risk of adverse pregnancy outcomes among aborigines in Southern Taiwan. *Public Health* 113:189–192.