Semen quality as a potential susceptibility indicator to SARS-CoV-2 insults in polluted areas

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Abstract
High levels of air pollution can contribute to high rate of the COVID-19 outbreaks. Air pollutants induce oxidative stress, inflammatory process, immune imbalance and coagulation at systemic level, making the organism susceptible to complications caused by various pathogens, including viruses, resulting in a possible important damage co-factor. Sperm cells are highly sensitive to the pro-oxidant effects of environmental pollutants, and represent an important alarm bell indicating how the burden of environmental pressure in a certain area is becoming increasingly unsustainable.

We underline that overlapping among maps of case fatality rate of COVID-19, male infertility rate and air pollution can be a challenging idea to understand the dynamics of the virus impact, considering semen quality that is an early and sensitive environmental marker, and could be a potential susceptibility indicator to viral insults (including SARS-CoV-2 ) in heavily polluted areas. So that, assessing the burden of environmental exposure of a given population and its potential susceptibility

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to insults through early biological stress indicators able to predict the probability, nature and magnitude for the adverse effects is a major public health challenge.

Key words: air pollution, COVID-19, semen quality, environmental marker, health marker, oxidative stress

Air pollution and COVID-19
A recent review point out that chronic exposure to air pollutants in the most polluted areas of the world (figure 1) leads to more severe and lethal forms of COVID-19\(^1\). Indeed, a study, carried out in 3,080 counties in the United States of America (U.S.A.) calculated an 8% increase in the COVID-19 death rate adjusted by 20 potential confounding factors for each 1 microgram/m\(^3\) elevation of fine particulate matter with a diameter of 2,5 μm or less (PM\(_{2.5}\))\(^2\). Furthermore, in 2003, during SARS infection in China, scientists reported that Case Fatality Rate (CFR) in the most polluted areas was twice as high as in the least polluted ones\(^3\). A preprint study has recently reported a higher CFR of COVID-19 in Wuhan, China, with increasing of air particular matter with diameter of 10 μm or less (PM\(_{10}\)) and PM\(_{2.5}\) on a temporal scale after adjusting for humidity and temperature\(^4\). Moreover, some authors found that the regions of Northern Italy most affected by COVID-19, had the highest levels of PM\(_{10}\) and PM\(_{2.5}\) in Europe\(^5-7\). A recent preprint found a significant correlation between high levels of PM\(_{2.5}\), carbon monoxide (CO), nitrogen dioxide (NO\(_2\)) and COVID-19 spread and mortality in Italy, U.S.A. and China\(^8\).

It’s worth highlighting that COVID-19 spread after initial outbreaks (China, South Korea, Iran) is occurred in Italy, then in the rest of Europe and Eastern U.S.A. between latitude 30° and 50° North in the seasonal period (December to April) where similar weather patterns, such as temperature (between 5 and 11 °C), low specific and absolute humidity of 3-6 g/kg and 4-7 g/m\(^3\) respectively were consistent with the behaviour of a seasonal respiratory virus\(^9\). Furthermore, it is significant that in the same seasonal period (May for Brazilian winter) the highest local peak out of this belt is in Sao Paulo, Brazil, a heavily polluted city (figure 2)\(^10\). It’s known that in the winter period the air pollution rates are higher. Stability of SARS-CoV-2 in different environmental conditions revealed that accelerated transmission dynamics of COVID-19 in specific environments were due to two different mechanisms: air pollution-to-human transmission, and human-to-human transmission in a context of high density of population. In addition, these studies highlighted that virus spreading and as a consequence the number of infected individuals, is highly dependent on the extent of the pollution time to which cities have been subjected\(^1,11\).
Pollution and susceptibility to viral insults

The World Health Organization (WHO) estimates that about a quarter of diseases is due to prolonged exposure to environmental pollutants\textsuperscript{12,13}, including cardiovascular and chronic degenerative disease, premature deaths and reproduction dysfunctions\textsuperscript{12,14-16} along with lifestyle, as reported in the European Code against\textsuperscript{17}. Moreover, a particular concern is the increasingly evident susceptibility to non-communicable diseases (NCDs) and the significant decline in body’s defences, also thought to be due to transgenerational effects already detectable in the current generation of damages occurred to the previous generation and that seem to give a new interpretation of the worldwide disease exponential load from not only the chronic-degenerative, but also to the infectious ones (dengue, yellow fever etc.)\textsuperscript{17-29}. In this context, multiple results showed the link between some pollutants like dioxins and immune response alterations. Furthermore, it shows that this is transmitted to the following generations, by reducing the defence ability toward viral pathogens\textsuperscript{30}. Therefore, susceptibility to respiratory viral infections may be facilitate by pollutants\textsuperscript{19}.

In particular, the chronic exposure to the air-born finest fraction of particulate matter (PM\textsubscript{2.5}), not only induces inflammation to alveolar district, but, passing the alveolar barrier, it reaches the blood and hence the peripheral tissues, inducing oxidative stress both directly and through the guest response to the chemical insult with an excessive production of ROS (reactive oxygen species) which contribute to the activation of inflammasome and, particularly, NLRP3, influencing the maturation and secretion of Cytokine such as IL-1 beta and IL-18 both involved in the systemic inflammatory syndrome and in all the facilitating conditions of the pathogen agent virulence, including vascular leakage and coagulopathy\textsuperscript{31-34}. It is, therefore, plausible that inflammatory mediators produced in the lungs by atmospheric pollutants could have a systemic impact and facilitate a silent systemic inflammation.

SARS-CoV-2 is able to unleash a fast process of autoimmune dysregulation, by inducing a significant Cytokine storm, mainly TNF-\textalpha, IL-6 e IL-1\textbeta, IL-17, IL-18, in genetically predisposed individuals\textsuperscript{35}. Such a process could be even more important when pre-existing environmental factors have already altered regulatory mechanisms for Cytokine release and/or even when there are some polymorphisms for IL-6, such as in specific populations or ethnic groups who in fact make them more susceptible to virus complications\textsuperscript{36}. Specifically, all populations are susceptible to COVID-19, but the elderly people, individuals with chronic diseases or low immune defenses, pregnant women and newborns are most exposed to complications\textsuperscript{37-39}.

In addition, air pollutants induce oxidative stress, inflammatory process, immune imbalance and coagulation at systemic level, making the organism susceptible to complications arising from the
pathogen agent virulence, including SARS-CoV-2, resulting as a possible important damage co-factor\textsuperscript{40}. This is even more true in those areas where poor air quality could, favour viral contagion and/or increased virulence, disarming the antioxidant and immune defences of the organism.

**Sperm decline in polluted areas**

Many data suggest a decline in sperm parameters in different areas of the world, particularly in developed ones or those undergoing strong industrial development with high levels of air pollution\textsuperscript{41}. A systematic review and meta-regression analysis reported a decline of total sperm counts by 59.3% in Europe, U.S.A., Canada and New Zealand between 1971 and 2011\textsuperscript{42}. In Asia, the infertility rate of Iranian men has increased by 20% over the last 20 years and in China, out of a total of 30,636 young donors, a decrease in total spermatozoa number and morphology of 30% and 38% respectively has been reported between 2001 and 2015\textsuperscript{43,44}. In Brasil, in the past 23 years a reduction of 0.24 million/mL of spermatozoa per year was reported\textsuperscript{45}.

The male reproductive system is, indeed, extremely sensitive to environmental pollutants, in particular, chronic exposure to high levels of PM\textsubscript{10}, PM\textsubscript{2.5} and individual air pollutants as well as NO\textsubscript{2} and SO\textsubscript{2} are negatively associated with sperm count, motility and testicular volume in infertile subjects\textsuperscript{46,47}. The mechanisms of spermatogenesis damage by environmental agents are largely unknown, although radical oxygen species (ROS) imbalance and associated oxidative stress may be the common denominator through which pollutants alter the most sensitive parameters of seminal quality such as sperm count, motility, morphology and integrity of sperm DNA\textsuperscript{48-50}. As a matter of fact, sperm cells are highly sensitive to the pro-oxidant effects of environmental pollutants, due to the limited volume of the cytoplasmic space, with less antioxidant defence, and sperm membrane lipids are target of ROS\textsuperscript{51}. In this regard, we recently reported that male gametes are the most sensitive cells to the accumulation of damaged DNA and showed, through molecular investigations, that the sperm nuclear basic proteins from samples of men living in polluted areas have a new and unexpected behaviour, resulting involved in DNA oxidative damage\textsuperscript{52}. Thus, in the present paper, we correlated the CFR maps of the most important COVID-19 outbreaks with the world areas presenting, in recent decades, a negative trend in sperm quality and high average annual levels of PM\textsubscript{10} and PM\textsubscript{2.5}, observing a very suggestive overlapping (figure 2). It could be argued that sperm decline may represent the earliest clinical sign of environmental pressure.

**Human semen as environmental and health marker**
Therefore, we and other authors indicate human semen as a “sentinel biomarker” of subclinical biological effect suitable for monitoring the impact of adverse environmental exposures\textsuperscript{53-57}. After all, semen quality has also been found to reflect individuals’ general health condition. In fact, recent research show an association between semen quality and the onset of chronic diseases, with male infertility as a predictor of future hospitalization and overall mortality\textsuperscript{58-62}.

We speculate that this observation could help understanding the dynamics that may have facilitated the COVID-19 severity in polluted areas. As an early and sensitive environmental and health marker, semen quality could be considered as a potential susceptibility indicator of external insults to the health of the general population and be used for health risk management, innovative prevention programs and health surveillance, especially in heavily polluted areas\textsuperscript{56,57}. However, although high population density, climatic characteristics, age, comorbidity, different capacity of health systems to face the pandemic and prevention policies adopted in the various countries currently play the central role, we should not overlook the possible facilitating contribution of pollution in increasing the risk for people living in areas with higher environmental pressure to the Covid-19 impact. Moreover, it must be considered that higher incidence of non-communicable diseases (NCDs) and male infertility are reported in these same areas because of a complex interaction between factors of chronic chemical and physical exposure, along with the contribution of lifestyle behavioural risk factors and individuals’ genetic background. In particular, human sperm decline in the last decades, represent an important alarm bell indicating how the burden of environmental pressure is becoming increasingly unsustainable. In this perspective, the first signs of damage to organo-sentinel systems such as the male reproductive system, detectable by the reduction in semen quality over time can be an opportunity to know the health status of the population in a given environmental context, including susceptibility to the virus impact in that population, and predict the medium to long term adverse effects on human health.

However, in our opinion semen quality as an early environmental and health marker could help the policy makers to intervene promptly in areas with significant environmental criticalities in order to reduce air, water and soil pollution with an integrated approach in a One Health perspective, where the sharing of information between different professional figures (clinicians, biologists, chemists, virologists, veterinarians, economists, epidemiologists) can succeed to find a systemic approach that could be effective on a global scale\textsuperscript{63}. The environment and our health are in dire need of this and above all it is necessary to estimate of effectiveness of the measures adopted to safeguard the health of community and also its social and productive organization with the aim to avoid, or at least reduce, the rapid and destructive spread of future viruses.
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Author contributions
LM developed the concept and drafted the manuscript, PMB collected the data, IMB, AG, FD and MP edited and revised manuscript, LM, IMB, FD, PMB, AG and MP approved the final version of the manuscript.

Competing interests
The authors declare no competing financial interest.
Figure 1: World map of tropospheric NO₂ concentrations from the Copernicus Sentinel-5P satellite (2019)
Figure 2: Overlapping between Case Fatality Rate maps (from pink to brown) of the most important COVID-19 outbreaks, air pollution and world areas presenting, in recent decades a negative trend in sperm quality, is shown. Some cities of most important COVID-19 outbreaks with PM$_{10}$ and PM$_{2.5}$ annual average (2018) above the WHO recommended values of 20 μg/m$^3$ and 10 μg/m$^3$ respectively are also reported as examples.