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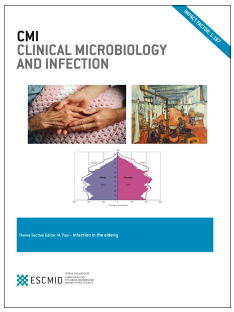

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Clinical Microbiology and Infection-Letter

Both SARS-CoV-2 infection and vaccination in pregnancy elicited neutralizing antibodies in pregnant women and newborns

Irene Cassaniti[1], Elena Percivalle[1], Paola Zelini[2], Kimta Ngaradoumbe Nanhorngue[3], Anna Parolo[3], Valeria Bernardi[4], Gianfranco Jorizzo[3], Peter Santer[4], Francesca Perotti[2], Arsenio Spinillo[2], Daniele Lilleri[1]*, Fausto Baldanti[1,5]

[1)]*Virologia Molecolare, Microbiologia e Virologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

[2)]*Ostetricia e Ginecologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*

[3)]*ASL 6 Euganea, Padova, Italy*

[4)]*Azienda Sanitaria dell'Alto Adige, Brunico, Italy*

[5)]*Dipartimento di scienze clinico-chirurgiche, diagnostiche e pediatriche, Università degli Studi di Pavia, Italy*

* Corresponding author: Molecular Virology Unit, Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy; email: d.lilleri@smatteo.pv.it

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To the Editor.

To date, few data on SARS-CoV-2 immune response after infection or vaccination have been reported in pregnant women. So far, maternal immunization during pregnancy inducing trans-placental antibody transfer to the newborn is currently supported to reduce morbidity and mortality from infectious diseases after birth.

After having signed written informed consent, two healthcare workers received complete BNT162b2 mRNA vaccination during pregnancy. The first vaccinated woman (VW#1) received the first dose at 31 weeks gestation and 4 days, the second woman (VW#2) at 27 weeks gestation and 6 days.

Serum samples from the mother/newborn pairs collected at delivery were tested by ELISA (Euroimmun, Luebeck, Germany) for anti-SARS-CoV-2 Spike IgG and IgA antibodies. Semi-quantitative results are expressed as optical density (OD) ratio with respect to an internal calibrator: a ratio ≥ 1.1 was considered positive.

SARS-CoV-2 Spike-specific IgA antibodies were documented in the two vaccinated women (OD ratio: 7.5 and 2.4); as expected, IgA were absent in the two newborns (N#1 and N#2). Spike-specific IgG were detectable in N#1 and N#2 (8.0 and 5.4) at higher levels than in VM#1 and VM#2 (6.8 and 4.0), with a newborn-to-maternal serum ratio of 1.2 and 1.4, respectively. As control, the newborn-to-maternal serum ratio for anti-cytomegalovirus (CMV) IgG measured by ELISA (Euroimmun) was 1.0 and 1.3. The neutralizing (NT) antibody titer [1] was higher in VW#2 than VW#1 (1:320 vs 1:20). Similarly, NT antibody titer was higher in N#2 than N#1 (1:160 and 1:10).

For comparison, seven women (median age 31 years old; range 23-35) who experienced SARS-CoV-2 infection during pregnancy were analyzed: one developed a mildly symptomatic infection during the first trimester, one developed pneumonia during the second trimester, and five women had an asymptomatic infection during the third trimester. The seven women were positive for Spike-specific IgA and IgG antibodies at delivery (with the exception of the women infected during the first trimester who was positive only for Spike-specific IgA), and only 3/7 were also positive for

Nucleocapsid IgG by ELISA (Euroimmun). The median newborn-to-maternal serum ratio was 1.4 (range 0.5-2.6) for Spike-specific IgG, and 1.0 (0.9-1.4) for CMV-specific IgG, while the median NT titer ratio was 0.5 (range: 0.03-1). Data are reported in Table 1 and Supplementary Table 1.

Current data suggest that pregnant women may be at increased risk to be admitted to an intensive care unit with respect to non-pregnant women, thus vaccination might represent a valuable preventive strategy.

The efficiency of trans-placental transfer of anti-SARS-CoV-2 antibody has been claimed to be lower than for other pathogens [2]. On the contrary, we observed that antibody transfer occurred efficiently from mothers showing anti-SARS-CoV-2 IgG at delivery (elicited either by infection or vaccination). Our results are in line with another study showing an efficient trans-placental transfer of anti-Spike IgG antibodies [3]. However, median NT titer was two-fold reduced in newborns with respect to mothers. This may be due to the contribution to neutralization in maternal serum of Spike-specific IgA, which are not transmitted to the fetus. It should be taken into account that, when evaluating placental transfer after natural infection, key determinants are time elapsed from infection, severity of the infection and maternal antibody titers. These factors may be at the basis of the conflicting results reported.

A recent report highlighted that the immune response elicited by SARS-CoV-2 vaccine in pregnant women was higher than that induced by natural infection [4]. Moreover, while it was suggested that third-trimester SARS-CoV-2 infection induced a poor trans-placental IgG transfer [5], in our study IgG elicited by either infection or vaccination appeared to be efficiently transferred to the fetus. While a sustained neutralizing response was observed in VM#2 and N#2, NT Abs were lower in VM#1 and N#1. These variable results are in the range of those observed in a cohort of immunocompetent vaccinated subjects (unpublished results).

On the other hand, a recent study conducted in Israel [6] reported a lower transfer ratio of anti-Spike IgG (median transfer ratio: 0.44) than that observed in our cases. The median time lapse between second dose administration and delivery was 11 days in the Israel cohort, whereas our

subjects received the second dose 33 and 42 days before delivery. Therefore, we can hypothesize that vaccination schedule should be completed at least one month before presumed date of delivery for a better antibody transfer.

As a major limitation, only two vaccinated pregnant women were analyzed. However, results are in line with those obtained in cohort of healthy immunocompetent subjects. On the other side this is the first report that compares trans-placental SARS-CoV-2 antibody transfer in vaccinated and infected pregnant women. These findings should be extended to a larger cohort and durability of vertically transmitted antibody after maternal vaccination should be investigated. Nevertheless, our preliminary study support the potentiality of maternal immunization in providing immune protection against SARS-CoV-2 in newborns.

Transparency declaration

Conflict of interests: the authors have no conflict of interest to declare.

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Contribution: FB, DL conceived the study; IC analyzed the data and drafted the initial manuscript; DL revised the manuscript and wrote final draft; EP, PZ performed serological analyses; KNN, AP, VB, GJ, PS, FP, AS enrolled the subjects and collected clinical data.

Ethical statement:

Blood samples were collected according to the Helsinki declaration and after ethical committee approval of Hospital of Padua, AULSS 6 Euganea (P-55422) and Pavia (P-20200046007).

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114 **Table 1.** Characteristics of two vaccinated pregnant women and seven SARS-CoV-2 seropositive at
115 delivery convalescent pregnant women
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	Convalescent pregnant women (median, range)	*VW#1*	*VW#2*
Age	31 [23-35]	37	36
Days between infection onset/2nd dose vaccination and delivery	76 [18-175]	33	42
Maternal immunity			
SARS-CoV-2 Spike IgG	1.9 [0.4-4.7]	4.0	6.8
SARS-CoV-2 NCP IgG	0.7 [0.2-2.9]	0.1	0.1
SARS-CoV-2 Spike IgA	1.8 [1.0-4.3]	2.4	7.5
SARS-CoV-2 NT Abs	1:160 [1:40-1:320]	1:20	1:320
CMV IgG	1.3 [0.7-1.5]	2.3	2.0
Newborn immunity			
SARS-CoV-2 Spike IgG	1.4 [1.2-3.3]	5.4	8.0
SARS-CoV-2 NCP IgG	0.9 [0.3-2.8]	0.1	0.1
SARS-CoV-2 Spike IgA	0.1 [0.1-0.1]	0.1	0.1
SARS-CoV-2 NT Abs	1:40 [<1:10-1:320]	1:10	1:160
CMV IgG	1.3 [1.0-1.5]	2.3	2.6

117 Legend. VW#1: vaccinated woman 1; VM#2: vaccinated woman 2; NCP: nucleocapsid protein; NT
118 Abs: neutralizing antibodies; CMV, cytomegalovirus.
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