SHORT COMMUNICATION

Preliminary Results for Personalized Therapy in Pregnant Women with Polycystic Ovary Syndrome During the COVID-19 Pandemic

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Abstract

Increased androgen level, hyperinsulinemia, diabetes, impaired fibrinolysis, obesity, hypertension, chronic inflammation, abnormal immune response to infections and hyperhomocysteinemia are the most common abnormalities related to polycystic ovary syndrome (PCOS) women and are the factors predisposing to the severe course of COVID-19. The SARS-Cov-2 infection during pregnancy is associated with an increased risk of complications (spontaneous abortion), similar to those in PCOS. The treatment of PCOS pregnant women with a history of fertility failures raises many doubts, especially during the COVID pandemic. However, due to the increasing incidence of infections among reproductive people and the potentially more serious course in pregnant women, numerous questions about the safety and effectiveness of the treatment are still very current. In our study we presented a series of cases of recurrent miscarriages or recurrent implantation failure PCOS pregnant women with confirmed COVID-19. The diagnosis of infertility confirmed the presence of plasminogen activator inhibitor type 1 and/or 5,10-methylenetetrahydrofolate reductase polymorphisms in each of them. Moreover, some of the women presented immune dysfunction associated with infertility. We have described the personalized treatments of each pregnant patient included: metformin, enoxaparin and tacrolimus. The treatment applied had the expected effect, supporting the implantation processes. Furthermore, despite the ambiguous data according to immunological therapy of infertile women during the COVID pandemic, we observed a mild or asymptomatic COVID-19 course and we noticed no pregnancy complications.

Keywords COVID-19 · PCOS · Pregnancy · Recurrent pregnancy loss · Metformin · Tacrolimus

Introduction

In December 2019 in Wuhan, China, a new strain of severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) emerged for the first time, causing a new coronavirus disease (COVID-19), which, due to its extremely rapid worldwide spread, reached pandemic status in March 2020. In most cases, COVID-19 is an asymptomatic or mild infection, and the clinical symptoms are dominated by: increased body temperature, headache, dry cough, fatigue, muscle aches, shortness of breath, gastrointestinal disorders (abdominal cramps, diarrhea, nausea), vomiting, smell and taste disorder (Fu et al. 2020). However, among high-risk patients, it is associated with the development of acute respiratory distress syndrome (ARDS) and the systemic disorder–micro-CLOTS syndrome (i.e., obstructive thrombo-inflammatory syndrome associated with microvascular SARS-CoV-2), associated with a high mortality rate (Ciceri et al. 2020). Therefore, it is extremely important to identify the factors predisposing to the severe course of COVID-19. According to existing data, male sex and age > 65 years is associated with a more severe course of the infection. Moreover, the presence of comorbidities such as: diabetes, hyperinsulinemia, hypertension, heart disease, and obesity has also been widely recognized as a key risk factor for severe COVID-19 (Richardson et al. 2020). Much effort has been made to elucidate the pathomechanism of the increased predisposition to more severe symptoms, especially for males. According to existing studies, it is believed that the effect of high

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androgen levels could explain the sex-specific differences in outcomes (Jin et al. 2020).

Considering the key role of androgens in the pathophysiology of infection, it is worth taking into account what risks are for women suffering from hyperandrogenism. According to Morgante et al. (2021) women with polycystic ovary syndrome (PCOS) are more prone to COVID-19 infections. Moreover, SARS-CoV-2 infection during pregnancy, was associated with an increased risk of complications such as: spontaneous abortion, preterm labor, intrauterine growth restriction and, in the mother, renal failure or disseminated intravascular coagulopathy (Li et al. 2020). According to the latest data, it was found that in women with COVID-19, the risk of stillbirth was twice as high as in pregnant women without coronavirus. In the case of the delta variant, it was four times higher (DeSisto et al. 2021). Based on the current literature, it is worth considering if a COVID-19-related cytokine storm and metabolic disturbances in PCOS may contribute to a more severe course of infection and if they are more predisposed to pregnancy complications.

Polycystic ovary syndrome is the most common endocrine disorder, occurring in about 10–15% of reproductive aging women. Increased androgen level, hyperinsulinemia, diabetes, obesity, hypertension and other cardiovascular diseases are the most common abnormalities related to PCOS women. Moreover, some authors have pointed at the relationship between immunological and hematological abnormalities in PCOS women and their connection with pregnancy failures. Undoubtedly, much attention is drawn to the fact that a number of comorbidities in PCOS overlap with the risk factors of severe COVID-19 course.

As already mentioned, the increased level of androgens, which was confirmed in the male population, undoubtedly influences the course of COVID-19. The molecular mechanisms take into account the role of the angiotensin-converting enzyme (ACE2) and its receptor, as well as the role of the transmembrane protease, serine 2 (TMPRSS2) which acts as a key mediator contributing to the SARS-CoV-2 entering into the host cell. In both the ACE2 and TMPRSS2 promoter sites there is an androgen receptor which activates the transcription of regulated genes (Moradi et al. 2020). The influence of androgen on COVID-19 infection was also confirmed in the female population and the results of this study may be extrapolated to the group of women with PCOS (Moradi et al. 2020). Testosterone seems to play an important role not only in the activation and entry of the virus into the host cell, but also in the regulation of the immune response. Androgen receptors are found on the surface of immunocompetent cells, such as macrophages and neutrophils. It is believed that the immunomodulatory effect of androgens is associated with an increase in the production of interleukin (IL-1β, IL-10, IL-2), transforming growth factor β1 and a decrease in the concentration of immune antibodies. As a result, there are changes in the immunological milieu that are similar to the cytokine storm seen in patients with severe COVID-19, which may in consequence lead to respiratory and multi-organ injury.

The cytokine storm observed in COVID-19 may also result from genetic predisposition to excessive cytokine secretion. Polymorphisms in genes encoding proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-6 have been confirmed in women with PCOS (Guo et al. 2015). Moreover, obesity co-occurring with PCOS also predisposes to chronic inflammation and an abnormal immune response to infections. Dysfunctional adipocytes which secrete pro-inflammatory cytokines (including TNF-α, IL1-β, IL-6) may intensify the inflammatory process (Kyrou et al. 2020). Based on the presented data, it can be concluded that chronic inflammation may be another aspect of PCOS pathophysiology that could also be of importance for COVID-19-related hyperinflammation.

Another important pathomechanism associated with the serious symptoms of COVID-19 and increased mortality is an increased risk of thrombosis, which is also observed in PCOS patients. Therefore, it can be hypothesized that PCOS women may be potentially at a higher risk of severe COVID-19 symptoms.

The aim of our study is to present a series of cases of recurrent miscarriages or recurrent implantation failure PCOS pregnant women with confirmed COVID-19. Moreover, we present the personalized treatment of each patient and its potential influence on the pregnancy COVID-19 infection course.

Materials and Methods

Retrospective analysis was performed on ten pregnant women with a history of reproductive failure, confirmed to be infected with COVID-19 during pregnancy between January 2021 and April 2021. All information was obtained from the patients' medical documentation from Medical Private Practice. The study was approved by the institutional review (27/WIM/2017). All patients gave informed consent to use their medical records provided that their information would be kept confidential and anonymous. All information on the diagnosis of reproductive failures was collected from the medical records and including: a panel of hormonal tests, results of thyroid function, oral glucose tolerance test with the assessment of insulin levels, tests for thrombophilia and for antiphospholipid syndrome, immunological analysis and polymorphisms of selected genes. The diagnostic test results obtained from the medical records were performed by the patients in external laboratories.

The concentrations of selected cytokines were measured with the double-antibody sandwich enzyme-linked

immunosorbent assay (ELISA), and were calculated from the standard curve of linear regression according to the manufacturer's instruction (ELISA-kits, Sun Red, Biotechnology Company Co. Ltd., Shanghai, China). Selected gene polymorphisms were marked using the GeneProof PAI-1, MTHFR C677T, A1298C Genotyping PCR Kit. All of the women included met the Rotterdam criteria of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). Most of them met the criteria of recurrent miscarriages and some met the criteria of recurrent implantation failure (Practice Committee of the American Society for Reproductive Medicine 2012). All abnormalities observed in each of the patients, which may have a link with previous pregnancy failures, are presented in Table 1. According to the medical documentation, before trying to get pregnant, each of the women had personalized treatment, the scheme of which is presented in Table 1. Except for the treatment presented, according to the SMART (specific, measurable, achievable, realistic, timely) procedure, all women had a Mediterranean and low glycemic index diet and physical activity of 150' per week (Teede et al. 2018).

Each woman made an effective attempt at conception during the therapy. The presented treatment continued throughout the entire pregnancy. According to the medical records, each of the pregnancies was successful, with no complications. Moreover, the performed ultrasound examinations of the fetus confirmed its well-being. However, despite compliance with the recommendations on limiting interpersonal contact, due to the COVID-19 pandemic, the presented patients reported a positive COVID PCR test result. The tests were commissioned by a general practitioner and performed in accordance with the guidelines of the Ministry of Health in force in Poland. Eight patients performed the test due to the appearance of symptoms characteristic of COVID-19, while two patients due to contact with a sick person. All women were tested for COVID-19 with deep nasal and oral swabs. Symptoms related to the course of COVID-19 and the information at the time of pregnancy when COVID-19 infection occurred are presented in Table 1.

Result

Among the patients presented in our study, we observed numerous risk factors of a severe course of COVID-19: PCOS, diabetes, plasminogen activator inhibitor type 1 (PAI-1) and 5,10-methylenetetrahydrofolate reductase (MTHFR) polymorphisms, thyroid dysfunction and immunological abnormalities. However, all cases were asymptomatic or mildly symptomatic. None of the women required hospitalization. The examination assessing the basic parameters (blood pressure, heart rate and blood oxygen saturation) remained normal. Only paracetamol was administered in the event of elevated body temperature. Despite the diagnosis of COVID-19, each of the patients continued the treatment according to the previously planned schedule, including immunosuppressive therapy. Table 1 shows the treatment schedules for each patient. The exact doses of the preparations used are presented in Table 2. All drugs were administered orally, with the exception of enoxaparin, which was administered subcutaneously. Despite previous concerns, we did not observe an exacerbation of COVID-19 in our patients during immunosuppressive treatment.

No pregnancy complications that could be associated with COVID-19 infection have been observed. The control tests were carried out according to the recommendations for pregnancy management in Poland. No additional tests were performed on patients. Apart from the symptoms presented in Table 1, no other abnormalities related to COVID-19 infection were observed. Each of the pregnancies came to term with the birth of a healthy child. Based on the current literature and our own experiences, the therapy including tacrolimus, metformin, enoxaparinum seems to be safe during pregnancy (Albaghdadi et al. 2021; Hyer et al. 2018; Jacobson et al. 2020; Paizis 2019).

Discussion

It is well-known that adaptive changes physiologically occur in pregnant women, usually predisposed to the development of serious complications caused by infections. In relation to SARS-CoV-2 infection, it is worth noting that the ACE2 has been shown to be strongly increased during pregnancy. As we mentioned above, ACE2 works as a virus receptor and in this way, pregnant women may be more prone to infection (Li et al. 2020). According to an article, SARS-CoV-2 infection during pregnancy, was associated with an increased risk of complications, such as: spontaneous abortion, preterm labor, intrauterine growth inhibition and, in the mother, renal failure or disseminated intravascular coagulopathy (Li et al. 2020). It has been suggested that the infection may lead to pregnancy complications indirectly through Treg/Th17 cell imbalance and subsequent uncontrolled systemic inflammation (Muyayalo et al. 2020). In addition, based on the data presented by the Center for Disease Control, it should be noted that pregnant women hospitalized for COVID-19 had more serious symptoms and required mechanical ventilation more often than non-pregnant women (Delahoy et al. 2020). Taking into account the above factors and considerations, it may be hypothesized that pregnant PCOS women may be in the higher risk group of pregnancy complications.

In each of the women analyzed in our study, except for PCOS, the presence of the PAI-1 and/or MTHFR polymorphisms were confirmed. Moreover, some of the women were confirmed for the immunological imbalance of Th1/

Table 1 Descriptive characteristic of PCOS SARS-CoV-2 positive pregnant women

	Patient 1 33 years 20 HBD	Patient 2 35 years 16 HBD	Patient 3 36 years/ 26 HBD	Patient 4 33 years 12 HBD	Patient 5 38 years 30HBD	Patient 6 37 years 37 HBD	Patient 7 33 years 32HBD	Patient 8 37 years 20HBD	Patient 9 32 years 8HBD	Patient 10 39 years 12HBD
Numbers of pregnancy	4	3	0	3	2	2	4	4	2	1
Miscarriages (number)	3	2	-	3	2	2	3	3	1	0
RIF	–	–	+	–	+	+	–	–	–	+
Comorbidities										
Hashimoto	+	+	+	+	+	–	+	+	–	–
MTHFR										
A1298C	Heterozygous	Wild type	Heterozygous	Wild type	Wild type	Heterozygous	Wild type	Heterozygous	Heterozygous	Heterozygous
C677T	Wild type	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Wild type	Heterozygous	Wild type	Heterozygous	Heterozygous
PAI-1 4G	Heterozygous	Homozygous	Wild type	Homozygous	Heterozygous	Wild type	Heterozygous	Wild type	Wild type	Heterozygous
Other	GDMG1	Hyperprolact[a]	Hyperprolact[a]	Hyperprolact[a]	Allergy to aspirin	No	No	GDMG1	No	No
Immunological abnormalities	No	No	TNF-α/IL-10: 17.2	TNF-α/IL-10: 3.5	TNF-α/IL-10: 3.6	TNF-α/IL-10: 10.9	No	TNF-α/IL-10: 4.3	No	TNF-α/IL-10: 4.9
Therapy	Aspirin Enoxaparin Metformin Inositol	Aspirin Enoxaparin Metformin Inositol	Aspirin Enoxaparin Metformin Inositol Tacrolimus	Aspirin Enoxaparin Metformin Inositol Tacrolimus NAC[c]	Enoxaparin Metformin Inositol Tacrolimus	Aspirin Enoxaparin ALA[b] Tacrolimus NAC	Aspirin Enoxaparin Metformin Euthyrox	Aspirin Metformin Tacrolimus	Aspirin Enoxaparin Metformin	Aspirin Enoxaparin Metformin Tacrolimus
Symptoms of COVID infection	Conjunctivitis Diarrhea Loss of smell	Dyspnoea	Cough	No symptoms	Cough	Cough	No symptoms	Cough	Loss of smell	Cough

[a] Hyperprolactynemia

[b] Alpha lipoic acid

[c] N-acetylcysteine

Table 2 List of drugs used in therapy

Name of medication	Dose
Aspirin	75–150 mg orally[a]
LMWH—Enoxaparin	40 mg subcutaneous[a]
Metformin	500–1500 mg orally[a]
NAC	400 mg orally[a]
Inositol	1000–2000 mg orally[a]
Tacrolimus	0.5–2 mg orally[a]
ALA	300–600 mg orally[a]

LMWH low-molecular-weight heparin; *NAC* N-acetylcysteine; *ALA* alpha lipoic acid

[a]Once a day

Th2 response. MTHFR is an enzyme responsible for folate metabolism, and the polymorphisms present in its gene are associated with lower enzyme activity. The effect of the decreased enzyme activity is an increase in homocysteine levels. According to several studies, homocysteine has been recognized as an independent risk factor for degenerative and atherosclerotic processes in the circulatory system). Many data have confirmed that high homocysteine concentrations can activate the production of pro-inflammatory cytokines (TNF-α, IL1-β, IL-6, IL-8) which consequently are associated with damaging the vascular endothelium of both small and large vessels (Ponti et al. 2020). The common pathomechanism of vascular endothelial damage suggests that high levels of homocysteine may exacerbate pathologies appearing in COVID-19. In addition, homocysteine, in a similar pathomechanism to COVID-19, leads to damage to the vascular endothelium, inhibits the synthesis of nitric oxide and increases the risk of thrombosis. In reference to existing data, combined folic acid and B-vitamin therapy reduces homocysteine levels). Moreover, Acosta-Elias and Espinosa-Tanguma (2020) showed that folic acid supplementation can reduce coronavirus replication. Another common feature of the presented patients is the presence of PAI-1 4G/5G polymorphism which is associated with increased transcription and higher levels and activity of type 1 PAI (Liu et al. 2014). The main function of a type 1 PAI is to reduce fibrinolysis which leads to fibrin accumulation and venous thrombosis. In the analyzed group of women, some of them presented an abnormal profile of secreted pro- and anti-inflammatory cytokines, which are crucial in the establishment of immune tolerance. Verma et al. (2019) confirmed that the increased activity of Th1 lymphocytes and a higher level of pro-inflammatory cytokines (TNF-α, IL-10; TNF-α/IL-4; INFG/IL-4) are associated with recurrent miscarriages and implantation disorders. Moreover, Albaghdadi et al. (2019) also pointed at an abnormal expression of Treg, IL-2, and IL-17, in PCOS women with a history of reproductive failure. Similar abnormalities were confirmed

in pregnancy complications related to COVID-19 infection (Muyayalo et al. 2020).

Due to present abnormalities, each woman was administered metformin. It is worth remembering the historical indications of metformin, which has been used as an antiviral drug. The pleiotropic effects of metformin, both anti-inflammatory and antiviral, have prompted many researchers to use it in the treatment of COVID patients. By activating the protein kinase, metformin has the ability to reduce inflammation. In addition, it reduces TNF, especially in women, and has an immunomodulatory effect on lymphocytes, macrophages and neutrophils. Interestingly, it also causes conformational and functional changes in the ACE2 receptor, which consequently limit the entry of the virus into the cell. When analyzing the outcomes of metformin treatment, a lower incidence of ARDS and lower mortality rate was observed in COVID patients (Luo et al. 2020). Moreover, it is worth mentioning the effect of metformin on the coagulation pathway. Velazquez et al. (1997) demonstrated the ability of metformin to lower PAI-1 levels). Similar results were also shown by other researchers, thus confirming the pleiotropic effect of metformin and the ability to decrease abortion risk in women with PCOS (Palomba et al. 2005). It has been confirmed many times that thromboembolic complications are a characteristic feature of COVID-19, even in the asymptomatic course of the infection. The entry of the virus into the endothelial cell and its replication causes the infiltration of inflammatory cells and, consequently, cell damage. The local cytokine-storm and endothelial damage promote a hypercoagulable state (Connors and Levy 2020).

The biology of the virus itself and overlapping individual patient predispositions, such as increased homocysteine value and PAI-1 justify the use of low molecular weight heparin (LMWH). All of the presented women were taking enoxaparin. It is worth underlining that LMWH not only has an anticoagulant, but also an anti-inflammatory effect. They increase the binding of TNF-α by plasma proteins, inhibit the production of TNF-α, IL-1β, IL-10 and inhibit the activation of the complement system. Heparin plays an important role in blastocyst adhesion by combining selectins, integrins and heparin-binding epidermal growth factor (HB-EGF), thus improving implantation (Mekinian et al. 2016). The use of LMWH in the case of COVID-19 infection seems to be justified, especially in the case of a severe course requiring hospitalization. The doses of heparin have been the subject of numerous discussions. However, the standard prophylactic dose for venous thromboembolism is recommended (Connors and Levy 2020).

Immunosuppressive treatment of reproductive failure in the context of the COVID-19 pandemic has raised numerous controversies and concerns about an increased risk of a more severe course of infection. However, numerous data have shown that an important part of the damage caused by

SARS-CoV-2 is linked to an altered inflammatory response and for this reason, anti-inflammatory drugs which inhibit the immune response were used in the COVID-19.

In the presented cases, patients with confirmed immunological abnormalities received tacrolimus at a dose of 1 or 2 mg per day during pregnancy. Tacrolimus inhibits the proliferation of T cells, NK cells and macrophages, IL-2 receptor expression, and the production of IL-2 and interferon γ. In addition, it induces the processes of dendritic cell differentiation leading to the activation of Treg lymphocytes (Kwak-Kim et al. 2020). Yamaguchi (2019) showed that tacrolimus activates the progesterone receptor, inducing endometrial maturation in the implantation window, it inhibits the processes of immune rejection, while inducing tolerance processes. The use of tacrolimus in the group of obese women with PCOS restores the disturbed IL-17/Treg balance, reducing the risk of reproductive failure (Nakagawa et al. 2015). As mentioned above, the pregnancy complications in COVID-19 patients are mainly related to IL-17/Treg imbalance. The applied treatment brought the expected effect, supporting the implantation processes. Moreover, despite multiple risk factors, no severe course of COVID-19 was observed in any of the patients.

Conclusions

In summary, we want to emphasize the importance of the diagnosis and treatment of women with a history of reproductive failure, especially during the COVID-19 pandemic. Concomitant abnormalities in PCOS, polymorphisms of selected genes, and immunological disorders require rather complicated, personalized treatment, which should be continued during a possible COVID-19 infection. Despite numerous risk factors for the severe course of COVID, the pregnant women presented by us have had little or no symptoms of infection. Continued treatment of pregnant women, also in the case of COVID-19 infection, allowed for good obstetric results and, it might have reduced the risk factors of a severe course of COVID-19.

Availability of Data and Materials All data generated in this study are included in the manuscript and are available for presentation upon request.

Declarations

Conflict of Interest The authors declare that there is no conflict of interests regarding the publication of this article.

Ethical Approval This study design was approved by the Institutional Review Board of the Military Institute of Medicine in Warsaw.

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