Central Australian Aboriginal women's placental and neonatal outcomes following maternal smokeless tobacco, cigarette or no tobacco use

Angela Ratsch,[1,2] Fiona Bogossian,[3,4] Elizabeth A. Burmeister,[1,4] Kathryn Steadman[5]

Abstract

Objective: To describe the placental characteristics and neonatal outcomes of Central Australian Aboriginal women based on maternal self-report of tobacco use.

Methods: Placental and neonatal variables were collected from a prospective maternal cohort of 19 smokeless tobacco chewers, 23 smokers and 31 no-tobacco users.

Results: Chewers had the lowest placental weight (460 g) while the no-tobacco group had the heaviest placental weight (565 g). Chewers and the no-tobacco group had placental areas of similar size (285 cm^2 and 288 cm^2, respectively) while the placentas of smokers were at least 13 cm^2 smaller (272 cm^2). There were two stillbirths in the study and more than one-third (36%) of neonates (newborns) were admitted to the Special Care Nursery, with the chewers' neonates having a higher admission rate compared with smokers' neonates (44% vs. 23%). The cohort mean birthweight (3348 g) was not significantly different between the groups. When stratified for elevated maternal glucose, the chewers' neonates had the lowest mean birthweight (2906 g) compared to the neonates of the no-tobacco group (3242 g) and smokers (3398 g).

Conclusions: This research is the first to demonstrate that the maternal use of Australian *Nicotiana* spp. (pituri) as smokeless tobacco may negatively impact placental and neonatal outcomes.

Implications for public health: Maternal smokeless tobacco use is a potential source of placental and foetal nicotine exposure. Maternal antenatal screening should be expanded to capture a broader range of tobacco and nicotine products, and appropriate cessation support is required.

Key words: pregnancy, maternal, perinatal, placental, foetal, neonatal outcomes, smoking, smokeless tobacco, pituri, Central Australia, Australian Aboriginal and Torres Strait Islander people.

Maternal tobacco smoking and maternal exposure to combusted tobacco vapour are associated with adverse maternal, placental, foetal and neonatal outcomes, with sequelae through childhood and adolescence[1-10] and into adulthood.[11-16] Reducing both the maternal use of smoked tobacco and exposure to the vapour from combusted tobacco are recognised as the most significant foetal and neonatal risk-reducing behaviours that can occur during pregnancy.[17,18]

Tobacco smoking is commonplace in Westernised populations, however, in low- and middle-income countries and in Indigenous populations, the use of smokeless tobacco (ST) is often more common.[19] ST is a term that describes tobacco products that are not combusted and are instead chewed, sucked or applied to the gums or nasal lining as powders and pastes. Products include chewing tobacco, snuff, chimo and khaini, and there are an estimated 356 million adult users in 140 countries (one in 10 males and 1 in 20 females).[19] This prevalence is likely an underestimate due to non-reporting of ST by more than 58 World Health Organization member states (including Australia and New Zealand), nevertheless, an estimated 90 million women >15 years of age use ST globally.[20]

Note to readers: In this research, the Central Australian Aboriginal women chose the term 'Aboriginal' to refer to themselves, and 'Indigenous' to refer to the broader group of Australian First Peoples. That choice has been maintained in the reporting of the research findings.

In Australia, Central Australian Aboriginal populations in the Northern Territory (NT) and adjacent state areas utilise wild tobacco plants (*Nicotiana* spp.) called *pituri,* as ST.[21] Portions of the dried plant are chewed to a pulp and placed in the lip, cheek and buccal space for extensive periods. If the quid of tobacco is removed from the oral space, it is stored on skin sites, for example under a headband, armband or behind the ear, possibly providing transdermal nicotine administration.[22] Female pituri use

1. Wide Bay Hospital and Health Services, Queensland
2. Rural Clinical School, The University of Queensland, Queensland
3. School of Health and Behavioural Sciences, University of the Sunshine Coast, Queensland
4. School of Nursing, Midwifery and Social Work, The University of Queensland, Queensland
5. School of Pharmacy, The University of Queensland, Queensland
Correspondence to: Dr Angela Ratsch, Wide Bay Hospital and Health Services, Hervey Bay, Queensland, 4655; e-mail: Angela.ratsch@health.qld.gov.au
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commences in early life and does not cease during pregnancy and lactation.[23] There has been no general health research related to pituri use, or any specific research examining the effects of pituri use on placental or neonatal outcomes.

Tobacco and nicotine: placental and foetal impacts

The question as to whether the maternal use of ST could affect placental and neonatal outcomes is premised on the pharmacological knowledge of nicotine. Nicotine is a potent vaso-constrictor and is the primary active and dose-dependent lethal component of tobacco.[22] Nicotine binds with and activates nicotinic acetylcholine receptors (nAChRs) in central and peripheral neuronal and non-neuronal tissue.[24-27] Receptor type and individual variability, including genetics and pregnancy, result in receptor up-regulation or desensitization in a biphasic manner.[22,28]

In the placenta, nicotine effects are thought to be due to mediation of the placental nAChRs, adversely affecting placental vessels and inhibiting trophoblast interstitial migration, invasion and differentiation, which impacts the establishment and development of the placenta.[29,30] An observational study in Pakistan compared 40 placentas of ST users to those of 40 non-ST users and demonstrated no difference in placental weights and the absence of gross morphological differences. However, at the micro-morphology level, there were significant abnormalities in the placental structures of ST users that would impact perfusion at the placental-uterine interface including: doubling of villi with excessive collagen ($p<0.001$), doubling of sub-trophoblastic basement membrane ($p<0.001$), doubling of syncytial buds ($p<0.001$), and tripling of apoptotic cells (i.e. programmed cell deaths; $p<0.001$).[31]

The placenta is critical to the survival and growth of the neonate (newborn), consequently, nicotine-induced changes to the placenta and its functionality flow on to changes in neonatal outcomes including lower birthweight, intrauterine growth retardation (which results in a small for gestational age [SGA] neonate), prematurity and admission to Special Care Nursery (SCN).[32] Birthweight is one of the sentinel predictors for neonatal mortality and morbidity,[33] and maternal cigarette exposure research shows a dose-dependent neonatal birthweight reduction of 320–435 grams (g),[34] while ST research shows birthweight reduction of between 100 g and 395 g.[35-39] In addition, there is a dose-dependent increased risk for preterm birth (<37 weeks gestation) and decreased length of gestation associated with both smoking and ST exposure.[36,38-44]

Foetal nicotine exposure also results in a dampened response to intrauterine and post-birth hypoxic episodes.[45-47] Research in low- and middle-income countries shows a stillbirth rate of 27–89/1000 births in ST chewers compared to 6–31/1000 in non-ST chewers.[36,48,49] Systematic reviews of studies in high-income countries show a 36–46% increase in the likelihood of stillbirth in the presence of maternal smoking.[50,51]

Nicotine: glucose homeostasis impacts

In addition to the foetal impact of nicotine exposure at CNS nAChRs, nicotine increases maternal blood glucose levels via the stimulation of the pancreas.[52] Insulin resistance is a normal aspect of pregnancy;[53] however, smoking in pregnancy increases the risk (AOR 1.9) for gestational diabetes.[54] At the foetal level, rat studies[13,55] show that the pancreas is vulnerable to nicotine exposure both during foetal life and during lactation, resulting in a loss of beta-cell mass and impaired glucose homeostasis. This permanent beta-cell damage triggers a cascade of physiological responses including glucose and insulin intolerance, hyperinsulinaemia and increased body weight.[56,57]

For Aboriginal neonates, exposure to elevated maternal glucose levels increases birthweight (mean increase 280 g), while for Caucasian neonates, exposure decreases birthweight (mean decrease 43 g).[58] Both Aboriginal and Caucasian neonates exposed to elevated glucose have lower APGAR scores at 5 minutes (8.78 and 9.08, respectively), compared to non-exposed neonates (9.09 and 9.15, respectively).[58] Gestational age (both preterm and post-term), birthweight (both low birthweight <2500 g and higher birthweight > 4000 g[59]) and elevated glucose independently increase the likelihood of caesarean section (CS) birth,[60,61] which in turn increase the likelihood of admission to SCN.[62] A well neonate is expected to have an APGAR score at 5 minutes ≥7 and is not expected to be admitted to SCN. A neonatal APGAR score at 5 minutes <7 indicates the neonate is taking longer to transition to extra-uterine life and signals the likelihood of admission to SCN.[62] Admission to SCN physically distances the mother from her neonate and extends the neonate's length of stay in hospital with resultant social, cultural, clinical and economic implications.

Objective

In Central Australia, the maternal use of *Nicotiana* spp. exposes the placenta and neonate to nicotine[63] and this exposure has not previously been examined. This paper presents the placental and neonatal findings from a larger descriptive research study, the complete protocol of which is published elsewhere.[64] The purpose of this paper is to address the primary research question: What are the placental characteristics and neonatal outcomes of Aboriginal women who self-report no-tobacco use, chewing pituri or smoking during pregnancy? Pregnancy, labour and birth outcomes[65] suggest an association between chewing pituri and the development of elevated maternal glucose levels. Elevated maternal glucose adversely affects gestational age and birthweight and increases the likelihood of admission to SCN and of a CS birth.[62,66] Consequently, a secondary research question was added: Is there an association between elevated maternal glucose and neonatal outcomes?

Methods

The research questions were addressed through a cohort study of prospectively enrolled pregnant Central Australian Aboriginal women who planned to birth at the Alice Springs Hospital, NT, Australia. The design, methodology and protocols were informed, directed and approved by a regional Aboriginal Women's Council. Ethical approval was obtained from the Central Australian (#2010.06.04) and The University of Queensland Human Research Ethics Committees (#2010000548 and # 2015001429). All participants provided written informed consent for themselves and their neonate prior to enrolling in the study, and all methods were conducted in accordance with the guidelines and regulations of the National Statement for the Ethical Conduct in Human Research.[67]

Sampling frame, sample size and exclusion criteria: The extent of pituri chewing by pregnant Central Australian Aboriginal

women had not been previously established. Observation suggested approximately 33% did not smoke or use pituri, 33% of women used pituri, and 33% of women smoked (R. Carroll, personal communication, 16 July 2009). This smoking estimate was supported by the NT Mothers and Babies Report,[68] which indicates a self-reported rate of 30% for Indigenous mothers in the Alice Springs District compared with an NT-wide rate of 52% in the first 20 weeks of pregnancy. The lower smoking rates in Central Australia are surmised to be a result of the 'local practice of chewing tobacco (pituri) in that region'.[69,70]

Detecting statistically significant adverse placental and neonatal outcomes in association with maternal tobacco and nicotine exposure requires an extensive sample size, which was not feasible in this study due to the relatively small Central Australian Aboriginal maternal population. Based on the observed rates of no-tobacco use, pituri use, and smoking, a sample of 20 participants in each group was considered sufficient to provide preliminary descriptive placental and neonatal data to inform further studies. Known maternal predictors of adverse placental and neonatal outcomes were not exclusion criteria for this study. These predictors are endemic in the target population and include: limited access to health and antenatal care, unemployment and poverty, poor nutrition, cardiac and renal disease, anaemia and hypertension.[70-72] Exclusion due to the presence of these predictors would have significantly reduced the eligible population sample. The only maternal exclusion criterion was self-reported dual pituri and cigarette use as the study was not resourced to distinguish between placental and neonatal effects arising from tobacco and nicotine absorbed through the maternal respiratory tract, and those arising from the maternal oral and transdermal routes.[73]

Population and recruitment: This study population is the singleton neonates ≥28 weeks gestation and their placentas born from a maternal sample of conveniently recruited Central Australian Aboriginal women who planned to birth at the Alice Springs Hospital, who were ≥18 years of age at the time of enrolment, and who consented to enrol themselves and their neonate in the research.

Data collection: Informed by the neonatal and placental literature[74-80] and by the pregnancy, labour and birth outcomes,[65] maternal, neonatal and placental variables were included in the data collection. The maternal variables were: age at enrolment (years and months); parity (number of births after 20 weeks or of at least 400 g); elevated glucose – any pre-pregnancy or gestational report of diabetes (yes/no); CS (yes/no); and tobacco use (yes/no and type if yes). The placental variables were: weight (g), and area (cm^2), and the neonatal outcomes were: viability (liveborn/stillborn); gender (male/female); gestational age (weeks and days); birthweight (g); head circumference in centimetres (cm); neonatal length (cm); APGAR score (</≥ 7); and admission to SCN (yes/no).

Accordingly, three data collection strategies were used. The first was a maternal interview on enrolment conducted by Aboriginal Health Workers (AHWs), Aboriginal Liaison Officers (ALOs) and midwives to capture self-report of tobacco use and variables such as maternal education, which are not routinely collected. Secondly, routinely collected data were drawn from the maternal and neonatal demographic and birth record contained in the NT Perinatal Data Report housed in CARESYS® (the NT electronic medical record system). Thirdly, placental weight and area were measured by midwives.

Data analysis: All analyses were completed using SPSS® and Stata 15 (Statacorp, Texas). The maternal self-report of tobacco use at interview was used to categorise the neonates into maternal tobacco exposure groups: a) no-tobacco exposure; b) pituri exposure; or c) cigarette smoking exposure. Missing data were examined for patterns and outliers identified through standard processes,[81] and both were reported but excluded from the analysis. Descriptive statistics with means and 95% confidence intervals (CI) if normally distributed, or medians with ranges for continuous data, or frequency and proportions for categorical data were reported. Maternal self-reported tobacco use was used as the independent variable for comparative analyses with statistical significance reported at the 0.05 alpha level.

Results

Maternal and birthing characteristics

The maternal and birthing characteristics are reported in full elsewhere,[65] in summary, the data in Table 1 show that of the 73 maternal participants, 31 mothers reported no-tobacco use, 19 reported pituri use and 23 reported cigarette use. The median maternal age of the cohort on enrolment was 24 years with no significant differences between the groups. The pituri chewing group experienced less than half the rate of CS (21%) compared with the smoking (48%) and slightly less than half of the no-tobacco group (39%). The rate of elevated glucose was higher in the pituri users (n = 9, 47%) compared with the smoking group (n = 5, 22%) and no-tobacco group (n = 5, 16%). The likelihood of the pituri chewing group having elevated glucose levels was four times that of no-tobacco use (OR: 4.68, 95%CI 1.26-17.42).

Placental characteristics

Placental weight and size data were not available for 30 (41%) births. There were no reports of antepartum haemorrhage, and one chewer was reported to have a retained placenta. Table 2 shows that the mean placental weight was 598 g (95%CI

Table 1: Maternal and birth characteristics by maternal self-reported tobacco use (N=73).

Variable	Maternal self-reported tobacco use			
	Total N=73	No-tobacco use n=31	Chewer n=19	Smoker n=23
Maternal age in years				
Median (range)	24 (18–38)	22 (18–37)	26 (18–34)	23 (18–38)
Maternal age categorised, n (col %, 95%CI)				
< 20	15 (21, 13–32)	11 (35, 20–54)	1 (5 ,1–31)	3 (13, 4–35)
20–29	41 (56, 44–67)	15 (48, 31–66)	10 (53, 30–74)	16 (70, 48–85)
30–39	17 (23, 15–35)	5 (16, 7–34)	8 (42, 22–65)	4 (17, 6–39)
Elective caesarean section	10 (14, 7–24)	2 (6, 2–23)	3 (16, 5–40)	5 (22, 9–44)
Emergency caesarean section	17 (23, 15–35)	10 (32, 18–51)	1 (5, 1–31)	6 (26, 12–48)
Elevated glucose[a]				
Yes	19 (26, 17–38)	5 (16, 7–34)	9 (47, 26–70)	5 (22, 9–44)
No	54 (74, 62–83)	26 (84, 66–93)	10 (53, 30–74)	18 (78, 56–91)
Odds ratio (95%CI) of elevated glucose		Reference group	4.68 (1.26–17.42)	1.44 (0.36–5.73)

Notes:
a: CARESYS® data did not specify if condition was pre-existing or gestational.

Table 2: Placental characteristics by maternal self–reported tobacco use (N=43).

	Total[a] N=43	Maternal self–reported tobacco use		
		No–tobacco n=22	Chewer n=11	Smoker n=10
Placental weight (g)				
n=43 mean (95% CI)	598 (502–694)	574 (528–620)	485 (385–585)	774 (349–1199)
n=40 mean (95% CI)[b]	548 (509–587)	574 (528–620)	485 (385–585)	564 (466–663)
n=40 median (range)[b]	555 (280–800)	565 (380–800)	460 (280–750)	500 (460 –690)
Placental area (cm^2)[b]				
n=43 mean (95% CI)	286 (264–308)	301 (273–328)	279 (220–339)	259 (209–310)
n=40 mean (95% CI)[b]	290 (269–312)	301 (273–328)	279 (220–339)	276 (229–323)
n=40 median (range)[b]	288 (156–480)	288 (208–480)	285 (156–450)	272 (180–340)

Notes:

a: Missing placental data n = 30 (no tobacco, n = 9 (30%); chewer, n = 8 (27%); smoker, n = 10 (43%))

b: Placenta of 3 smoker group participants not included in weight analysis and area as extreme outliers (90 g, 1740 g and 1960 g)

Table 3: Neonatal outcomes and characteristics by maternal self-reported tobacco use (N = 73).

	Total N=73	Maternal self–reported tobacco use		
		No–tobacco n=31	Chewer n=19	Smoker n=1230
	n (col %, 95% CI)			
Viability				
Liveborn	71 (97,89–99)	30 (97, 79–99)	18 (95, 69–99)	23 (100,–)
Still born	2 (3,1–11)	1 (3, 1–21)	1 (5, 1–31)	0 (0)
Neonate gender				
Male	40 (55, 43–66)	19 (61, 43–77)	11 (58, 35–78)	10 (43, 25–64)
Female	33 (45, 34–57)	12 (39, 23–57)	8 (42, 22–65)	13 (57, 36–75)
Gestational age, weeks				
< 28 weeks	1 (1, 0–9)	0 (0)	0 (0)	1 (4, 100)
28–36 weeks	6 (8, 4–17)	3 (10, 50)	2 (11, 33)	1 (4, 17)
37+ weeks	66 (90, 81–95)	28 (90, 42)	17 (89, 26)	21 (91, 32)
Mean (95 % CI)[a]	38.8 (38.3–39.2)	38.8 (38.2–39.5)	38.4 (37.6–39.1)	39.0 (38.1–40.0)
Birthweight				
<1,500 g	2 (3, 1–11)	0 (0)	0 (0)	2 (9, 2–30)
1,500–2,499 g	6 (8, 4–17)	3 (10, 3–27)	3 (16, 5–40)	0 (0)
2,500–2,999 g	12 (16, 9–27)	5 (16, 7–34)	4 (21, 8–46)	3 (13, 4–35)
3,000–3,499 g	23 (32, 22–43)	12 (39, 23–57)	4 (21, 8–46)	7 (30, 15–52)
3,500–3,999 g	21 (29, 19–40)	9 (29, 16–48)	5 (26,11–51)	7 (30, 15–52)
4,000–4,499 g	6 (8, 4–17)	1 (3, 1–21)	3 (16, 5–40)	2 (9, 2–30)
> 4,500 g	3 (4, 1–12)	1 (3,1–21)	0 (0)	2 (9, 2–30)
Mean (95% CI)[a]	3,348 (3,189–3,507)	3,278 (3,065–3,491)	3,286 (2950–3,622)	3,500 (3,153–3,848)
Head circumference, cm				
Mean (95% CI)	34.3 (33.8–34.8)	34.1 (33.2–34.9)	33.8 (32.9–34.7)	35.0 (34.0–35.9)
Missing,[b] n	7	3	3	1
Body length, cm				
Mean (95% CI)	49.8 (49.0–50.6)	49.9 (48.5–51.2)	49.2 (47.7–50.7)	50.2 (48.9–51.6)
Missing,[b] n	4	1	2	1
CS birth				
Yes	27 (37,27–49)	12 (39, 23–57)	4 (21, 8–46)	11 (48, 28–68)
No	46 (63, 51–73)	19 (61, 43–77)	15 (79, 54–92)	12 (52, 32–72)
APGAR at 5 minutes (liveborn neonates n = 71)				
< 7	7 (10, 5–20)	4 (14, 5–32)	2 (11, 3–37)	1 (5, 1–28)
≥ 7	60 (90, 80–95)	25 (86, 68–95)	15 (89, 63–97)	20 (95, 72–99)
Missing,[b] n	4	2	1	1
Neonate admitted to Special Care Nursery[c]				
Yes	25 (36, 25–48)	12 (40, 24–59)	8 (44, 23–68)	5 (23, 9–45)
No	45 (64, 52–75)	18 (60, 41–76)	10 (56, 32–77)	17 (77, 55–91)

Notes:

a: N=72, 1 extreme outlier omitted from calculation

b: Missing data not included in percentage or p value calculation

c: N=70, 1 extreme outlier (birthed at 27 weeks) and 2 stillbirths omitted from calculation

502-694). The smoker group had two very large placentas (1740 g and 1960 g) and one very small placenta (90 g) that met the outlier criteria and were removed from the analysis. The median placental weight for pituri chewers was 460 g, which was 40 g below that of the smokers and 105 g below that of the no-tobacco use group. Comparison of the placental area data shows the cohort median placental area was 288 cm^2, with the placentas of no-tobacco use group slightly larger in area (288 cm^2) than those of pituri users (285 cm^2), and the placentas of smokers (272 cm^2) were approximately 16 cm^2 smaller than those of the no-tobacco use group.

Neonatal characteristics

The neonatal findings are shown in Table 3 and are summarised as follows:

Viability and gender. Of the 73 neonates born in the study, 71 were liveborn. Two foetal deaths in utero (stillbirths) were reported, both at 40 weeks gestation; a neonate from a pituri chewing mother and a neonate from a no-tobacco using mother. There were 40 male neonates (55%) and 33 female neonates (45%) born in the study with no gender difference apparent across the cohort, although when considered by the tobacco exposure group, differences in the male:female ratios were evident. The male:female ratio in the no-tobacco use group was 19:12, 61% male; the ratio shifted to a closer equivalence in the pituri chewing group (11:8, 57% male), and was reversed in the smoking group with the birth of fewer males than females (10:13, 43% male).

Gestational age. The cohort mean gestational age was 38.8 weeks and no significant difference between the groups. In total seven neonates (10%) birthed before term (< 37 weeks). Analysis of these data indicated that four of the seven neonates met the outlier labelling rule; three "reasonable" (neonate of no-tobacco use mother = 34 weeks, neonate of pituri chewing mother = 34 weeks; neonate of smoking mother = 31 weeks), and one "extreme" outlier (neonate of smoking mother = 27 weeks). Removal of the data from three reasonable outliers resulted in no change in the difference in gestational age data between the groups and their results were retained; however, the extreme outlier skewed the gestational age findings and was subsequently removed from the analysis. There were no post-term outlier births.

Birthweight. Comparable mean birthweight findings were demonstrated in the cohort, with no significant difference between the groups, although at the 50% birthweight percentile, the neonates of pituri chewers weighed 160 g less than those of smokers; 3300 g vs. 3460 g. Eight neonates were categorised as low birthweight (< 2500 g). Analysis indicated one neonate's data (smoking mother = 27-weeks gestation, 900 g birthweight) impacted the birthweight range of the smoking cohort and met the outlier labelling rule and was subsequently removed from the analysis. Nine neonates had birthweights > 4000 g, none of which met the outlier criteria.

Head circumference and body length. The mean head circumference of the group was 34.3 cm (95%CI 33.8-34.8) and body length was 49.8 cm (49.0-50.6). The neonates of pituri chewers had the smallest mean head circumference (33.8 cm, 95%CI 32.9-34.7) and were shorter in mean length (49.2 cm, 95%CI 47.7-50.7) compared to the length of the no-tobacco use group (49.9 cm, 95%CI 48.5-51.2) and smoking groups (50.2 cm, 95%CI 48.9-51.6).

CS birth. The neonates of smoking mothers were more likely to be born via CS (48%) compared with the no-tobacco use group (39%) and pituri chewers (21%). Clinically, it was expected that the neonates born following CS would have more likelihood of being admitted to SCN; however, there were between-group differences with 75% for the no-tobacco group, compared with 27% for the smoking group and 25% for the chewing neonates being admitted to SCN post-CS birth.

APGAR score. The data show that 90% of the cohort had an APGAR ≥ 7 at five minutes, with no differences between the groups.

Admission to SCN. Proportionally, the neonates from the pituri chewing cohort (44%) were more likely to be admitted to SCN compared with the neonates from the no-tobacco group (40%) and the smoking group (23%).

Gestational age and birthweight: Association with elevated maternal glucose

Gestational age impacts birthweight, and both are affected by elevated maternal glucose,[66] accordingly, analysis of data relating to gestational age, birthweight and elevated maternal glucose was undertaken (Table 4). The data show that the glucose-exposed neonates had a shorter gestation by a mean of seven days and a higher mean birthweight (3698 g, 95%CI 3376-4019) than the neonates without exposure to elevated glucose (mean birthweight 3231 g, 95%CI 3054-3409). The data indicate between-group differences, with the rate of neonates exposed to elevated glucose being higher in the pituri group (n = 9, 47%) compared with the smoking group (n = 4, 18%) and no-tobacco use group (n = 5, 16%).

There were tobacco exposure in-group birthweight differences based on elevated glucose exposure. The neonates of pituri chewers exposed to elevated glucose had a mean birthweight increase of 803 g (28%) compared with the neonates of maternal chewers without exposure. The neonates of smokers with exposure to elevated maternal glucose had a higher mean birthweight of 564 g (17%) compared with the neonates of smokers without elevated maternal glucose exposure. Considering only the neonates from the no-tobacco use group, exposure to elevated maternal glucose was associated with a higher mean birthweight of 224 g (7%) compared to neonates without exposure to elevated glucose.

Analysis of the data from all neonates who were not exposed to elevated maternal glucose indicates that the neonates of pituri chewers were the lowest birthweight group (mean 2906 g, 95%CI 2465-3347), with a mean birthweight 335 g (10.4%) less than the non-exposed neonates of no-tobacco users (mean 3242 g, 95%CI 3045-3438) and 492g (14.5%) less than the non-exposed neonates of smokers (mean 3398 g, 95%CI 2987-3808).

Neonatal characteristics and outcomes: Association with admission to SCN

Clinically, several birthing and neonatal characteristics are predictors for SCN admission including lower gestational age, lower and higher birthweight, CS birth, an APGAR score < 7 at five minutes, and exposure to elevated maternal glucose. Table 5 shows that across the cohort, 36% of neonates were admitted to SCN, comprising all neonates (n = 6) less than 37 weeks gestation, and all neonates < 2499 g (n = 7) and 50% of those above 4000 g (n = 4).

Following CS birth, 48% (n = 13) of neonates were admitted to SCN, with a higher proportion (75%, n = 9) of neonates of the no-tobacco use group admitted compared with smokers' neonates (27 %, n = 3) and neonates of pituri chewers (25%, n = 1). The data show

Table 4: Gestational age, birthweight and elevated maternal glucose by maternal self-reported tobacco use (N = 72).

	Elevated maternal glucose		Maternal self-reported tobacco use					
	All N = 72[a]		No tobacco n = 31		Chewer n = 19		Smoker n = 22	
Elevated glucose	No n = 54	Yes n = 18	No n = 26	Yes n = 5	No n = 10	Yes n = 9	No n = 18	Yes n = 4
Gestation, weeks[a]								
Mean (95% CI)	39.0 (38.5–39.5)	38.0 (37.3–38.7)	39.0 (38.3–39.7)	37.6 (35.7–39.5)	38.8 (37.7–39.9)	37.9 (36.6–39.1)	39.1 (38.0–40.2)	38.8 (37.2–40.3)
Median (range)	39 (31–41)	38 (34–40)	39 (34–41)	37 (36–40)	39 (36–41)	38 (34–39)	39 (31–41)	39 (38–40)
Pre-term <37; n (col%, 95%CI)	4 (7, 3–19)	2 (11, 3–37)	2 (8, 2–27)	1 (20, 2–75)	1 (10, 1–50)	1 (11, 1–54)	1 (6,1–33)	0 (0)
Term 37- 41; n (col%, 95%CI)	50 (93, 81–97)	16 (89, 63–97)	24 (92, 73–98)	4 (80, 25–98)	9 (90, 50–99)	8 (89, 46–99)	17 (94, 67–99)	4 (100, –)
Birthweight, g[a]								
Mean (95%CI)	3,231 (3,054–3,409)	3,698 (3,376–4,019)	3,242 (3,045–3,438)	3,466 (2,223–4,709)	2,906 (2,465–3,347)	3,709 (3,299–4,119)	3,398 (2,987–3,808)	3,961 (3,480–4,443)
Median (range)	3,275 (1,420–5,380)	3,850 (2,020–4,600)	3,430 (2,160–3,940)	3,440 (2,020–4,600)	2,885 (1,930–3,860)	3,840 (2,850–4,290)	3,325 (1,420–5,380)	4,014 (3,580–4,238)

Notes

a: N=72, low gestational age neonate omitted from calculation

that 32% (n = 20) of the cohort with an APGAR ≥ 7 at five minutes were admitted to SCN admission consisting of 44% (n = 7) of neonates of pituri chewers compared with 32% (n = 8) neonates of no-tobacco users and 24% (n = 5) of neonates of smokers. Of the neonates exposed to elevated glucose (24%, n = 17), all no-tobacco-exposed neonates (n = 4) and 50% (n = 2) of neonates of smokers were admitted to SCN, compared with 44% (n = 4) of neonates of pituri chewers.

Discussion

Mindful of the gaps in the literature around the use of ST by Central Australian Aboriginal women and the pharmacological potential for ST to impact pregnancy outcomes, this paper reports on the placental characteristics and neonatal outcomes associated with maternal tobacco exposure. The findings show that more than half (57%) of the neonates were exposed to maternal tobacco use (26% ST use, 31% cigarette use) and there were differences in placental and neonatal outcomes based on this exposure.

Placental weight and size. The placenta and its functionality are critical to the survival and growth of the foetus. The smallest median placental area was evidenced in the smoking group (272 cm^2), which was 13 cm^2 smaller than the pituri chewing group (285 cm^2), and 16 cm^2 smaller than the placentas from the no-tobacco use group (288 cm^2). Placenta research[82] shows that the effect of cigarette smoking at different stages of pregnancy and different doses of exposure has a non-linear effect on placental size and weight, thus while the smaller placental area findings in this study are supported by some previous research,[83] they are counter to other research that shows larger placentas in the presence of maternal smoking with an elevated odds ratio (OR) of placenta praevia in a dose-related response (OR 1.42 95%CI: 1.30, 1.54).[84]

In terms of placental weight, the pituri chewing group demonstrated the lowest median placental weight (460 g) in comparison to the smoking group (500 g) and the no-tobacco group (565 g); however, there were two exceptionally large placentas in the smoking group (1740 g and 1960 g) and one very small placenta (90 g), which were excluded from the analysis. The evidence around heavier placentas in smokers is mixed, with some reports refuting the association[83] while others are supportive.[85,86] In the latter, there is speculation of placental inflammation induced by smoked tobacco exposure, as well as an increase in placental angiogenesis in response to pathological hypoxia from nicotine exposure, which results in heavier placentas in smokers. Similar to the smoked tobacco research, the finding of lower placental weight in the ST users in this study is corroborated by some reports[31] and contrary to other reports.[87] Nevertheless, the findings in this research show the placentas of smokers have a smaller area and are heavier compared with those of pituri chewers, who have a wider area and lighter placentas, and both are different to the placentas of the no-tobacco use group. The mechanism and impact of different types, doses and durations of tobacco and nicotine exposure at different stages of placental development requires sound biochemical, genomic and imaging assessment to inform the consideration of findings.

Gender: Worldwide the ratio of male to female births is 106:100 or 51.4% male.[88] In this research, of the 73 neonates, 40 were male (55%) and 33 were female (45%); however, gender ratio differences between tobacco exposure groups were evident. There were more males in the no-tobacco group (19:12, 61%) than the pituri chewing group (11:8, 59%), and a reversal of the male:female ratio in the smoking group (10:13, 43%). Evidence from both maternal and paternal cigarette smoking research shows similar findings to the smoking-exposed group in this research, with a reduction in the

Table 5: Neonatal characteristics, outcomes and admission to special care nursery by maternal self-reported tobacco use (N = 70).

	Elevated maternal glucose		Maternal self-reported tobacco use					
	All N = 70[a]		No tobacco n = 30		Chewer n = 18		Smoker n = 22	
Admitted to Special Care Nursery	No n = 45 (37–52)	Yes n = 25 (18–33)	No n = 18 (12–26)	Yes n = 12 (7–19)	No n = 10 (5–17)	Yes n = 8 (4–14)	No n =17 (11–25)	Yes n = 5 (2–10)
Gender n (95%CI)								
Male	25 (18–33)	14 (8–21)	10 (5–17)	9 (5–16)	6 (3–12)	4 (1–9)	9 (5–16)	1 (0–5)
Female	20 (13–28)	11 (6–18)	8 (4–14)	3 (1–8)	4 (1–9)	4 (1–9)	8 (4–14)	4 (1–9)
Gestation n (95%CI)								
<37 weeks	0	6 (3–12)	0	3 (1–8)	0	2 (0–6)	0	1 (0–5)
≥37 weeks	45 (37–52)	19 (12–27)	18 (12–26)	9 (5–16)	10 (5–17)	6 (3–12)	17 (11–25)	4 (1–9)
Birthweight g n (95%CI)								
<2,499	0	7 (3–13)	0	3 (1–8)	0	3 (1–8)	0	1 (0–5)
2,500–3,999	41 (33–49)	14 (8–21)	18 (12–26)	8 (4–14)	9 (5–16)	3 (1–8)	14 (8–21)	3 (1–8)
>4,000	4 (1–9)	4 (1–9)	0	0 (0–5)	1 (0–5)	2 (0–6)	3 (1–8)	1 (0–5)
CS n (95%CI)								
No	31 (23–39)	12 (7–19)	15 (9–22)	3 (1–8)	7 (3–13)	7 (3–13)	9 (5–16)	2 (0–6)
Yes	14 (8–21)	13 (8–20)	3 (1–8)	9 (5–16)	3 (1–8)	1 (0–5)	8 (4–14)	3 (1–8)
APGAR 5 minutes n (95%CI)[b]								
< 7	2 (0–6)	3 (1–8)	1 (0–5)	2 (0–6)	0	1 (0–5)	1 (0–5)	0
≥ 7	42 (34–49)	20 (13–28)	17 (11–25)	8 (4–14)	9 (5–15)	7 (3–13)	16 (10–23)	5 (2–10)
Exposure to elevated glucose								
Yes, n (col%, 95%CI)	7 (41, 20–66)	10 (59, 34–80)	0 (0)	4 (100, –)	5 (56, 23–84)	4 (44, 16–77)	2 (50, 9–91)	2 (50, 9–91)

Notes

a: N=70. Two stillbirth and low gestational age neonate omitted from calculation.

b: Three AGPAR scores missing from calculation.

male:female newborn gender ratio (82-92:100) in a tobacco dose-response manner and the mechanisms still to be defined.[89-91] ST research also confirms reductions in the male:female ratio in ST chewers (80-81:100, 45% males) compared with non-ST users (106-109:100, 52% males).[36,92] Research is required to explore the possible changes in gender ratios associated with maternal (and paternal) tobacco and nicotine use and exposure. The findings of such research could be influential in pregnancy-related tobacco cessation strategies.

Gestational age and birthweight: Gestational age and birthweight are key variables that are strongly associated with neonatal and infant mortality[93] and with the development of chronic diseases in adulthood.[94] The cohort demonstrated a mean gestation age of 38.8 weeks and comparable mean birthweights. The similarity in mean birthweights was contrary to the smoking in pregnancy literature, which describes lower birthweights in smoked tobacco-exposed pregnancies.[18] In this research, the use of mean birthweight as an indicator of group neonatal health may be misleading if considered outside the potential confounder of elevated maternal glucose.

Elevated maternal glucose can result in an SGA or LGA birthweight, which can result in an admission to SCN and/or earlier induced labour with lower gestational age birthing.[95,96] Smoking has the reverse effect, lowering birthweight.[97] Previous research shows that elevated glucose during pregnancy is associated with birthweight after adjusting for the smoking group.[98,99] This research showed similar mean birthweights across the three groups; however, the effect of elevated maternal glucose may have masked lower birthweights in the tobacco-exposed groups and particularly so for the neonates of pituri chewers. In the presence of elevated glucose, the mean birthweight increase was greater for the neonates of pituri chewers (803 g), than for neonates of smokers (563 g), and the neonates of the no-tobacco exposure group (255 g). Comparison between the tobacco-exposed neonates who were not exposed to elevated glucose showed the neonates of pituri chewers weighed 492 g less than those of smokers. That is, the neonates of pituri chewers had a lower mean birthweight than the neonates of smokers in the absence of elevated maternal glucose.

Pregnancy-specific diabetes research generally categorises smoked tobacco and ST use together as tobacco use[100-103] and shows that tobacco use before and during pregnancy increases the risk of gestational diabetes.[54,104] In this study, the increased proportion of elevated glucose for participants in the pituri chewing group suggests that it may be a tobacco/nicotine-specific mechanism that is involved in altering glucose metabolism, as distinct from a combusted tobacco mechanism.

A discussion on maternal tobacco and nicotine exposure and elevated glucose in pregnancy is incomplete without consideration of the long-term neonatal outcomes. Epidemiological studies show a relationship between maternal smoking and an increased risk of developing type 1 diabetes in childhood when genetic predisposition was controlled,[12] and increased hypertension, obesity and type 2 diabetes in the adult offspring of smoking mothers.[14,56,105] Research in animals exposed in utero to nicotine consistently demonstrates impaired neonatal glucose homeostasis, hyperinsulinaemia, increased body weight and dyslipidaemia.

For the neonate, the intrauterine environment is critical to its development and predicts lifelong health. Adverse exposures in that environment impact on foetal programming and short-, medium- and long-term health and cognitive outcomes. The glucose-exposed neonates of pituri users and smokers experience a double impact, with exposure to high glucose and high nicotine in-utero environment, and the possibility of continued nicotine exposure through the breast milk after birth.

CS, APGAR and SCN admission: In this research, the neonates of smoking mothers were twice as likely to be born via CS compared with the pituri chewers (48% vs. 21%). It may be that differences in maternal or pregnancy characteristics and/or foetal characteristics contributed to this difference. It is also possible that exposure to tobacco and nicotine products and the cumulative effect of tobacco and nicotine contributes to these differences. Nicotine has a biphasic effect at nAChRs with intermittent administration (such as with smoking) increasing a range of maternal physiological responses, which are then translated to foetal responses through the maternal–foetal transfer of nicotine.[22] In the presence of maternal smoking, there is an increased likelihood of stillbirth (OR 1.46 95%CI 1.36-1.55),[50,51] and the presence of a non-reassuring foetal heart rate pattern and foetal tachycardia is cited as influencing higher CS rates in maternal smokers.[106] Conversely, continued and accumulated nicotine administration (such as with high dose and frequent smoking, and ST use) produces a decrease in nAChRs responses and a dampening of neuronal activity.[24,107]

SCN admission occurred more often in the neonates of pituri chewers than of smokers (44% vs. 23%) and more often in the neonates of pituri chewers with APGARs ≥7 compared with the neonates of smoking mothers (44% compared to 24%), with these admissions unrelated to CS birth. It is theorised that the nAChR responses of the pituri users' neonates are more blunted than the smokers' neonates due to the cumulative effect of maternal pituri use and the administration method,[23,108] which perhaps produces elements of the nicotine narcolepsy[109,110] known and highly desired by the adult Aboriginal pituri users as 'pituri dreaming'.[23]

Limitations

The paper reports the placental characteristics and neonatal outcomes from an observational study that conveniently enrolled the maternal participants categorised on their self-reported use of tobacco. Self-report is the global standard for reporting tobacco use in pregnancy, however, this method may produce under-reporting.[111,112] The maternal participants were enrolled after 28 weeks gestation. Potential maternal participants who experienced a miscarriage, or birthed, or were transferred to another health service prior to 28 weeks were not included, which possibly underestimates the impact of tobacco and nicotine exposure on early- and mid-pregnancy outcomes. The data collection included data from the healthcare reporting systems, and data entry errors could have occurred, and the extracted data were not checked against medical records. While differences between tobacco and nicotine exposure groups are suggested in these findings, and these findings have been reported back to the regional Aboriginal Women's Council, caution needs to be applied to the interpretation of the results given the imprecision of the estimates as indicated by wide confidence intervals.

Conclusion

In vivo evidence demonstrates that nicotine, the principal pharmacologically active element in tobacco cigarettes, adversely affects the placenta and is fetotoxic, and this study provides the first evidence that maternal pituri use is a potential contributory risk factor in adverse placental and neonatal outcomes. Aside from cigarettes, tobacco and nicotine are contained in a range of other products including smokeless tobacco, e-cigarettes and nicotine replacement therapies. Worldwide, the curing of tobacco for ST use and the formulation of ST products differs extensively, and in addition, ST self-administration practices vary widely with population demographics. These factors challenge the external validity of the findings of this study. Nevertheless, 35 years ago, the 1986 Surgeon General's Report on the Health Consequences of Using Smokeless Tobacco[113] evidenced a range of adverse general health outcomes. Since then, further research has extended the adverse general health outcomes[114-116] and begun to establish pregnancy-specific adverse findings for the neonates of mothers who use ST.[41,117-120]

As an outcome of sustained public health education in Australia over the past 20 years, there has been a decline in the self-reported rates of smoking in pregnancy from 19% in 2001 to 9.6% in 2018.[121,122] In parallel, there has been an increase in the use and availability of ST and nicotine products.[20] This generational shift in tobacco and nicotine use is not reflected in the Australian Perinatal Data Collection.[123] That is, women continue to be asked about their own cigarette use only, and there is no standardised inquiry about second-hand smoke exposure, e-cigarettes, nicotine gum, patches, drops, mists or ST. This limited tobacco and nicotine screening has ramifications for the mother, her children, the clinician, Indigenous populations and the broader profile of Australian health. It is timely to review the pregnancy assessment of tobacco and nicotine exposure to capture the growing use of novel tobacco and nicotine products, as well as the pre-colonisation use of ST by Australian Indigenous populations.[21] In doing so, more comprehensive information that reflects the multicultural and contemporary nature of Australian populations and their use of tobacco and nicotine will be available to consider against placental and neonatal outcomes.

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