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# Influence of maternal oral microbiome on newborn oral microbiome in healthy pregnancies

Monica Russo<sup>1\*</sup> , Maria Grazia Calevo<sup>2</sup>, Gloria D'Alessandro<sup>3</sup>, Matteo Tantari<sup>3</sup>, Marco Migliorati<sup>4</sup>, Ilaria Piccardo<sup>4</sup>, Paola Polo Perucchin<sup>1</sup> and Cesare Arioni<sup>1</sup>

## Abstract

**Background** Periodontal disease and its bacteria can be responsible for pregnancy complications and transmission of periodontal bacteria from mother to newborn.

**Methods** A salivary swab to 60 healthy, full-term newborns and their mothers was taken immediately after birth. The test was performed with Real Time PCR method to evaluate the expression of the gene through DNA amplification. The species considered were: *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum* ssp.

**Results** The newborn oral microbiome was composed primarily by saprophytes (98.38 + 4.88%), just like the mothers (98.8 + 3.69%). There was a statistically significant difference of the total microbiological density in newborns and mothers ( $p = 0.0001$ ). Maternal and neonatal oral microbiome had a correlated total microbiological density only in 33.3% ( $N = 20/60$ ) of cases. The analysis of the oral microbiome showed a pathological composition only in 12/60 babies (20%). The most frequent detected specie in newborns was *Fusobacterium nucleatum* (9/12 babies, 75%), as well as for the mothers (53.3%). However, the pathogen was present both in baby and his mother only in 3 dyads. *Porphyromonas gingivalis* showed the highest association mother-baby (4/12 dyads, 33%). *Porphyromonas gingivalis* was the pathogen with the highest bacterial load in the 12 mothers. We found a statistically significant difference in the total load of *Porphyromonas gingivalis* in mothers and babies ( $p = 0.02$ ).

**Conclusions** There was a statistically significant difference in the richness of the microbiome from newborns and mothers. Even comparing the microbiological density in the oral cavity of the individual mother-child pairs, we did not find a significant concordance. These results seem to suggest a low influence of maternal oral microbiome on the richness of the oral neonatal one. We didn't find mother-child concordance ( $p = 0.0001$ ) in the presence of pathogenic periodontal micro-organisms. *Fusobacterium nucleatum* was the most frequent specie detected. *Porphyromonas gingivalis* instead was the bacteria with the higher possibility of transmission. In conclusion in our study maternal oral health doesn't affect healthy, full-term newborns' oral microbiome. Further studies are needed to understand the maternal influence on newborn's oral microbiome and its effects on babies long-term health.

\*Correspondence:

Monica Russo  
monica.russo@hsanmartino.it

Full list of author information is available at the end of the article



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**Keywords** Oral microbiome, Full-term newborn, Mother-infant colonization

## Background

Even if the origin of the neonatal oral microbiome is poorly understood, it is clearly that richness and change in composition of neonatal oral microbiome impact both short and long term outcomes [1, 2]. It is assumed that the initial development and maturation of the neonatal oral microbiome is largely determinate by maternal-offspring exchanges of microbiome during and after delivery [3, 4]. There are evidences that newborn's oral microbiome is influenced first of all by the mode of delivery [5, 6] and several studies demostred the impact of this on the infant's future health. It has been infact demostred the influence of C-section in microbioma's composition and the association with an increased incidence of celiac disease, asthma, type 1 diabetes and obesity [7–10]. Also use of use of antibiotics in pregnancy may increase offspring risk of childhood desease [11, 12]. However, accumulating evidences show that neonatal oral microbiome has a prenatal origin [13, 14]. Gingivitis is the most common oral disease in pregnancy. The species characterized by high pathogenicity are: *Aggregatibacter actinomycetemcomitans*, *Phorphyromonas gingivalis*, *Tanarella forsythia* and *Treponema denticle*. They are also added, with less pathogenicity, species such as the *Prevotella intermedia* and the *Fusobacterium nucleatum*. The latter is less harmful individually than the first, but a synergy between these two complexes can lead to an increase in virulence. The scientific literature, in the last twenty years, has a growing interest in showing that periodontal disease and its bacteria can be responsible for pregnancy complications such as preterm births or low birth weight and transmission of periodontal bacteria from mother to newborn [15]. Two pathogenic mechanisms have been proposed to explain the connection from maternal oral dysbiosis and placental and fetal biology: the direct pathway is based on the presence of gram-negative anaerobic bacteremia originating in the gingival biofilm [16], whereas the indirect pathway involves the production of pro-inflammatory markers which enter the bloodstream from the gingival submucosa [17].

The influence of maternal oral microbiome to early oral newborn colonization isn't well understood and there is a need for more in-depth research to understand if cariogenic bacteria colonize the fetus' mouth in healthy pregnancies too.

Oral diseases are progressive, cumulative and grow in complexity over time, which is why it is very important for good oral health to be established early in life.

In order to motivate the oral hygiene of women of childbearing age and to prevent future diseases in the systemic and oral health of children, we analyzed the

neonatal oral microbiome to establilh if there is an influence of the maternal oral microbiome in healthy pregnancies on the neonatal mouth colonization at birth.

## Patients and methods

This Retropective observational cohort study was performed in the Neonatal Unit of the IRCCS Ospedale Policlinico San Martino Genoa, Italy in collaboration with the Academy Unit of Obstetrics and Gynecology and the Orthodontics Department of Genoa University between 2017 and 2018.

A total of 60 newborns (34 F, 26 M) and their mothers were enrolled to study their oral microbiome. The average birth weight was 3205.9 g, ranged 2600–3850 g. Women ages was ranging from 20 to 42 years old (mean 32.08 y.o.).

Inclusion criteria were: newborns must have to be born by vaginal delivery, a term (37th –41th gestational week), in health and adequate for gestional age (AGA). Babies just after birth must stay skin to skin with their mothers. Mothers must not have received antibiotics during delivery and must not have taken antibiotics during the last 6 mounths of pregnancy. Furthermore, the women in this study must not have drunk or eaten or brushed their teeth half an hour before the test. None of the mothers had received dental treatment during pregnancy.

Exclusion criteria were: newborns by caesarean section, prematurity (<37th gestational week), newborns with difficult birth or any health problem who don't permitte them to stay immediatly after birth skin to skin with the mother because they necessity hospitalization in Neonatal Intensive Care Unit.

The outcome of this study was to analyze oral neonatal microbiome and to evaluate the trasmission in healthy pregnancies of the major pathogenic bacterias in oral diseases comparing it with the maternal oral cavity microbiome.

The study provides for the execution of a salivary swab to the neonate and his mother; it was a multi-site microbiological test. The samples were taken from the baby's immediately after birth, before start breastfeeding, during skin to skin to accurately reflect colonization prior to and during birth. Samplings were obtained using steril paper cones swiped on the oral mucose of the babies and inserted into the periodontal sulcus of the mothers for at least 1 min. The test was performed with Real Time PCR method, to evaluate the expression of the gene through DNA amplification.

The microbial density in the test was expressed in number of bacterias (copies per  $\mu$ l).

The species considered for this research were: *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum* ssp.

Written informed consent was obtained from parents or caregiver of patients after full explanation of the study, in according to the declaration of Helsinki.

Data are described as mean and standard deviation (SD) or median and range for continuous variables, and as absolute and relative frequencies for categorical variables. Non-parametric analysis (Mann-Whitney U-test, Wilcoxon test) for continuous variables and the Chi square or Fisher's exact test for categorical variables were used to measure differences between groups. P values  $\leq 0.05$  were considered statistically significant, and all P values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois USA).

Ethical clearance for the publication of this study was obtained from the Regional Ethical Committee (CER Liguria: 415/2022 – DB id 12,565).

## Results

This study analyzed 60 babies' oral microbiome at birth. All infants were born at full term by vaginal, eutocic delivery. Newborns were adequate for gestational age (AGA) and had not health problems.

We analyzed and compared newborn's oral microbiome at birth with their mothers' oral microbiome to understand if it could be influenced by their mothers during pregnancy.

We found a microbial community density lower than  $10^3$  copies per  $\mu\text{l}$  in 10/60 newborns (16.7%); 17/60 babies (28.3%) were between  $10^3$  and  $10^4$  copies per  $\mu\text{l}$ ; 14/60 babies (23.3%) had microbiological density higher than  $10^4$  but lower than  $10^5$  copies per  $\mu\text{l}$ . Richer microbiome ( $>10^5$  copies per  $\mu\text{l}$ ) was found in 19/60 babies (31.7%), only 4 of them had a microbial community density  $>10^6$  copies per  $\mu\text{l}$ .

There was a statistically significant difference of the total microbiological density in newborns and mothers ( $p=0.0001$ ). Maternal and neonatal oral microbiome had a correlated total microbiological density only in 33.3% ( $N=20/60$ ) of cases. 18 mothers and babies had both a microbiome  $>10^5$  copies per  $\mu\text{l}$ . In 2 cases both mother and neonate had microbiological density  $<10^5$  copies per  $\mu\text{l}$ . In all the other couples, mothers had a richer microbiome  $>10^5$  copies per  $\mu\text{l}$ , but their children weren't.

The oral cavity microbiome of the 60 full term babies was composed primarily by saprophytes ( $98.38 \pm 4.88\%$ ), just like the mothers ( $98.8 \pm 3.69\%$ ). The analysis of the oral microbiome showed a pathological composition only in 12/60 babies (20%). Only 4/12 of these newborns had a richer microbiological density too ( $>10^5$  copies per  $\mu\text{l}$ ). In

comparison, the oral microbiome of mothers showed the presence of pathogenetic bacteria in oral diseases in 80% ( $N=48/60$ ), so in 36/60 cases we didn't find mother-child concordance ( $p=0.0001$ ) in the presence of pathogenic periodontal micro-organisms.

We studied the neonatal oral microbiome in these 12 babies and compared it with their mother's.

Because mothers had richer microbiome than newborns, in these 12 dyads was confirmed a statistically difference in the total microbiological density ( $p=0.002$ ). In addition, comparing the percentage of saprophyte and pathogens in the microbiome, there was also a significant difference in the microbiome composition of the 12 babies and their mothers ( $p=0.03$ ).

About investigation of the periodontal micro-organisms in the 12 babies, in 4/12 babies (33.3%) there was a polymicrobial contamination: in 1 case of them we found contamination by 3 different species, the other 3 cases was contaminated by 2 different species, they had higher total microbial community  $>10^5$  copies per  $\mu\text{l}$ .

We found *Fusobacterium nucleatum* in 9/12 babies (75%): it was the most frequent specie present in these 12 newborns. Even in mothers *Fusobacterium nucleatum* was the most frequent oral bacteria detected: the frequency in the 60 mothers was high 53.3%. In 6 mothers of these 9 babies, *Fusobacterium nucleatum* wasn't found, so only in three of the dyads the presence of *Fusobacterium nucleatum* spp was associated.

The frequency of the species *Prevotella intermedia* and *Porphyromonas gingivalis* in the babies' oral microbiome was the same ( $N=4/12$ ; 33%), lower than *Fusobacterium nucleatum*. The frequency of *Prevotella intermedia* in all 60 mothers was 31.7% ( $N=19/60$ ). *Prevotella intermedia* was present in 4/12 mothers, but only in 2 of the 12 dyads (16.6%) *Prevotella intermedia* was observed in both mother and newborn. *Porphyromonas gingivalis* was present in 29/60 mothers (48.3%) and in 7 of the 12 mothers (58.3%). It showed an higher association mother-baby than all the others specie examined because we observed transmission of *Porphyromonas gingivalis* in 4 of the 12 dyads (33%).

Despite the specie with the highest bacterial load in newborns was *Fusobacterium nucleatum* ( $1266 \pm 2634$  copies per  $\mu\text{l}$ ), *Porphyromonas gingivalis* was the oral pathogen with the highest bacterial load in the 12 mothers. There was a statistically difference in the total load of *Porphyromonas gingivalis* in mothers and babies ( $6459 \pm 13,106$  vs.  $40 \pm 60$  copies per  $\mu\text{l}$ ;  $p=0.02$ ). This difference wasn't observed for the other species examined, in fact the bacterial count of *Fusobacterium nucleatum*, *Prevotella intermedia* was similar in the 12 dyads mother-newborn ( $p>0.05$ ).

None of the 12 babies showed the presence of *Aggregatibacter actinomycetemcomitans* in their oral

microbiome. *Aggregatibacter actinomycetemcomitans* was the less frequent in the mothers' oral microbiome too: it was present in only 1 mother of the 12 dyads and in 7/60 mothers (11.7%).

## Discussion

Several studies confirm that the microbiome in the first years of life is fundamental for health in future. Even if the most of oral microbial colonization is traditionally considered to take place after birth, the beginning of the development of the microbiome seems to take place just at the fetal level with the passage of bacteria through the placenta and then becomes more complex from birth onward [18]. The human gut is the first most rich microbiome with a great diversified microbial community, meanwhile the second is the oral cavity [19]. Many studies have shown the presence of a rich microbiome just in intestinal fetus and newborn: it is very likely that this is due to the fact that the fetus ingests large amounts of amniotic fluid during the last trimester of pregnancy. Several mechanisms have been proposed to explain how bacteria may be able to colonize the uterine cavity during pregnancy. In relation to healthy pregnancies, two main pathways are currently considered: by blood, through the placenta after translocation from the digestive tract (oral cavity and intestines) or by vertical transmission from the vaginal tract. A recent systematic review summarizes studies on oral microbiome in infants, children and adolescents: evidence indicates that a stable core microbiome is present just in newborns and it becomes more differentiated within the first four years of life [20].

In our study, the microbiological test executed at full term birth by a salivary swab, shows us the density of microbiological population in the mouth of the neonates and their mothers. We examined the richness of oral microbial community of the babies immediately after birth, before skin to skin contact with the mother and before start breastfeeding, to reduce the influence of them on the density of the microbial community in the mouth at birth, so to accurately reflect colonization prior to and during birth. It is discussed if the delivery mode influence oral microbiome, some recent studies conclude that newborn microflora isn't related to the kind of delivery but instead primarily driven by body habitats [1, 21]. In any case, to reduce the influence of delivery mode on microbial density, the babies of the study were born exclusively by vaginal delivery. Furthermore mothers were not given antibiotics during delivery and hadn't taken antibiotics during the last 6 months of pregnancy. In spite of everything samples from the oral cavity of our neonates showed low microbial richness, in fact only 4 babies had a very rich microbiome with more than  $10^6$  copies per  $\mu\text{l}$ . There was a statistically significant difference in the richness of the microbiome from the 60

newborns and mothers ( $p=0.0001$ ). Even comparing the microbiological density in the oral cavity of the individual mother-child pairs, we did not find a significant concordance (33.3%). It is supposed that the presence of caries in mothers doesn't influence microbiome density and composition in infants in the first year of life [22, 23], results of this study seem to suggest a low influence of maternal oral microbiome on the richness of oral newborns microbiome at birth too. A so low microbiological density in the mouth of the full term babies immediately after birth could also effort the consideration that, even if the foetal microbiome colonization may begin already in utero, oral microbiome composition matures throughout the first period of life and it is shaped by factors including host genetics and the environment [14]. Microbiome is a dynamic ecosystem and most of the development of the composition and function of the child's oral microbiome occurs in the first years [20] and in particular probably just in the first hours of life [3, 4, 24]. So, the contact with the mother and our interventions on the environment around the mother and the newborn just after birth are very important for future richness and composition of the infant oral microbiome: the initial microbial exchanges between mother and infant at birth are fundamental as these early colonisers play a very important role in the development of the neonate's immune system and long term in the activity and function of the microbiome [25].

Oral microbiome is a complex community and its composition and persistence is strictly influenced by food, oral hygiene practices and salivary flow [26]. Several studies investigate oral microbiome composition using advanced techniques of DNA sequencing, they found that the main phyla present in oral cavity are: Firmicutes, Bacteroides, Proteobacteria, Actinobacteria, Fusobacteria and Spirochaetes [20, 24, 27, 28]. To show the influence of maternal oral pathogens on the babies, we analyzed the presence at full term birth of major pathogenic bacteria in oral diseases: *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum* ssp.

Oral diseases are progressive, cumulative and grow in complexity over time, which is why it is very important for good oral health to be established early in life. The etiology of both dental caries and periodontal disease is polymicrobial and occurs when there is a shift in the overall ecological balance of microbes in the oral cavity [29].

It is known that the oral health and oral microbiome of a woman may directly affect her pregnancy and her developing fetus: if the mother has periodontal disease, she has higher risk for giving preterm birth, for delivering a low-birth-weight infant, for preeclampsia, and 3.4 times higher risk for preterm birth plus delivery of an

infant of low birth weight [15]. So, even if there is still insufficient evidence to conclude, it has been proposed that periodontal pathogens or their products some way reach the placenta and spread beyond it to the fetus [30].

Studies have found that in the case of oral diseases (gingivitis or periodontitis), bacteria in the oral cavity may reach amniotic fluid through transient bacteremia, indicating that maternal microbes may be transmitted to the amniotic fluid with blood.

The available studies have focused their attention on the immediate complications of fetal and neonatal colonization by these pathogenic germs of the oral cavity, but it isn't yet understood whether transmission of these pathogens is possible even in uncomplicated pregnancies, in healthy full-term infants and it is not possible to exclude that a colonization already at birth can determine a worse prognosis of oral health in the child.

The genera considered in this study, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, are all Gram negative oral pathogens responsible for periodontal disease. They are characterized by the production of various metabolites and virulence factors that lead to the destruction of periodontal tissue or inactivation of the local defenses of the immune system.

We found that the newborns' oral cavity microbiome was composed primarily by saprophytes. The analysis of the oral microbiome showed in fact a pathological composition only in 20% of babies, this data doesn't correlate with the incidence of periodontal pathogens in the mothers (N=48/60; 80%). So in our samples there weren't significant transmission of periodontal micro-organisms and we could conclude that the oral health and oral microbiome of the mothers don't affect a full term pregnancy. So the hypothesis of colonization in utero is still controversial and these data would make us suspect that in some pregnancies, but not in all, there may be a bacteremia which may be followed by a complication of gestation. However, from the analysis of these data it would not be clear what is the mechanism that leads to the unleashing of bacteremia, since the presence of pathogens of the oral cavity in our 12 children did not correlate with the highest maternal bacterial charges.

*Fusobacterium nucleatum* was the most frequent species detected in both mothers and babies, although again there was no correlation in the dyads. *Fusobacterium nucleatum* is an opportunistic periodontal pathogen of the oral cavity, but the dysbiosis can determine its pathogenicity with local and systemic consequences. We can't determine what influence will have for the future the presence of *Fusobacterium nucleatum* in the oral cavity immediately at birth but it is interesting that, even if in few babies of our sample, this bacteria was in some way able to trough the placenta also in healthy gestations.

Analysis of the other pathogenic genera of the oral cavity of our study showed a lower incidence of presence than *Fusobacterium nucleatum* in the oral mouth at birth. *Porphyromonas gingivalis* showed an higher correlation mother-babies (N=4/12; 33%) than all the other genera examined, so it could be the bacteria with the higher possibility of transmission, but it is at the moment a too low evidence to demonstrate it. None of the babies showed the presence of *Aggregatibacter actinomycetemcomitans* in their oral microbiome. Even in mothers it was the bacterium with the lowest incidence in the oral cavity.

In 4 babies there was a polymicrobial contamination too. Sometimes the association between two or more pathogens can be even more aggressive and harmful, polymicrobial infections in fact can be more serious than those caused by a single pathogen, when the interactions between individual species turn a mixed infection into a synergistic infection.

We cannot still know exactly what influence the presence of *Fusobacterium nucleatum* and other periodontal microorganisms in the oral cavity just at birth will have for the future infant oral health, but we could assume for these newborns a greater future risk of pathology if the balance between the different species of the microbiome under the influence of environmental factors will be broken.

**In conclusion**, in our study maternal oral microbiome doesn't influence healthy, full-term newborn's oral microbiome. There are currently not enough studies that analyze the oral microbiome at full-term birth and compare it with the maternal one. Research into oral pathogenic microorganisms in newborns has also focused on the effects on gestation, but the possible transmission to healthy full-term infants and its possible effects on long-term health has not yet been investigated. Further studies are needed.

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#### Authors' contributions

Conceptualization, C.A. and M.R.; methodology, M.R. and P.P.P.; software, M.R. and P.P.P.; validation, M.R., C.A. and M.M.; formal analysis, M.G.C.; investigation, M.R., G.D. and M.T.; writing—original draft preparation, M.R. and M.M.; writing—review and editing, M.R., I.P. and M.M.; supervision, M.R., C.A. All authors have read and agreed to the published version of the manuscript.

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#### Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Ethical clearance for the publication of this study was obtained from the Regional Ethical Committee at the date 17/10/2022. Registration Number CER Liguria: 415/2022 – DB id 12565. Written informed consent was obtained from parents or caregiver of patients after full explanation of the study, in according to the Declaration of Helsinki. The study was conducted in compliance with the Good Clinical Practice.

### Consent for publication

This research doesn't require consent for the publication.

### Competing interests

The authors declare that they have no competing interests.

### Author details

<sup>1</sup>Operative Unit of Neonatology, IRCCS Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, Genoa 16132, Italy

<sup>2</sup>Epidemiology and Biostatistics Unit, Scientific Direction, IRCCS Istituto Giannina Gaslini, Genoa, Italy

<sup>3</sup>Academy Unit of Obstetrics and Gynecology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

<sup>4</sup>Department of Surgical Sciences and Integrated Diagnostics (DISC). Orthodontics Department, Genoa University, Genoa, Italy

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