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REVIEW

COVID-19 and fertility—at the crossroads of autoimmunity and thrombosis

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Abstract

The SARS-CoV-2 virus is known to mediate attack via ACE-2 Receptor, thus having adverse effects on cardiovascular, respiratory, digestive and reproductive systems, the latter being an area of emerging concern, due to the associated impact on fertility, with potential for an outsized effect on population distribution and socioeconomic road map in subsequent years. This narrative review aims to put forth the current evidence of effect of SARS-CoV-2 on human fertility from a multipronged immunologic, haematologic, and gynaecologic perspective; highlighting the areas of contradiction and potential future measures. A literature search was conducted through the MEDLINE and SCOPUS databases to identify articles on the subject in English. Relevant information was extracted from around 300 articles for this review. The existing data give non-conclusive evidence about the impact of SARS-CoV-2 infection on fertility; however, a greater impact on male fertility as compared to females merits further exploration. However, reproduction and fertility is a key concern and considering the pandemic is prolonged, natural conception or ART require extra precautions.

Keywords COVID-19 · Female fertility · Male fertility · Sexual/vertical transmission · Autoimmunity

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Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ACE-2	Angiotensin converting enzyme-2
TMPRSS2	Transmembrane serine protease 2
ART	Assisted reproductive techniques
RAAS	Renin–angiotensin–aldosterone system
HPA	Hypothalamic–pituitary–adrenal axis
AMH	Anti-Müllerian hormone
ITP	Immune thrombocytopenic purpura
GBS	Guillain-Barré Syndrome
MFS	Miller-Fisher Syndrome
ANA	Anti-nuclear Antibodies
aCL	Anti-cardiolipin antibodies
ANCA	Anti-neutrophil cytoplasmic antibodies
Anti-β2 GPI	Anti-β2 glycoprotein
aPL	Anti-phospholipid antibodies

Introduction

The COVID-19 pandemic has led to a remarkable upheaval in global health and economy in a span of 18 months. While steady research on the subject has thrown light on the pathogenic mechanisms of the disease, a better understanding

has also paved the way to newer concerns. It is now well-accepted that human cells that express angiotensin converting enzyme-2 (ACE-2) and transmembrane serine protease 2 (TMPRSS2) receptors act as portal of entry for the virus into the human body and immune system. The viral attack spans various systems, ranging from cardiovascular, respiratory, and digestive, to urinary and gonadal organs. The latter has led to emerging concerns regarding potential effect of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2 on human fertility [1, 2]). COVID-19 is also emerging as a disease that potentially triggers autoimmunity, and this raises the case for severe and lasting effects on various systems, including reproductive capacity, as seen with several autoimmune rheumatic diseases [3–5]. Moreover, several new drugs being used to treat these conditions may potentially have a bearing on future fertility, a risk that remains largely unexplored [6, 7].

ACE-2 receptor is present in higher concentrations in testes and in ovaries. It is hypothesized and proved by some small cohorts that SARS-CoV-2 can result in impaired spermatogenesis, by direct viral mediated destruction or via autoimmune orchitis or thrombosis in males; and adversely affects the oocyte quality in females [8, 9]. Therefore, COVID-19 is known to cause alteration in both male and female reproductive functions, raising the concern of infertility. A keen understanding of these effects lies at the intersection of viral microbiology, immunology, reproductive medicine and hematology.

Effects of this kind may plausibly impact mankind and the generations to come in ways never imagined, have an outsized impact on population distribution in subsequent years, and even turn the economic roadmap upside down. In addition, the impact on fertility and birth trends in response to the pandemic may potentially vary according to the socioeconomic conditions, accessibility to contraception and assisted reproductive techniques (ART) [10]. Understanding these effects may be the first step towards formulating further course of action to prevent long-standing population-level morbidity. Therefore, this narrative review explores the effects of SARS-CoV-2 on human fertility and possibility of its sexual transmission from a gynecological, immunological, endocrinological and hematological viewpoint.

Methods

A literature search was conducted through the MEDLINE and SCOPUS databases to identify articles on the subject in English. Several types of articles, ranging from case reports, case series, letter to editors, systematic reviews, narrative reviews, and observational studies were reviewed published anytime till 13th June 2021. The search terms included: "COVID-19 OR SARS-CoV2 OR SARS-COV-2 OR novel coronavirus OR nCOV", "Fertility OR Reproduction OR Spermatogenesis OR Pregnancy OR Sexual Health OR Birth OR Testes OR Ovaries OR Placenta OR ACE-2 OR Breast", "Male OR Men", "Female OR Women", "Autoimmune OR Immunological" and "Vertical transmission, Sexual transmission". Different combinations of the above-mentioned terms were used to identify around 4900 articles on 13th June 2021 (Supplementary figure). After an initial screening of Title and abstracts, 600 relevant articles were retained. Full text screening was then carried out independently by two co-authors; JT and LG, to shortlist approximately 250 articles meeting the inclusion criteria and relevant information was extracted from 73 articles for this review. Since, there is ample data on the effects of COVID-19 on pregnancy, articles dealing exclusively with this topic were excluded from review.

COVID-19 and female fertility

The ACE-2 receptor is widely expressed in uterus, ovaries, fallopian tubes, vagina and placenta; hence female reproductive system is predisposed to effects as a result of SARS-CoV-2 infection, although the risk is thought to be lesser as compared to males [11, 12]. The SARS CoV-2 affects the renin angiotensin aldosterone system (RAAS) which is involved in follicular maturation, ovulation phases, luteal angiogenesis and degeneration, and embryo development. Thus, COVID-19 infection may potentially adversely impact the ovarian granulosa cells or interfere with follicular growth, consequently affecting the quality of oocytes [11]. The ACE-2 receptor is also found in endometrium and the virus might intervene with implantation of embryo or lead to miscarriage [13].

A study by Ding et al. [14] showed the effect of COVID-19 on the ovarian function in women whereby higher levels of testosterone and prolactin, and lower levels of AMH (Anti-Müllerian hormone) were observed in infected patients as opposed to their healthy counterparts. Therefore, ovarian reserve can be significantly reduced in such patients [14]. On the contrary, Li et al.'s study did not show any alteration in sex hormones and AMH levels; but did notice delayed menstrual cycle and changes in menstrual volume in some patients [15]. Another study did notice raised LH levels in SARS-CoV-2-infected women, indicative of hypogonadism [9].

It is further suggested that stress and panic associated with the COVID-19 pandemic contribute to menstrual irregularities and adversely affect the quality of oocytes [16]. These psychological effects can also translate into sexual dysfunction; indirectly impacting conception [16]. It has been noticed that after SARS-CoV-2 infection, women had a decrease in frequency of sexual intercourse and satisfaction [17].

COVID-19 and male fertility

Studies in the past have shown that viruses like HPV, HIV, HSV, HBV, and HCV can adversely affect male fertility by causing orchitis or affecting the quality, motility, count, liquefaction time and morphology of sperms [18]. Thus, it is reasonable to extrapolate that SARS-CoV-2 too may have some effect on male fertility. The male spermatozoa has a high concentration of ACE-2 receptors and they can be a major target of direct destruction by SARS-CoV-2 which raises the concern about resulting male infertility and the risk of sexual transmission of the virus [1]. A study by Wang et al. [19] showed the highest concentration of ACE 2 receptors, within the testes, are in the spermatogonia, Sertoli and Leydig's cells. When compared to ACE-2 negative cells, the ACE-2 receptor positive spermatogonia showed higher frequency of viral reproduction, viral gene expression and transmission. ACE-2 positive spermatogonia also showed significantly reduced spermatid differentiation, sperm-egg recognition, acrosome reaction, sperm chromatin condensation and male meiosis [19].

A study by Ma et al. [20] showed deranged ratios of testosterone to LH and of FSH to LH, indicating potential adverse effect on spermatogenesis. Some other studies also support the finding of decreased testosterone levels in SARS-CoV-2-infected males [21, 22]. Sperm quality was also seen to be affected in those with active infection particularly, sperm count and motility [23]. SARS-CoV-2 infection has been associated with orchitis. The possible mechanisms of orchitis could be autoimmune inflammatory orchitis or direct destruction of the testicular cells by the cytopathic effect of the virus [24, 25]. Another hypothesis is vascular thrombosis and vasculitis like phenomenon which may result in ischemic orchitis [26]. Elevated core body temperature during fevers caused by COVID could also negatively impact the physiology of spermatogenesis [27]. Another interesting aspect that has been discussed in literature is the derangement of the hypothalamic pituitary adrenal axis due to psychological stress of the disease, thus having adverse effects on spermatogenesis [16]. However, presence of SARS-CoV-2 in semen was not noticed in the majority of studies [28–31], but Li et al.'s study did show the presence in few patients [32].The possibility of sexual transmission cannot be completely excluded, since most studies are based on small sample sizes and have contradictory results. Similar to the effect on female fertility, current evidence on SARS-CoV-2's effect on male fertility is divided.

Table 1 highlights the major findings about male and female infertility during COVID-19.

COVID-19—sexual and vertical transmission

A study conducted by Pan et al. [33] showed no evidence of presence of SARS-CoV-2 in the semen of infected patients, ruling out sexual transmission; however, long term effects are still unclear. Several other studies listed in Table 1, demonstrate the absence of viral shedding in semen; but Li et al.'s study demonstrated positive semen samples both in acutely infected and recovering patients [32]. Thus, current literature is non-conclusive regarding this aspect of COVID pathophysiology.

Data on the risk of vertical transmission of SARS-CoV-2 from mother to fetus is disputed, with most studies against it [34, 35] but some do favor the finding [36]. The co-expression of ACE-2 and TMPRSS2 was found to be negligible in placental tissues, thus minimizing the potential of entry of virus into the products of conception [37]. It was also proposed that Caveolin, a membrane bound structure which allows endocytosis of viruses is not present in syncytiotrophoblast, thus preventing inflammation [38]. However, the virus could use alternate entry routes which are yet to be discovered.

There are no reports of vertical transmission for SARS (severe acute respiratory syndrome) and MERS (middle east respiratory syndrome), but the same cannot be assumed for SARS-CoV-2. A study by Schwartz et al. [39] investigating 38 pregnant women did not show any vertical transmission, with negative RT-PCR results for placenta and no maternal deaths were recorded. Another study by Chen et al. investigating nine pregnant patients with COVID-19 infection, did not find presence of the virus in amniotic fluid, cord blood and breast milk, however; all births were via Cesarean section, all nine mothers did develop some symptoms, fetal distress was noticed in two cases but no death was reported [34].

A recent case report published in JAMA, supports the possibility of vertical transmission. The baby was born via cesarean to a COVID-19 positive female and tested positive for both IgG and IgM against SARS-CoV-2. IgM antibody cannot be attributed to placental transfer, and is indicative of in utero infection [13]. Another case reported a miscarriage in second trimester which seemingly was attributed to the inflammation at placenta based on the histopathological findings [40].

A study by Menter et al. [41] evaluated the placentas of 5 SARS-CoV-2 positive pregnant women which showed signs of placental villitis and maternal–fetal malperfusion; thus indicative of placental infection. These findings can further support the hypothesis of a potential vertical transmission to fetus due to inflammation and subsequent infection at placenta [41]. Also, the maternal vascular malperfusion and inflammation are known to be causes of earlier

Table 1 Covid-19 and its effects of fertility

Author	*n*	Disease state	Sample type	Findings	Limitations
COVID-19 and female fertility					
Ding et al. [14]	78		Blood	Alteration of ovarian reserve (3.2% decrease in AMH, 14.3% rise in Testosterone, 20.7% rise in Prolactin) in COVID-19-infected women as compared to healthy counterparts	Hormone levels were not collected at the same time in menstrual cycle Limited sample size Some older peri-menopausal women with already fluctuating hormonal levels The casual relation between COVID-19 and hormonal markers is not clear
Li et al. [15]	237	90 = severely ill 147 = mild infection	Blood	No changes in sex hormones and AMH Changes in menstrual cycle and volume observed (20% had decreased volume, 19% had delayed cycle)	Absent menstrual history of some patients due to retrospective study design Hormone levels were not followed up after recovery No biopsy of ovary to confirm presence of virus
COVID-19 and male fertility					
Li et al. [32]	38	23 = recovered 15 = acute stage	Semen	RT-PCR was positive for SARS-CoV-2 in 15.8% patients	Small sample size and short follow-up Different co-morbid
Ning et al. [31]	17	9 = positive 8 = negative	Semen	None of the patients was positive for N gene and ORF1ab gene	Small sample size and short follow-up
Holtmann et al. [23]	18	16 = recovered 2 = active infection	Semen	RT-PCR was negative for SARS-CoV-2 Impaired quality of sperm in those with active infection 7% patients had scrotal discomfort	Small sample size No semen analysis before infection Medication used for COVID-19 might have a confounding effect on findings
Pan et al. [33]	34		Semen	19% had discomfort in scrotum during infection RT-PCR was negative for SARS-CoV-2 Sparse expression of ACE-2 and TMPRSS2	Small sample size Semen quality was not assessed
Guo et al. [34]	23	11 = recovered 12 = acute infection	Semen	RT-PCR was negative for SARS-CoV-2 No effect on sperm motility, morphology and concentration	Small sample size
Pavone et al. [35]	9		Semen	RT-PCR was negative for SARS-CoV-2	Small sample size Severely infected patients were not included
Kayaslaan et al. [36]	16	Acute infection (hospitalized)	Semen	RT-PCR was negative for SARS-CoV-2	
Paoli et al. [30]	1		Semen and Urine	RT-PCR was negative for SARS-CoV-2	Case report
Song et al. [29]	13	12 = recovery stage 1 = acute stage	Semen and testes	RT-PCR was negative for SARS-CoV-2	Small sample size
Zhang et al. [37]	10		Prostatic secretion	RT-PCR was negative for SARS-CoV-2	Variation in days for collection of sample

Table 1 (continued)

Author	*n*	Disease state	Sample type	Findings	Limitations
Li et al. [16]	29	23 = recovering inpatients 6 = deceased	Autopsy of epididymis and testicular specimen And Semen	-Interstitial edema, congestion and red blood cell exudation in testes -Higher number of apoptotic cells in seminiferous tubules as compared to healthy counterparts -Oligozoospermia in 39.1% -Marked leukocytosis in semen of 60.9% -Impaired spermatogenesis with decreased sperm concentration -Increased seminal levels on IL-6, TNF-alpha	Small sample size Prospective evaluation of patients could not be done
Rastrelli et al. [38]	31		Blood	Total and free testosterone levels were lower in those with severe COVID-19 infection	
Ma et al. [21]	81		Blood	Markedly raised LH levels, and decreased ratio of FSH: LH and Testosterone: LH were noticed in infected patients as compared to the non-infected group	Pre-print
Schroeder et al. [22]	(Not specified)	Critically-ill	Blood	Males had significantly lower testosterone and dihydrotestosterone levels as compared to females and their healthy counterparts	Pre-print
Guo et al. [39]	41	Recovered patients after 56 days of hospital discharge	Semen	Total sperm count, sperm concentration and motility was significantly decreased as compared to controls; but showed improvement in next sampling after a further 29 days	Pre-COVID infection sperm parameters of the participants were not available for comparison Small sample size

pregnancy loss, and might also be the reason for losses seen with COVID-19 infection [42]. In a small cohort study, Bergen reported histopathological findings of placentas of 20 COVID positive patients, out of which eight showed fetal vascular malperfusion without any umbilical cord abnormalities. This is suggestive of thrombosis in fetal vasculature as a possible etiology [43].

A possibility of transmission of SARS-CoV-2 infection through breast milk also exists. Some case reports showed presence of the virus in breast milk; however, only one infant tested positive for COVID-19 amongst these; however, the route of transmission in this child was not confirmed [44]. Periera et al. [45] did not find any transmission through breast milk.

Effect of COVID-19 on sexual health from an immunologic perspective

It has been proposed that SARS-CoV-2 could trigger an autoimmune reaction in the genetically predisposed population [46]. Immunologically mediated conditions like Immune thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), Miller-Fisher syndrome (MFS) have been reported in COVID-19 patients [47]. A study by Sacchi et al. investigated the presence of autoimmune markers in 40 SARS-CoV-2 positive patients to support their hypothesis of association of COVID-19 with autoimmunity: 57.5% patients were positive for ANA (anti-nuclear antibodies), 12.5% had anti-cardiolipin antibodies (aCL), 25% tested positive for ANCA (anti-neutrophil cytoplasmic antibodies), and 5% had anti-β2 glycoprotein (anti-β2 GPI). Therefore, a significant prevalence of autoantibodies were found in COVID-19 patients as compared to healthy counterparts [48]. Another study by Wang et al. shows higher prevalence and reactivity of autoantibodies in SARS-CoV-2-infected patients which are suggestive of their role in the associated pathology [49].

The findings of deep vein thrombosis, stroke, disseminated intravascular coagulopathy and other vascular manifestations in COVID-19 infection have been associated with presence of aPL (Anti-phospholipid antibodies) [47]. However, studies have noticed that COVID-19-associated aPL do not seem to be anti-domain 1 which are the very pathogenic antibodies in APS [50]. Auto-immune antibody-associated thrombosis have been reported in three SARS-CoV-2-infected patients [50]. aPL are autoantibodies known to be directly involved in pathogenesis of thrombotic damage in several organs and of obstetric complications with reports of miscarriages. Although the rate of pregnancy loss has been no different during the COVID-19 pandemic, some aPL-associated conditions like HELLP syndrome (hemolysis; elevated liver enzymes, and low platelet count) have been reported [47]. A case of ovarian thrombosis in a pregnant women with COVID-19 infection was also reported [51]. Based on scarce data it can't be concluded confidently whether or not aPL autoantibodies play a role in determining pregnancy outcomes in COVID positive patients; but studies do suggest that aPL-induced thrombosis is enhanced during an infection or hyper-inflammatory condition which is noticed in COVID-19 [52].

It has been reported that prednisone used in the management of Juvenile Systemic Lupus Erythematosus (JSLE) resulted in amenorrhea with marked decrease in FSH and LH levels [53]. The high doses of steroids used to treat severe COVID-19 may have similar effect on the menstrual cycle. Also, considering COVID-19 is likely an autoimmune disease, it was proposed to use immunosuppressants for its management [53], which may potentially impact fertility and/or pregnancy outcomes [54].

SARS-CoV-2 infection is well-known to cause a cytokine storm which leads to overproduction of cytokines like IL-6, TNF-alpha that could affect the sexual health adversely [55, 56]. The therapeutic effects of steroids and IL-6 inhibitors in COVID-19 infection are suggestive of the underlying inflammatory mechanism as pathogenic [57]. In males, the associated inflammation disrupts the blood-testis barrier [58] and cause an orchitis-like syndrome [59]. The cytokines could also suppress the hypothalamic-pituitary–testicular axis, leading to hypogonadism and thus decreased testosterone levels [60]. Since SARS-CoV-2 is known to cause hypercoagulation due to vasculitis, damage to testes could also be due to segmental vasculitis [61]. It is suggested that orchitis could also be a result of vasculitis; hence, SARS-CoV2-induced immune response might be the reason behind damage to testes and alteration in hormone levels [60]. Moreover, IgG detected on immunohistochemistry of seminiferous tubules which is indicative of an autoimmune response leading to auto-immune orchitis [62, 63]. Anti-phospholipid antibodies were detected in COVID-positive patients which are hypothesized to intervene with fertility by acting against sperm, although this remains largely unproven [64–66].

A recent study addressing the hypothesis of role of autoimmunity in COVID-19 identified 28 human proteins harbouring regions homologous to SARS-CoV-2 peptides that could possibly be acting as autoantigens in COVID-19 patients displaying autoimmune conditions. Interestingly, these conserved regions are amongst the experimentally validated B cell epitopes of SARS-CoV-2 proteins. The reported human proteins have demonstrated

presence of autoantibodies against them in typical autoimmune conditions which may explain the frequent occurrence of autoimmune conditions following SARS-CoV-2 infection. Moreover, the proposed autoantigens' widespread tissue distribution is suggestive of their involvement in multi-organ manifestations via molecular mimicry [67]. Another study found the presence of anti TPO (thyroid peroxidase antibodies) in long COVID patients on follow-up [68].

Likewise, Lingel et al. [69] noticed raised titers of anti-CCP (Cyclic Citrullinated peptide antibodies) and anti-TG (Tissue Transglutaminase) in SARS-CoV-2-infected patients on follow-up indicating the formation of autoantibodies and hence the role of autoimmunity in COVID-19. COVID-19-associated viral myositis is also thought to be a result of the autoimmunity [70]. Also many patients with severe infection were noticed to have autoantibodies against NET (Neutrophil Extracellular Traps) which play a role in decreased clearance of NET, therefore, further exacerbating the severity of infection [71].

Areas of contradiction

Several areas still require extensive research since most of the currently available data is contradictory, rendering it difficult to make a conclusive statement. It is still unclear whether or not sexual and vertical transmission occur, and, if it does, is it only restricted to certain stages of infection or depends or severity of infection. Although studies do highlight the role of autoimmunity in COVID-19, the crossroads of infection, autoimmunity and immunosuppression are yet to be solved. Also the extent of effect on fertility is not yet clear, but it is known that male fertility can be affected more than female fertility. Figure 1 summarizes the current findings.

Conclusion

The existing data give non-conclusive evidence about the impact of SARS-CoV-2 infection on fertility; however, a greater impact on male fertility as compared to female has been noticed. The presence of ACE2 in testes, with reports of autoimmune orchitis and impaired spermatogenesis, alteration in sex hormones and some findings of viral shedding in semen are definite areas of concern. However, most studies are observational with small sample size and therefore large, controlled trials or prospective studies are needed to make a definite conclusion. As for females, the SARS-CoV-2 infection has so far shown to be less dreadful to the pregnancy outcomes as compared to SARS and MERS. However, reproduction and fertility is a key concern and considering the pandemic is prolonged, natural conception or ART require extra precautions. The impact on fertility can change the socio-economic dynamics of all countries and that's why it deserves prime attention, requiring an urgent need for global studies to address the plausible issue about male infertility.

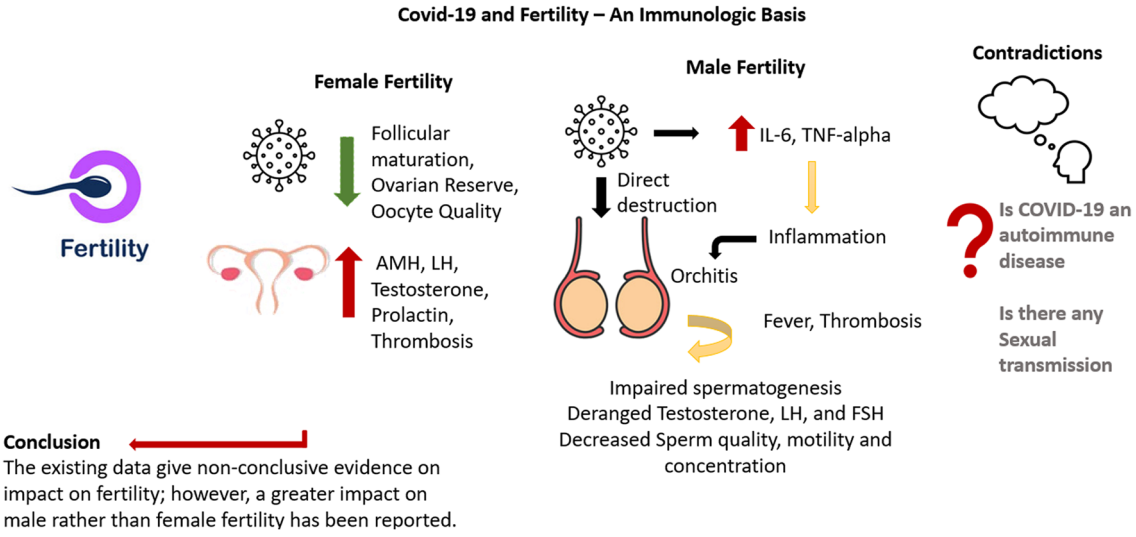

Fig. 1 Covid-19 and fertility—an immunologic basis

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Author contributions LG was involved in the conceptualization and methodology. JT was involved in investigation/data curation. JT and LG were involved in writing of the original draft and LG, JT, TC and LA were involved in manuscript review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declarations

Conflict of interest JT, LG, TC and LA report no conflicts of interest/competing interests.

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