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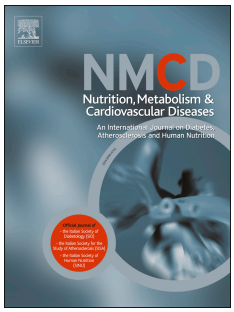

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COVID-19 Vaccination in Pregnant and Lactating Diabetic Women

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Abstract

Aim. To discuss available information on the opportunity for pregnant women affected by diabetes/obesity to receive COVID-19 vaccine.

Data Synthesis. Pregnant women with SARS-CoV-2 (COVID-19) infection are at high risk for severe acute respiratory syndrome and adverse outcomes. Pregnant women with severe COVID-19 present increased rates of preterm delivery (<37 gestational weeks), cesarean delivery and neonatal admissions to the intensive care unit. Comorbidity such as diabetes (pregestational or gestational) or obesity further increased maternal and fetal complications. It is known that diabetic or obese patients with COVID-19 present an unfavorable course and a worse prognosis, with a direct association between worse outcome and suboptimal glycol-metabolic control or body mass index (BMI) levels. Critical COVID-19 infection prevention is important for both mother and fetus. Vaccination during pregnancy is a common practice. Vaccines against COVID-19 are distributed across the world with some population considered to have a priority. Since pregnant women are excluded from clinical trials very little information are available on safety and efficacy of COVD-19 vaccines during pregnancy. However, it is well known the concept of passive immunization of the newborn obtained with transplacental passage of protective antibodies into the fetal/neonatal circulation after maternal infection or vaccination. Moreover, it has been reported that COVID-19 vaccine-induced IgG pass to the neonates through breastmilk. Therefore, maternal vaccination can protect mother, fetus and baby.

Conclusions. After an individual risk/benefit evaluation pregnant and lactating women should be counselled to receive COVID-19 vaccines.

INTRODUCTION

Aim of this document is to evaluate the available data on coronavirus disease 2019 (COVID-19) vaccination for diabetic women during pregnancy and/or breastfeeding.

First the effects of SARS-CoV-2 infection on pregnancy were discussed, pregnant women are at an increased risk for severe illness of COVID-19 when compared to non-pregnant people. Then we focused on diabetes (pregestational or gestational) and obesity which represent important risk factors for both adverse pregnancy outcomes (maternal and fetal) and severe COVID-19.

Next the available information regarding vaccination against COVID-19 during pregnancy or lactation for people affected by diabetes and/or obesity were assessed. During pregnancy many vaccines are recommended, because maternal antibodies through transplacental passage into the fetal circulation result protective for neonate. Thus maternal vaccination can protect mother, fetus and baby. On the base of the available data on COVID-19 related adverse outcomes and due to the absence of scientific evidence on possible harmful effect of COVID-19 vaccination during pregnancy, we suggest to evaluate the individual risk/benefit and consider vaccination in diabetic/obese women during pregnancy and lactation.

COVID-19 in pregnancy

Pregnant women are at high risk for severe pulmonary influenza-related diseases. The immunological conditions related to pregnancy cause a special susceptibility to infection disease complications as suggested by the greater risk of hospitalization, preterm delivery and still birth in pregnant women affected by influenza illness [1–3].This susceptibility to infection complications has been confirmed by data obtained during the current coronavirus pandemic. Pregnant women with COVID-19 seem to be at increased risk for admission to an intensive care unit, invasive ventilation, and extra corporeal membrane oxygenation compared to non-pregnant, reproductive aged women with COVID-19 [4,5].

Available data regarding SARS-CoV-2 "vertical mother-fetus transmission" showed that it represents a rare event [6] not associated with the development of comorbidities in the newborn [7]. Intrauterine transmission appears to be rare, probably due to reduced expression of the ACE2 receptor and serine protease needed for entry SARS-CoV2 into the cell [8]. Moreover, transmission via breast milk is unlikely, indeed out of 64 samples taken from affected mothers only one tested positive for SARS-CoV-2 RNA, but no active replication virus was found [9].

Regarding COVID-19 effects on fetal outcomes it has been observed that pregnant women with COVID-19 presented higher rates of preterm delivery (<37 gestational weeks) as compare to

controls [4]. In this regard the UK Pregnancy and Neonatal Outcomes in COVID- 19 (PAN-COVID) and the US American Academy of Pediatrics Section on Neonatal Perinatal Medicine (AAP SONPM) registries monitored over 4,000 pregnant women with confirmed or suspected COVID-19. Common to both registries was a high proportion of cases with pre-term delivery: 12.0% in PAN-COVID and 15.7% in AAP SONPM. The rate was 60% higher in PAN-COVID than is expected for England and Wales based on Office of National Statistics (ONS) data for January-September 2020 (7.5%) [10], and 57% higher in AAP SONPM than expected based on US National Vital Statistics Reports for 2018 (10%) [11]. Extremely preterm delivery (< 27 gestational weeks) occurred in 0.5% of cases in PAN-COVID and 0.3% in AAP SONPM [12]. In addition, some reports indicate that COVID-19 infection in pregnant women is associated with high rates of cesarean delivery and neonatal admissions to the intensive care unit while intrauterine and neonatal death rates remain low [5,13]. On the other hands several studies highlighted possible risk factors able to worsen COVID-19 during pregnancy, these include obesity, hypertension, gestational diabetes and ethnicity [4,14]. COVID-19 has also been associated to a hypercoagulable state (already high during pregnancy) thus increasing the maternal thromboembolic risk already associated to obesity and diabetes [15].

COVID-19 and Diabetes and/or Obesity during pregnancy

It has been observed that in diabetic patients SARS-CoV-2 infection is related to an unfavorable course and a worse prognosis, with a direct association between worse outcome and suboptimal glycol-metabolic control [16,17]. Several studies and meta-analysis showed that COVID-19 patients with diabetes are exposed to a high risk of severe disease, critical illness with higher rate of ICU admissions and death [18–22]. In addition, as compare to subject without diabetes, patients with diabetes infected with SARS-CoV-2 and with poor blood glucose control (i.e. higher HbA1c) before hospital admission, show an increased high risk of death [23,24], together with a high risk of composite outcomes (ICU admission, mechanical ventilation and death) (OR 5.47, 95%CI 1.56-19.82) [25].

Similarly, obese COVID-19 patients present a severe illness, longer hospital stay and increased risk of admission to the ICU, proportionally with body mass index (BMI) levels [26,27]. Moreover, BMI above 40 kg/m^2 was an independent risk factor associated with mortality, especially in patients younger than 50 years (OR: 5.1) [28]. Furthermore, plasma soluble ACE2, the entry receptor of SARS-CoV-2, is increased in type 2 diabetes mellitus and is associated with hyperglycemia and with indexes of insulin resistance, suggesting a possible role of insulin resistance in COVID-19

severity [29]. Therefore, the clinical course and prognosis of COVID-19 in obese and/or diabetic patients is significantly more severe.

Scant data on COVID-19 in pregnancy complicated by diabetes and/or obesity are currently available. An analysis conducted by the Vaccine Safety Datalink (VSD) on surveillance of COVID-19 admissions during the period March 1 to May 30, 2020, indicates that conditions such as pre-pregnancy obesity and gestational diabetes (GDM) are more common among pregnant women hospitalized for COVID-19, than pregnant women hospitalized for obstetric reasons (44% versus 31% and 26% vs 8%, respectively) [30]. In a case series of critically ill pregnant women with COVID-19 in need of intensive care the 60% of patients had gestational diabetes and BMI >25 kg/m^2 [31]. Moreover, it has been reported that in pregnant women with SARS-CoV-2 infections who were hospitalized for severe disease the most common underlying conditions were pre-pregnancy BMI ≥30 kg/m^2 (41.7%) and type 2 diabetes (12.5%). Among them, women who died due to COVID-19 disease (12.5%) were all obese before pregnancy [5].

The data so far available regarding the effects of COVID-19 in pregnancy and in patients affected by diabetes and/or obesity place these conditions among important risk factors for severe COVID-19 or death, therefore pregnant patients with diabetes and/or obesity should be considered in especially vulnerable position [32].

COVID-19 Vaccines during pregnancy

Based on the aforementioned information the scientific community agrees to consider pregnancy, especially when complicated by diabetes and/or obesity, a priority for COVID-19 vaccine. Despite the recognition of the need for inclusion of pregnant women in clinical trials, the speed at which the COVID-19 vaccines were developed precluded the inclusion of pregnant in the trials conducted. Thus, very little information is currently available on safety and efficacy of COVD19 vaccines during pregnancy [33]. It is known the concept of passive immunization of the newborn obtained with transplacental passage of protective antibodies into the fetal/neonatal circulation after maternal infection or vaccination. According to that, maternal vaccination can protect the mother, fetus and baby. Therefore, a single intervention offers powerful protection for two susceptible individuals who are at increased risk for a disease and its complications [34]. No previous experience with mRNA vaccines (the first type of COVID-19 vaccines approved) in pregnant women is available. However, there is no reason to expect that different effects of mRNA vaccines in pregnant as compare to non-pregnant women. To date no data are available for COVID-19 vaccines using a viral vector. However, other vaccines using similar technology have previously been successfully and safety used in pregnancy. In general, it must be considered that different types of vaccines are

allowed during pregnancy when the benefit of the vaccination is considered to outweigh the potential risk [35,36]. Although developmental and reproductive toxicology studies in pre-clinical models conducted to assess the potential effects of a new medication or vaccine on the full spectrum of reproduction, have not yet been completed for any of the COVID-19 vaccines, the results so far available indicate these vaccines as safe [37]. Among participants of phase 3 COVID-19 vaccines clinical trials in non-pregnant adults, a few unplanned pregnancies occurred (12 in the vaccine group for Pfizer and 6 for Moderna) however the pregnancies exposed to vaccine are still ongoing [33]. Clinical trials of COVID-19 vaccines safety and immunogenicity for pregnant women have begun in January 2021. As of February 16, 2021, there have been over 30,000 pregnancies reported in CDC's v-safe post-vaccination health checker [38]. Based on limited self-reported information, no specific side effects have been observed in pregnancy. In a prospective cohort study the mRNA vaccine-induced immune responses and the side effects were evaluated in 84 pregnant and in 31 lactating women. A strong humoral immune response was observed in all vaccinated women with higher levels of SARS-CoV-2 antibodies compared to pregnant women with natural infection in the previous 4-12 weeks [39]. No adverse pregnancy outcomes were observed, except the 8% of spontaneous preterm delivery [39]. As for other vaccines, injection site soreness, fever, fatigue, headache, chills, together with muscle and joint pain are the most frequent systemic reactions to COVID-19 vaccines. Fever (38°C or higher) was more common after the 2nd dose [39]. Vaccine-induced IgG pass across the placenta to the fetus and in neonates through breastmilk. Whether breastmilk IgG will offer neonatal protection remains unclear [39]. Neonates of pregnant who experienced fever in their first trimester of pregnancy showed an increased risk for birth defects, although the absolute risk remains small. The birth defect risks associated with fever appear even lower if antipyretic medications are used [40].

Taking into account the risks of severe COVID-19 in pregnant women, the important practice and benefits of vaccination in pregnancy, the demonstrated efficacy and safety of COVID-19 vaccines in non-pregnant populations and the encouraging data so far available during pregnancy, it can be inferred that the benefits of COVID-19 vaccination outweigh the risks. For this reason, the majority of scientific societies and federal agencies indicate that pregnant and lactating women should not be excluded from vaccination [37,41–44].

In conclusion, pregnant women should be counselled to receive COVID-19 vaccine since SARS-CoV-2 infection increases the risk for both the mother and the fetus (Table). The presence in pregnant women of other risk factors such as diabetes (pregestational and gestational), cardiovascular disease and obesity, exposed them to severe complications in case of COVID-19. In

addition, the assessment of the individual risk of contracting the infection in relation to the spread of the virus in the community and degree of exposure in the workplace (e. g. working as a health worker or caregiver) are further elements to consider [43]. Healthcare providers should recommend SARS-CoV-2 vaccination in diabetic women during the phase of pregnancy planning, since there are not evidence or theoretical concerns about effects of COVID-19 vaccines on fertility. Moreover, a delay of pregnancy after COVID-19 vaccination is not necessary. Lactating women may receive the vaccine without discontinuing breastfeeding. All these considerations should be examined to evaluate the risk/benefit profile of vaccination [4,41,42,45].

Table. Considerations for the use of COVID-19 vaccines in pregnant or lactating diabetic women

- Pregnant women with pre-gestational or gestational diabetes complicated by SARS-COV-2 infection have a higher risk of complications. The presence of obesity further increased the maternal risk.

- Diabetic pregnant women who do not have a history of SARS-COV-2 infection may be candidate for COVID-19 vaccine at any trimester of pregnancy.

- Other recommended vaccinations are allowed in addition to COVID-19 vaccine during pregnancy. However, as a precaution, it is appropriate to observe a 14-day interval between vaccines.

- Women with type 1 or type 2 diabetes mellitus of childbearing age should consider the vaccination against COVID-19 during pregnancy planning.

- To date, the safety data produced for both types of available vaccines (based on mRNA or on non-replicative adenoviral vector) are not sufficient to suggest which one should be preferred during pregnancy and breastfeeding.

- Lactating women may receive the vaccine without discontinuing breastfeeding.

- All women, either vaccinated or not, should adopt preventive measures such as protective masks, physical distancing and frequent hand washing.

Competing Interests: All the authors (M.A.S., G.F., L.S.) declare no conflict of interest in connection with submitted material.

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