An Evaluation of Infertility Among Women in the Republic of Palau, 2016

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Abstract

Fertility challenges are a personal and important part of a woman's reproductive health and are associated with health and lifestyle factors. Limited data exist on infertility among women in Palau. We describe the lifetime prevalence of self-reported infertility in a nationally representative sample of women in Palau and investigate the association between tobacco and/or betel nut use and infertility. During May-December 2016, a population-based survey of noncommunicable diseases was conducted in Palau using a geographically stratified random sample of households (N=2409). Men and women ≥18 years of age were chosen randomly from each selected household. The prevalence of a self-reported lifetime episode of infertility (having tried unsuccessfully to become pregnant for ≥12 months) was evaluated among 874 women aged ≥18 years by key health and lifestyle factors. Prevalence ratios (PR) and 95% confidence intervals (CI) were calculated. Of 315 women who ever tried to become pregnant, 39.7% (95% CI: 34.2%, 45.3%) reported a lifetime episode of infertility. Prevalence was higher in women of Palauan vs other ethnicity (PR=1.6, 95% CI: 1.1, 2.3), those who self-reported poor/not good vs. excellent/very good health status (PR=2.1, 95% CI: 1.4, 3.3), and those with a body mass index (BMI) ≥30 vs <30 (PR=1.7, 95% CI: 1.3, 2.2). Adjusted models showed that tobacco and/or betel nut users were almost twice as likely to report infertility versus non-users (PR=1.8, 95% CI: 1.3, 2.5). More research is needed to understand the infertility experiences of women in Palau and to promote lifestyle factors contributing to optimal reproductive health.

Keywords

Palau, infertility, tobacco, betel nut, obesity

Abbreviations

BMI = body mass index
CI = confidence interval
CT = Chlamydia trachomatis
LBW = low birth weight
NSFG = National Survey of Family Growth
PID = pelvic inflammatory disease
PR = prevalence ratio
STI = sexually transmitted infection

Introduction

The Republic of Palau is an island nation in the western Pacific Ocean with a population of approximately 18000 people.[1] Palau is 1 of 3 Pacific Island nations that have a Compact of Free Association with the United States, along with the Federated States of Micronesia and Republic of the Marshall Islands.[2] Similar to other countries in the Pacific, Palau has a high prevalence of noncommunicable diseases, as well as a high prevalence of the known risk factors for noncommunicable disease, including unhealthy diet, physical inactivity, obesity, excessive alcohol consumption, and tobacco use.[3,4]

An estimated 24.7% of adults in Palau smoke cigarettes daily, and many chew tobacco with betel nut, also known as areca nut.[4,5] Betel nut chewing, common in countries in the Pacific Islands and South/Southeast Asia, generally consists of chewing betel nut along with slaked lime in a piece of a betel leaf. In Palau, betel nut chewing is more common than cigarette smoking, with an estimated 52.6% of adults regularly chewing betel nut (within the last 30 days), with 87% of those adding tobacco to the mixture.[6-9] A higher proportion of women in Palau chew betel nut compared to men (55.1% vs 47.5%, respectively), both with and without tobacco.[8] Chewing betel nut has psychoactive effects, including activation of the sympathetic nervous system to heighten alertness and reduce fatigue.[9,10] This popular local custom is also known to have carcinogenic effects.[6,11,12] Both tobacco and betel nut chewing are associated with oral cancers and both have been identified as public health problems in Palau.[12,13] It is possible that the synergistic effect of combined tobacco and betel nut chewing may increase the risk of adverse carcinogenic outcomes.[12]

Tobacco and betel nut use can also affect a woman's reproductive health. Use of either during pregnancy can result in adverse outcomes, including impaired fetal growth, preterm delivery, low birth weight (LBW), cardiovascular problems, neonatal withdrawal symptoms, and infant mortality.[14-21] Previous studies have also shown an association of tobacco use with infertility, and a meta-analysis of 12 studies found a 60% increased risk of infertility in women smokers vs. non-smokers of reproductive age.[22]

Infertility, typically defined as the inability to conceive for ≥12 months of unprotected sexual intercourse, affects many women throughout the world.[23] Given that fertility declines steadily in women with age, some clinicians consider ≥6 months of unprotected sex without conception an episode of infertility in women aged ≥35 years.[24] In industrialized countries, about 15% of couples who try to conceive will fail to obtain a recognized

pregnancy.[25] Although infertility affects many women, there are limited data estimating its prevalence in many resource-constrained settings.

Despite the known adverse reproductive health outcomes associated with tobacco and betel nut use and the high prevalence of these lifestyle factors among women in Palau, no previous studies have examined the prevalence of and risk factors associated with infertility in these women. Therefore, the aim of this study was to estimate the lifetime prevalence of infertility in a nationally representative sample of women in Palau and investigate the association between tobacco and/or betel nut use and infertility.

Methods

Study Population and Design

We conducted a secondary data analysis using data from a population-based survey conducted in the Republic of Palau from May to December 2016 to assess noncommunicable diseases and associated risk factors. In the original survey, hereafter referred to as the Palau Hybrid Survey, 2409 households were surveyed. The household sample size was determined based on the most populated islands in Palau (Koror = 1592 households, Babeldaob = 704, Peleliu = 70, Angaur = 21, Kayangel = 11, Sonsorol = 6, Hathobei = 5). Households were randomly selected according to geographical stratification on 2 levels: island and state. Men and women aged ≥18 years were then randomly selected from each household for inclusion in the survey using the KISH selection method.[26] Individuals were eligible if they were able to comprehend either the English or Palauan language and provide consent. Due to the secondary data analysis nature of this study, the number of exclusions at each stage of sampling were unavailable to the author; however, most exclusions were due to vacant houses, with the true refusal rate being extremely low. Also, because of the large sample size relative to the total population of Palau (13.3% based on 2015 Census data) and the representativeness of the sample compared to the general population of Palau (the demographic distributions of the 2015 Census are relatively similar to the distributions of the survey sample demographics), these data were not weighted.[1,8] See Supplemental Table 1 for a comparison of the selected sample to the total Palauan population based on 2015 Census data.[8]

Survey respondents answered questions about various health, dietary, and lifestyle factors, and had a range of physical and biochemical measurements taken. Modeled after the questions used in the National Health and Nutrition Examination Survey and the National Survey of Family Growth (NSFG),[27,28] women who reported ever trying to become pregnant were asked "At any time, did you try for more than 12 months and not become pregnant?"; those answering "Yes" were considered to have had a lifetime episode of infertility.[29] We estimated the prevalence of

Table 1. Characteristics of Women Respondents of the Palau Hybrid Survey (n=874), Republic of Palau, 2016.		
Characteristic	Sample Size	% (95% CI)
Age Group, in Years		
18-29	119	13.6 (11.4, 16.1)
30-39	159	18.2 (15.7, 20.9)
40-49	209	23.9 (21.1, 26.9)
50-59	196	22.4 (19.7, 25.3)
≥60	191	21.9 (19.2, 24.7)
Ethnicity[a]		
Palauan	647	74.0 (71.0, 76.9)
Other	227	26.0 (23.1, 29.0)
General Health Status[b]		
Poor/Not good	162	19.4 (16.8, 22.3)
Good/Fair/Okay	545	65.3 (61.9, 68.5)
Excellent/Very good	128	15.3 (13.0, 18.0)
Missing	39	
Body Mass Index		
<18.5	167	19.1 (16.6, 21.9)
18.5-24.9	169	19.3 (16.8, 22.1)
25-29.9	237	27.1 (24.2, 30.2)
≥30	301	34.5 (31.3, 37.7)
Lifetime Episode of Infertility[c]		
Yes	125	39.7 (34.2, 45.3)
No	190	60.3 (54.7, 65.8)
Missing	559	
Any Tobacco Use[d]		
Yes	466	53.3 (50.0, 56.7)
No	408	46.7 (43.3, 50.1)
Any Betel Nut Use[e]		
Yes	481	55.1 (51.7, 58.4)
No	392	44.9 (41.6, 48.3)
Missing	1	
Any Tobacco and/or Betel Nut Use[d,e]		
Tobacco use only	38	4.4 (3.1, 5.9)
Betel nut use only	53	6.1 (4.6, 7.9)
Both betel nut and tobacco use	428	49.0 (45.7, 52.4)
Neither	354	40.5 (37.3, 43.9)
Missing	1	

[a] "Other" consists of Filipino or self-reported "Other" ethnicity.
[b] General health status was based on self-report.
[c] Of those who (1) responded "Yes" to ever having tried to get pregnant and (2) provided a response to the question "At any time, did you try for more than 12 months and not become pregnant?" Women answering "Yes" to the question "At any time, did you try for more than 12 months and not become pregnant?" were defined as having a self-reported lifetime episode of infertility.
[d] Any tobacco use defined as reporting use of any of the following: cigarette sticks, e-cigarette, or betel nut with tobacco.
[e] Any betel nut use defined as report of using betel nut, with or without tobacco.

Supplemental Table 1. Comparison of Palau Hybrid survey sample to 2015 Palauan population based on Census data.[8]		
	Survey Sample N=1768	2015 Census Data N=13,299
Gender		
Male	894 (51%)	7373 (55%)
Female	874 (49%)	5926 (45%)
Age Group		
18-24 years	143 (8%)	1660 (12%)
25-44 years	651 (37%)	5475 (41%)
45-64 years	754 (43%)	4874 (37%)
65+ years	220 (12%)	1289 (10%)
Ethnicity		
Palauan	1253 (71%)	(73%)*
Non-Palauan	515 (29%)	(27%)

*For all ages

self-reported infertility among women who had tried to become pregnant and investigated the association between tobacco and/or betel nut use and self-reported infertility. Data on pregnancy subsequent to an episode of infertility were not obtained.

Data Collection

Public health staff from the Palau Ministry of Health were trained to perform all interviews and measurements. Surveys were translated into Palauan and English and were performed in-person. The survey questions were taken from validated questionnaires, then piloted and modified as necessary for specificity to Palau (Supplemental Table 2). The translations into the Palauan language also underwent piloting. Information was collected on various sociodemographic (eg, age, ethnicity, education, marital status), health (eg, general health status, physical/dental exams, presence of noncommunicable diseases) and lifestyle (eg, tobacco, betel nut, and alcohol use, physical activity) characteristics and subsequent physical measurements were taken the following morning (including height and weight, fasting glucose, cholesterol, and blood pressure measurements). The temporality of lifestyle factors in relation to the episode of infertility was not assessed. Body mass index (BMI) was calculated using the measurements for height and weight. Data on reproductive outcomes or infectious diseases, including sexually transmitted infections (STIs) or their sequelae, were not collected. All data were collected electronically using a tablet and were uploaded weekly at the Palau Ministry of Health. The Palau Institutional Review Board approved and a Research Determination was received from the Centers for Disease Control and Prevention for this analysis.

Statistical Analysis

The prevalence of self-reported lifetime infertility and 95% confidence intervals (CIs) were estimated overall and by various sociodemographic, health, and lifestyle characteristics, including age group (18-29, 30-39, 40-49, 50-59, ≥60 years), ethnicity (Palauan vs. other), self-reported general health status (excellent/very good, good/fair/okay, poor/not good), BMI (<18.5, 18.5-24.9, 25-29.9, ≥30), any tobacco use (use of cigarette sticks, e-cigarettes, or betel nut use with tobacco), any betel nut use (with or without tobacco), and any tobacco and/or betel nut use (tobacco use only, betel nut use only, both tobacco and betel nut use, or neither). Bivariate associations were estimated using prevalence ratios (PRs) and 95% CIs.

We estimated the association between any tobacco and/or betel nut use and infertility using a generalized linear model using a log link and assuming a binomial distribution adjusted for confounders. We first assessed for any effect measure modification by adding terms to the model specific to the interaction between tobacco and/or betel nut use and covariates, such as age, ethnicity, general health status, and BMI. Any interaction term with a *P*-value ≤.05 was considered an effect measure modifier. We then assessed for confounding for covariates with any tobacco and/or betel nut use through a change-in-estimate approach, with covariates changing the any tobacco/betel nut use and infertility association by >10% remaining in the model. All analyses were conducted using SAS statistical software (version 9.4, SAS Institute, Cary, NC).

Results

A total of 1768 individuals aged ≥18 years completed the Palau Hybrid Survey; 874 were women. Of the women respondents, nearly half were ≥50 years of age (50-59 years: 22.4%, 95% CI: 19.7%, 25.3%; ≥60 years: 21.9%, 95% CI: 19.2%, 24.7%; Table 1) and the majority were of Palauan ethnicity (74.0%, 95% CI: 71.0%, 76.9%). Nearly 1 in 5 women respondents (19.4%, 95% CI: 16.8%, 22.3%) reported their general health status to be poor/not good, with the majority (65.3%, 95% CI: 61.9%, 68.5%) reporting to be of good/fair/okay health. More than one-third had a BMI defined as obese (BMI ≥30; 34.5%, 95% CI: 31.3%, 37.7%). Any tobacco and any betel nut use were both highly prevalent in this population, at 53.3% (95% CI: 50.0%, 56.7%) and 55.1% (95% CI: 51.7%, 58.4%), respectively, with 49.0% (95% CI: 45.7%, 52.4%) using both tobacco and betel nut.

Approximately 36.0% (n=315) of women reported that they had ever tried to become pregnant. Of these women, 39.7% (95% CI: 34.2%, 45.3%) reported a lifetime episode of infertility. Among women who had ever tried to become pregnant, those of Palauan ethnicity were significantly more likely to report an episode of infertility compared to those of "other" ethnicity (PR: 1.6; 95% CI: 1.1, 2.3; Table 2). Those reporting good/fair/okay health had nearly equal prevalence of self-reported infertility to those reporting excellent/very good health (PR: 1.1; 95% CI: 0.7, 1.7); however, those reporting poor/not good health had 2.1 times the prevalence of self-reported infertility

Supplemental Table 2. Palau Hybrid Survey Indicators.[8]		
Variable	**Source Question**	**Response Options**
General Health	Would you say that your general health is…	Excellent, very good, good, fair or okay, poor or not good
Last doctor visit	About how long has it been since you last visited a medical provider for an annual checkup?	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Last dental visit	How long has it been since you last visited a dentist or a dental clinic for any reason?	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Teeth missing	How many of your permanent teeth have been removed because of tooth decay or gum disease?	1-5, ≥6 but not all, all, none
Body Mass Index category	Calculated by weight (kg) over height (cm) squared.	Underweight <18.5, normal 18.5-24.9, overweight 25-29.9, obese ≥30
Hypertension	Measured blood pressure and self-reported high blood pressure and medication status was used to categorize hypertension.	Hypertension = BP ≥140/90 and/or if they self-reported being diagnosed with hypertension and were taking medication for their hypertension
High blood sugar or diabetes	Measured fasting blood glucose and self-reported diagnosis of diabetes and medication status was used to categorize high blood sugar/diabetes.	Diabetes = fasting blood glucose ≥126mg/dL and/or self-report for diabetes and were on medication for their diabetes.
High Total Cholesterol	Measured total cholesterol was used.	Elevated cholesterol = total cholesterol ≥190mg/dL; high total cholesterol = total cholesterol ≥240mg/dL.
Low HDL Cholesterol	Measured HDL cholesterol was used.	Low HDL = HDL cholesterol <40mg/dL.
Diseases	Have you ever been told by a doctor that you have gout, arthritis, asthma, ulcer, other heart disease, heart disease, tuberculosis, depression, stroke, lung disease, cancer? (separate variables for each)	Yes or no
Infertility	At any time did you try for more than 12 months and not become pregnant?	Yes or no
Ectopic pregnancy	Were you ever told that you had an ectopic pregnancy (tubal pregnancy that resulted in a miscarriage)?	Yes or no
Pelvic Inflammatory Disease	Have you ever been treated with antibiotics for an infection in your fallopian tubes, womb, or ovaries, also called a pelvic infection, pelvic inflammatory disease, or P.I.D.?	Yes or no
Cigarette Use	During the past 30 days, on how many days did you smoke cigarettes?	0 days = no use; 1-29 days = some use; 30 days = everyday use
Quit cigarette use	Do you want to quit smoking cigarettes?	Yes or no
E-cigarette use	During the past 30 days, on how many days did you use E-Cigarettes or a personal vaporizer (PV), or electronic nicotine?	0 days = no use; 1-29 days = some use; 30 days = everyday use
Home 2nd hand smoke	During the past 7 days, on how many days did someone other than you smoke tobacco inside your home while you were at home?	0 days = no exposure; 1-7 days = some exposure
Work 2nd hand smoke	During the past 7 days, on how many days did you breathe tobacco smoke at your workplace from someone else other than you who was smoking tobacco?	0 days = no exposure; 1-7 days = some exposure
Vehicle 2nd hand smoke	During the past 7 days, on how many days did you ride in a vehicle where someone other than you was smoking tobacco?	0 days = no exposure; 1-7 days = some exposure
Any 2nd hand smoke exposure	Answered yes to any of the 2nd hand smoke questions	Yes or no
Betel nut use	During the past 30 days, on how many days did you chew betel nut?	0 days = no use; 1-29 days = some use; 30 days = everyday use
Use tobacco in betel nut use	What kind of tobacco do you most often add to your betel nut chew?	Cigarette Sticks, imported loose tobacco, locally grown tobacco, other type of tobacco
Quit betel nut use	Do you want to quit chewing betel nut with tobacco?	Yes or no
Alcohol consumption	During the past 30 days, on how many days did you have at least one standard drink of any alcohol?	0 days = no use; 1-29 days = some use; 30 days = everyday use
Binge alcohol frequency	During the past 30 days, how many days did you have (for men, ≥5 standard alcoholic drinks; for women ≥4 standard alcoholic drinks):	0 days = no binge, 1-29 days = some binge, 30 days = everyday binge
Fruit and vegetable consumption	Sum of usual daily fruit consumption and daily vegetable consumption.	<1 servings, 1-<3 servings, 3-<5 servings, ≥5 servings
Watching salt intake	Are you currently watching or reducing your sodium or salt intake?	Yes or no
Importance of lowering salt in diet	How important is lowering salt in your diet?	Very important, somewhat important, not at all important
Processed meat consumption	In a regular day, how many times do you eat processed meats? This does not include canned fish.	0 servings, 1 serving, ≥2 servings

Supplemental Table 2. Palau Hybrid Survey Indicators.[8] (Continued from Previous Page)		
Variable	**Source Question**	**Response Options**
Sugar-sweetened beverage consumption	In a regular day, how many sugary drinks do you drink? This does not include diet drinks made with artificial sweeteners.	0 servings, 1 serving, ≥2 servings
Physical activity level	Based on GPAQ questions and calculations which is a combination of how many weeks a person is vigorously or moderately active due to work, transportation, or recreational activities AND the total number of METs in a week. METs are commonly used in the analysis of physical activity. MET (Metabolic Equivalent): The ratio of the work metabolic rate to the resting metabolic rate. One MET is defined as 1 kcal/kg/hour and is equivalent to the energy cost of sitting quietly. A MET is also defined as oxygen uptake in ml/kg/min with one MET equal to the oxygen cost of sitting quietly, around 3.5 ml/kg/min.	**High-Level**
		• If vigorous PA due to work or leisure on more than 3 days a week and Total physical activity MET minutes per week is greater than or equal to 1500
		• If moderate PA due to work or leisure on 7 days a week and Total physical activity MET minutes per week is greater than or equal to 3000
		Moderate-Level
		• If vigorous PA due to work or leisure on more than 3 days a week that totals 60 or more minutes
		• If moderately PA due to work or leisure on 5 days a week that totals 150 or more minutes
		• If moderate PA due to work or leisure at least 5 days a week and Total physical activity MET minutes per week is greater than or equal to 600
		Low-Level
		• Doesn't meet any of the above criteria
Colonoscopy screening	How long has it been since your last colonoscopy? (adults ≥50)	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Blood stool test	A blood stool test is a test that determines whether the stool contains blood. How long has it been since your last blood stool test? (adults ≥50)	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Mammogram screening	How long has it been since you had your last mammogram? (women 50-74)	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Clinical breast exam	A clinical breast exam is when a doctor, nurse, or other health professional feels the breasts for lumps. How long has it been since your last clinical breast exam?	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Pap smear screening	How long has it been since you had your last Pap test? (women 21-65)	≤1 year, ≤2 years, ≤5 years, ≥5 years, never
Drug use	During the past 30 days, report on how many days you used any of the following substance: prescription drugs, inhalants, LSD, heroin, marijuana. (separate variables for each)	No use = 0 days, use = ≥1 day
Perceptions of drugs as risky	How much do people risk harming themselves physically and in other ways when they engage in the following behaviors? Cigarettes, alcohol, marijuana, betel nut with tobacco, heroin, LSD, inhalants, prescription drugs without doctor's orders	Great risk, moderate, slight, no risk
Disapproval of drug use	How much do you approve or disapprove of the following substances? ≥1 pack of cigarettes per day, betel nut with tobacco everyday, marijuana ≥1 time a month, ≥2 alcohol beverages a day	Strongly disapprove, somewhat disapprove, don't disapprove (includes: approve, somewhat approve, and neither approve or disapprove)

compared to those reporting excellent/very good health (95% CI: 1.4, 3.3). Women with a BMI ≥30 were also significantly more likely to self-report infertility compared with women with a BMI <30 (PR: 1.7; 95% CI: 1.3, 2.2). Women with any tobacco and/or betel nut use were significantly more likely to self-report infertility compared with women using neither (PR: 2.0; 95% CI: 1.4, 2.7).

Among women who had ever tried to become pregnant, ethnicity, general health status, and BMI were also associated with any tobacco and/or betel nut use and were considered as possible confounders (Supplemental Table 3). Women of Palauan

ethnicity, those with a BMI ≥30, and those in good/fair/okay or poor/not good health (compared with excellent/very good health) were more likely to report any tobacco and/or betel nut use. In multivariate analysis, no covariate modified the association between any tobacco and/or betel nut use and infertility, and only BMI was identified to confound the association (age, ethnicity, and general health status were all not identified as confounders). Among women who had ever tried to become pregnant, those reporting any tobacco and/or betel nut use vs. those without had 1.8 times the prevalence of a self-reported lifetime episode of infertility, adjusting for BMI (adjusted PR: 1.8; 95% CI: 1.3, 2.5; Table 2).

Supplemental Table 3. Characteristics of Women Respondents of the Palau Hybrid Survey Associated with Any Tobacco and/or Betel Nut Use[a] (n=315)[b], Republic of Palau, 2016.		
Characteristic	**Prevalence (95% CI)**	**Prevalence Ratio (95% CI)**
Age Group, in Years		
18-29	60.0 (40.6, 77.3)	Ref
30-39	47.9 (35.9, 60.1)	0.8 (0.5, 1.2)
40-49	58.0 (47.0, 68.4)	1.0 (0.7, 1.4)
50-59	65.3 (53.5, 76.0)	1.1 (0.8, 1.5)
≥60	52.9 (38.5, 67.1)	0.9 (0.6, 1.3)
Ethnicity[c]		
Palauan	76.0 (69.8, 81.5)	6.5 (3.7, 11.4)
Other	11.7 (6.0, 20.0)	Ref
General Health Status[d]		
Poor/Not good	81.5 (68.6, 90.8)	3.8 (2.2, 6.5)
Good/Fair/Okay	59.4 (52.2, 66.3)	2.8 (1.6, 4.7)
Excellent/Very good	21.6 (11.3, 35.3)	Ref
Body Mass Index		
≥30	75.2 (66.2, 82.9)	1.6 (1.3, 1.9)
<30	46.5 (39.5, 53.7)	Ref

[a] Any tobacco and/or betel nut use defined as tobacco use only, betel nut use only, or both tobacco and betel nut use. [b] Of those who 1) responded "Yes" to ever having tried to get pregnant and 2) provided a response to the question "At any time, did you try for more than 12 months and not become pregnant?" (lifetime episode of infertility). [c] "Other" consists of Filipino or self-reported "Other" ethnicity. [d] General health status was based on self-report.

Table 2. Characteristics of Women Respondents of the Palau Hybrid Survey Associated with a Self-reported Lifetime Episode of Infertility (n=315)[a], Republic of Palau, 2016.			
Characteristic	**Prevalence (95% CI)**	**Prevalence Ratio (95% CI)**	**Adjusted Prevalence Ratio (95% CI)[b]**
Age Group, in Years			
18-29	40.0 (22.7, 59.4)	Ref	
30-39	42.3 (30.6, 54.6)	1.1 (0.6, 1.8)	
40-49	40.9 (30.5, 51.9)	1.0 (0.6, 1.7)	
50-59	44.0 (32.6, 55.9)	1.1 (0.7, 1.8)	
≥60	27.5 (15.9, 41.7)	0.7 (0.4, 1.3)	
Ethnicity[c]			
Palauan	44.8 (38.1, 51.6)	1.6 (1.1, 2.3)	
Other	27.7 (18.9, 37.9)	Ref	
General Health Status[d]			
Poor/Not good	66.7 (52.5, 78.9)	2.1 (1.4, 3.3)	
Good/Fair/Okay	34.0 (27.4, 41.1)	1.1 (0.7, 1.7)	
Excellent/Very good	31.4 (19.1, 45.9)	Ref	
Body Mass Index			
≥30	53.1 (43.5, 62.6)	1.7 (1.3, 2.2)	
<30	32.2 (25.8, 39.1)	Ref	
Any Tobacco and/or Betel Nut Use[e]			
Any betel nut or tobacco use	50.3 (42.7, 57.8)	2.0 (1.4, 2.7)	1.8 (1.3, 2.5)
Neither	25.7 (18.6, 33.9)	Ref	

[a] Of those who 1) responded "Yes" to ever having tried to get pregnant and 2) provided a response to the question "At any time, did you try for more than 12 months and not become pregnant?" (self-reported lifetime episode of infertility). [b] Calculated with a generalized linear model using a log link and assuming a binomial distribution, adjusting for BMI. [c] "Other" consists of Filipino or self-reported "Other" ethnicity. [d] General health status was based on self-report. [e] Any tobacco and/or betel nut use defined as tobacco use only, betel nut use only, or both tobacco and betel nut use.

Discussion

This is the first study to report on the prevalence of and associations with female infertility in the Republic of Palau, which is an under-represented population in the public health literature. Nearly 40% of women who had ever tried to become pregnant self-reported having had an episode of infertility at some point in their lifetime. The estimates of infertility in this population (39.7%) are notably higher than those from the United States (6.7%).[30] Lifestyle risk factors, such as tobacco and betel nut use, were also highly prevalent, with more than half of women in Palau regularly using either or both.

Women in Palau using any tobacco and/or betel nut were significantly more likely than non-users to report a lifetime episode of infertility.[22,31] Estimates of rates of cigarette smoking among women in Palau are lower than those of women in the United States, with estimates of 9.7% and 13.5%, respectively.[8,32] Prior studies have shown relationships between smoking tobacco and female infertility, with smoking more than half of a pack of cigarettes per day associated with reduced fecundity.[33,34] More than half (55.1%) of women in Palau reported betel nut chewing in the past 30 days, with or without tobacco.[8] Although no prior studies have been performed evaluating the association between betel nut use and infertility, previous studies have found betel nut use to be associated with adverse pregnancy outcomes.[4,20] Prior studies have also found that mothers who chewed tobacco with betel nut had 2.4 times the risk of having a LBW baby at full term compared to non-chewers.[20]

Women who are obese are at increased risk for reproductive health complications compared to their non-obese counterparts, including higher rates of preterm birth and poorer fertility outcomes following assisted reproductive technology.[20,35-39] In this population-based study, we found that more than one-third of women in Palau had a BMI defined as obese (≥30), similar to prior estimates from the 2013 Palauan National Health Profile and lower than US estimates.[4,40] In our analysis, obese women had a higher prevalence of self-reported infertility compared to women of all other BMI categories and BMI confounded the association between tobacco and/or betel nut use and infertility. It is possible that BMI also modifies this association (e.g., obese women who use tobacco and/or betel nut may experience higher rates of infertility than normal weight women who use tobacco and/or betel nut). However, given our small sample size, we may not have been able to detect meaningful differences. It is also possible that other health and lifestyle risk factors affecting women's reproductive health, such as nutrition, exercise, stress, caffeine, alcohol use, and environmental exposures, could affect the association between tobacco and/or betel nut use and infertility in this population.[41] Studies with larger sample sizes could help disentangle the potential interactions of these health and lifestyle risk factors and refine interventions to reduce reproductive health complications.

Other factors known to be associated with infertility are STIs. Infection with *Chlamydia trachomatis* (CT) is the leading preventable cause of tubal factor infertility, and is assumed to act via the intermediate development of pelvic inflammatory disease (PID) which subsequently leads to tubal scarring resulting in infertility.[42,43] PID, and subsequent infertility, can be prevented with prompt detection and treatment of infections, most commonly infections with CT.[44,45] CT is the most commonly reported infection in the Republic of Palau.[4] Data from the 2013 National Health Profile in Palau indicate that the CT case rate in 2011 was 1149 cases per 100 000 population, 2.5 times the rate for the general US population that year (453.4 per 100,000 population); 75% of reported cases were among women.[4,46] Given that 2 out of every 5 women in Palau self-report infertility, the typical association of infertility with a prior chlamydial infection, and the high rates of reported CT in women in Palau, future research should investigate possible associations between a prior chlamydial infection and infertility in this population. Including questions on CT and other STI history, including partner history, and potential sequelae would be useful in future surveys.

There were a number of limitations to this analysis. First, although the survey was population-based, the data were not weighted to account for the stratified sampling design used to recruit survey participants. Point estimates may be subject to non-response bias and may over- or under-represent subpopulations in Palau. Second, the overall sample size was small, particularly when restricted to women who reported having tried to become pregnant. This limited our ability to estimate the prevalence of infertility among sub-populations (eg, young women of other ethnicity). For the same reasons, we were unable to evaluate associations of tobacco and betel nut use separately with infertility. It is also possible that we could not detect important effect measure modifiers, limiting our ability to evaluate the likely complicated association between tobacco and betel nut use and other lifestyle characteristics. The existence of a dose-response effect between tobacco and reduced fecundity has been reported and was of interest in evaluating in this population.[33] However, sample size limitations prevented the analysis of data to that level of granularity. Third, although the survey covered a number of lifestyle questions, some possible important confounders, such as a history of STIs, were not collected. There are a variety of other causes of infertility, including polycystic ovarian syndrome, premature ovarian failure, endometriosis, and autoimmune diseases, such as lupus. These conditions were also not mentioned in the survey and should all be considered valuable areas for future research. Fourth, with the exception of BMI, the variables used in this analysis were based on self-report, including the general health status of the participants, as well as the main outcome of a lifetime episode of infertility, which may have biased our estimates. Questions regarding former vs current tobacco and/or betel nut use were not asked as a part of the survey and would have been an important distinction

to have evaluated. In addition, women reporting an episode of infertility were not asked whether they had a subsequent pregnancy. Finally, the temporality of the presence of health and/or lifestyle factors in relation to a self-reported episode of infertility was not assessed. For example, a woman could report an episode of infertility that occurred when she was 20 years old and was using tobacco, but responded to the survey when she was 40 years old and did not use tobacco, resulting in a misclassification of exposure. In light of these limitations, the results of these analyses should be interpreted as showing that women in Palau who have experienced an episode of infertility during their lifetime are more likely to have used tobacco and/or betel nut during their lifetime and have a higher BMI.

Based on a population-based survey, we document a high prevalence of self-reported infertility among women in Palau and illustrate a complex web of interrelated health and lifestyle factors, including tobacco and betel nut use, which may affect the reproductive health of women in the Republic of Palau. Since betel nut chewing is a cultural norm in Palau and the prevalence of tobacco use, obesity, and poor general health are all high, it is important to understand how these factors may be leading to a serious public health issue and to identify the most effective ways to intervene. Similarly, a better understanding of the role of a variety of health problems as causes of infertility in Palau is important. The high prevalence of and associations between health and lifestyle factors with infertility identified in this study may also be informative for other Pacific island nations that have customs similar to those of Palau. The results of this study highlight the need for more research to understand the infertility experiences of women in Palau and to promote healthy lifestyle factors contributing to optimal reproductive health in the Pacific island nations.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of Interest

The authors report no conflicts of interest.

Acknowledgments

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