Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Adverse effects on female fertility from vaccination against COVID-19 unlikely

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ABSTRACT

This opinion paper briefly presents arguments that support the unlikelihood of an impact on female fertility from current covid-19 vaccines.

Vaccination is a success story in modern medicine, yet the number of vaccination critics is increasing (Greenwood, 2014). The current COVID-19 pandemic with the resulting fear and uncertainty in the public is also a breeding ground for vaccination opponents (Romer and Jamieson, 2020). Misinformation and conspiracy theories have accompanied the pandemic since its inception, and especially, concerning the newly developed vaccines (Ball and Maxmen, 2020). Distinct types of vaccines have been approved or are under development in different countries. Their global aim is the induction of antibody and T cell generation targeting the SARS-CoV-2 spike protein (Park et al., 2021; Voysey et al., 2021).

Claims have circulated in social media that these antibodies also act against placental components, leading to infertility (Fauzia, 2020). This has led to an enormous public interest in the topic reflected by 34,900 % increase of respective internet search terms in the U.S. (Sajjadi et al., 2021). The suspected target is syncytin-1 (endogenous retrovirus group W member 1, envelope; ERVW-1), mostly localized to villous syncytiotrophoblast. Binding to its main receptor SLC1A5, almost exclusively expressed in villous cytotrophoblast, initiates the fusion process to form the syncytiotrophoblast (Lavillette et al., 2002; Roberts et al., 2021). In the female or male reproductive tract, a lower syncytin-1 expression has been described also for oocytes, testes, and spermatozoa (Bjerregaard et al., 2014; Bergallo et al., 2021), but also for adrenal tissue, bone marrow, white blood cells, breast, colon, kidney, ovary, prostate, skin, spleen, thymus, thyroid, brain and trachea (de Parseval et al., 2003).

The corona spike protein (1273 amino acids) contains the sequence VVNQN. A similar but not identical sequence of 5 amino acids (VVLQN) is expressed in syncytin-1 (538 amino acids) at position 378–382 (homology approximately 0.75 %) (Laufer et al., 2009; UniProt, 2021). In syncytin-1, VVLQN forms part of a heptad repeat region at position 363–391 (HRA2), localized in a transmembrane subunit, with slight fusion inhibiting functions and not directly accessible to antibodies. The sequences of syncytin-1 responsible for fusion are mostly localized in its surface domain (Chang et al., 2004). All other similar sequences are shorter (maximum of 3 concordant subsequent amino acids) resulting in a total identity of $< 7\%$ as calculated by UniProt alignment (UniProt, 2021).

A therapeutic humanized IgG4 monoclonal antibody (GNbAC1, Temelimab; geneuro) targeting the surface domain of human endogenous retrovirus type W family (HERV-W), also named multiple sclerosis associated retrovirus (MSRV), has been developed for treatment of multiple sclerosis (Curtin et al., 2015). This protein has an overall homology of 81 % with syncytin-1, and even 87 % homology with the syncytin-1 surface domain (Laufer et al., 2009). Despite the high similarity with MSRV, the therapeutic antibody does not bind to syncytin and has no effect on syncytin functionality in relation to syncytiotrophoblast cell fusion, which is fundamental for normal placental development (Kornmann and Curtin, 2020). It may be presumed that a potential antibody against a very short transmembrane sequence would not disturb the functionality of syncytin-1.

In consideration of the suspected generation of anti-syncytin-1 antibodies induced through the SARS-CoV-2 vaccines, a far stronger

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antibody inducing effect may be expected through the virus itself. In an active infection, the corona spike protein antigen exposure is significantly higher and more incalculable than after vaccination. SARS-CoV-2 infection causes an elevated risk for on average 1 week earlier birth, preterm delivery and newborns that require phototherapy (Dumitriu et al., 2021; Mirbeyk et al., 2021). In the early phase of the pandemic in 2020, it has been reported that SARS-CoV-2 infection does not seem to impact frequency of further pregnancy disorders such as gestational diabetes, preeclampsia, intrauterine growth restriction, preterm rupture of membrane, stillbirth, hemorrhage, neonatal intensive care unit admission or neonatal sepsis (Pirjani et al., 2020). These observations have been done on low numbers of patients and do not justify the statement that SARS-CoV-2 infection is not harmful in pregnancy (Mirbeyk et al., 2021). Thus far, no significantly increased risk of pregnancy loss for women with anti-SARS-CoV-2 antibodies has been reported (la Cour Freiesleben et al., 2021). A recent study has shown that the pregnancy rate upon transfer of in vitro fertilized frozen embryos is not different between vaccinated or recovered anti-SARS-CoV-2 immunoreactive and non-reactive women (Morris, 2021). In 2002/2003, a SARS-CoV (frequently named SARS-CoV-1) pandemic has emerged. This virus expresses the same VVNQN sequence in its spike protein as SARS-CoV-2, and thus, shows the same similarity with syncytin-1, potentially leading to similar antibodies against the respective epitope. Nonetheless, long-term effects of SARS-CoV on female fertility have not been reported (Segars et al., 2020).

Therefore, from the perspective of reproductive medicine and placental research, the widespread claims concerning fertility disturbing effects through COVID-19 vaccines appear unfounded and we strongly recommend to avoid the potential risk of pregnancy complications through vaccination.

Declaration of Competing Interest

The authors report no declarations of interest.

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