Received: 27 April 2023 | Revised: 3 July 2023 | Accepted: 7 July 2023

DOI: 10.1111/odi.14683

ORIGINAL ARTICLE

ORAL DISEASES WILEY

Maternal periodontal diseases affect the leukocyte profiles of umbilical cord blood: A cohort study

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Funding information
This study was supported by the Shenzhen/Hong Kong Innovation Circle Programme-Type D project from the Science, Technology & Innovation Commission of Shenzhen Municipal Government (SGDX2019081623060946 to L.J. Jin); the Research and Transformation Platform for Maternal and Child Oral Health Promotion & Disease Control in the Guangdong-Hong Kong-Macao Greater Bay Area; and Beijing Stomatological Hospital of Capital Medical University Young Scientist Program (No. YSP202011) to D. Zhao.

Abstract

Aim: This study evaluated the connection of periodontal status with the leukocyte profiles of maternal peripheral blood (MPB) and umbilical cord blood (UCB).

Materials and Methods: Ninety-nine pregnant females were recruited, and their data were collected via questionnaire and from medical records, including demographics, systemic conditions, complete blood count (CBC) and C-reaction protein (CRP) level in MPB. Full-mouth periodontal assessment was performed. CBC and CRP levels in UCB were measured after parturition.

Results: All subjects and their neonates were generally healthy. 30.3% of the participants presented with periodontal health condition, whereas 69.7% had different severities of periodontal diseases. The counts/percentages of eosinophils and monocytes in UCB from the subjects with periodontal diseases elevated, and the percentage of neutrophils decreased referencing to that from the counterparts ($p < 0.05$). There were positive correlations for total leukocyte count, neutrophils and lymphocytes counts/percentages in MPB and UCB among the periodontally healthy subjects ($r > 0.4$, $p < 0.05$), but such findings did not exist in those with periodontal diseases. Moreover, periodontal diseases independently accounted for the counts/percentages of neutrophils and eosinophils in UCB after controlling confounders in four testing models (ANCOVA, $p < 0.05$).

Conclusion: Maternal periodontal diseases could to some extent disturb the leukocyte profiles of umbilical cord blood.

KEYWORDS
complete blood count, leukocyte profiles, maternal periodontal diseases, maternal peripheral blood, neonates, umbilical cord blood

1 | INTRODUCTION

Periodontal diseases including gingivitis and periodontitis, one of the major inflammatory oral diseases and global oral healthcare burdens, are initiated by dysbiotic plaque biofilms and crucially driven by the resultant dysregulated immuno-inflammatory response (Feres et al., 2016; Hajishengallis & Chavakis, 2021; Hajishengallis & Lambris, 2012; Kassebaum et al., 2014; Tonetti et al., 2017). Importantly, periodontitis considerably affects oral health and yet closely connects to common extraoral comorbidities like diabetes and cardiovascular disease (Feres et al., 2016; Hajishengallis & Chavakis, 2021; Hajishengallis & Lambris, 2012; Kassebaum et al., 2014; Tonetti et al., 2017). Over the past 30 years, various studies have been undertaken to evaluate the association of maternal periodontal diseases with the delivery and health of neonates as well as the relevant clinical implications (Beck et al., 2019). It is worth noting that the first epidemiologic evidence in 1996 reveals the connection of periodontitis with adverse pregnancy outcomes (APOs) (Offenbacher et al., 1996). Afterward, further efforts have been made on generating more scientific data sets and possible benefits of clinical interventions (Beck et al., 2019; da Silva et al., 2017).

Meanwhile, the underlying mechanisms involved in periodontal diseases and APOs have been hypothesized and elucidated in both direct and indirect pathways (Figuero et al., 2020). It has been demonstrated that the hematogenous dissemination of periodontopathogens and/or their virulence components could reach the fetal-placental unit and critically contribute to pregnancy complications (Han & Wang, 2013; Vander Haar et al., 2018). Yet, the increased release of pro-inflammatory cytokines enables it to circulate to the fetal-placental unit and stimulate the liver for elevating systemic levels of inflammation, consequently accounting for the unwanted fetal-placental effects (Madianos et al., 2013). The evidence of these proposed pathways is commonly reflected in the presence of oral bacteria in fetal and placental compartments which are normally absent in the vaginal flora, or with the increased levels of antibodies to periodontal pathogens and pro-inflammatory biomarkers in maternal peripheral blood (MPB) and umbilical cord blood (UCB) (Sanz et al., 2013). For instance, *Fusobacterium nucleatum*, one of the most prevalent oral microorganisms in intra-amniotic infection which can cause many APOs, has been isolated from amniotic fluids, UCB, and even lungs of the stillborn infants (Chaim & Mazor, 1992; Gonzales-Marin et al., 2013; Han et al., 2010). On the contrary, the findings on the association of elevated systemic levels of periodontitis-induced inflammation with APOs remain controversial. It has been reported that pro-inflammatory cytokines like interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) in MPB are positively correlated with periodontal attachment loss, but the levels of both mediators are not significantly different among 131 pregnant women with or without preterm delivery (Mesa et al., 2016). Whereas, another pilot study demonstrates that the subjects with a higher risk of preterm birth exhibit markedly more severe periodontal diseases and higher levels of various cytokines in MPB (Latorre Uriza et al., 2018).

Taken together, the exact interconnection of periodontal conditions in pregnant females to the inflammatory profiles of their neonates remains unclear. It is known that the profile of white blood cells (WBC) in MPB from healthy mothers was significantly correlated with UCB (Qaiser et al., 2013), and yet there is a significant correlation between the WBC of UCB and neonatal peripheral venous blood (Rotshenker-Olshinka et al., 2014). Moreover, the mother's unhealthy condition affects inflammatory response in the UCB. For instance, SARS-Cov-2 infection among pregnant women could induce considerable inflammatory responses at the maternal–fetal interface and account for a mild cytokine release in the UCB (Garcia-Flores et al., 2022). It should be noted that cytokines can activate immune cells in UCB (e.g., cord blood macrophages) (Dreschers et al., 2019). Vertical transfer of immune cells may also account for the effect of maternal immune condition on the inflammatory profile in UCB (Hall et al., 1995). Therefore, maternal periodontitis-induced host response may to some extent link with the inflammatory profiles in UCB. As such, it is hypothesized in the present study that maternal periodontal status could affect the leukocyte profiles of MPB and UCB.

2 | MATERIALS AND METHODS

2.1 | Participants

This cohort study was jointly undertaken at the Departments of Obstetrics and Periodontics, Shenzhen Maternity & Child Healthcare Hospital (SMCHH). A group of Chinese pregnant women (34–36 gestational weeks) was recruited, and the individual data sets (i.e., demographic and socioeconomic characteristics, lifestyles, and oral hygiene behaviors) were obtained through a questionnaire survey. The exclusion criteria were listed as follows: (i) aged over 35 years; (ii) pre-pregnant body mass index (BMI) either <18.5 kg/m^2 or ≥28 kg/m^2; (iii) conception by assisted reproductive technology; (iv) having periodontal treatment during pregnancy; (v) presence of any infections, systemic inflammatory diseases and/or any immuno-compromised conditions; (vi) presence of threatened abortion or taking medication during pregnancy; (vii) unavailability of medical and/or clinical records in the data sets of SMCHH; (viii) lack of willingness to receive the assessment at any time points of the study; and (ix) loss of follow-up for delivery. The Ethics Committee of SMCHH reviewed and approved this project (SFYLS [2020]013). All subjects gave their oral and written informed consent prior to the study. The project was carried out following the 2013 Declaration of Helsinki.

2.2 | Periodontal examination

A calibrated single investigator (HJL) performed a full-mouth periodontal assessment at six sites of each tooth present (excluding the third molars) using the UNC 15 probe (Hu Friedy) during the 34–36 gestational weeks, along the timeline of routine prenatal check-ups. The intra-examiner reliability was deemed to be good with a κ-value of 0.887. The following parameters were documented, consisting of the number of remaining teeth, full-mouth plaque score (FMPS), bleeding on probing (BOP), probing depth (PD), and number of tooth loss due to periodontitis. Periodontal inflamed surface area (PISA) was determined by using an EXCEL form, so-called Calculate PISA Probing Pocket Depth (Miki et al., 2021). The periodontal status was broadly categorized as periodontal health or periodontal diseases. Herein, the subjects with periodontal health presented with <10% of BOP sites with PD ≤3 mm and no history of periodontitis (Chapple et al., 2018), while those without the healthy condition defined above were classified as the periodontal diseases group. In addition, the subjects with BOP% ≥ 10% were further divided into low level (<30%) or high level (≥30%) of periodontal inflammation groups, respectively.

2.3 | Medical records

The clinical and laboratory records at 34–36 gestational weeks were retrieved from the medical data sets of SMCHH prior to periodontal assessment, such as BMI, blood pressure, levels of total protein, and various parameters including glycosylated hemoglobin ($HbA1_c$), insulin, blood and urine glucose, total cholesterol, lipoproteins, triglyceride, total bilirubin and bile acid, alanine aminotransferase, aspartate aminotransferase, serum albumin, urine albumin and creatinine, urinary albumin creatinine ratio, and uric acid as well as complete blood count (CBC) and C-reactive protein (CRP).

2.4 | Collection and analysis of UCB

UCB was collected within 10 min immediately following the delivery using the cannulation of the umbilical vein (Carroll et al., 2018). All samples were drawn by a 21-gauge needle and transferred to a 3-mL ethylenediaminetetraacetic acid (EDTA) tube (BD Vacutainer). Both CBC and CRP levels were measured by an automated analyzer (BC-7500 CRP) at the Clinical Laboratory of SMCHH.

2.5 | Data analysis

The sample size was determined using a software tool (G*Power 3.1.9.7). As there were no studies investigating the profiles of CBC in UCB among pregnant women with different periodontal status, the effect size (count of total leukocytes in MPB) comparing subjects with or without periodontal diseases ranged from 0.55 to 0.74 (*t*-test-means) with reference to previous findings (Botelho et al., 2021; Kolte et al., 2014; Ustaoglu et al., 2020). Thus, 30–53 individuals per group should be enrolled to reach a 5% level of significance and 80% detection power. Considering the potentially unequal allocation (1:3), the sample size was therefore considered to be 78–144 subjects. To allow a 20% loss of follow-up rate, the final sample size was set as 94–173 subjects.

All data were presented appropriately, for categorical variables (number/percentage) and normally (mean ± standard deviation) or abnormally distributed continuous variables (median with interquartile range, IQR). The Chi-square test was used to determine the intergroup difference in categorical variables. The profiles of CBC and CRP levels in MPB and UCB were compared using paired *t*-test or related samples Wilcoxon-signed ranks test. According to the periodontal status, all subjects were generally categorized into the periodontal health group and periodontal diseases group. The ratio of each variable of CBC in UCB with respect to that in MPB was calculated as well. Independent two-sample *t*-test and Mann–Whitney *U* test were further undertaken to determine any intergroup difference for continuous variables. Moreover, univariate linear regression examined the correlation of CBC in both MPB and UCB for the whole sample and individual group. Analysis of covariance (ANCOVA) was employed to evaluate the potential influence of various variables on the selected continuous dependent ones with significant relations to periodontal conditions. A software tool (SPSS version 28, IBM Corporation, New York, USA) was employed for all data analysis, and the statistical significance was identified as two-sided $p < 0.05$.

3 | RESULTS

3.1 | General conditions

A total of 539 pregnant females at 34–36 gestational weeks were screened. Five individuals aged over 35 years were not included, and yet 66 subjects were excluded due to their general conditions prior to or during pregnancy. After searching the datasets of SMCHH, 119 subjects were ineligible due to a lack of medical records and/or clinical and laboratory results. Consequently, two subjects who had periodontal treatment during pregnancy and 228 subjects without willingness of receiving periodontal examination were further excluded. Among the 119 remaining subjects who received oral examination, 20 of them could not be followed up for delivery. Therefore, 99 participants with median age of 30.0 years were finally recruited for data analysis (Figure S1).

As shown in Table 1, 77.8% of subjects graduated from university. Nearly half had a monthly household income equal to or over 20,000 RMB, and performed physical exercise daily with the duration of <30 min. The median of gravidity, parity, and abortion in order was 2, 0, and 0. The 25%, 50%, and 75% percentiles of delivery age were 39 + 0, 39 + 4, and 40 + 2 weeks, respectively. 42.4% of neonates were female. These participants brushed their teeth twice a day, and 39.4% of them flossed their teeth. Five subjects had prior periodontal treatment within 12 months, and 33 subjects were regular dental visitors.

TABLE 1 Demographic characteristics, lifestyles, obstetric history, and oral hygiene behaviors of all 99 subjects.

Variables	Median (IQR)/*n* (%)
Age, years	30.0 (28.0, 32.0)
Educational attainment	
High School	22 (22.2)
University	77 (77.8)
Monthly household income	
<9000 RMB	20 (20.2)
9000–19,999 RMB	31 (31.3)
≥20,000 RMB	48 (48.5)
Exercise	
<1 per week	16 (16.2)
1–3 per week	18 (18.2)
4–6 per week	16 (16.2)
Everyday	49 (49.5)
Duration of exercise	
<30 min	47 (47.5)
≥30 min	52 (52.5)
Gravidity	2.0 (1.0; 2.0)
Parity	0.0 (0.0; 1.0)
Abortion	0.0 (0.0; 1.0)
Delivery age, weeks + days	39 + 4 (39 + 0; 40 + 2)
Gender of neonate	
Female	42 (42.4)
Male	57 (57.6)
Toothbrushing, times per day	2.0 (2.0; 2.0)
Flossing	39 (39.4)
Periodontal treatment experience within 12 months	5 (5.1)
Regularly dental visitors	33 (33.3)

Furthermore, the follow-up period is from 11 to 45 days, and the average time is 32.18 ± 1.0 days. The results of systemic conditions are presented in Table S1. A total of 21 parameters evaluating metabolism as well as hepatic and renal functions were within the normal range for all subjects. In addition, the APGAR Scores evaluating the general conditions of neonates (i.e., appearance, pulse, grimace, activity, and respiration) were 10 (full scores) for all babies at 1, 5, and 10 min after birth. No neonates had a birth weight <2500 g.

3.2 | Periodontal conditions

Overall, 30 subjects presented with healthy periodontal conditions and 69 with periodontal diseases (Table 2). Among all participants, the median of FMPS and BOP was 77.0% and 18.5%, respectively. According to the BOP%, 42 subjects had a low level of periodontal inflammation and 27 showed a high one. More than half (54.5%) of them exhibited PD with 4–5 mm, and none had over 30% of tooth sites with PD >5 mm or tooth loss due to periodontitis. The median (IQR) of PISA was 234.3 (388.3) mm^2. The median (1st; 3rd quartiles) number of remaining teeth was 28 (27; 28). Furthermore, demographic data, lifestyles, obstetric history, and oral hygiene behaviors among participants with various periodontal status are presented in Table S2. Generally, most of the findings were comparable among the pregnant women with or without periodontal diseases, except for age, gravidity, and parity. The subjects were significantly older in the Periodontal diseases group (31.0 with IQR 29.0; 33.0) than those from the Periodontal health group (29.0 with IQR 27.0; 31.0) ($p < 0.01$). Gravidity and parity in subjects with periodontal diseases notably increased compared with their counterparts ($p < 0.05$).

TABLE 2 Periodontal status of all 99 participants.

Variables	Median (IQR)/*n* (%)
FMPS, % of sites per subject	77.0 (60.0, 93.0)
BOP, % of sites per subject	18.5 (8.3, 32.1)
Health (BOP% <10%)	30 (30.3)
Low level of periodontal inflammation (BOP% ≥10% and <30%)	42 (42.4)
High level of periodontal inflammation (BOP% ≥30%)	27 (27.3)
PD	
<4 mm	36 (36.4)
4–5 mm	54 (54.5)
>5 mm	9 (9.1)
PISA	234.3 (388.3)
Number of remaining teeth	28 (27; 28)
Number of tooth loss due to periodontitis	0 (0; 0)
Periodontal status	
Health	30 (30.3)
Periodontal diseases	69 (69.7)

Abbreviations: BOP, bleeding on probing; FMPS, full-mouth plaque score; PD, probing depth; PISA, periodontal inflamed surface area.

3.3 | CBC and CRP levels in MPB and UCB

The overall profiles of leukocytes, erythrocytes, and platelets were considerably different between MPB and UCB ($p < 0.001$, Table 3). The cell count for leukocytes (i.e., total leukocytes, neutrophils, lymphocytes, eosinophils, basophils, and monocytes) was significantly greater in the UCB compared with those of the MPB ($p < 0.001$). Moreover, the percentages of eosinophils, basophils, and monocytes were 2.80%, 0.30%, and 7.70% in the UCB, respectively, which considerably increased with reference to those in the MPB (1.00%, 0.20%, and 5.50%, respectively, $p < 0.001$). Furthermore, the cell counts for total erythrocytes and platelets were generally elevated in UCB compared with those in MPB. There was a similar trend for hemoglobin, hematocrit, corpuscular volume (MCV), corpuscular hemoglobin (MCH) and red cell distribution width (RDW) as well ($p < 0.001$). Interestingly, platelet

TABLE 3 CBC and CRP levels in maternal peripheral blood and umbilical cord blood.

Variables	Maternal peripheral blood	Umbilical cord blood
Total leukocytes, 10^9/L	9.29 (7.91; 10.65)	13.52 (11.17; 15.60)*
Neutrophils, 10^9/L	6.87 (5.78; 8.18)	7.89 (6.31; 10.15)*
Lymphocytes, 10^9/L	1.62 (1.40; 1.89)	3.85 (3.29; 4.76)*
Eosinophils, 10^9/L	0.09 (0.06; 0.13)	0.38 (0.29; 0.56)*
Basophils, 10^9/L	0.02 (0.01; 0.02)	0.04 (0.02; 0.06)*
Monocytes, 10^9/L	0.50 (0.40; 0.63)	1.13 (0.79; 1.47)*
Neutrophils, %	74.42 ± 5.00	59.02 ± 7.31
Lymphocytes, %	18.53 ± 4.39	29.33 ± 6.59
Eosinophils, %	1.00 (0.60; 1.40)	2.80 (2.00; 4.10)*
Basophils, %	0.20 (0.10; 0.30)	0.30 (0.20; 0.40)*
Monocytes, %	5.50 (4.80; 6.40)	7.70 (6.60; 9.20)*
Total Erythrocytes, 10^{12}/L	3.87 ± 0.27	4.35 ± 0.46
Hemoglobin, g/L	125.00 (120.00; 130.00)	158.00 (146.00; 168.00)*
Hematocrit, %	36.90 (35.20; 38.20)	46.70 (42.80; 49.80)*
MCV, fL	94.70 (92.40; 97.80)	106.10 (104.10; 109.90)*
MCH, pg	32.20 (31.10; 33.20)	36.00 (35.40; 37.10)*
MCHC, g/L	338.00 (334.00; 342.00)	338.00 (334.00; 344.00)
RDW, %	13.30 (13.00; 13.80)	14.90 (14.40; 15.60)*
Total Platelets, 10^9/L	209.11 ± 50.89	288.54 ± 55.94
Plateletcrit, %	0.19 ± 0.04	0.26 ± 0.04
MPV, fL	9.00 (8.30; 9.80)	8.90 (8.40; 9.40)
PDW, fL	16.30 (16.00; 16.70)	16.10 (15.90; 16.30)*
CRP, mg/L		
<1	1 (1.0)	97 (98.0)
1–3	31 (31.3)	0 (0.0)
>3	62 (62.6)	0 (0.0)
NA	5 (5.1)	2 (2.0)

Note: The data are shown as Median (IQR), Mean ± SD, or *n* (%) as appropriate.

Abbreviations: CBC, Complete blood count; CRP, C-reaction protein; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; MPV, Mean platelet volume; PDW, Platelet distribution width; RDW, Red cell distribution width.

*$p < 0.001$ (0.05/11, 0.05/7, 0.05/4). Related samples Wilcoxon-signed rank test/paired *t*-test.

distribution width (PDW) in UCB was slightly lower than that in MPB (16.10 vs. 16.30 fL, $p < 0.001$). Moreover, nearly all UCBs (98.0%) had CRP levels less than 1 mg/L, while 93 MPBs (93.9%) had CRP levels ≥1 mg/L.

3.4 | CBC and CRP levels in MPB and UCB from subjects with periodontal health and diseases

The profiles of CBC and CRP levels in MPB from the subjects with healthy or inflamed periodontium are presented in Table 4. There was no significant intergroup difference in the profiles of leukocytes, erythrocytes, and platelets from MPB. Furthermore, there were 56.7% (17/30) of individuals with CRP levels over 3 mg/L in the periodontal health group and 60.9% (42/69) of subjects in the counterparts.

Although the profiles of CBC and CRP levels were similar in MPB from subjects with or without periodontal diseases, the difference in leukocyte profiles in UCB was statistically significant ($p < 0.05$, Figure 1 and Table 4). The cell count (0.46×10^9/L, IQR $0.29–0.64 \times 10^9$/L) and percentage (3.3%, IQR 1.9–4.7%) of eosinophils in the Periodontal diseases group were notably higher than those from the Periodontal health group (0.32×10^9/L and 2.4%, respectively) ($p < 0.05$, Figure 1 and Table 4). The percentage of monocytes in the UCB was considerably higher in the subjects with periodontal diseases than that in the counterparts (8.19% ± 2.00% vs. 7.46% ± 1.33%, Figure 1b) ($p < 0.05$), whereas the percentage of neutrophils was significantly lower in the Periodontal diseases group (57.9% ± 7.7%) than that in the healthy group (61.6% ± 5.5%) ($p = 0.01$, Figure 1b). The profiles of erythrocytes and platelets were similar in UCB from Periodontal health and disease groups

TABLE 4 Comparison of CBC and CRP levels in maternal peripheral blood and umbilical cord blood from subjects with different periodontal conditions.

	Maternal peripheral blood		Umbilical cord blood	
Variables	**Periodontal health**	**Periodontal diseases**	**Periodontal health**	**Periodontal diseases**
Total leukocytes, 10^9/L	9.4 (8.1; 10.5)	9.2 (7.8; 10.7)	13.0 (10.8; 17.0)	13.6 (11.4; 15.3)
Neutrophils, 10^9/L	7.0 (6.1; 8.2)	6.8 (5.7; 8.2)	8.1 (6.6; 11.0)	7.9 (6.2; 9.7)
Lymphocytes, 10^9/L	1.6 (1.4; 1.8)	1.6 (1.4; 1.9)	3.7 (3.2; 4.5)	3.9 (3.3; 4.9)
Eosinophils, 10^9/L	0.08 (0.05; 0.12)	0.09 (0.06; 0.15)	0.32 (0.27; 0.42)	0.46 (0.30; 0.65)**
Basophils, 10^9/L	0.02 (0.01; 0.03)	0.02 (0.01; 0.02)	0.04 (0.03; 0.05)	0.04 (0.02; 0.06)
Monocytes, 10^9/L	0.52 (0.40; 0.65)	0.50 (0.41; 0.63)	0.93 (0.77; 1.38)	1.18 (0.81; 1.49)
Neutrophils, %	75.31 ± 4.30	74.03 ± 5.26	61.55 ± 5.52	57.92 ± 7.75*
Lymphocytes, %	18.00 ± 3.76	18.76 ± 4.65	28.04 ± 5.35	29.90 ± 7.03
Eosinophils, %	0.9 (0.5; 1.1)	1.1 (0.7; 1.5)	2.4 (2.0; 3.0)	3.3 (2.1; 4.9)*
Basophils, %	0.2 (0.1; 0.3)	0.2 (0.1; 0.3)	0.3 (0.2; 0.4)	0.3 (0.2; 0.4)
Monocytes, %	5.55 ± 1.18	5.75 ± 1.19	7.46 ± 1.33	8.19 ± 2.00*
Total Erythrocytes, 10^{12}/L	3.85 ± 0.28	3.89 ± 0.26	4.29 ± 0.51	4.38 ± 0.44
Hemoglobin, g/L	125 (119; 129)	123 (120; 130)	155.80 ± 18.80	157.12 ± 14.58
Hematocrit, %	37.0 (34.3; 38.3)	36.9 (35.2; 38.1)	46.07 ± 5.56	46.47 ± 4.41
MCV, fL	96.2 (92.7; 99.0)	94.4 (92.2; 97.0)	106.6 (105.0; 110.7)	105.6 (103.8; 109.8)
MCH, pg	32.5 (31.6; 33.2)	31.9 (31.0; 33.2)	36.3 (35.6; 37.1)	36.0 (35.1; 37.1)
MCHC, g/L	338 (333; 342)	337 (334; 343)	339 (334; 343)	338 (334; 344)
RDW, %	13.2 (12.9; 13.9)	13.3 (13.0; 13.7)	14.9 (14.4; 15.5)	14.9 (14.4; 15.6)
Total Platelets, 10^9/L	200.40 ± 43.64	212.90 ± 53.60	288.03 ± 59.79	288.75 ± 54.63
Plateletcrit, %	0.186 ± 0.037	0.190 ± 0.042	0.24 (0.23; 0.28)	0.26 (0.23; 0.29)
MPV, fL	9.3 (8.7; 9.9)	9.0 (8.1; 9.7)	8.91 ± 0.74	8.94 ± 0.63
PDW, fL	16.5 (16.3; 16.8)	16.3 (15.9; 16.7)	16.1 (15.9; 16.3)	16.1 (15.9; 16.3)
CRP, mg/L				
<1	0 (0.0)	1 (1.4)	28 (93.3)	69 (100.0)
1–3	11 (36.6)	23 (33.3)	0 (0.0)	0 (0.0)
>3	17 (56.7)	42 (60.9)	0 (0.0)	0 (0.0)
NA	2 (6.7)	3 (4.3)	2 (6.7)	0 (0.0)

Note: The data are shown as Median (IQR), Mean ± SD, or *n* (%) as appropriate.

*$p < 0.05$, ** $p < 0.01$; Mann-Whitney *U* test/Independent two-sample *t*-test.

Abbreviations: CBC, Complete blood count; CRP, C-reaction protein; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; MPV, Mean platelet volume; PDW, Platelet distribution width; RDW, Red cell distribution width.

(Table 4). Moreover, except for two neonates without the data of CRP, all neonates had CRP levels below 1 mg/L. Additionally, the ratio of each variable of CBC in MPB with respect to that in UCB was calculated and presented in Table S3. Here, the ratio of eosinophils count (UCB/MPB) significantly increased among those with periodontal diseases compared with that in the counterparts (4.33 vs. 4.00) ($p < 0.05$).

The potential correlation of CBC in MPB and UCB was further examined (Table 5). Interestingly, such correlations were markedly different in the two groups. Among the periodontally healthy individuals, the count of total leukocytes, count and percentage of neutrophils as well as percentage of lymphocytes in UCB were positively correlated with those in MPB ($p < 0.05$), with a considerable strength ($r > 0.4$). However, these notable correlations of leukocyte profiles were not detected in the Periodontal diseases group. In addition, regarding the profiles of platelets, a negative correlation for plateletcrit was found in the periodontal health group with moderate strength ($p < 0.05$, $r = -0.363$), whereas there was a positive correlation for mean platelet volume (MPV) with weak strength ($p < 0.05$, $r = 0.254$) in the periodontal diseases group. Moreover, the correlations of CBC between UCB and MPB among subjects with low or high levels of periodontal inflammation were evaluated as well (Table S4). Similarly, significant correlations existed among subjects with low but not those with high levels of periodontal inflammation. Positive correlations with moderate strength occurred for the count of eosinophils and count/percentage of basophils between UCB and

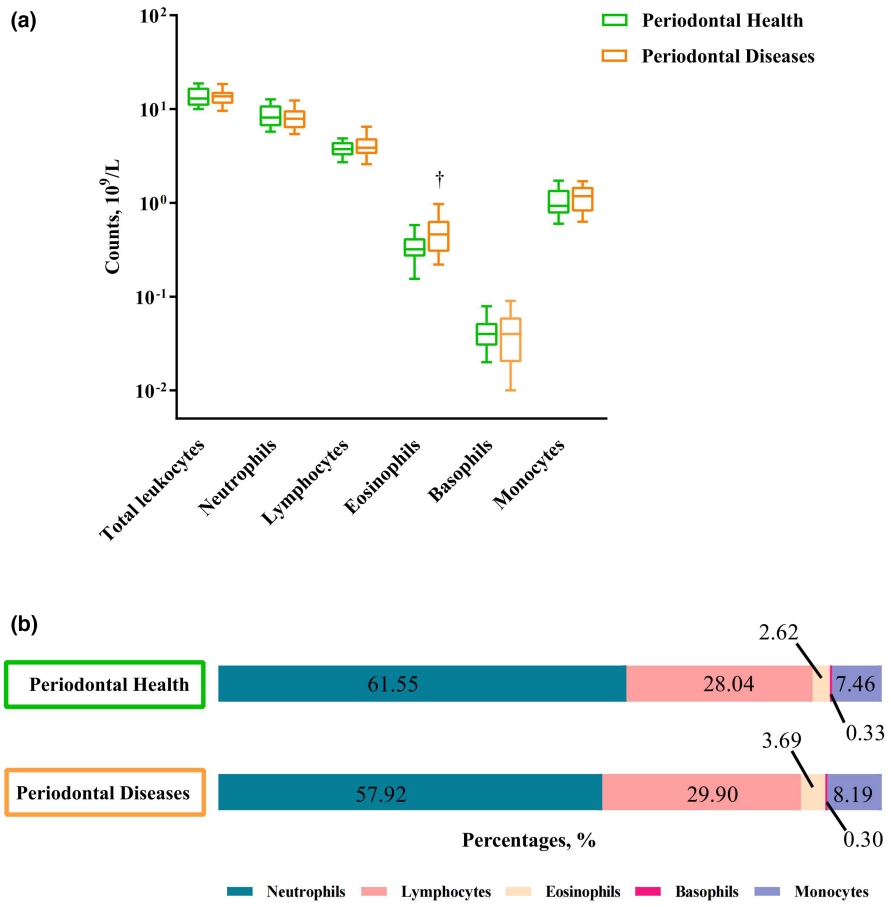

FIGURE 1 (a). The counts of leukocytes in the umbilical cord blood from subjects with different periodontal conditions. (b). The percentages of leukocytes in the umbilical cord blood from subjects with different periodontal conditions. $^{\dagger}p < 0.01$.

MPB ($p < 0.05$, $r > 0.3$), whereas plateletcrit in UCB was negatively correlated with that in MPB ($p < 0.05$, $r = -0.338$).

Furthermore, the correlation analyses of periodontal parameters (FMPS and BOP%) and PISA with CBC for both MPB and UCB were conducted, and the results are shown in Table S5. Notably, the percentage of neutrophils in UCB was negatively correlated with maternal BOP% and PISA, respectively ($p < 0.05$). Whereas, the percentage of monocytes in UCB was positively correlated with maternal BOP% and PISA, respectively ($p < 0.05$). Additionally, PISA was negatively correlated with MPV and PDW in MPB ($p < 0.05$).

3.5 | Effect of periodontal status on the leukocyte profiles in UCB

A total of four models were established for further analyzing the potential effects of the periodontal status of mothers-to-be on the leukocyte profiles in UCB (Table 6). Based on the previous findings, the counts of eosinophils and percentages of neutrophils, eosinophils, and monocytes were selected to be dependent variables to represent the profiles of leukocytes.

In Model 1, periodontal diseases independently affected the count and percentage of eosinophils (coefficient 0.12 and 0.90, respectively) and percentage of neutrophils with a coefficient of −3.79 ($p < 0.05$), after adjusting for age and leukocyte profiles in MPB. Then, four demographic confounders were further adjusted (i.e., educational attainment, monthly household income, exercise, and duration of exercise), and similar results were documented (Model 2). The count of eosinophils as well as percentages of neutrophils and eosinophils independently affected with the coefficient in order of 0.13, −4.45, and 1.04, respectively ($p < 0.05$). On the basis of Model 1, the gender of neonates, delivery age, gravidity, parity, and abortion of pregnant women were considered in Model 3. The effect of periodontal diseases on the percentage of neutrophils remained to be significant with a coefficient of −3.68 (95%CI −7.26; −0.11) ($p < 0.05$). Finally, the systemic conditions of mothers-to-be at 34–36 gestational weeks were analyzed together with the confounders in Model 1, which was then defined in Model 4. Interestingly, periodontal diseases, with reference to periodontal health, independently affected the count and percentage of eosinophils with the coefficients of 0.14 (95% CI 0.009; 0.27) and 1.34 (95% CI 0.28; 2.39) ($p < 0.05$), respectively.

4 | DISCUSSION

This study evaluated for the first time the potential connection of different periodontal conditions in pregnant females with the individual leukocyte profiles of both MPB and UCB. With no surprise, the CBC was markedly different between MPB and UCB. However,

TABLE 5 Correlation of CBC in maternal peripheral blood and umbilical cord blood.

Variables	Periodontal health	Periodontal diseases	Total sample
Total leukocytes count	0.438 (0.191)*	0.078 (0.006)	0.193 (0.037)
Neutrophils count	0.500 (0.250)**	0.113 (0.013)	0.246 (0.061)*
Lymphocytes count	0.349 (0.122)	0.086 (0.007)	0.125 (0.016)
Eosinophils count	0.050 (0.002)	0.140 (0.020)	0.175 (0.031)
Basophils count	−0.199 (0.039)	0.213 (0.046)	0.117 (0.014)
Monocytes count	0.280 (0.078)	0.220 (0.048)	0.232 (0.054)*
Neutrophils percentage	0.407 (0.165)*	0.097 (0.009)	0.180 (0.032)
Lymphocytes percentage	0.431 (0.186)*	0.059 (0.003)	0.145 (0.021)
Eosinophils percentage	−0.147 (0.022)	0.051 (0.003)	0.075 (0.006)
Basophils percentage	−0.205 (0.042)	0.106 (0.011)	0.030 (0.001)
Monocytes percentage	0.251 (0.063)	0.163 (0.026)	0.190 (0.036)
Total erythrocytes	0.228 (0.052)	0.051 (0.003)	0.119 (0.014)
Hemoglobin	−0.024 (0.001)	−0.076 (0.006)	−0.060 (0.004)
Hematocrit	0.030 (0.001)	−0.036 (0.001)	−0.015 (0.000)
MCV	0.010 (0.000)	0.100 (0.010)	0.094 (0.009)
MCH	−0.230 (0.053)	0.036 (0.001)	0.001 (0.000)
MCHC	0.270 (0.073)	0.033 (0.001)	0.105 (0.011)
RDW	−0.175 (0.031)	−0.038 (0.001)	−0.037 (0.001)
Total platelets	−0.045 (0.002)	−0.055 (0.003)	−0.051 (0.003)
Plateletcrit	−0.363 (0.132)*	−0.123 (0.015)	−0.189 (0.036)
MPV	0.245 (0.060)	0.254 (0.064)*	0.245 (0.060)*
PDW	0.094 (0.009)	−0.077 (0.006)	−0.037 (0.001)

Note: The data are shown as r (r^2).

*$p < 0.05$, ** $p < 0.01$; univariate linear regression.

Abbreviations: CBC, Complete blood count; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; MCV, Mean corpuscular volume; MPV, Mean platelet volume; PDW, Platelet distribution width; RDW, Red cell distribution width.

it is interesting to note that maternal periodontal conditions could significantly impact the overall profiles of leukocytes in UCB instead of those in MPB. Indeed, the count and percentage of eosinophils in UCB and the corresponding ratio of eosinophils count in UCB to MPB from the periodontal diseases group were notably elevated compared with those from the periodontal health group. Moreover, the percentage of monocytes in UCB was significantly higher among the subjects with periodontal diseases than that in their counterparts, while the percentage of neutrophils in UCB was significantly lower in the subjects with periodontal diseases than that in the healthy ones. It is worth noting that periodontal diseases could markedly affect the link of CBC in MPB and UCB. Notably, there were positive correlations of total leukocyte count, count and percentage of neutrophils as well as percentage of lymphocytes in UCB with those from MPB only among the periodontally healthy individuals. Moreover, significant correlations of CBC between UCB and MPB were shown only among the subjects with low levels of periodontal inflammation but not those with high levels of periodontal inflammation. Importantly, periodontal diseases independently impacted the count/percentage of neutrophils and eosinophils in UCB after adjusting for confounders in four different models. Taken together, these findings may imply that such natural intrinsic MPB-UCB connection could to some extent be disrupted by periodontal disease-induced and resultantly elevated levels of systemic inflammation.

It is well noted that the blood placental barrier separates maternal circulation from fetal blood in the placenta (Burton & Fowden, 2015; Maltepe & Fisher, 2015). It functions as a semipermeable membrane and single syncytiotrophoblast layer to protect the embryo from harmful effects of substances in MPB and yet appropriately regulates the exchange of nutrients, oxygen, carbon dioxide, and other waste products between the mother's body and fetus (Burton & Fowden, 2015; Tetro et al., 2018). Thus, it is anticipated from this study that there is a marked difference in the profiles of CBC between MPB and UCB. Indeed, our findings are supported by the previous report that the number of total leukocytes and differential leukocyte count are significantly higher in the UCB than those in the MPB (Qaiser et al., 2013). On the other hand, despite the existing blood placental barrier, maternal immune cells can be detected in UCB, indicating there is a vertical transfer pathway from the maternal circulation to the fetus (Hall et al., 1995). Indeed, these vertically transferred maternal immune cells promote neonatal immunity (Stelzer et al., 2021).

TABLE 6 Multivariate analyses (ANCOVA) for the leukocyte profiles in umbilical cord blood.

	Multivariate analysis			
	Eosinophils (10^9/L)	Neutrophils (%)	Eosinophils (%)	Monocytes (%)
	p value	*p* value	*p* value	*p* value
	MD/coefficient	MD/coefficient	MD/coefficient	MD/coefficient
Models	(95%CI)	(95%CI)	(95%CI)	(95%CI)
Model 1				
Periodontal diseases	**0.032** 0.12 (0.01, 0.24)	**0.020** −3.79 (−7.67, −0.66)	**0.036** 0.90 (0.06, 1.74)	0.082 0.78 (−0.10, 1.67)
Adjusted R^2	0.098	0.033	0.072	0.035
Model 2				
Periodontal diseases	**0.040** 0.13 (0.006, 0.25)	**0.019** −4.45 (−8.14, −0.77)	**0.024** 1.04 (0.14, 1.93)	0.109 0.76 (−0.17, 1.70)
Adjusted R^2	0.044	0.013	0.033	0.011
Model 3				
Periodontal diseases	0.066 0.11 (−0.008, 0.23)	**0.044** −3.68 (−7.26, −0.11)	0.085 0.74 (−0.11, 1.59)	0.059 0.90 (−0.03, 1.83)
Adjusted R^2	0.080	0.068	0.130	0.012
Model 4				
Periodontal diseases	**0.043** 0.14 (0.009, 0.27)	0.210 −3.13 (−8.06, 1.81)	**0.014** 1.34 (0.28, 2.39)	0.051 1.06 (−0.03, 2.13)
Diastolic pressure				**0.041** 0.09 (0.004, 0.18)
HbA_{1c}	**0.021** 0.27 (0.04, 0.50)			
Total cholesterol	**0.027** −0.23 (−0.43, −0.03)			
Low-density lipoprotein	**0.031** 0.24 (0.02, 0.46)			
Triglyceride	**0.045** 0.08 (0.002, 0.16)			**0.021** −0.75 (−1.38, −0.12)
Lymphocytes (10^9/L)				**0.025** 25.35 (3.24, 47.45)
Neutrophils (%)				**0.018** −2.27 (−4.13, −0.40)
Lymphocytes (%)				**0.009** −2.83 (−4.92, −0.74)
Adjusted R^2	0.278	−0.079	0.097	0.170

Note: Independent variable: periodontal status (periodontal health vs periodontal diseases). Confounders: Model 1: age and counts/percentages of leukocytes in maternal peripheral blood. Model 2: Model 1 + educational attainment; monthly household income; exercise; and duration of exercise. Model 3: Model 1 + gravidity; parity; abortion; delivery age; and gender of neonates. Model 4: Model 1 + systemic conditions (i.e., body mass index; total protein; systolic pressure; diastolic pressure; HbA_{1c}, glycosylated hemoglobin; glucose; urine glucose; insulin; total cholesterol; high-density lipoprotein; low-density lipoprotein; triglyceride; total bilirubin; total bile acid; ALT, alanine aminotransferase; AST, aspartate transaminase; urine albumin; urine creatinine; urine albumin creatinine ratio; serum albumin; and uric acid). Bold font indicates statistical significance ($p < 0.05$). When adjusted $p < 0.05$, MD (mean difference) or coefficient is presented for continuous or categorical confounders, respectively.

A cross-sectional study with 314 healthy mothers and their neonates also shows that there is a positive correlation of total leukocyte count between UCB and MPB (Qaiser et al., 2013), whereas another study including 60 healthy mothers and 54 anemia mothers reports that there is no significant correlation for total leukocytes between UCB and MPB (Timilsina et al., 2018). These findings suggest that unhealthy conditions of mothers-to-be could to some extent disrupt the intrinsic MPB–UCB connection of leukocyte profiles.

The current evidence shows that the severity of periodontal diseases and general conditions crucially affect the systemic level of inflammation. For instance, patients with more severe

periodontitis show increased levels of CRP and counts of total leukocytes, neutrophils, and lymphocytes (Torrungruang et al., 2018). In female adults, the percentage of eosinophils is found to be positively correlated with the levels of periodontal inflammation and tissue destruction (Senpuku et al., 2007). Moreover, periodontitis patients with type 2 diabetes mellitus (T2DM) exhibit notably higher levels of pro-inflammatory biomarkers in circulation like TNF-α and CRP than those of the controls (Pradeep et al., 2014; Singhal et al., 2016), which could be attributed to periodontitis-related exaggeration of inflammatory response under the compromised systemic conditions such as uncontrolled hyperglycemia (Kumar et al., 2020). In the present study, the pregnant females were systemically healthy prior to pregnancy and had no administration of medication during the pregnancy as well. Additionally, the majority of the subjects presented with periodontal health and/or shallow periodontal pocket, and only nine exhibited localized deep periodontal pockets. Further studies including subjects with various degrees of periodontitis severity and host susceptibility could determine the exact effect of maternal periodontal diseases on the profiles of circulatory leukocytes in MPB.

A recent study demonstrates that the immuno-inflammatory response in MPB and UCB may differ (Dreschers et al., 2019). The immune cells from UCB exhibit a higher diversity and more unique subtypes than those from fetal or adult peripheral blood (Ng et al., 2023). Indeed, the present study reveals that the profiles of leukocytes like eosinophils are significantly different in UCB between the mothers with or without periodontal diseases, but such findings were not observed in MPB. It is well known that eosinophils actively participate in the immune response against parasitic infection (Klion & Nutman, 2004; Maizels & Yazdanbakhsh, 2003). Atopic manifestation is a kind of aberration in immune response such as asthma and acts as an ongoing airway inflammation and remodeling leading to reversible airway hyperresponsiveness and obstruction (Trivedi & Lloyd, 2007). It has been reported that the count of eosinophils in UCB could independently predict the incidence of common allergic diseases from birth to age four among neonates (Crnkovic et al., 2019). Moreover, the newborns with eosinophilia (count of eosinophils $>0.7\times10^9$/L in UCB) show a 5.3-fold increased risk of suffering from these diseases compared with their counterparts (Crnkovic et al., 2019). Interestingly, there were 14 neonates with eosinophilia in our study, and none of their mothers had healthy periodontal conditions. Indeed, all of them had maternal periodontal inflammation with BOP% ≥10%; and the majority (12/14) presented with periodontal pockets (PD ≥4 mm). These observations imply that uncontrolled periodontal diseases of these mothers may be associated with the presence of eosinophilia in their neonates. Furthermore, eosinophils are important regulators of local immunity and play notable roles in the maintenance of tissue homeostasis (Jacobsen et al., 2012; Lee et al., 2010). The role of eosinophils in modulating the immune system is reflected by their biological function in the synthetization, storage, and production of various cytokines (Long et al., 2016). The followings are some examples, such as T helper 1 (Th1) cytokines like interferon-gamma (IFN-γ) and IL-12; Th2 cytokines (e.g., IL-4, IL-13); pro-inflammatory cytokines (e.g., IL-1β, IL-6, IL-8); and anti-inflammatory cytokines like transforming growth factor-beta (TGF-β) and IL-10 (Lacy & Moqbel, 2001; Spencer et al., 2009). Additionally, the potential role of eosinophils in maintaining metabolic homeostasis has been suggested (Fukui et al., 2009; Wu et al., 2011). Indeed, there is an independent relationship between peripheral eosinophil count with albumin excretion rate (Fukui et al., 2009). Currently, there are very limited studies addressing the potential effects of maternal periodontal diseases on these cytokines in UCB. It is noted from a previous study in pregnant women with mild/moderate periodontitis shows that periodontal treatment does not significantly affect the levels of pro-inflammatory cytokines in UCB (Pirie et al., 2013). Further clinical trials could clarify this important issue. Collectively, these findings suggest that periodontal diseases in pregnant females could affect the CBC profiles in UCB, and consequently influence to some extent the general health of newborns.

The limitations of the present study have to be elaborated. The current cohort is relatively young and well-educated with a high socioeconomic scale. It has been documented that education and socioeconomic status could influence the awareness of health and determine the costs of spending on healthcare and related issues, which subsequently may affect the external validity (Larsen et al., 2018). The subjects were systemically healthy prior to pregnancy and only several individuals had severe periodontal disease. These factors may to some extent account for the present observations on the association of maternal periodontal diseases with the leukocyte profile of the fetus. Moreover, although 21 parameters were selected to investigate the systemic conditions of the subjects, there are still some potential confounders not fully adjusted, such as pregnancy weight gain and nutrition status in UCB (e.g., iron) that could be significantly associated with the count of eosinophils (Weigert et al., 2015). Further large sample size investigations with subjects having various severities and susceptibilities of gingivitis and periodontitis as well as adequate adjustment of confounders are highly warranted to clarify the current results. Yet, the potential translational values need to be explored for better oral and general healthcare of pregnant women and their neonates.

5 | CONCLUSION

The current findings suggest that maternal periodontal diseases may affect the leukocyte profiles in UCB, showing the importance of oral/periodontal health promotion and care for further improving the well-being of mothers-to-be and their neonates.

AUTHOR CONTRIBUTIONS

Dan Zhao: Methodology; writing – original draft; formal analysis; visualization. **Tianfan Cheng:** Methodology; writing – original draft. **Dangli Hu:** Investigation; writing – original draft; data curation. **Xiaoyi Xu:** Investigation; data curation; formal analysis. **Feng Zhang:** Investigation; data curation. **Rong Yu:** Investigation; data curation.

Huijun Li: Investigation; validation. **Ping Wen:** Investigation. **Lihua Chen:** Investigation. **Mali Fu:** Investigation. **Hong Yang:** Investigation. **Hanyu Zhang:** Investigation. **Jilong Yao:** Writing – original draft; funding acquisition; project administration; resources. **Lijian Jin:** Conceptualization; supervision; writing – review and editing; funding acquisition; project administration.

ACKNOWLEDGMENTS

The authors thank Fengli Shi, Tongtong Wang and Yinwan Li for appropriately recruiting the subjects, Cun Duan and Yuchi Gao for profiling the blood cells, and Richard Yang for retrieving all clinical and laboratory records. The great cooperation of all participants is highly appreciated.

FUNDING INFORMATION

This study was supported by the Shenzhen/Hong Kong Innovation Circle Programme-Type D project from the Science, Technology & Innovation Commission of Shenzhen Municipal Government (SGDX2019081623060946 to L.J. Jin); the Research and Transformation Platform for Maternal and Child Oral Health Promotion & Disease Control in the Guangdong-Hong Kong-Macao Greater Bay Area; and Beijing Stomatological Hospital of Capital Medical University Young Scientist Program (No. YSP202011) to D. Zhao.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhao, D., Cheng, T., Hu, D., Xu, X., Zhang, F., Yu, R., Li, H., Wen, P., Chen, L., Fu, M., Yang, H., Zhang, H., Yao, J., & Jin, L. (2023). Maternal periodontal diseases affect the leukocyte profiles of umbilical cord blood: A cohort study. *Oral Diseases*, *00*, 1–13. https://doi.org/10.1111/odi.14683