How has COVID-19 affected sex and fertility?

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COVID-19 pandemic has had an effect on our sex lives, but whether it has an impact on fertility or can be sexually transmitted are yet to be determined.

By the second anniversary of the start of the pandemic, PubMed had recorded more than 200 000 papers on SARS-CoV-2. By definition, none could record long-term clinical outcomes. With new data appearing daily, it is not surprising that some are conflicting and some conclusions have been overturned within a short time. Despite the great importance of sexual activity and fertility, only 0.01% and 0.17% respectively are on these subjects.

Genital ACE2 receptors

Males

The SARS-CoV-2 virus attaches to any cells that express angiotensin-converting enzyme-2 receptors (ACE2). Transmembrane serine protease 2 (TMPRSS-2) is needed for cell entry. ACE2 receptor expression is found throughout the male genital tract except in the epididymis. It is particularly strong in Sertoli cells and sperm stem cells.

A study of testicular biopsies has shown ACE2 receptors in somatic and germ cells, with a higher level of expression in infertile men.[1] Spermatozoa have ACE1 and ACE2 receptors of several subtypes.[2] TMPRSS-2 is highly expressed in elongated spermatids and moderately in the epididymis and sperm stem cells.[3]

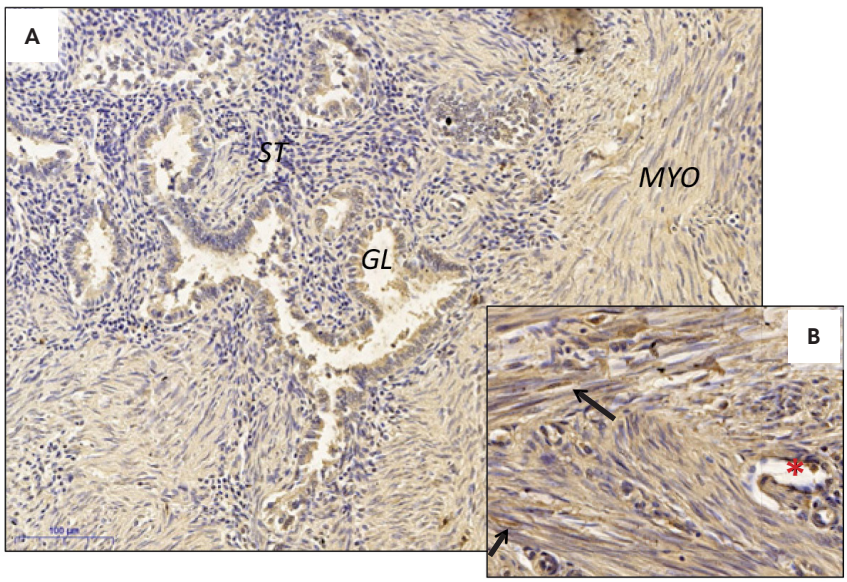

Figure 1. Localisation of ACE2 in human uterine tissues by immunohistochemistry. (A) Panoramic view of the endometrium-myometrium transition, where ACE2 staining predominates in the epithelium of endometrial glands (GL) contrasting with the surrounding endometrial stroma (ST). (B) Detail of myometrium (MYO) showing ACE2 expression in smooth muscle fibres (arrows) and vascular endothelium (asterisk).[5] Reproduced with permission from Reis FM, Reis AM. Angiotensin-converting enzyme 2 (ACE2), angiotensin-(1–7) and Mas receptor in gonadal and reproductive functions. *Clin Sci (Lond)* 2020;134:2929–41

Females

There is a conflict in the literature on females. Two recent reviews have concluded that ACE2 expression is found in the ovaries, endometrium, myometrium (Figure 1) and decidua, and in the vagina. Expression is increased in first-trimester trophoblast, and in late-gestation placenta, chorion, amnion and umbilical cord.[4,5]

However, a new study on fresh tissue from the female genital tract (excluding the vagina) and on breast cells, showed very low expression of ACE2 receptors (less than 5% of cells). Furthermore, TMPRSS-2 expression was also low or absent. The authors concluded that infection of the female genital organs with SARS-CoV-2 was unlikely.[6]

It is difficult to know how these views can be reconciled. Several articles are literature reviews, some quoting other reviews. Going back to the original papers, there is good evidence that there is some expression of ACE2 in the female genital tract (Figure 2).[7–10] It may be that the extent of the expression is low, although several papers do not quantify it.

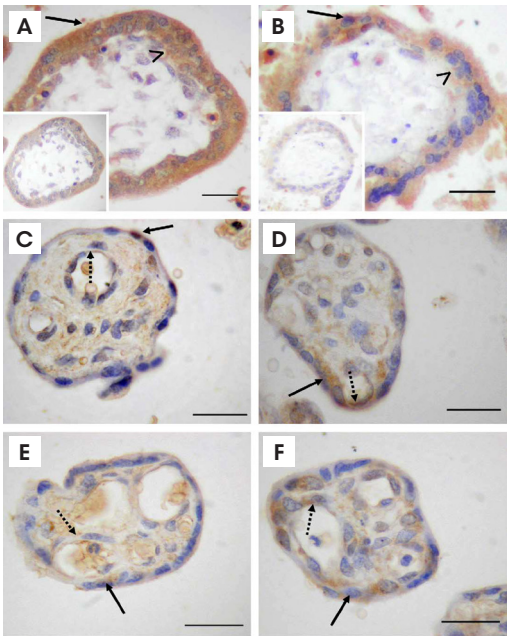

Figure 2. There is good evidence that there is some expression of ACE2 in the female genital tract, as evidenced by immunohistochemical expression of Ang-(1-7) (sections A, C, E) and ACE2 (sections B, D, F) in the syncytiotrophoblast (arrows), cytotrophoblast (arrow heads) and fetal endothelium (dashed arrows) of terminal placental villi of ectopic pregnancy (A, B), normal term pregnancy (C, D) and pre-eclamptic pregnancies (E, F). Positive staining is brown and nuclear counterstaining is blue. Inserts in panels A and B represent sequential sections incubated with preabsorbed antibodies. Scale bar = 25µm.[9] Reproduced with permission from Valdes G, Neves LAA, Anton L, *et al*. Distribution of angiotensin-(1–7) and ACE2 in human placentas of normal and pathological pregnancies. *Placenta* 2006;27:200–7

SARS-CoV-2 virus in the genital tract

Males

Although several viruses can be found in semen, it is difficult to prove that there is transmission by intercourse because other modes of transmission between partners must be excluded. It is easier with the Zika virus, which is normally transmitted via mosquitoes. Sexual transmission can occur by vaginal, oral or anal intercourse.[11]

Despite the blood/testis barrier, some viruses, particularly mumps, can cause testicular atrophy and azoospermia.

The results of searching for the SARS-CoV-2 virus in semen are varied, with an incidence between 0% and 27% of patients studied. In a Chinese study, 4 of 15 men in the acute stage of the disease and 2 of 23 recovering men had positive results in semen by PCR testing (Table 1). The study group included all hospitalised men with COVID-19 in the city of Shangqiu over a three-week period in 2020. Apparently, none declined to join the study unless comatose or impotent.[12] Conversely, a USA study of 18 men with mild or moderate COVID-19 symptoms (none requiring hospitalisation) produced no positive results.[13] Overall, seven of nine studies have found no virus in semen.[14]

It is not known whether there is viable virus in the semen.[15] The conflicting findings suggest that the virus can enter semen with severe infections but, probably, not with milder ones.

Females

The finding of SARS-CoV-2 virus in the vagina is probably very rare. Six of eight prospective series of women with generalised COVID-19 produced no positive results. Rectal swabs were also done in one of these studies and 27% of participants were found to be positive, none of whom had virus in the vagina.[16]

In the other two studies, 98 women (63 of whom were pregnant) produced four positive results.[17,18] Interestingly, one of the pregnant women was found to have the virus in the placenta even though the vaginal swab was negative (Figure 3).[18]

Sexual activity

The effects of the COVID-19 pandemic on sexual activity, especially during lockdown periods, depends on a variety of factors and may be different in some countries. For example, a study in Turkey showed increased frequency but decreased quality.[19]

Despite reports by some of the UK popular press that lockdown increased the quality and frequency of intercourse,[20] most evidence is that the reverse has happened.[21] Throughout the world, it is reported that the sex life of couples has deteriorated during the pandemic. This applies to the measurable components such as potency, frequency and duration of intercourse, foreplay, and to more subjective aspects such as lubrication, enjoyment and libido. Medical staff are particularly at risk of sexual dysfunction.[22–24]

Sexual behaviour has also changed. There has been a significant increase in the use of pornography sites. Pornhub, which is one of the larger sites in the UK, reported a

Patient	Approximate age in years*	Days of illness before specimen	Days since clinical recovery
1	20s	6	Still ill
2	20s	10	Still ill
3	30s	11	Still ill
4	40s	9	Still ill
5	50s	12	2
6	30s	16	3

*Precise ages not given

Table 1. Characteristics of men whose semen tested positive for SARS-CoV-2 during and after infection[12]

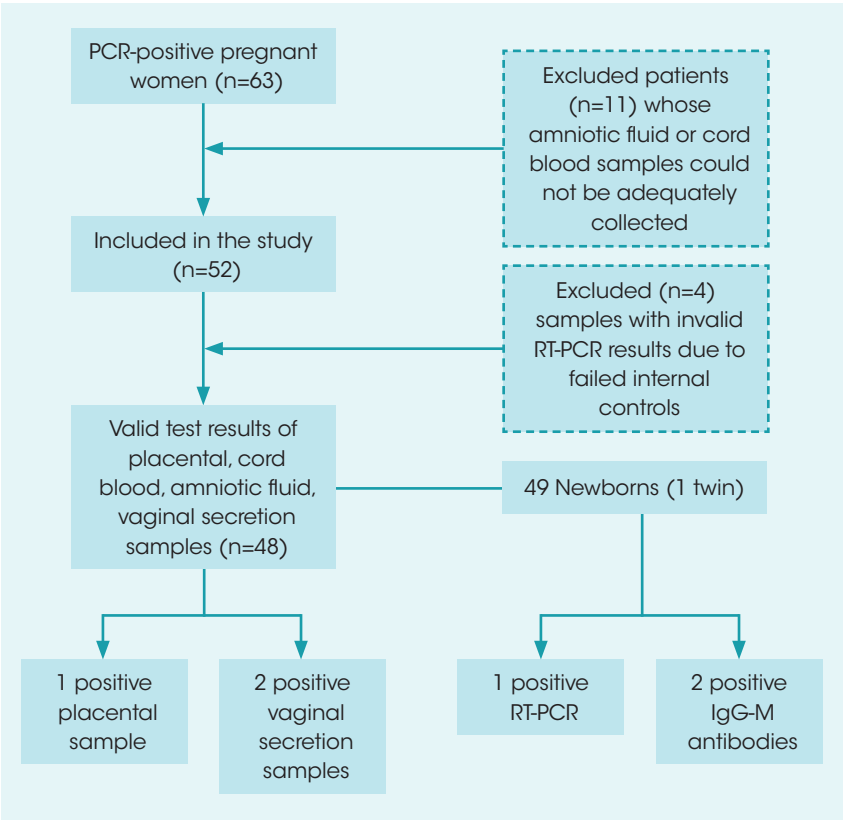

Figure 3. Results of PCR tests of the genital tract in pregnant women with SARS-CoV-2.[18] Reproduced with permission from Sinaci S, Ocal DF, Seven B, *et al.* Vertical transmission of SARS-CoV-2: a prospective cross-sectional study from a tertiary center. *J Med Virol* 2021;93:5864–72

worldwide increase of 11% in traffic during February and March 2020. When it became free to users in many countries the increase was up to 24%.[25]

Several countries have noted a decrease in risky behaviour such as use of multiple casual partners and mouth-to-mouth kissing, especially among gay men. There has been an increase in online sex, both with established partners and sex workers.[26,27]

Much has been written about mental health during the pandemic. Within relationships there has been an increase in sexual violence and emotional abuse. This most commonly occurs within the home and can be difficult to identify. Stalking and other sexually abusive behaviour beyond the home may have also increased.[28]

Not surprisingly, however, it is better to have sex than not to. In a web-based cohort study of nearly 7000 subjects, about a third of whom were having regular sex and two thirds were not, the haves were happier than the have-nots. Happiness and sexual satisfaction were measured by standard anxiety, depression and sexological instruments. By all measures, the cohort who were having sex during lockdowns were highly significantly better off than the celibate.[29]

Although warnings about the possibility of transmission with intercourse have appeared in COVID-19 articles, there is no evidence that it has occurred. There are several features of sexual activity that are much more likely to result in viral transmission. However, as it takes up to 72 days for sperm to reach maturity, it might be possible for sperm to remain infected even after clearance from other sites had occurred. This would be a possibility particularly if antibodies against the virus could not cross the blood/testis barrier.

Fertility

So far, the possible impact of the SARS-CoV-2 virus on fertility is based on limited human data and work in rats. It is very important not to translate the very limited literature into fact.

Perhaps more worrying than the birth rate is the widespread fake news among young women that the COVID-19 vaccines reduce fertility.[30] There was a 30-fold increase in internet searches on this subject after the emergency use authorisation in December 2020.[31]

An online survey in the USA published in December 2021 showed that this remains a problem. In 914 unvaccinated heterosexual adults (42% female), 218 believed that their 'reproductive health or fertility' would be impaired and 199 had 'concerns' about it (46% in total). Such views were more common among the rich and well educated.[32] There have been similar findings in other countries.

Studies in rats have shown no effect of vaccine on fertility or pregnancy outcome. Neutralising antibodies were found in the offspring of the vaccinated cohort.[33]

Males

The direct effect of the virus on semen is unknown. In the study with longest follow-up, on 84 men with COVID-19 infection requiring hospitalisation, all standard WHO criteria for semen analysis were significantly impaired. Specimens were examined at 10-day intervals up to 60 days. Controls were 108 volunteers with proven fertility. The

infected men had about a half of the normal seminal volume; the sperm concentration was a mean of $10x10^6$/ml.

Progressive motility was halved and the morphology was very poor. There were statistically significant improvements in the number of sperm in each specimen and their motility with time, but by 60 days none of the improvements appeared to be clinically significant although they had a significant *p*-value. The specimens were not tested for the COVID-19 virus.[34]

There were similar findings in other studies. Specimens were tested for viral RNA but none were positive.[35,36] In one of these, there was no correlation with severity of disease, but there was strong correlation between sperm abnormalities and the titres of SARS-CoV-2 IgG antibody against portions of the viral spikes. Three of 120 men developed high levels of antisperm antibodies.[36]

Increased luteinising hormone and decreased testosterone levels have been found in men with COVID-19 infections. The more severe the infection, as judged by white cell counts and CRP levels, the more severe were the changes.[37]

SARS-CoV-2 virus can damage sperm, especially with severe disease, but the mechanism is unknown. A transient fall in the conception rate has been shown in a prospective study of infected men.[38] More data are required to confirm this effect.

Females

As with any other severe illness, COVID-19 causes some menstrual changes, mainly prolonged cycle and reduced volume. Sex hormone changes have not been found.[39] The main concern with this might be a woman's fear that she was pregnant when she was not.

The Times reports that COVID-19 is 'associated' with the lowest fertility rate since 1938.[40] In fact, if the ultimate measure of fertility is the number of live births, COVID-19 seems not to have had any effect so far. There has been a steady decrease in the UK birth rate since 2012, of about 4% per year. However, the latest figures from the Office for National Statistics are for 2020 and the first quarter of 2021, which show the same decline.[41] Most of these babies must have been conceived or planned before the pandemic took hold.[40]

A prospective study of 2126 women in North America who wished to become pregnant showed that neither infection nor vaccination had any effect on rate of conception per menstrual cycle.[38]

There are problems in pregnancy due to COVID-19 that are beyond the scope of this article. It is, at least, reassuring to find that in the first trimester the viability of the fetus in women with COVID-19 is no different to that in uninfected women.[42]

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