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Integrative Approach on Post COVID-19 and Infertility: A Literature Review

Review Article

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Abstract

Introduction: Post COVID-19 Syndrome is term given to multitudinous health impacts that persist more than four weeks after being infected with SARS CoV-2. Viral infections are one of the causative factors which lead to infertility by affecting the hypothalamic–pituitary–adrenal, gonad axes. Covid-19 can be corelated with *Janapadodhwansajanya Vyadhi* and *Abhishangaja Jvara* while Post COVID-19 can be corelated with *Jeerna Abhishangaja Jvara*. Methodology: Information for present review is compiled from classical texts of Ayurved with commentary and variety of scientific search databases including Google Scholar, NCBI, PubMed and Science Direct by using keywords like Post COVID-19 infertility, Ayurved and Post COVID-19 infertility etc. Articles studied in detail after screening for relevancy to synthesize qualitative review. Result: The result reviewed on semen analysis, Renin angiotensin system, sperm DNA and morphology, cytokine storm, oxidative and mental stress. This review also illustrates the reproductive organ histology related to inflammatory responses, receptors like ACE-2, TMPRSS2 etc., various cases reported like orchitis, irregular menstruation, premature birth, caesarean delivery etc. due to SARSCOV-2 exposure. This showed association between Long COVID and infertility. Discussion: Information discussed are focused on various study conducted on impact of COVID crisis related to various infertility parameters associated with Long COVID. Due to *Jirna Avastha* of *Jvara* (~Fever persists after 21 days from onset), *Uttarottar Sapta Dhatu Dushti* occurs which ultimately can land up in *Dushti* of *Shukra Dhatu, Shukravaha Strotas* and *Aartavavaha Strotas (*~Reproductive system*)*. The integrative approach of Ayurvedic management will be beneficial in such cases.

Keywords: *Janapadodhwansajanya Vyadhi, Jeerna Abhishangaja jwara,* Post COVID-19, *Vandhyatva*.

Introduction

Global novel pandemic COVID-19 caused by SARSCoV-2 continues to rampage across the world leading to severe painful humanity healthcare crisis in the form of acute infection of COVID-19 and Long COVID even after a year from its first emergence which was in December 2019.(1) Post COVID-19 Syndrome is term given to multisystemic, long-lasting inflammatory effect that persist more than three weeks after being infected with SARS CoV-2.(2) As of on 10th November 2022, there have been 630,387,858 confirmed cases of COVID-19, including 6,583,163 deaths worldwide while in India there have been 44,662,952 confirmed cases and 530,511 deaths as reported by WHO.(3) COVID 19 is multisystem disease with extra respiratory complication affecting the cardiac (arrythmias and myocardial injury), gastro-intestinal, nervous (neuropathy, encephalopathy), endocrine and musculoskeletal systems, reproductive system and also cause thrombo-embolic complications.(4) Infertility is the inability to reproduce by natural means in person, animal or plant.(5)

As described in Ayurved Infertility means biological inability of reproductive age to contribute to conception and the state of a woman who is not capable to carry pregnancy to full term. (6) Shushruta has described *Ritu* (~menstrual cycle regulation), *Kshetram* (~Reproductive organs), *Ambu* (~Nutrition), *Beejam* (~sperm and ovum) as *Garbha Sangraha Samagri* i.e., essential factor for pregnancy. (7) Any abnormalities in any of these factors lead to *Vandhyatva.*

As SARS-Cov-2 spike protein receptors like ACE2 and TMPRSS2 which facilitate the virus-receptor fusion found within the reproductive system, it is susceptibility to being infected by COVID-19.(8) Various biotic and abiotic factors, malnutrition, toxicants, psychological stress and viral infections are known to be causative factors for infertility of humans through various mechanism.(9) A various viral infections like HIV, HTLV-I, HHV-8, Epstein-Barr virus, Hepatitis viruses etc. causes changes in the endocrine and reproductive systems in humans and animals. The hypothalamic–pituitary–adrenal, gonad axes can be affected by viral infections which can lead to infertility. (10)

COVID-19 can be corelated with *Janapadodhwansajanya Vyadhi* and *Abhishangaja Jvara* while Post COVID-19 can be corelated with *Jeerna Abhishangaja Jvara*. There may be *Utorottar*

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Sapta Dhatu Dushti in post COVID-19 syndrome like *Jeerna Jwara.* In *Ayurved*, communicable diseases are clearly mentioned under a broad term *Janpadodhwansa (11)* and *Aupasargik –Roga (12) by* Charak and Sushrut respectively.

Janapadodhwansha specifies the disease of large number of people within a specific region from disease probably infections and communicable in nature. [10]

According to Charak *Yonidushti* (~genital organ abnormality), *Manas Abhitapa* (~psychological distress), *Shukra*(~Sperm*), Aartava*(~ovum) *Dushti*(~vitiation*), Apathya Aahara Vihar, Balakshaya* are causes of infertility. (13) *Janapadodhwansha* can be prevented and controlled by using *Panchakarma (*~purification procedures) like *Vamana* (~therapeutic emesis), *Virechana* (~therapeutic purgation)*, Basti* (~medicated enema), *Nasya* (Nostril instillation of medication) and also by *Rasayana* (~Rejuvenation) and following the *Sadavritta* (~personal and social code of conduct) can be useful in the risk-prone areas to improve immunity and minimize the risk of infection. (14)

Aims and Objectives

- To review literature related to COVID crisis effect on progeny production.
- To evaluate integrative approach in terms of pathophysiology, management, prevention of infertility due to COVID-19.

Material and Methods

Information for present review is compiled from classical texts of Ayurveda with commentary and variety of scientific search databases including PubMed, NCBI, Science Direct and Google Scholar by using keywords like Post COVID-19 infertility, Ayurveda and Post COVID-19 infertility. Articles and classical texts studied in detail to synthesize qualitative review regarding integrative approach towards Post COVID-19 infertility.

Observations and Results

COVID-19 receptors, mediators and infertility

COVID-19 mediators like Renin angiotensin system(RAS) disrupted due to COVID crisis which can lead to infertility as RAS maintains ovarian blood pressure, paracrine signaling pathways, spermatogenesis, sperm maturation, tubular contractibility and acrosomal exocytosis. Excess of RAS components cause reduction of testosterone, Cancer of cervix, breasts, ovarian and endometrial. SARS-CoV-2 infection can increase ANG-II by down-regulating ACE-2 receptors.

COVID-19 mediators cytokine storm, oxidative stress, fever, and frustration, mental stress due to social isolation, confinement promotes abnormal quality of sperm and ovum as gametogenesis, reproductive cycles are depended on all this factors. Proteins like ACE-2, CD147, TMPRSS2, lysosomal cathepsin (CTSL), cluster of differentiation (CD147) and neuropilin-1 which are entry factors for SARS-CoV-2 present in the testes, prostrate, epididymis, seminal vesicles, fallopian tube, endometrium, cervix, uterus, vagina, ovary, placenta and ovarian follicles. (9)

Case reports regarding COVID-19 and infertility:

Cases have been reported of orchioepididymitis, interstitial edema, red blood cell exudation in testes, oligozoospermia, thinning of seminiferous tubules, bilateral orchitis, priapism, testicular pain and numerous degenerated germ cells due to COVID-19 infection in male while in female cases reported of cycle prolongation and decreased menstrual volume. (9)

In vitro fertilization case study showed oligo-astheno-teratozoo spermia with sperm DNA damage, no acrosome in semen analysis after 43 days of recovery from being infected with SARS-CoV-2 while semen analysis after135 days showed improvement in sperm motility and count but sperm DNA remain severely damaged with teratozoospermia. (15)

In utero SARS-CoV-2 exposure:

Pregnancy is principally a sensitive phenomenon being more vulnerable for infection which requires additional care. (16) Case report have been reported of preterm birth, maternal morbidity, fetal distress, fibrinoid necrosis, mural hypertrophy of membrane arterioles, vessel ectasia, placental injury, persistence of intramural endovascular trophoblast. Pre-eclampsia during pregnancy manifest due to upregulated ANG-II/ AT1R. Placental villi, syncytiotrophoblasts, cytotrophoblast and smooth muscles of the umbilical cord have been observed to contain ACE-2. (9)

Infections during pregnancy raises the concern of transmission of the infection from the mother to the baby, either in utero or during the intrapartum and early postpartum period. ACE2 has been shown to be expressed by fetal kidney, ilium, and rectal cells from as early as 15 weeks, barely detectable at 15 weeks in the lungs. Pregnant women with COVID-19 might be at increased risk of problems such as stillbirth, pre-eclampsia, premature birth, birth by emergency caesarean delivery, neurodevelopmental abnormality and pregnancy loss. infants born to women infected with SARS-CoV-2 had higher immunoglobulin (Ig)G and IgM levels for SARS-CoV-2. (17) Acharya Kashyap has stated that fever in a pregnant woman is the most troublesome disease as the foetus suffers due to the transfer of heat of fever from the mother to the foetus. (18)

SARS-CoV2 and male reproductive system

TMPRSS2 significantly expressed in the prostate which is essential entry factor of virus. Viral infections led to epididymitis, orchitis and defective spermatogenesis by crossing blood–testis barrier. (6) According to available epidemiological data steadily increasing testicular cancer have viral infection as an etiology factor. (10)

A case study showed low level of testosterone and follicle-stimulating hormone level whereas prolactin and luteinising hormones were high. (19) The median TSN of men previously infected with SARS-

CoV-2 was 12.5 million which is less than the 5th percentile of normal TSN. Additionally, 83.3% of cohort study showed TSN less that the 25th percentile while 50% had a TSN less than the 2.5th percentile. (20)

SARS-CoV-2 and female reproductive system

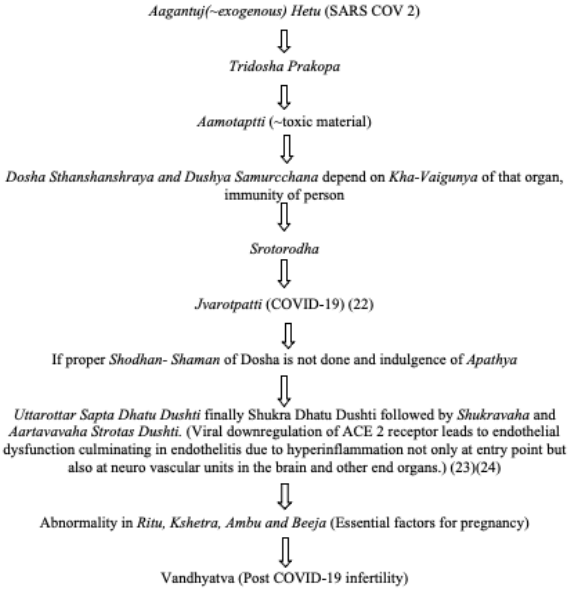
Infiltration of the SARS-CoV-2 in the ovary lead to menstrual abnormality in form of short, increases volume or prolonged menstrual cycles. Infertility causes due to HPA axis dysfunction, decreased ovarian reserves, dysfunctional uterine bleeding, hypercoagulability which prevent implantation. HIV infection causes earlier menopause suggests viral infection affects female fertility capability. (21)

Charak has described healthy *Yoni*, *Garbhashaya Marga* and maintenance of *Vatadi Dosha* are essential for conception and maintenance of pregnancy. (5)

Probable pathophysiology of Post COVID-19 infertility

- *Hetu:* Improper *Shodhan, Apathya Ahara- Vihara*
- *Status* of *Agni: Agnimandya(~dyspepsia)*
- *Dosha: Pruthak / Sansrusta / Sannipataj*
- *Dushya: Ras (*~Tissue Fluids/Plasma), *Rakta(*~Blood), *Mansa(*~Muscle), *Meda (*~Fat & Connective Tissues), *Asthi (*~Bone Tissue), *Majja (*~Bone Marrow) and *Shukra (~sperm or ovum)*
- *Strotas* Involved: *Rasvaha, Shukravaha/ Aartavavaha*
- *Adhishtan: Sharir, Mana*
- *Abhivyakti Sthan: Shukravaha* and *Aartavavaha Strotas*
- *Avastha: Jirna(~chronic)*

Figure 1: Showing the *samprapti*



Management:

Integrative approach of Ayurvedic management in Post COVID-19 infertility:

The traditional Indian medicinal system 'Ayurved' has holistic approach, not confined within symptomatic relief; treatment will work better to overcome and prevent COVID-19 crisis complication. It can include *Deepana* (~appetizer), *Pachana*(~digestives), *Panchakarma*(~purification), *Rasayana, Vajikarana (*~strengthening virility*), Shamana drugs* (~oral drugs), *Uttarbasti (*~medicines instillation through urethral or vaginal routes*), Yoga-Pranayama, Sadavritta Palan* which will work at a level of various smallest channel of multisystem of body to eliminate diseases from the root and to prevent re-occurrence. The equilibrium state of *Dhatu* is called *Swasthya*. (25) The person who is desirous to be healthy should adopt healthy practices related to diet, conduct and activities

Panchakarma

Post COVID-19 immune over-reaction causes multisystemic symptoms due to persistent fragment of viral genes by triggering factors. (26) Charak also has explained importance of proper *Shodhan* of *Leena Dosha* (~merged toxins) and *Pathyapathya* in consequence to avoid the re-occurrence of diseases. (27) As we know in COVID 19, nostrils and throat are the sites which get initially affected. So, *Nasya* may be the choice of *Shodhana* in Post COVID-19 syndrome. (28) *Nasya Karma* used for *Punsavan Vidhi* suggests that it acts up to the level of *Shukra/Aartava Dhatu* i.e., it not only acts locally but also acts at multisystemic level of body. (29) *Uttarbasti* of *Shukra Shodhan, Shukrajanana* and *Prajasthapana Mahakashaya Dravya* can be beneficial to overcome condition like post viral infertility.

Importance of immunomodulation in Post COVID-19 Syndrome:

The immune system violent-triggering response through mediators plays an important role in manifestation of post viral complications. Enhancement of immunity will maintain optimum health by preventing such communicable diseases. (30) Immunity can be considered in Ayurved as *Vyadhikshmatva* and *Ojas* (essence of *Dhatus* i.e., structural elements); which depends on the condition of *Agni*, *Dosha*, and *Dhatu*. (31) It is found that patients with co-morbidities tend to have low immunity level suffer more than the healthy individual. (32)

Rasayana

Rasayana potentiates *Ojas* in other words boosts the immune system, for example, researches have proved that intake of *Amalaki, Pippali, Haritaki, Shilajatu* increases gamma globulin leading to increase in nonspecific resistance. Ayurved emphasizes this aspect of controlling the infectious diseases. (33)

"*Rasayana Chikitsa*" is therapy which produces the best quality of *Raas*, *Rakta* and other *Dhatus* by enhancing *Agni* i.e., digestion, metabolism and absorption and used for rejuvenation by boosting the immune system and alleviating disease condition. (34) *Rasayana* increases the longevity, increases mental as well as physical strength, destroys the disease process and decreases the ageing process. (35)

Discussion

However, underlying mechanism for these findings remains as a debate, possible mechanism according to review literature are infection-induced hypothalamic–pituitary axis dysfunction, cytokine storm, oxidative stress, mental stress and reproductive organ damage, *Tridosha Prakopa, Aamotaptti, Srotorodha, Dhatudourbalya due* to acute severe infection which causes direct gonadal damage. According to Ayurved it can be correlated with *Jeerna Abhishangaja Jwara* for understanding clinical pathophysiology behind these cases and for management purpose.

As there is possibility of impaired fertility parameters via SARS-CoV-2 infection, it is better to adopt preventive majors by means of *Shodhan, Rasayan* etc. More studies are required for investigating information about SARS-CoV-2 effect on fertile capability to overcome drawbacks like small sample size, no long-term follow up. In Ayurved, no study, review is found regarding COVID-19 effect on *Shukravaha, Aartavavaha Strotas* till now. Most of the studies on SARS-CoV-2 effect on semen analysis have denied the presence of the virus in the seminal plasma and study also showed SARS-CoV-2 infection can affect total sperm count though not detected in semen. Whether SARS-CoV-2 can affect spermatogenic function long-term remains to be evaluated.

Conclusion

Hence it is concluded SARS-CoV-2 infection led to disturbance of functions and histology of the reproductive system which ultimately land up into infertility. The integrative approach of Ayurvedic management will be beneficial in such cases which will help to improve quality of public health.

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