

Corona and Reproduction, or Why the Corona Vaccination Does Not Result in Infertility

„Corona und Reproduktion“ oder warum die Coronaimpfung nicht unfruchtbar macht



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ABSTRACT

Background As the COVID-19 pandemic persists and new vaccines are developed, concerns among the general public are growing that both infection with the SARS-CoV-2 virus and vaccinations against the coronavirus (mRNA vaccines) could lead to infertility or higher miscarriage rates. These fears are voiced particularly often by young adults of reproductive age. This review summarizes the current data on the impact of SARS-CoV-2 infection and corona vaccinations on female and male fertility, based on both animal models and human data.

Method A systematic literature search (PubMed, Embase, Web of Science) was carried out using the search terms “COVID 19, SARS-CoV-2, fertility, semen, sperm, oocyte, male fertility, female fertility, infertility”. After the search, original articles published between October 2019 and October 2021 were selected and reviewed.

Results Despite the use of very high vaccine doses in animal models, no negative impacts on fertility, the course of pregnancy, or fetal development were detected. In humans, no SARS-CoV-2 RNA was found in the oocytes/follicular fluid of infected women; similarly, no differences with regard to pregnancy rates or percentages of healthy children were found between persons who had recovered from the disease, vaccinated persons, and controls. Vaccination also had no impact on live-birth rates after assisted reproductive treatment. No viral RNA was detected in the semen of the majority of infected or still infectious men; however, a significant deterioration of semen parameters was found during semen analysis, especially after severe viral disease. None of the studies found that corona vaccines had any impact on male fertility.

Discussion Neither the animal models nor the human data presented in recent studies provide any indications that fertility decreases after being vaccinated against coronavirus. However, there is a growing body of evidence that severe SARS-CoV-2 infection has a negative impact on male fertility

and there is clear evidence of an increased risk of complications among pregnant women with SARS-CoV-2 infection. The counseling offered to young adults should therefore take their fears and concerns seriously as well as providing a structured discussion of the current data.

ZUSAMMENFASSUNG

Hintergrund Mit Fortschreiten der COVID-19-Pandemie und der Entwicklung neuer Impfstoffe wächst in der Öffentlichkeit die Sorge, dass sowohl eine Infektion mit dem SARS-CoV-2-Virus als auch eine Coronaimpfung (mRNA-Impfstoffe) zu einer Infertilität bzw. einer erhöhten Abortrate führen könnten. Besonders junge, in der Reproduktionsphase befindliche Menschen äußern diese Ängste. Der vorliegende Übersichtsartikel fasst die aktuellen Daten zum Einfluss einer SARS-CoV-2-Infektion bzw. einer Coronaimpfung auf die weibliche und männliche Fertilität am Tiermodell und auf humaner Seite zusammen.

Methoden Anhand der Schlüsselwörter „COVID 19, SARS-CoV-2, fertility, semen, sperm, oocyte, male fertility, female fertility, infertility“ wurde eine systematische Literaturrecherche durchgeführt (Pubmed, Embase, Web of Science). Im Anschluss wurden Originalarbeiten von Oktober 2019 bis Oktober 2021 ausgewählt und aufgearbeitet.

Ergebnisse Im Tiermodell war trotz des Einsatzes von sehr hohen Impfdosen kein negativer Effekt auf die Fruchtbarkeit, den Schwangerschaftsverlauf und die fetale Entwicklung nachweisbar. Auf humaner Seite wurde bei infizierten Frauen keine SARS-CoV-2-RNA in Oozyten/Follikelflüssigkeit nachgewiesen; ebenso zeigten sich zwischen Genesenen, Geimpften und Kontrollen keine Unterschiede hinsichtlich Schwangerschaftshäufigkeit und des Anteils gesunder Kinder. Ferner beeinflusste die Impfung auch nicht die Lebendgeburtenrate nach einer assistierten reproduktionsmedizinischen Behandlung. Bei infizierten und noch infektiösen Männern wurde in der Mehrzahl der Fälle keine Virus-RNA im Ejakulat nachgewiesen; allerdings zeigten sich deutliche Einschränkungen im Spermogramm, insbesondere nach schwerwiegend verlaufender Infektion. Bisherige Studien zeigen keinen negativen Einfluss einer Coronaimpfung auf die männliche Fertilität.

Diskussion Die aktuellen Studien geben weder im Tiermodell noch auf humaner Seite einen Hinweis auf eine Einschränkung der Fertilität nach einer Coronaimpfung. Demgegenüber gibt es zunehmende Hinweise für negative Auswirkungen einer schweren SARS-CoV-2-Infektion auf die männliche Fertilität und klare Evidenz für ein erhöhtes Komplikationsrisiko von Schwangeren bei einer SARS-CoV-2-Infektion. Die Beratung von jungen Menschen sollte daher sowohl die Ängste und Sorgen ernst nehmen als auch die aktuelle Datenlage strukturiert erörtern.

Introduction

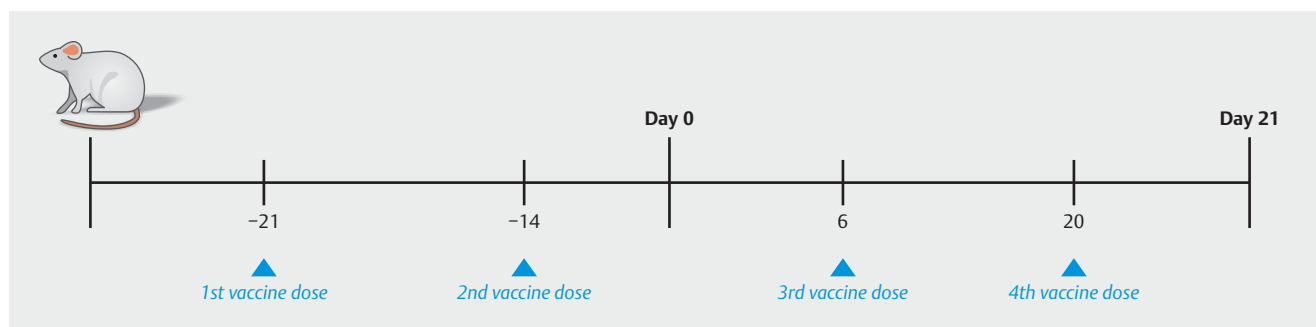
Coronavirus disease 2019 (COVID-19) is caused by the new beta-coronavirus, referred to by the WHO as 2019-nCoV and by the International Committee on Taxonomy of Viruses as severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Emerging in the final months of 2019, the disease has since triggered a global pandemic which has infected at least 326.3 million people and led to 5.53 million deaths (as per 17 January 2022) [1, 2].

Although the prevalence of disease has been approximately the same, a significant gender bias has been found with regard to both severity of disease and mortality [3, 4]: men have a higher risk of requiring intubation and spend a longer time in hospital compared to women. In addition, the mortality rate in men is higher, even after comparing age groups and ethnicities and taking co-morbidities into account [5]. A possible protective effect of female but also male sexual hormones is currently being discussed in this context [6, 7]. After acute infection, 2.3% of persons who fell ill report persistent side effects (> 12 weeks) in the form of so-called long/post-COVID syndrome [8, 9]. The syndrome is characterized by symptoms such as fatigue, headache, dyspnea and anosmia and occurs more commonly in older patients (> 52 years), patients with a higher body mass index (BMI > 26), patients who have previously had severe COVID-19, and women [10, 11]. In patients below the age of 52 years, SARS-CoV-2 infection is generally associated with lower morbidity and mortality rates than in older infected persons, with a lower percentage (25%) of “critically” ill patients according to the COVID-19 score

[12–14]. However, the delta variant of the virus has also led to an increasing rate of hospitalizations among young adults aged between 18 and 34 years. 21% of patients in this patient population require intensive care. The mortality rate of 2.7% is twice as high as that occurring following myocardial infarction in the same age group [15].

Initial studies have shown an impact on male fertility in severely or critically ill patients with COVID-19, particularly on sperm motility and morphology [16–18]. There is not much current data on the impact of SARS-CoV-2 infection on female fertility, particularly on oocyte quality, as assisted reproductive treatment is not carried out in cases with acute infection and oocytes are therefore not examined [19].

Caring for pregnant women during a pandemic is a challenge. At the beginning of the pandemic, it was assumed that placental transmission of maternal infection did not occur [20]; however, recent data have shown changes in the placenta of SARS-CoV-2-positive mothers, such as vascular malperfusion with increased syncytial knots and focal perivillous fibrin depositions [21, 22]. Moreover, a reduction in mtDNA values was found in the placentas of pregnant women with SARS-CoV-2 infection. This is significantly associated with oxidative DNA damage and indicates that the placenta is under severe oxidative stress [23]. Pregnant women with COVID-19 also have a more severe course of disease compared to non-pregnant women [24]. The time spent in hospital is longer and the likelihood that they will require ventilatory support and may need to be moved to intensive care is higher for pregnant women [25]. Moreover, rates of cesarean section



► **Fig. 1** Study design and timing of administration of the vaccine (BNT162b2). Day 0 = start of gestation period, Day 21 = C-section or delivery [37].

and preterm birth rates for fetal distress are higher for pregnant women who are SARS-CoV-2-positive [26–28].

To date, the EU has approved two mRNA vaccines and two viral vector vaccines to contain the pandemic. Both mRNA vaccines have been shown to be 95% effective for the prevention of severe COVID-19 disease in the age group between 12–17 years, 85% effective in persons aged 18–39 years, and 86% effective in persons older than 40 years [29,30]. Vaccination with the vector vaccine by AstraZeneca resulted in 61% protection from SARS-CoV-2 infection with severe symptoms of disease for persons aged 18–39 years, 72% protection for persons aged 40–59 years and 80% protection for people above the age of 60 years [29–32].

The rapid development and approval of these vaccines combined with the simultaneous spread of misinformation across social media has not just raised fears among persons strongly opposed to vaccinations. Such fears can include worries about possible long-term consequences, including the long-term impact on the fertility of vaccinated persons [33,34]. Such fears and concerns can only be countered by a detailed, structured presentation of the data available in recent studies. This article therefore presents the current data on possible impacts of corona vaccination or SARS-CoV-2 infection on fertility using both animal models and human data.

Available Vaccines and Currently Established Animal Models

Two different types of vaccine are currently approved for use against the SARS-CoV-2 virus in the European Union (EU): two mRNA vaccines (BNT162b2 from BioNTech/Pfizer and mRNA-1273 from Moderna) and two viral vector vaccines (AZD1222 from AstraZeneca, JNJ-78436735 from Janssen).

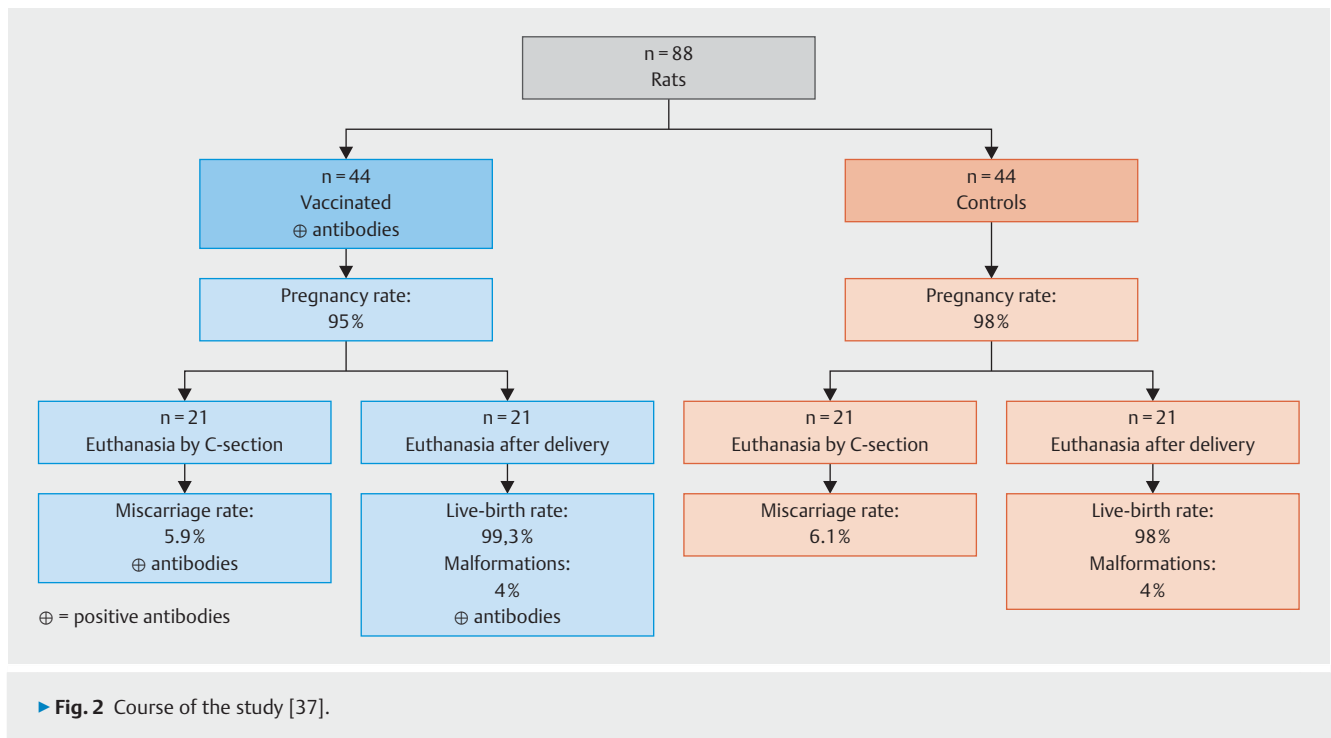
Viral vector vaccines function by incorporating the DNA for the spike protein of the SARS-CoV-2 virus in a modified adenovirus; the DNA is introduced into the cell's nucleus and transcribed into the RNA, which results in the production of spike proteins. The spike proteins are then transported to the cell surface, where they induce a targeted cellular and humoral immune response. This leads to the production of specific antibodies against the spike protein on the surface of the virus. In the event of an infection,

the spike protein epitopes of the SARS-CoV-2 virus are recognized and neutralized with the help of the available antibodies [32,35]. With mRNA vaccines, the viral RNA needed to create spike proteins is directly absorbed by the cells around the vaccination site through endocytosis. With this type of vaccine, the mRNA is enveloped by lipid nanoparticles to protect and allow it to enter cells of the body without being immediately broken down again. The viral RNA is then decoded, translated into spike proteins by the body's own ribosomes, and the antigen is transported to the surface of the cell. As with the immune response elicited by vector vaccines, the use of mRNA vaccines also results in the production of specific antibodies [29,31,36]. What is important is that just a few days later, no adenoviruses can be detected in persons who received vector vaccines and no spike protein-coding mRNA can be detected in the human organism of persons who received mRNA vaccines [29,31,32].

Several animal models have been used to investigate the possible side effects of a corona vaccine on fertility, pregnancy and offspring. Bowman et al. analyzed the impact of vaccinations using the mRNA vaccine (BNT162b2) on female fertility and the course of pregnancy in rats (► **Fig. 1**). The study was carried out in a total of 88 female rats of reproductive age. The control group was injected with a saline solution, while the rats in the study group received a total of 4 doses of the mRNA vaccine (30 µg/vaccination). Dosages were selected to be similar to the doses given to humans (70 kg) and were therefore 300× higher than human doses on a µg/kg basis (220 g) [37].

Injections were administered to all of the animals before the start of gestation (Day 0) and during pregnancy. Half of the rats in both the control group and the study group (n = 21/group) were euthanized and classified as the cesarean section group. The remaining animals and their offspring were examined after delivery. No differences with regard to fertility, duration of pregnancy, miscarriage or live-birth rates were found between the study group and the control group, although the rats received a 300-fold dose of the vaccine. In addition, all animals and their offspring in the study group had positive antibody titers against the SARS-CoV-2 spike protein (► **Fig. 2**) [37].

Another study investigated the safety of the vector vaccine Vaxzevria manufactured by AstraZeneca (AZD1222), with regard to the fertility and development of offspring in a mouse model.



Both study phases focused on the developmental and postpartum period. In the 1st phase, the first dose of vaccine (0.035 ml) was injected on Day 14 (= Day 0 of gestation) and the second on Day 6 of gestation. Day 0 corresponded to the date of fertilization and C-section was carried out on Day 17. As the dose in humans (70 kg) is 0.5 ml, the dose administered to each mouse (30 g) was 163× higher. In a 2nd phase, vaccines were administered after fertilization (Day 0), with the first vaccine dose administered on Day 6 after gestation and the second dose on Day 15. Animals and their offspring were investigated post partum. The viral vector vaccine used had no impact on fertility, the course of pregnancy, or offspring.

After having received the vaccination, animals showed no loss of appetite and experienced no weight loss. The pregnancy rate (PR) in the study group was 92% and the rate of spontaneous abortion was 6.8%, which did not differ from the control group (PR 94%, abortion rate 7.5%). The malformation rate for the offspring of the study group was 0.6% compared to 1.8% in the control group [38].

Female Fertility and SARS-CoV-2 Infection or Vaccination

To determine the impact of an infection on individual cell types, the first questions that need to be answered are the fundamental questions whether and how cells can be infected. To understand the impact on female fertility, there must be an impact on the ovaries, particularly on the oocytes. Stanley et al. [33] showed in a small study population (n = 18) that human cumulus cells show no or only minimal RNA expression of transmembrane protease

serine 2 (TMPRSS2) which is a point of entry for the SARS-CoV-2 virus.

The same study detected RNA expression of TMPRSS2 and angiotensin-converting enzyme 2 (ACE2) in the ovarian cells of primates. SARS-CoV-2 uses ACE2, which is encoded on the X chromosome, as a receptor to enter human cells. The more advanced the developmental stage of the oocytes, the more it was possible to detect expression of both proteins. The highest expression was found in the antral follicles [39]. This means that in a primate model, oocytes are most vulnerable just before ovulation or just prior to follicular atresia during the physiological cycle. The data on human oocytes is limited; there are only 3 case reports of women proven to have SARS-CoV-2 infection at the time of follicular aspiration during assisted reproductive treatment [19,40]. No viral RNA was found in either the follicular fluid of a symptomatic patient [19] or the oocytes of two asymptomatic patients [40]. No infection was detected in the oocytes of these women even though, according to the animal model, they were in the most vulnerable phase of folliculogenesis.

A long-term impact of SARS-CoV-2 infection on ovarian function or ovarian reserve has not been detected. Wang et al. [35] reported on 4043 ART cycles in Wuhan, 70 of which were in patients found to be positive for IgG/IgM SARS-CoV-2 antibodies compared to women without detected antibodies. There was no significant difference between the two groups with regard to anti-Müllerian hormone (AMH) levels, antral follicle count (AFC), follicle-stimulating hormone (FSH) levels, number of retrieved oocytes, and pregnancy rate [41].

A recently published study also found no differences in ovarian reserve (measured using AMH over the course of one year) between patients who had recovered from SARS-CoV-2 infection and patients who had not been infected [43].

► **Table 1** Impact of corona vaccinations on assisted reproductive treatment (ART) cycles.

	Bentov et al. [43]			p-value	Orvieto et al. [40]		
	Vaccinated	Recovered	Control		Before	After	p-value
Number of patients	9	9	14		36	36	
Age in years	35.3 ± 3.97	34.1 ± 4.7	32.5 ± 5.3	ns	37.3 ± 17.5		
Antral follicle count	13.3 ± 4.7	13.6 ± 4.1	15.6 ± 6.7	0.008	–	–	–
Estradiol peak (Pmol/L)	8874 ± 2555	10810 ± 5867	8379 ± 4167	ns	6041 ± 4052	7708 ± 7640	ns
Progesterone peak (nmol/L)	3.29 ± 2.09	3.31 ± 1.14	1.64 ± 0.67	ns	2.3 ± 1.8	2.2 ± 1.2	ns
Number of oocytes	12.4 ± 8.7	10.89 ± 4.8	11.2 ± 6.7	ns	9.7 ± 6.7	10.1 ± 8	ns
Number of mature oocytes	7.25 ± 2.77	8.37 ± 4.1	7.75 ± 4.7	ns	7.94 ± 5.7	8.0 ± 6.5	ns
Number of good-quality embryos	0.43 ± 0.5	0.55 ± 0.14	0.72 ± 0.34	ns	2.8 ± 2.7	2.8 ± 3.3	ns

Data are given as mean ± SD, ns = not significant

Another study analyzed AMH values as well as serum concentrations of testosterone, estradiol, progesterone, LH and FSH in patients who had been infected with SARS-CoV-2. The study found no differences compared to age-matched controls [44]. However, changes in menstrual cycles did occur after SARS-CoV-2 infection, irrespective of the severity of infection [44].

Two further studies investigated the question whether vaccination has a significant impact on ovarian reserve [42, 45]. One study compared the outcomes of assisted reproductive treatment (ART) cycles in couples who were not yet vaccinated and in couples who received two vaccinations with an mRNA vaccine; no differences were found in the number of (mature) oocytes or blastocysts [42]. The second study also found no differences in follicular function during ART cycles between women who had recovered from SARS-CoV-2 infection, women vaccinated with an mRNA vaccine (BNT162b2), and healthy patients [45] (► **Table 1**). The effects of a corona vaccination on menstrual cycles are still largely unknown. The Eunice Kennedy Shriver National Institute of Child Health and Human Development has recently provided \$1.67 million in research funding to investigate possible associations.

One of the first vaccine myths centered on the fear that corona vaccines could lead to infertility. The reason given for this assumption was a supposed similarity between the SARS-CoV-2 spike protein and syncytin-1, a protein that plays a role in implantation and placental development. This led to concerns being voiced on social media about the possible effect of vaccines on fertility. However, it has been shown that there is no evidence or functional basis for this hypothetical cross-immunity as the two proteins are completely different with regard to their composition and immunogenicity. It has also been shown that neither antibodies which develop after receiving a SARS-CoV2 vaccine nor antibodies which are present after infection with SARS-CoV2 bind to syncytin-1 and they can therefore not cause infertility [46]. This was also highlighted in post-marketing observational studies after the mRNA vaccines had been approved, which found no differences between vaccinated and unvaccinated women with regard to the incidence of pregnancies with no complications [47]. A recent study of 993 pregnant women who were vaccinated with a mRNA vaccine in their 2nd or 3rd trimester of pregnancy found no differences

with regard to the course of pregnancy and birth compared to unvaccinated women [48].

The data presented here show that concerns that corona vaccines may make women infertile are unfounded.

Male Fertility and SARS-CoV-2 Infection or Corona Vaccination

To investigate possible effects on the male reproductive system, it is necessary to study the impact of SARS-CoV-2 infection on the hypothalamic-pituitary-gonadal axis, spermatogenesis/spermio-genesis, and testosterone production [49]. It is also important to differentiate between SARS-CoV-2 infections which take a severe course and those that do not. Severe SARS-CoV-2/COVID-19 infection is accompanied by high fever and a significant decrease in overall health; the unspecific effects on male fertility which also occur in the context of other infectious diseases must be differentiated from the specific effects caused by SARS-CoV-2 [50].

As some of the men who fell ill with COVID-19 complained of testicular pain, it became clear early on that gonadal involvement could not be excluded in cases with serious infection [55].

Histological examinations of testicular tissue obtained from men who had died either from or with COVID-19 showed damage to the seminiferous tubules and to Sertoli and Leydig cells [51].

As ACE2 is expressed in the spermatogonia and Sertoli and Leydig cells in the testes, there is a suspicion that the virus might be targeting these cells and that infection could affect male fertility [52, 53]. SARS-CoV-2 uses spike proteins to bind to ACE2. TMPRSS2 then breaks down the S protein into S1 and S2 subunits. The S2 subunit promotes fusion of the membranes of the virus with those of the host cell, allowing viral RNA to enter the infected cell [54]. The data on the expression of TMPRSS2 in male genitalia is still contradictory [54]. As ACE2 receptors and TMPRSS-2 are influenced by androgens, it is important to consider possible specific effects of an infection with SARS-CoV-2 on the male organism and genital tract [55–61].

A total of 21 original studies were found which investigated to what extent it is possible to detect SARS-CoV-2 in semen and

whether SARS-CoV-2 infection reduces male fertility [16–18,62–73] (► **Table 2**). Two papers investigated semen parameters before and after COVID-19 vaccination [74,75].

SARS-CoV-2 Infection

At the start of the pandemic, one of the important issues was whether SARS-CoV-2 could be sexually transmitted. Most of the 21 studies which examined this issue reported that no SARS-CoV-2 RNA could be detected in semen [16–18,62,63,65,69–73,76–81] (► **Table 2**). Only two studies reported positive findings [16,72]. In the study by Baldi et al. [13], RT-PCR analysis for SARS-CoV-2 in semen was positive in one patient with critical symptoms. However, SARS-CoV-2 was also detected in the urine of this patient and it is therefore assumed that the semen sample was contaminated. Similarly, it was not possible to exclude contamination in the study by Li et al. [57], which reported on six patients with a positive RT-PCR, as the time of last micturition was

not recorded. The study also had a number of methodological errors. It is therefore currently assumed that the semen of men who are positive for SARS-CoV-2 is not infectious.

In the studies discussed here, male fertility during and after SARS-CoV-2 infection was evaluated using individual sperm parameters in accordance with the 5th edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen, published in 2010 [82]. Because of the possible RNA-genome interaction, some of the studies additionally carried out reverse transcriptase-polymerase-chain reaction (RT-PCR) to detect SARS-CoV-2 in semen samples. A few of the studies additionally analyzed semen samples to identify cytokines and other immune parameters [18,65].

Semen analysis of patients was carried out in 13 of the original studies discussed here [16–18,62–69,77,80]. Four of the 13 found abnormalities with regard to sperm concentrations (million/ml) [16,18,65,69]. In 11 of the 13, semen analysis included an examination of sperm motility, and 4 of the 11 detected a de-

► **Table 2** Summary of recent studies on SARS-CoV-2 infection and male fertility.

Author (year)	COVID-19 status ¹	Characteristics	Study population (n, patients/controls)	Age (median)	SARS-CoV-2 RNA detected in semen	Sperm: concentration (million/ml)	Sperm: motility, WHO A+B (%)	Sperm: morphology (%)
Holtmann N (2020)	no infection	–	14	33	negative	normal range ²	normal range	not investigated
	could not be classified based on Guidelines	recovered; two patients with acute infection	14	43	negative	normal range	normal range	not investigated
	severe		4	41	negative	normal range	pathological ²	not investigated
Paoli D (2020)	not tested; no symptoms	patients with different malignant neoplasms	10	31	negative	normal ranges	normal range	normal range
Gacci M (2020)	could not be classified based on Guidelines	recovered; not hospitalized	12	44	negative	normal range	normal range	pathological
		recovered; hospitalized (normal ward)	26	52	negative	normal range	pathological	pathological
	critical	recovered; hospitalized (intensive care unit)	5	59	one person was positive	pathological	pathological	pathological
Temiz MZ (2020)	moderate	smoker	10	38	negative	normal range	normal range	normal range
			10	37				
Maleki BH (2021)	mild	corticosteroid therapy, semen quality analysis during and after infection	1	35	not investigated	pathological	pathological	pathological
	moderate		23					
	severe		27					
	critical		33					
Pazir Y (2021)	mild	50% nicotine abuse, semen quality analysis before and after infection	24	35	not investigated	no significant change	no significant change	not investigated
Honggang L (2020)	could not be classified based on Guidelines	–	23	41	negative	pathological	not investigated	not investigated

Continued next page

► **Table 2** Summary of recent studies on SARS-CoV-2 infection and male fertility. (Continued)

Author (year)	COVID-19 status ¹	Characteristics	Study population (n, patients/controls)	Age (median)	SARS-CoV-2 RNA detected in semen	Sperm: concentration (million/ml)	Sperm: motility, WHO A+B (%)	Sperm: morphology (%)
Guo TH (2021)	mild to severe	–	41	26	not investigated	normal range	normal range	normal range
Erbay G (2021)	could not be classified based on Guidelines	before and after COVID-19 infection	69	31	not investigated	normal range	normal range	normal range
Koç E (2021)	not reported	before and after COVID-19 infection	21	32	not investigated	no significant change	significant deterioration	significant deterioration
Best JC (2021)	not reported	–	30	40	negative	pathological	not investigated	not investigated
Pan F (2020)	could not be classified based on Guidelines	50% of men had a BMI > 25; 3 men had hypertension	34	37	negative	not investigated	not investigated	not investigated
Song C (2020)	could not be classified based on Guidelines	one man (age: 67) died of SARS-CoV-2	13	33	negative	not investigated	not investigated	not investigated
Li D (2020)	could not be classified based on Guidelines	23 men recovered; 15 men with acute infection	38	not specified	6 people positive	not investigated	not investigated	not investigated
Paoli D (2020)	moderate	dyslipidemia (treatment with simvastatin 20 mg/d for 1 year); androgenetic alopecia (topical treatment with finasteride 1 mg/d); criculate ligament reconstruction	1	31	negative	not investigated	not investigated	not investigated
Huang C (2020)	not reported	qualified sperm donors	100	not specified	negative	not investigated	not investigated	not investigated
Ruan Y (2021)	could not be classified based on Guidelines	tested positive with RT-PCR and recovered completely	55	31	negative	normal range	normal range	not investigated
Burke CA (2021)	tested positive	no one hospitalized	19	32	negative	not investigated	not investigated	not investigated
Kayaaslan B (2020)	could not be classified based on Guidelines	all hospitalized	16	34	negative	not investigated	not investigated	not investigated
Ma L (2021)	could not be classified based on Guidelines	11 already recovered	12	32	negative	normal range	normal range	normal range
Pavone C (2020)	tested positive	no one hospitalized	9	42	negative	not investigated	not investigated	not investigated

¹ Severity of the SARS-CoV-2 infection was classified according to the COVID-19 Guideline (Xu et al. 2020 [13]). Mild: clinical symptoms are mild and there are no indications of pneumonia on chest imaging. Moderate: patients present with fever and respiratory symptoms; pneumonia is detected on chest imaging. Severe: adult patients have at least one of the following symptoms: respiratory frequency of 30/min, oxygen saturation $\leq 93\%$ at rest, partial arterial pressure of oxygen ≤ 300 mmHg. Children present with at least one of the following symptoms: dyspnea (except when crying), oxygen saturation $\leq 92\%$ at rest, ventilatory assistance, cyanosis, lethargy, unconscious, food is rejected, dehydration. Critical: at least one of the following symptoms is present: respiratory failure requiring mechanical ventilatory assistance, shock, organ failure requiring monitoring and ICU.

² Sperm parameters above WHO reference values are referred to as “normal range”: sperm concentration $\geq 15 \times 10^6$ /ml; sperm motility: percentage of progressive motile sperm $\geq 32\%$; percentage of morphologically unremarkable sperm $\geq 4\%$. Values below WHO reference values are referred to as “pathological” (Nieschlag et al. 2021 [82, 84]).

³ In studies which compared sperm parameters before and after SARS-CoV-2 infection, non-significant differences ($p > 0.05$) are reported as “no significant change” and significant deterioration ($p < 0.05$) as “significant deterioration”.

terioration of motility [16–18,68]. Eight of the 13 studies also analyzed sperm morphology, and three of the studies reported higher rates of morphologically abnormal sperm [16,18,68]. Two of the 13 original studies compared semen quality parameters of patients before and after having had COVID-19. One of these two studies reported a significant deterioration in motility and morphology after recovering from disease [64,68].

In summary, it is important to be aware that the total number of semen analyses from men infected with SARS-CoV-2 examined in original studies is <500. One third of the studies found changes, some of them significant, in the three relevant semen parameters. Severe COVID-19 disease in particular was found to lead to a reduction in sperm concentrations and motility and an increase in morphological abnormalities. It is also important to be aware of additional effects on spermatogenesis and spermio-genesis, particularly in men who have severe COVID-19 and experience a significant overall deterioration requiring hospitalization and treatment in an intensive care unit including life-sustaining measures.

Corona Vaccination

The data on the effects of SARS-CoV-2 vaccination on male fertility includes two papers which studied the impact of the mRNA vaccine BNT162b2. Safrai et al. investigated the sperm quality of 43 men (37.1 ± 6 years) before and after being vaccinated [74]. Their semen was examined before and 33.6 ± 20.2 days after the first vaccination. Sperm concentrations before and after the vaccination were unaffected ($43.6 \pm 58 \times 10^6/\text{ml}$ vs. $47 \pm 54.8 \times 10^6/\text{ml}$; $p = 0.7$); there were also no significant changes in sperm motility (percentage of motile sperm $\times 10^6$: 48.5 ± 83.4 vs. 61.7 ± 92.9 ; $p = 0.4$). A second study included a total of 45 men (aged 28 ± 3 years) who were investigated before and after receiving two doses of BNT162b2 [75]. Sperm samples were investigated before and on average 75 days (70–86 days) after receiving the second vaccination. Sperm concentrations before and after the vaccination were unaffected (respective median and interquartile interval: 26 [19.5–34] $\times 10^6/\text{ml}$ vs. 30 [21.5–40.5] $\times 10^6/\text{ml}$; $p = 0.2$). Sperm motility was also unaffected (respective median and interquartile interval for the percentage of motile sperm $\times 10^6$: 58 [52.5–65] vs. 65 [58–70]; $p = 0.001$). Both studies confirm that sperm quality does not deteriorate after a corona vaccination.

Another study by Carto et al. investigated the association between approved COVID-19 vaccines and the occurrence of orchitis and/or epididymitis within 1–9 months after receiving the vaccine. A total of 663 774 men who had received at least one vaccination were compared with 9985 154 men who were not vaccinated. Orchitis and/or epididymitis occurred significantly less often in men who had been vaccinated (OR = 0.568; 95% CI: 0.497–0.649; $p < 0.0001$) [83].

Importance for Male Patients

In some men, infection with SARS-CoV-2 will negatively affect the quality of their sperm, depending on the severity of infection. The SARS-CoV-2 vaccine does not result in any deterioration of sperm. In view of the potential impact of disease on male fertility, vaccinations should be recommended to men, especially as the possibility cannot be excluded that other testicular functions, for example the function of Leydig cells, could also be negatively affected by infection with SARS-CoV-2.

Conclusion

In the animal models, vaccination with BNT162b2 or AZD1222 was found to have no effect on fertility and had no negative impact on existing pregnancies compared to placebo [38]. Moreover, antibodies against the SARS-CoV-2 spike protein were detected in the offspring in animal models [37]. This is particularly remarkable given the fact that animals were given far higher doses of the vaccines compared to humans.

Up to now, SARS-CoV-2 RNA has not been detected in the oocytes or follicular fluid of women proven to have had SARS-CoV-2 infection [19,40]. Similarly, no changes in ovarian reserve, specifically, no changes in AMH concentrations, were found in women who had recovered from COVID-19 infection [32,43]. Likewise, vaccination with mRNA vaccines did not change the ovarian response and was associated with good success rates in cases who were undergoing ART [42,45].

Numerous studies found no traces of SARS-CoV-2 RNA in the sperm samples of infected men [16,17,62,63,65,69–71,73,76,78–81]. As regards the two studies which detected viral RNA in sperm samples, the international debate has highlighted specific methodological errors made in the two studies [16,72]. In contrast to these studies, comparisons of semen parameters taken before and after men were vaccinated found that corona vaccines had no negative impact on male fertility [74,75,83]. However, male fertility was found to be at least temporarily impaired after SARS-CoV-2 infection, particularly in severe cases of disease, with more than one third of studies showing a deterioration of all 3 relevant semen parameters.

Based on the available data, the perennial question whether COVID vaccines lead to infertility can be answered with a resounding “No!”. But the erroneous belief that vaccines cause infertility has unfortunately taken hold among many young people wishing to have children and those who may wish to have children in future. Providing factual information is essential when attempting to change such beliefs, but it is also important to take the anxieties and concerns of target groups seriously and discuss them in detail. Social media channels which are able to reach a big audience, particularly channels used extensively by people under the age of 30, could be useful in this context.

Conflict of Interest

The authors declare that they have no conflict of interest.

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