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ORIGINAL ARTICLE

Olfactory sensory evaluation in newborn children of women infected with COVID-19 during pregnancy

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Abstract

Introduction: In adults, olfactory loss is one of the earliest and most frequent acute clinical manifestations of SARS-CoV-2 infection. The number of children infected with SARS-CoV-2 is relatively small, perhaps due to the lower expression of Angiotensin Converting Enzyme 2 (ACE2) in children compared to adults. Little is known about foetal impairment in mothers infected with SARS-CoV-2. This paper describes an ongoing scientific project on smell perception in infants.

Objective: The goal of the study is to develop and validate a behavioural evaluative scale of olfactory perception in healthy newborns and to apply this scale to newborn children of women infected with COVID-19 during pregnancy comparing to newborn children of women without COVID-19 infection history, in order to compare these groups.

Methods: This is a retrospective comparative analytical cohort study of 300 newborns exposed and unexposed to COVID-19 during pregnancy. The data collection will follow the experimental procedure in a previous study that explored odours of the maternal breastmilk, vanilla (sweet) and distilled water (neutral). A coffee smell was implemented as an addition to this previous study in order to include acid/bitterness category to the categories of stimuli.

Discussion: It is feasible to argue the hypothesis of the involvement of the foetus' olfactory bulb as one of the indelible pathophysiological manifestations to the clinical diagnosis of COVID-19 with neurosensory olfactory deficit in foetuses and newborns affected by intrauterine infection. This study aims to investigate if newborn children of women infected with COVID-19 during pregnancy have olfactory sensory changes. The clinical trial was registered in the Brazilian Registry of Clinical Trials (ReBEC- RBR-65qxs2).

Keywords: newborn, perception, odors, COVID-19, SARS-CoV-2

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Authors summary

Why was this study done?
Olfactory loss in adults is one of the initial and most frequent acute clinical manifestations of SARS-CoV-2 infection. The few studies that have evaluated this alteration in the paediatric range have shown that children have less olfactory sensory loss than adults. One possible explanation would be the lesser expression of ACE2 in the nasal mucosa compared to adults with consequently less binding of SARS-CoV2. The authors propose to evaluate the action of SARS-CoV-2 at the intrauterine level regarding the foetus' olfactory sensory impairment.

What did the researchers do and find?
This study aims to assess the olfactory sensory perception of newborns of women who previously tested positive for COVID-19 during pregnancy compared to newborns of women who did not test positive for COVID-19 during pregnancy. It also aims to develop and validate a behavioural evaluation scale of olfactory sensory-perceptual perception in newborns. This work is based on the scientific literature on the sensory-perceptual development of smell in foetuses and newborns. Newborns will be exposed to four odours: breast milk, vanilla (sweet), coffee (bitter) and distilled water (neutral). The exposure order will be the same in all experiments.

What do these findings mean?
There is a lack of data in the literature regarding foetal impairment by SARS-CoV-2. Younger children have a lower incidence of COVID-19 symptoms compared to adults including low frequency of sensory impairment, especially smell. The results of this study will clarify whether intrauterine SARS-CoV-2 can affect the foetal sensory system or not.

INTRODUCTION

The natural history of COVID-19, caused by the SARThe natural history of COVID-19, caused by the SARS-CoV-2 virus, is still being explored. Little is known about its effects on pregnancy, the puerperium and the health of the mother and foetus, as well as the impact on the long-term development of the children of infected mothers during pregnancy. Based on the positive data to date, the clinical picture of COVID-19 during pregnancy does not seem to differ when observed outside this period. The disease can be asymptomatic or present with clinical manifestations that vary in severity and symptomology, with the most common symptoms being fever (67%) and cough (66%), accompanied less frequently by malaise, dyspnoea, and diarrhoea[1].

Vertical transmission of SARS-CoV-2 was previously thoroughly assessed in six pregnant women affected by the disease in the third trimester[2]. This study tested the amniotic fluid, umbilical cord blood, breast milk and nasopharyngeal swab of newborns, which were all negative for the virus. Subsequently, two systematic review and two studies describing cases of pregnancy infection in hospitals of Wuhan, China and New York City, United States, found no evidence of vertical transmission[1,3–5]. Inconclusive reports of vertical transmission include that of newborns with specific anti-SARS-CoV-2 IgM, but with negative RT-PCR[5], as well as that of a 16h newborn with positive RT-PCR with 16h of life, but specific IgG and IgM remained negative until the 5th day[6]. The interpretation of these results requires prospective studies, which are known for the accuracy of molecular tests and the kinetics of anti-SARS-CoV-2.

Maternal SARS-CoV-2 infection does not expose the foetus and newborn only to the effects caused directly by the virus, but also to a variety of indirect effects. The consequences of the maternal and foetal inflammatory response, with the production of potentially cytotoxic cytokines, as well as the effect of the use of antiviral medications, have not been studied to date. Another important aspect concerns the risk of contamination of the newborn during or shortly after birth. Practices such as delayed cord clamping and skin-to-skin contact between mothers and newborns are not universally recommended and evidence on the risk of contagion during breastfeeding is still limited[7,8].

There are studies reporting infected adults who developed neurological diseases, such as mental confusion, stroke, seizure, or loss of smell, due to a direct or indirect effect on the central nervous system (CNS). Likewise, a picture of acute haemorrhagic encephalopathy diagnosed through magnetic resonance imaging was reported in a woman in the sixth decade of life affected by COVID-19[9]. The prevalence of neurological impairment by the disease is still being observed, but a study of 214 patients in Japan showed that 36% had some clinical finding related to the nervous system[10]. Though, not enough data is provided about the risk of fetuses or newborn infants being vulnerable to neurological sequels due to the COVID-19 infection.

Problem

Among the symptoms provided by carriers of the new coronavirus, is an olfactory sensory alteration. Olfactory loss in adults is one of the earliest and most frequent acute clinical manifestations of SARS-CoV-2 infection. It is feasible to hypothesize the involvement of the foetus' olfactory bulb during intrauterine life as one of the indelible pathophysiological manifestations to the clinical diagnosis of COVID-19 with neurosensory olfactory deficit in foetuses and newborns affected by intrauterine infection. Based on these evidences, the following research question was raised: do newborn children of women infected with SARS-CoV-2 during pregnancy have olfactory sensory changes? Hence, this work is based on the scientific literature on the sensory-perceptual development of smell in foetuses and newborn babies[11-18] and aims to replicate methodological procedures of studies such as Bartocci *et al.*[12], adapting this to the hospital context and expanding it as categories of olfactory stimulus for the implementation of a measure of discrimination sensitivity.

The main goal of the study is to assess the olfactory sensory perception of newborn children of women infected with SARS-CoV-2 during pregnancy. The specific objectives are to develop a behavioural evaluation scale of olfactory perception in infants; to validate this scale in healthy newborns; and to compare the responses with that of newborn children of women infected with COVID-19 during pregnancy.

METHODS

Study Design

The present study is a retrospective comparative analytical cohort research of 300 newborns as part of a major project aiming to follow-up the development of children born from mothers that tested positively for COVID-19 during pregnancy entitled "Clinical outcomes of children of mothers exposed to SARS-CoV-2 infection during pregnancy".

Sample size calculation

No precise figure is available about the prevalence of SARS-CoV-2 infection among pregnant women in Brazil, but international reports estimate up to 15.3% of all pregnancies being exposed[1-4]. Recent data accounts for a birth rate of 44,195 newborns per year in the Federal District area, where Brasilia the capitol of Brazil, is located. Thus, considering an "infinite" population (>20.000 pregnant women), and assuming a 15% prevalence of SARS-CoV-2 exposed pregnancies, a confidence level of 95% and margin of error of 5%, the minimum size for a random sample of exposed women would be 195, yielding an expected similar figure for the exposed children. Taking into consideration an expected drop-out rate of up to 20% in the BORN sub-study, the required number of exposed mothers (to give birth to the BORN participants) would raise to 234.

Nevertheless, our sampling approach is based on convenience, not random chance, as eligible subjects present to the recruitment centres. The aforementioned calculations served primarily as a reference, so as not to overestimate the inclusion of participants. Given the limited available knowledge regarding the effects of SARS-CoV-2 on pregnancy and child development, thus conferring upon the study an eminently exploratory character, we adopted an approach of "as much as feasible, but no more than reasonable" for the sample size definition.

Everything considered, we set an a priori number of 300 exposed women in the PREGNANT phase, which would result in expected 300 exposed children in the BORN phase. We adopted a 1:1 allocation rate between exposed and controls, thus implying another 300 mothers and 300 children who did not test positive for COVID-19 to constitute the non-exposed control group. Hence, the overall sample size of the PROUDEST study was finally set at 1200 participants (600 mother-child dyads: 300 exposed, 300 control).

Study Location and Period

This study would take place at the outpatient clinic for newborns born to pregnant women with COVID -19 (and Regular Growth and Development Outpatient clinic with newborns born to pregnant women without Covid-19). This outpatient clinic was developed at the University Hospital of Brasília (HUB) aiming at accompanying these newborns up to five years of age. It is composed of a multidisciplinary team, such as paediatric doctors, nurses, occupational therapists, speech therapists and neuropsychologists. This study will investigate infants born between July 2020 and March 2021.

Study Population and Eligibility Criteria

The target group will be composed of newborns up to 14 days old, whose mothers tested positive on a test that detects genetic material of the virus using a laboratory technique called polymerase chain reaction (PCR) for SARS-CoV-2 during pregnancy. The control group will be composed of newborns up to 14 days old, whose mothers did not test positive for SARS-CoV-2 during pregnancy. The inclusion criteria for exposed mother-baby dyads are a maternal age of ≥18 years and laboratory evidence of SARS-CoV-2 infection during pregnancy through RT-PCR or serology (searching for IgG and IgM antibodies) markers. The results of the rapid test accompanied by information about the clinical symptoms or characteristic tomography were collected as supplementary data. For the control group of unexposed mother-baby dyads, the inclusion criteria are a maternal age of ≥18 years and serology for SARS-CoV-2 (IgG and IgM antibodies) at admission for delivery assistance. Exposed newborns will be included evidence of maternal SARS-CoV-2 infection during pregnancy.

Exclusion criteria for exposed women and unexposed women are: pre-existing chronic diseases requiring continuous use of medications, except diabetes and hypertension; smoking and / or alcohol consumption; suspected or confirmed other congenital infections such as toxoplasmosis, syphilis, rubella, herpes, Chagas and ZIKA; and impossibility of sequential follow-up until delivery. Exposed and unexposed newborns will be excluded if there are indications or confirmation of genetic disorder; suspected or confirmed other congenital infections, such as toxoplasmosis, syphilis, rubella, herpes Chagas and ZIKA; and impossibility of sequential follow-up until the age of five.

Data Collection

The maternal epidemiological data will be obtained at the first meeting with the pregnant woman or her legal representative and are those contained in the "Epidemiological data spreadsheet". Clinical data will be obtained during prenatal care, which will occur in consultations with the following maximum interval: monthly between 0 and 34 weeks, twice a week between 34 and 36 weeks and weekly between 36 weeks and delivery. The data referring to childbirth and puerperium assistance will be obtained during hospitalization in the maternity hospital from medical reports. The monitoring of child growth and development will follow the intervals determined by the Ministry of Health of Brazil and will take place in an outpatient clinic specifically created for this purpose, composed of a multidisciplinary team of paediatrics, psychologists, occupational therapists, speech therapists, physiotherapists and nurses. The assessment of child neurodevelopment up to 42 months of life will include cognitive, motor, socioemotional aspects, and aspects related to language and adaptive behaviour and will be carried out with the validated version of the Bayley III Child Development Scale[19]. As of two and a half years of age, aspects related to intellectual performance will also be assessed through the Wechsler Pre-School and Primary Intelligence Scale[20], with a half-yearly interval.

The metabolic evaluation will be carried out by measuring blood glucose, insulin, lipid profile (total cholesterol and fractions, triglycerides), thyroid function (TSH, free T4) and basal cortisol at the end of the 12th and 24th months of life. Blood, CSF and placenta samples will be stored following the current rules for handling biological materials until their analysis.

Data Collection Procedure

The data collection will follow an experimental procedure from Bartocci *et al.*[12] that explores odours of the maternal breastmilk, vanilla (sweet), coffee (acid/bitter) and distilled water (neutral). The coffee smell is an addition to the previous study in order to include the acid/bitterness category to the categories of stimuli. Each test epoch consists of 30 s of baseline definition followed by 30 s of smell exposure with a two-minute interval for washout effect (figure 1).

The research assistants will wear surgical gloves for each handling of the solutions, and they will be prepared in an auxiliary room to avoid the spread of the smell of the solutions in the environment. Each solution will be kept in a hermetically sealed flask before and during all session to avoid smell impregnation. The room temperature will be maintained between 19-21ºC. The baby will be accommodated and cuddled on the lap of a familiar caregiver to prevent social stress and in a calm, relatively quiet (between 40 and 50dB(A)) environment reserved inside the Hospital Paediatric Follow-Up facility. The behavioral state[21] during the session will be monitored and registered for each stage of smell exposure ranging from state 1 (deep sleep) to sate 6 (crying). In case of the baby achieving state level six (cry – intense cry or high motor activity) or in need of a diaper change, the session will be paused and resumed as soon the baby returns to the state five or less. Mothers will be instructed to not use moisturizers or perfumes and to bring the babies already breastfed at least 15 min before the session.

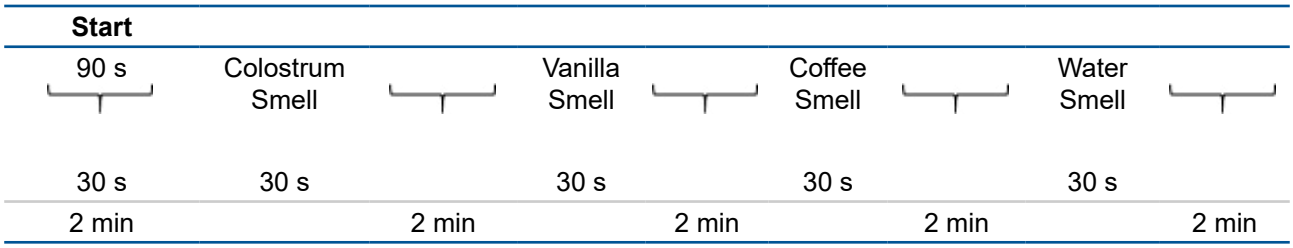

Figure 1: Timeline of odour exposure during one session adapted from Bartocci *et al.*[12]

Session phases

Step I

Collection of socio-demographic and clinical information through specific instruments and consultation of the electronic medical record.

Step II

1.Select the sample according to the inclusion criteria – participant invitation.
2.Explain to the mother how the research will be carried out and collect the consent form from the person responsible for the newborn.
3.Ask if the mother had followed the requirement to not use moisturizers or perfumes.
4.Ask the mother to remove 1 ml of breast milk and put it on a hermetic flask.
5.Turn on the video recorder.
6.Follow the following steps with the baby sitting on the companion's lap (not the mother):

A. Basal Phase: start filming the baby's face for at least 30 seconds before the first odour presentation and keep filming the entire session.
B. Stimulus Phase I: present the cotton swab soaked in breast milk for 30 seconds 2 cm from the baby's nose, maintaining the filming throughout this period, discard the cotton swab.
C. Wash out phase I: continue filming the baby for 2 minutes while the research assistant discards the cotton swab dipped in breast milk.
D. Stimulus Phase II: present the cotton swab soaked in vanilla solution for 30 seconds 2 cm from the baby's nose, maintaining the filming throughout this period, discard the cotton swab.
E. Wash out phase II: continue filming the baby for 2 minutes.
F. Stimulus Phase III: present the cotton swab soaked in coffee solution for 30 seconds 2 cm from the baby's nose, maintaining the filming throughout this period, discard the cotton swab.
G. Washout phase I: continue filming the baby for 2 minutes.
H. Control Phase: present the cotton swab soaked in water for 30 seconds 2 cm from the baby's nose, maintaining the filming throughout this period, discard the cotton swab.
J. Washout phase II: continue filming the baby for 2 minutes.

Step III - Image coding

1.Phase I coding: will be carried out for the development of the olfactory sensory evaluation scale. The videos will be analyzed frame by frame to survey categories of behavioural responses to the four different olfactory stimuli. The rating levels will consider two response categories "yes" or "no", for present and absent reaction to the smell. Factor Analysis will be performed with analyses of the main components for the construction of the instrument and analysis of the sample data.

2.Phase II coding: will be carried out for comparative evaluation of newborn children of pregnant women with and without a diagnosis for Covid-19.

Data Analysis

A mixed design will be run, with treatment (colostrum, vanilla, coffee, water) as within-subject variable and COVID-19 (covid vs. noncovid babies) as between-subject variable (group variable). The dependent variable will be the dichotomous responses. Continuous variables will be described as mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables will be described as frequencies and percentages. The analyses will be run to determine the perception thresholds, sensitivity parameters, and ROC curves (Receiver Operating Characteristic). In addition to fixed effects models, random effects models are estimated and also adjusted for possible confounders. Statistical significance will be considered when the p value is less than .05. The data will be stored in a SPSS-21 file, with an alphanumeric code that prevents the identification of the patient; curve fitting will be done with the MATLAB curve-fitting tool. To control for possible selection bias, propensity score matching (PSM) will be performed, followed by re-analyses as part of the robustness analyses.

Ethical and Legal Aspects of the Research

The study was approved by the Research Ethics Committee from the University of Brasilia School of Medicine (http://www.fm.unb.br/cep-fm - CAAE 32359620.0.0000.5558) and was registered in the Brazilian Registry of Clinical Trials (ReBec) under number RBR-65qxs2. The complete protocol can be accessed at ReBec "Effects of COVID-19 on pregnancy, childbirth, puerperium, neonatal period and child development" [cited 2020 Sep 17]. Available from: http:// ensaiosclinicos.gov.br/rg/ RBR-65qxs2/).

DISCUSSION

Pregnant women can be infected with SARS-CoV-2, with a possible consequent infection of their foetuses and newborns. SARS-COV-2 infection can cause an immune overreaction that is manifested by the excessive activation of immune cells and the production of a large amount of interferon and cytokines that can affect foetal development and increase the risk of neurological diseases in the neonatal period[5].

Like SARS-CoV, SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as a functional receptor to infect human cells. Studies have shown that ACE2 is expressed mainly in the respiratory, cardiovascular and digestive systems, which makes these organs more susceptible to this new virus. ACE2 is less mature in the youngest children and thus may not function as an appropriate receptor for SARS-CoV-2. The number of children infected with SARS-CoV-2 is relatively small. Thus, one hypothesis for this low infection rate is the low expression of ACE2 in children. Bunyavanich[22] conducted a retrospective study that examined the nasal epithelium of 305 individuals aged 4 to 60 years and observed that the gene expression of ACE2 in the nasal epithelium was age dependent. ACE2 gene expression was lower in younger children and increased with age.

A neurological symptom that has been frequently described in patients who tested positive for COVID-19 is a temporary impairment of taste and smell, which has been reported in 49-70% of infected people[23]. Somekh *et al*.[24] evaluated sensory function in patients (children and adults) who had COVID-19 documented by laboratory tests. Of the 73 patients, 37 (51%) reported having had a change in taste or smell, 25.8% of which were children. Children aged 5 to 10 years did not report sensory impairment[23]. However, there are still no reports about infants, especially newborn infants on the risk of being infected during pregnancy or delivery time.

One of the proposed mechanisms for altering smell and taste related to COVID-19 is the ability of SARS-CoV-2 to bind to ACE2 in the nasal and oral mucosa. Among people who tested positive for COVID-19, olfactory sensory sensation was significantly less impaired in children than in adults ($p = .00014$). The significant difference in olfactory sensory impairment between children and adults, and particularly between younger children and middle-aged adults, is in line with the finding that the expression of ACE2 in the nasal epithelium and in the oral cavity is more intense among adults, corroborating the possibility that the distribution and expression of ACE2 in the oral cavity and nasal epithelium may contribute to differences in sensory impairment[22]. Little is known about foetal impairment in mothers infected with SARS-CoV-2. By evaluating the olfactory sensory perception of newborns of women infected with COVID-19 during pregnancy, we can quantify such involvement.

Author Contributions

RMT, GMF KSFC and LRM devised the original study protocol, which was amended by TL, JS, JALJ and KNC. RMT, KNC, KSFC wrote the first draft of the manuscript that was then critically reviewed and revised by the other co-authors. All authors approved the final version of the manuscript for submission. RMT is the guarantor, and affirms that the manuscript is an honest, accurate and transparent account of the study being reported; and that any discrepancies from the study as planned have been explained.

Conflicts of Interest

The authors have no conflict of interest to declare.

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Resumo

Introdução: Em adultos, a perda olfativa é uma das manifestações clínicas agudas mais precoces e frequentes da infecção por SARS-CoV-2. O número de crianças infectadas com SARS-CoV-2 é pequeno, talvez devido à menor expressão da Enzima Conversora da Angiotensina 2 (ACE2) em crianças em comparação com adultos. Pouco se sabe sobre o comprometimento fetal em mães infectadas com SARS-CoV-2. Este artigo descreve um projeto em andamento sobre a percepção olfativa em bebês recém-nascidos.

Objetivo: o objetivo do presente estudo é desenvolver e validar uma escala de avaliação comportamental da percepção olfativa em recém-nascidos saudáveis e aplicá-la a recém-nascidos de mulheres infectadas com COVID-19 durante a gravidez e comparar a recém-nascidos de mulheres sem histórico de infecção por COVID-19.

Método: Este é um estudo de coorte analítico comparativo retrospectivo de 300 recém-nascidos expostos e não expostos ao COVID-19 durante a gravidez. A coleta de dados seguirá o procedimento experimental de estudo anterior que explorou odores do leite materno, baunilha (doce) e água destilada (neutro). Um cheiro de café foi implementado como um complemento a este estudo anterior, a fim de incluir a categoria ácido / amargo nas categorias de estímulos.

Discussão: É possível argumentar a hipótese do envolvimento do bulbo olfatório do feto durante a vida intrauterina como uma das manifestações fisiopatológicas indeléveis para o diagnóstico clínico de COVID-19 com déficit olfatório neurossensorial em fetos e recém-nascidos afetados por infecção intrauterina. Este estudo tem como objetivo investigar se filhos recém-nascidos de mulheres infectadas com COVID-19 durante a gravidez apresentam alterações sensoriais olfativas. O ensaio clínico foi registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC-RBR-65qxs2).

Palavras-chave: recém-nascido, percepção, odores, COVID-19, SARS-CoV-2

摘要

嗅觉丧失是成人感染新型冠状病毒(SARS-CoV-2)最早和最常见的急性临床表现之一. 与成人相比，儿童血管紧张素转换酶2（ACE2）的表达水平较低，推测儿童发病人数较成人少

与此有关. 尽管如此，但对于在感染新型冠状病毒(SARS-CoV-2)孕妇子宫内胎儿的嗅觉损伤的情况还不清楚.

研究目的：本研究的目的是开发和验证健康新生儿的嗅觉行为评价量表，然后运用该量表对比评估妊娠期感染COVID-19的母亲分娩的新生儿和妊娠期未感染COVID-19的母亲分娩的新生儿的嗅觉感知.

研究方法：该研究是一个回顾性对比分析队列研究，研究对象为300个在妊娠期暴露和未暴露在新型冠状病毒（COVID-19）的新生儿. 数据采集将遵循一个早前对气味探究的实验程序. 本研究为了将将酸/苦也纳入刺激类别，在原先只有母乳、香草(甜)、和蒸馏水(中性)的气味的基础上又加入了咖啡气味.

讨论：一个可能的假说认为，胎儿的嗅球子宫内发育过程中受累是在临床诊断宫内感染SARS-CoV-2并伴神经感觉性嗅觉障碍的胎儿和新生儿中重要病理生理表现之一.

本研究旨在探讨妊娠期感染COVID-19的新生儿是否存在嗅觉改变. 该临床试验注册在巴西临床试验注册中心(ReBEC-RBR-65qxs2).

关键词：新生儿， 知觉，嗅觉，2019冠状病毒病，严重急性呼吸综合征冠状病毒2.