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Original Article

Maternal periodontal disease and perinatal mortality

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Background: Periodontal disease has been associated with increased perinatal mortality.

Aims: To examine the association between maternal periodontal disease and perinatal mortality.

Methods: We performed a retrospective and prospective matched case–control study of women with unexplained perinatal mortality at more than 20 weeks gestational age. Women were matched for socioeconomic status, smoking status and time since delivery. All women underwent a detailed periodontal examination and completed a questionnaire describing oral health symptoms. No intervention took place.

Results: Fifty-three women who had experienced a perinatal death and 111 controls completed the study. Thirty-two women were recruited retrospectively and 21 women were recruited prospectively. Twenty-three (43.4%) women who had experienced a perinatal death and 27 (24.3%) controls had periodontal disease. There were no differences in oral health behaviours or symptoms between cases and controls. Perinatal death was associated with periodontal disease (odds ratio (OR) 2.34, 95% confidence interval (CI) 1.05, 5.47). Periodontal disease was more strongly associated with perinatal mortality due to extreme prematurity (OR 3.60, 95% CI 1.20, 12.04). Multivariate analysis showed this relationship to be consistent after inclusion of higher parity, country of birth, advanced maternal age and maternal obesity in the model (OR 4.56, 95% CI 1.25, 21.27).

Conclusions: Maternal periodontal disease may contribute to perinatal mortality, especially that caused by extreme prematurity.

Key words: perinatal mortality, periodontal disease, preterm birth, stillbirth.

Introduction

Perinatal mortality remains a significant problem in modern obstetrics; the current perinatal mortality rate is approximately 9.5 per 1000 in developed countries.[1] Normally formed fetuses may succumb due to unexplained stillbirth, extreme prematurity and intrauterine growth restriction. These causes account for 38% of perinatal deaths in Australia and these rates have been stable in recent years.[2]

Periodontitis is a chronic inflammatory condition of the periodontal tissues supporting the tooth and the alveolar bone resulting in destruction of connective tissue and, in later stages, bone resorption. Periodontal disease has been associated with preterm birth, and treatment of periodontal disease has been shown to reduce the rate of preterm birth in some studies,[3,4] but not others.[5] Animal studies have suggested that periodontal disease may be associated with perinatal mortality[6–8] and there are two published studies investigating this association in humans.[9,10]

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We aimed to explore the association between clinical periodontal disease, maternal oral health symptoms and perinatal mortality caused by perinatal infection, antepartum haemorrhage, fetal growth restriction, spontaneous preterm birth and unexplained fetal death.

Methods

The study was a matched case–control study. Ethics approval was provided by the local institutional Ethics Committee and informed written consent was obtained from each woman. Subjects were excluded if the woman: was pregnant at the time of recruitment; had a history of cervical surgery, structural uterine anomalies or diethylstilbestrol exposure; had previous or ongoing periodontal treatment by a specialist periodontist; required prophylactic antibiotics for dental examination; or had insufficient English language skills to understand the consequences of participation in the study.

Cases were defined as women experiencing an 'idiopathic' fetal or neonatal death, classified by Perinatal Society of Australia and New Zealand (PSANZ) categories listed in Table 1, in a singleton pregnancy. We grouped unexplained perinatal mortality and deaths caused by fetal growth restriction, antepartum haemorrhage or preterm birth, in the absence of an underlying cause such as maternal hypertension,

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Table 1 Categories of Perinatal Society of Australia and New Zealand Perinatal Death Classifications defined as idiopathic perinatal death

Category 2 Perinatal infection
• 2.19 Unspecified bacterial infection†
Category 4 APH
• Placental abruption‡
• Other APH
• APH of undetermined origin
Category 8 Fetal growth restriction
Category 9 Spontaneous preterm
Category 10 Unexplained antepartum death

†Unspecified bacterial infection included pregnancies with a similar presentation to Category 9, Spontaneous preterm, but had funisitis on placental histology.
†Women with placental abruption were excluded if there was evidence of hypertension.
APH, antepartum haemorrhage.

maternal thrombophilia, fetal anomaly, placenta praevia, trauma, cervical incompetence or uterine structural anomalies. These cases of perinatal mortality may have an infective origin, such as periodontal disease. The definition of perinatal mortality used in this study was the death of babies weighing at least 400 g or greater than 20 weeks gestation where birthweight is not known, consistent with the Australian National Perinatal Statistics Unit definition. The cause of perinatal mortality was determined using the Perinatal Society of Australia and New Zealand coding system, the PSANZ PDC,[11] after a thorough investigation. A comprehensive maternal obstetric and medical history was performed on all the women experiencing a perinatal death as part of clinical care. Diagnosis of the cause of death was made by consensus in consultation with maternal fetal medicine specialists, perinatal pathologists and neonatologists. One of three specialised perinatal pathologists performed all the postmortem examinations.

The study was planned to include 100 cases and 200 controls. This sample size allowed detection of an odds ratio (OR) of 2.5 with 80% power in order to evaluate the strength of association between periodontal disease and perinatal mortality[12] (assuming 15% periodontal disease in controls, based on unpublished data from a pilot study performed in the same hospital). An interim analysis was planned to take place after 50 cases had been recruited, and following this analysis, recruiting was stopped.

Cases were recruited using two methods, retrospective and prospective. Initially the hospital records were examined and women who had delivered within the previous two years and conformed to the definition of perinatal mortality were contacted. A second group of women were recruited prospectively from those attending the hospital Perinatal Loss Clinic.

Controls were matched using the hospital obstetric database for women who had delivered a singleton liveborn infant at a gestational age of 37 weeks or greater. Women who experienced perinatal mortality (cases) were matched by smoking status during pregnancy (defined as smoking during pregnancy yes/no), time since delivery (within one month) and socioeconomic status (SES), in a ratio of one case to two controls. SES was determined using the surrogate marker of postcode of residence at the time of delivery. Local government areas are ranked according to the Australian Bureau of Statistics using the Index of Relative Socio-Economic Advantage/Disadvantage. Women who agreed to participate then attended for a periodontal examination and completion of a questionnaire as described below.

One periodontist (CW) performed all examinations and took a brief medical and dental history. The periodontal examination involved examining the patient's dentition, periodontium, soft tissues and fillings if present. The whole mouth was charted using the Florida Probe™ and six sites were assessed on each tooth. Periodontal pocket depth, clinical attachment loss (CAL) and bleeding on probing were recorded for each site. After the dental examination, each subject was advised of any treatment required and given a record of the examination findings to be taken to their dentist. No treatment was performed as part of the study. The examiner was blinded to the case or control status of the women, and participants were asked not to disclose this information.

Periodontal disease was defined as four or more sites with greater than or equal to 3 mm CAL and pocket depth greater than or equal to 4 mm. This definition was adapted from Offenbacher *et al.*[13] to account for the approximate 1 mm decrease in pocket depth seen in the non-pregnant state compared to pregnancy.[9,14,15] Participants completed a questionnaire following the dental examination regarding oral health symptoms and behaviours.

Continuous data were summarised using medians and interquartile ranges. Categorical data were summarised using frequency distributions. Univariate comparisons of continuous outcomes were performed using Mann–Whitney test or Kruskal–Wallis test. Comparisons of categorical outcomes were performed using chi-square test for association. Conditional logistic regression was conducted to investigate the effects of periodontal disease on pregnancy loss. Other covariates such as ethnicity, parity, body mass index (BMI) and age were also examined. SPSS (SPSS, Chicago, IL, USA) and LogXact 5 (Cytel, Cambridge, MA, USA) statistical software were used for statistical analysis. All hypothesis tests were two-sided and conducted at 5% significance level.

Results

Fifty three women who had experienced a perinatal death (50 stillbirths and three neonatal deaths) and 111 controls completed the study (Figs 1 and 2). Seven cases were matched with only one control, 35 cases with two controls, ten cases with three controls and one case with four controls.

There was no difference between the cases and the controls with respect to age, parity, marital status, educational achievement, BMI, ethnicity, infant gender, family income, pre-existing diabetes or hypertension (Table 2). Among

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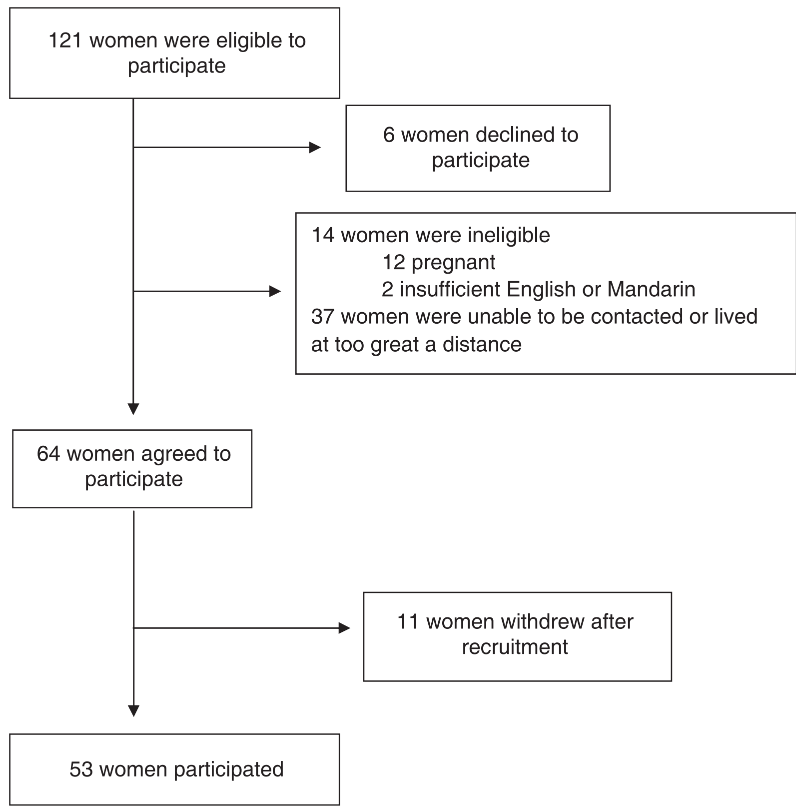

Figure 1 Participation of cases.

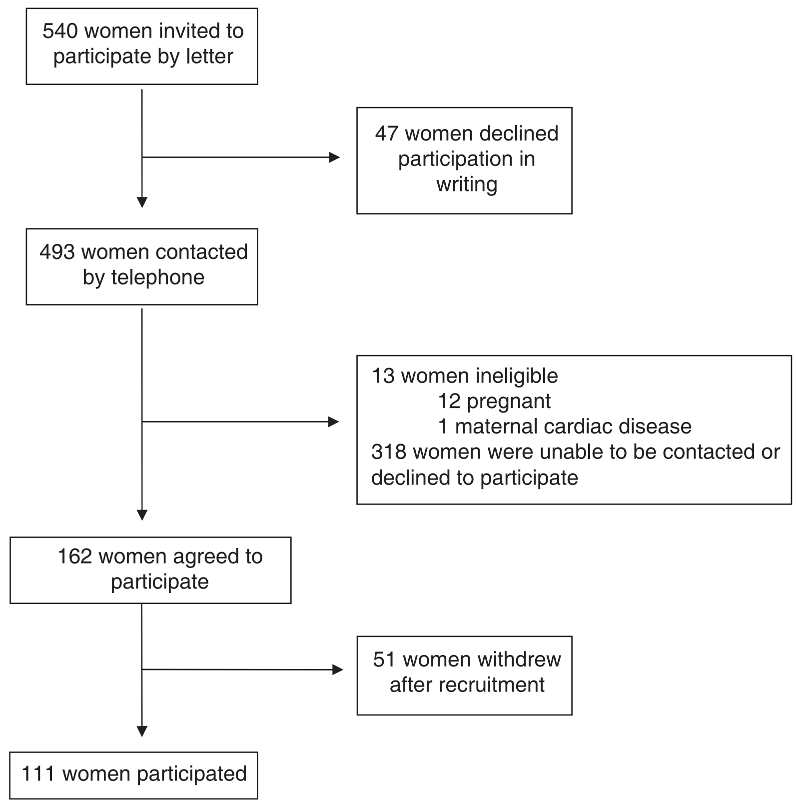

Figure 2 Participation of controls.

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Table 2 Demographic data

		Case	Control	*P*-value
Maternal age		31 (26,34)	33 (26.5,36)	0.05
Nulliparous		26 (49.1)	55 (49.5)	1.00
Completed secondary education		31 (58.5)	65 (58.6)	1.00
Body mass index > 25		21 (42.0)	42 (38.5)	0.93
Country of birth Australia*		40 (75.5)	71 (64.0)	0.21
Mode of delivery	Spontaneous vaginal	48 (90.4)	59 (56.8)	< 0.001
	Instrumental vaginal	0 (0.0)	20 (18.0)	
	Caesarean section	5 (9.4)	28 (24.3)	
Male infant		27 (50.9)	53 (47.7)	0.80
Infant birthweight (g)		447.5 (352 1007)	3487 (3235 3776)	< 0.001
Gestational age at delivery		22 (21,27)	40 (38.4,41)	< 0.001
Apgar 5 minutes		NA	9 (8,9)	NA
Family income	< $A40 000 per annum	12 (22.6)	28 (25.2)	0.05
	≥ $A40 000 per annum	33 (62.3)	62 (55.9)	
	Not stated	8 (15.1)	11 (9.9)	
Maternal diabetes		2 (3.8)	4 (3.6)	1.00
Maternal hypertension		2 (3.8)	3 (2.7)	1.00

Data missing for one control.
Data are *n* (%) or median (interquartile range) as appropriate.
NA, not applicable.
*One woman in each group was Aboriginal or Torres Strait Islander.

Table 3 Incidence of maternal periodontal disease in cases and controls

	Case	Control
	n = 53	*n* = 111
Periodontal disease†	23 (43.4)	27 (24.3)
≥ 4 sites with PD of ≥ 4 mm	27 (50.9)	36 (32.4)
≥ 4 sites with CAL of ≥ 3 mm	23 (43.4)	27 (24.3)

Data are presented as *n* (%).
†Periodontal disease as defined in text.
CAL, clinical attachment loss; PD, pocket depth.

women with perinatal death, as expected, gestational age was shorter, infant birthweight was lower and mode of delivery was more likely to be a vaginal delivery. Four of the cases had had a previous perinatal death; however, this information was not available for the women in the control group.

The study was concluded following interim analysis that demonstrated an effect of periodontal disease on perinatal mortality. The sample size calculations were performed for an expected effect size, however, the effect size was larger and so a positive finding was demonstrated earlier.

Fifty (30.5%) women had periodontal disease (Table 3). There was no difference in oral health behaviours or symptoms between cases and controls (Table 4). The cause of death, according to the PSANZ PDC classification, is described in Table 5. A complete post-mortem was performed in 36 of the cases, external examination and X-rays only in four cases, and a post-mortem was not performed in 13 cases. Other investigations were performed less frequently in the majority of cases, except in the women whose infants were classified as unexplained antenatal death.

Twenty-three (43.4%) women who had experienced a perinatal death and 27 (24.3%) controls had periodontal disease. Perinatal death was associated with periodontal disease (OR 2.34, 95% confidence interval (CI) 1.05, 5.47) and this relationship remained statistically significant when multivariate analysis was performed including parity, country of birth, advanced maternal age and maternal obesity (OR 2.57, 95% CI 1.03, 6.76). The association was also present when the periodontal parameters of four or more sites with pocket depth greater than equal to 4 mm (OR 2.58, 95% CI 1.08, 6.50), four or more sites with CAL greater than or equal to 3 mm (OR 2.64, 95% CI 1.26, 5.77) and number of sites with bleeding on probing (OR 1.52, 95% CI 1.21, 1.96) were analysed separately.

Data were analysed for the entire study and then for cases of bacterial infection, antepartum haemorrhage and spontaneous preterm birth together, as these clinical outcomes are thought to often originate from a common pathway. These patients were characterised by extreme prematurity, the mean gestational age at delivery was 21.8 weeks (interquartile range (IQR) 21–22 weeks). In comparison, the mean gestational age for the remaining patients was 29.6 weeks (IQR 25–35 weeks). Periodontal disease was associated with perinatal mortality due to extreme prematurity (OR 3.60, 95% CI 1.20, 12.04). Multivariate analysis again showed this relationship to be consistent after inclusion of higher parity, country of birth, advanced maternal age and maternal obesity in the model (OR 4.56, 95% CI 1.25, 21.27).

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Table 4 Oral health symptoms and behaviours in cases compared to controls

Symptom	OR	95% CI
Teeth brushing (twice a day or more)	1.38	0.66, 2.97
Cleaning between teeth (once a day or more)	2.54	0.97, 6.94
Regular dental visit	0.76	0.34, 1.72
Bad breath in morning (daily)	1.73	0.77, 4.04
Bad breath all day (daily)	0.88	0.01, 18.23
Bleeding gums when brushing (daily)	0.56	0.09, 2.31
Bleeding gums when flossing (monthly or more)	1.00	0.49, 2.47
Bad taste in mouth (daily)	0.47	0.08, 1.90
Reddened gums (monthly or more)	1.37	0.45, 4.15
Sensitivity of teeth (monthly or more)	0.78	0.32, 1.84

Responses were provided by between 114 and 151 subjects for each question.
CI, confidence interval; OR, odds ratio.

Table 5 Cause of death classified by PSANZ PDC

Category	Number of cases	Category	Number of cases
2 bacterial infection	6 (11.3)	2.19	6
4 antepartum haemorrhage	6 (11.3)	4.1	2
		4.9	4
8 fetal growth restriction	8 (15.1)	8.1	3
		8.2	1
		8.3	3
		8.8	1
9 spontaneous preterm	21 (39.6)	9.11	3
		9.12	4
		9.17	1
		9.21	10
		9.22	3
10 unexplained antepartum death	12 (22.6)	10.3	12
Total	53		53

Data are *n* (%).

Discussion

Women with perinatal loss were more than twice as likely to have periodontal disease and women with perinatal loss due to extreme prematurity were more than four times as likely to have periodontal disease, compared to women with a full-term, liveborn infant. These risks to pregnancy could only be determined by a periodontal examination, not by maternal oral health behaviours or oral health symptoms.

Only pregnancies that were more than 20 weeks gestational age, consistent with Australian perinatal mortality definitions and were classified as an unexplained perinatal death, as defined above, were included. The majority of cases were thoroughly investigated to exclude known causes of perinatal mortality. A post-mortem was performed in 75% of cases and placental histology in 98%, which is high in comparison to data from other states in Australia and the UK, where post-mortem rates as low as 34% have been recorded.[16,17]

Two other studies have also found an association between perinatal mortality and periodontal disease. The largest was by Moore *et al.*[9] This study included women experiencing 'miscarriage' at any gestational age from 12 weeks. Women experiencing a 'miscarriage' had more evidence of periodontal disease. The cause of the perinatal mortality was not described, and so this population was likely to include fetuses that died from any of a range of causes including congenital anomalies, termination of pregnancy or iatrogenic prematurity. It is likely that these causes of perinatal mortality are equally distributed through the patients with or without periodontal disease, but this is not known.

Similarly, Lieff *et al.* published, in abstract form only, details of women experiencing perinatal mortality from the Oral Conditions in Pregnancy cohort.[10] Eighty eight women experienced a fetal loss, but data were only available on 36 of these. Fetal loss was defined as spontaneous abortion at less than 20 weeks or intrauterine fetal demise at greater than 20 weeks. The OR for fetal loss among women with periodontal disease was 5.0 (95% CI 1.1, 22.0).

Both these studies have similar results to our study; however, there were significant methodological differences.

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Perinatal mortality was not the primary endpoint, the definitions used were not consistent with widely accepted definitions of perinatal mortality and it is difficult to ascertain the cause of death of the fetuses or infants. Interestingly, although a recent large study evaluating the effects of treatment of periodontal disease in pregnancy did not find a reduction in preterm birth, there was a decrease in the composite outcome of spontaneous abortion and still birth in the group that received antenatal treatment for periodontal disease (*P*-value 0.04).[5]

A stronger association was seen between periodontal disease and perinatal mortality in the subgroup of extremely preterm birth, comprising PSANZ PDC Category 2.19 Bacterial infection; Categories 4.1, 4.8, 4.9 Antepartum haemorrhage; and Category 9 Spontaneous preterm, than in the entire perinatal mortality population of the study. This group was chosen as it is widely believed that these clinical presentations may all originate from a common intrauterine inflammatory pathway.[18] It may be that the association between periodontal disease and perinatal mortality exists solely in this group, and represents only an extension of the previously described association between periodontal disease and preterm birth. This finding is consistent with data describing a stronger association with periodontal disease with very early preterm birth rather than later in pregnancy.[13] It has been demonstrated previously that very preterm births have high rates of positive chorioamniotic membrane cultures and chorioamnionitis compared to pregnancies at a later gestational age, consistent with the role of infection in very early preterm birth.[19,20] The strong association with extremely preterm birth and periodontal disease was a secondary analysis and so must be treated with caution.

Maternal oral health symptoms were not predictive of perinatal loss or of periodontal disease. This is a surprising finding, as at the time of completing the questionnaire, women were aware of both their pregnancy outcome and their periodontal disease assessment, providing substantial opportunity for bias. This finding does not affect the validity of the study, as oral health symptoms are a poor predictor of periodontal disease in the wider community.[21]

Perinatal mortality has been associated with exposure to periodontal pathogens in a number of animal studies.[6–8] The mechanisms for the deaths are not clearly defined, and often the experimental protocols involve giving amounts of lipopolysaccharide that are above physiological doses to the fetus. Fetal hypotension may cause death, as demonstrated in fetal sheep given intravenous *Escherichia coli* lipopolysaccharide.[22] This response is more consistent with a single large bolus of lipopolysaccharide, instead of the tachyphylaxis expected with chronic low dose exposure via the maternal circulation. With regard to extremely preterm birth, it is believed that a number of infective pathways potentially triggered by periodontal disease may lead to the eventual common outcome of preterm birth.[19]

Microbial invasion of the amniotic cavity has a significant role to play in midpregnancy labour with intact membranes. It has been demonstrated that among women delivering between 20 weeks gestational age and term, inflammation is most strongly associated with lower gestational ages,[20] and is frequently not clinically evident.[23] It is also possible that women who are destined to deliver at mid-pregnancy have infection present prior to conception.[24] Thus, delivery in the second trimester may result from infective origins.

The parameters measured in a periodontal examination are pocket depth, CAL and bleeding on probing. Differences were found between the women experiencing perinatal loss and the controls in each of these parameters individually and when the definition of periodontal disease described above was used. CAL provides a record of previous disease, while pocket depth and bleeding on probing are better indicators of active inflammation.

Our study is potentially weakened by the retrospective design and delay between delivery and recruitment, necessitated by the infrequence of perinatal mortality. However, bias in recruitment was lessened because the symptoms of periodontal disease are usually silent and not apparent to the subject in the manner of dental caries or a toothache. Also, periodontal disease occurs in a pattern of activity and relative quiescence of inflammation, with slow progression in examination findings over many years. A strength of our study derives from using a single skilled examiner to perform all the periodontal examinations who was unaware of the subjects' pregnancy outcomes.

There appears to be an association between maternal periodontal disease and perinatal mortality. This relationship was demonstrated most strongly among women who experienced a perinatal death due to preterm birth. It is possible that periodontal disease does contribute to perinatal mortality in some women and that treatment of periodontal disease may reduce the risk of a subsequent loss.

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