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COMMENTARY



Assisted reproduction and thromboembolic risk in the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic has significantly increased mortality in many countries, with the number of infected cases increasing exponentially worldwide. One of the main determining factors of the poor prognosis in these patients is the development of coagulopathy. Moreover, it is well known that assisted reproductive technology procedures confer a risk of thromboembolic complications. This commentary analyses specific aspects coexisting between the thrombotic risk described during virus infection and that reported in the context of assisted reproduction treatments. Based on known pathophysiological aspects of virus infection and of ovarian stimulation, there are common elements that deserve to be taken into account. In the present context, any risk of hyperstimulation should be avoided. Gonadotrophin-releasing hormone agonist triggering should be mandatory in high-responder patients and/or those with COVID-19 infection. In both cases, the cycle should be segmented. A proposal is made for the use of prophylactic low molecular weight heparin not only in those cases in which oocyte retrieval has been performed, but also in those in which cancellation has been decided. In addition, endometrial preparation for frozen-thawed embryo transfers should use the transdermal route in order to minimize the higher thrombotic risk associated with the oral route.

INTRODUCTION

From the first case identified in Wuhan (China) in late December 2019 until today, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported to have affected more than 10 million people in 187 countries, resulting in more than 500,000 deaths. The outbreak has been brought to global attention and was declared a pandemic by the World Health Organization on 11 March 2020 (*WHO, 2020*). Mortality occurs mainly from severe lung involvement causing an acute respiratory distress syndrome, although sometimes multi-organ failure occurs, with significant coagulation disorders (*Zhou et al., 2020*).

Due to the large increase in number of reported cases and the impact of the COVID-19 coronavirus on public health, the European Society for Human Reproduction and Embryology (ESHRE) on 19 March 2020 and the American Society for Reproductive Medicine (ASRM) on 30 March 2020 recommended the cessation of any activity related to assisted reproduction. More recently, both societies, ESHRE on 23 April and ASRM on 24 April, have authorized the resumption of healthcare activity with the general safety recommendations established by government authorities in each country (*ESHRE Covid-19 Working group 2020/ASRM/Covid-19 Task force 2020*). These measures

pursue minimizing of contagion and are also based on the fact that infertility is a disease whose prognosis can worsen over time.

Protocols have been established in order to minimize the risk of contagion for both patients and staff. However, few measures have been established regarding ovarian stimulation protocols, triggering and other considerations related to the clinical management of patients. The aim of this review is to analyse a specific coexisting issue, looking at the thrombotic risk described during virus infection and that reported in the context of assisted reproduction treatments.

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THROMBOEMBOLIC RISK IN COVID-19 PATIENTS: CURRENT UNDERSTANDING OF THE PATHOGENESIS

As mentioned above, COVID-19 has a special affinity for the lungs; however, a key factor in the poor prognosis of the infection is the presence of coagulopathy and thromboembolic complications (Connors and Levy, 2020; Tang et al., 2020). The three essential elements of the so-called Virchow's triad for thromboembolic risk occur during virus infection. First, endothelial injury has been related to the virus's affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are present in many organs, including the vascular endothelium (South et al., 2020). Second, a stasis of blood flow is caused by immobilization during the hospitalization of critically ill patients. Third, a state of hypercoagulability occurs as a consequence of the large number of prothrombotic circulating factors that have been reported in patients with severe COVID-19 (Thachil et al., 2020).

Based on the currently available literature it has been suggested that some coagulation markers, such as D-dimers, prothrombin time and platelet count (in decreasing order of importance), are associated with high mortality in COVID-19 patients. In line with this, it has been demonstrated that anticoagulant therapy using heparin has been associated with a decrease in mortality, suggesting positive effects on the endothelial dysfunction and inflammatory state (Thachil, 2020).

Interestingly, high concentrations of D-dimer were able to predict the degree of coagulopathy even in asymptomatic COVID-19 patients. In this context, the International Society on Thrombosis and Haemostasis (ISTH) recommends the use of prophylactic low molecular weight heparin (LMWH) in all patients (including those who are not critically ill) who require hospital admission and those who have comorbidities (Thachil, 2020).

THROMBOEMBOLIC RISK IN ASSISTED REPRODUCTIVE TECHNOLOGY (ART): CURRENT UNDERSTANDING OF THE PATHOGENESIS

It is well known that ART procedures confer a risk of thromboembolic

complications. Most thrombotic complications have been reported in the context of ovarian hyperstimulation syndrome (OHSS), and prophylactic guidelines have been established in this regard that were not considered necessary during ovarian stimulation in the absence of risk factors. Even though the incidence is low in absolute terms, it is similar to the risk of venous thrombosis during pregnancy, which is 10 times higher than the risk in non-pregnant women of reproductive age. Thromboembolic complications can be arterial or venous, with differences in timing and location. Unlike arterial events, which occur preferentially at the start of OHSS, venous events can occur weeks later, even after the OHSS has resolved. On the other hand, while arterial thromboses are predominantly cerebrovascular accidents, venous events are mostly reported in unusual sites such as the upper extremities (Chan, 2009).

In addition, it is worth noting that the risk of venous thromboembolism (VTE) is higher in pregnant women who have had IVF compared with women who have had normal pregnancies. One study demonstrated that the risk is significantly higher in the first trimester of pregnancy after IVF (Rova et al., 2012). In addition, pregnancies complicated by OHSS showed a 100-fold increased risk of VTE, as opposed to the five-fold increased risk seen in the absence of OHSS. Therefore, ovarian stimulation, OHSS and pregnancy exponentially increase the risk of VTE (Grandoni and Villani, 2015).

Despite the fact the causes of the increased thrombotic risk in the context of ART are not well known, it is possible, in line with the scheme described in the previous section, to analyse the different aspects outlined in Virchow's triad.

Endothelial injury

In terms of endothelial injury, a relevant aspect regarding ovarian stimulation and OHSS can be identified. According to the knowledge on haemodynamics and neurohormonal systems during severe OHSS (Balasch et al., 1998), arteriolar vasodilation is a constant finding in patients with severe forms of the syndrome. This produces underfilling of the arterial vascular compartment (i.e. decreased 'effective arterial blood volume') and resulting arterial hypotension that leads to high-pressure baroreceptor-mediated

stimulation of endogenous vasoactive systems (renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone). The simultaneous occurrences of these compensatory mechanisms comprise the so-called 'hyperdynamic circulation' that characterizes conditions associated with oedema formation (Schrier et al., 1990).

In line with this, it has been shown that this haemodynamic alteration occurs universally during ovarian stimulation in IVF cycles, with significant activation of endogenous vasoactive systems in the luteal phase. The degree of activation of these endogenous vasoactive systems is lower than that observed in patients with severe OHSS (Manau et al., 1998). This suggests that the extreme circulatory dysfunction observed during severe OHSS appears to be more attenuated in all women undergoing IVF. In this context it can be speculated that the role of the renin-angiotensin system could be affected by the special affinity of COVID-19 for the ACE2 receptor and thereby give rise to new, unknown clinical scenarios (South et al., 2020).

According to what has previously been mentioned, the hyperdynamic circulation demonstrated in ovarian stimulation and in more intense cases of OHSS has been linked to the tissue factor that is essential for, and now considered to be the primary and most potent activator of, blood system coagulation. It is accepted that circulating monocytes are the cells of the vascular system that can trigger blood coagulation through the tissue factor-dependent pathway (Witkowski et al., 2016). The increase in vascular wall shear stress in conditions of hyperdynamic circulation and the arteriolar vasodilation can induce the formation of interstitial oedema by increasing capillary permeability. Due to the surface area available for filtration and hydrostatic pressure, it is possible that changes in the vessel wall occur during ovarian stimulation and make the blood monocytes more sensitive to tissue factor activity.

Conversely, concentrations of tissue factor pathway inhibitor, which play a relevant role in haemostatic equilibrium, progressively decrease throughout ovarian stimulation, which would explain the hypercoagulable state that occurs during assisted reproduction (Romagnuolo et al., 2014). In line with

this, a prothrombotic state has been demonstrated in women with OHSS, with an increase of markers such thrombin (thrombin–antithrombin complex and prothrombin fragments 1 + 2) and fibrin (D-dimer) (*Balasz et al., 1996*).

Stasis

In terms of stasis, it is evident that hospital admission and immobilization represent an added prothrombotic risk, as occurs in cases of severe OHSS. Furthermore, the haemoconcentration present in most patients has been shown to be a more serious factor in women with OHSS and should therefore be avoided (*Fabregues et al., 1998*). This situation should not occur in the absence of OHSS; however, it would be prudent to take it into account.

Hypercoagulability

The third aspect, related to the pathogenesis of hypercoagulability, is the hypercoagulable state, i.e. the changes in prothrombotic circulatory factors that have been reported during ovarian stimulation and with OHSS. It has been shown that concentrations of plasma fibrinogen increase and those of anti-thrombin decrease, together with decreasing markers of fibrinolytic activity, following ovarian stimulation in IVF (*Westerlund et al., 2012*). The increase in coagulation factors indicates a trend towards a procoagulable state. As noted above, an increase in tissue factor and consequently in D-dimer has been demonstrated in OHSS (*Balasz et al., 1996*). Furthermore, it has recently been reported that ovarian stimulation in IVF cycles, with its boost of endogenous oestrogens, is associated with increased concentrations of procoagulant microparticles. In relation to this, phenotyping of microparticles showed that the increase in concentration of oestrogens was correlated with platelet-derived microparticles, monocyte-derived microparticles and endothelial-derived microparticles (*Olausson et al., 2016*).

In summary, many aspects related to the hypercoagulable state are present during ovarian stimulation, very prominently so in the extreme situation of OHSS.

ADDED RISK IN CURRENT CLINICAL PRACTICE IN ART

Government recommendations in different countries, as well as those from ESHRE and ASRM, clearly minimize the

risks of COVID-19 transmission. However, there are aspects related to ovarian stimulation and the risk of OHSS that should be highlighted. Having ruled out patients with comorbidities who should obviously postpone assisted reproduction treatments, there are still aspects related to clinical management in the field of assisted reproduction that must be observed.

In the present context, any risk of hyperstimulation should be avoided. Gonadotrophin-releasing hormone agonist triggering should be mandatory in high-responder patients and/or those with COVID-19 infection. In both cases, the cycle should be segmented, which minimizes the possibility of OHSS even if it does not totally rule it out.

Based on what is mentioned in this article, we would propose prophylaxis with LMWH not only in those cases in which oocyte recovery has been performed, but also in those in which cancellation has been decided on. COVID-19 infection before oocyte recovery or during the luteal phase would significantly increase the risk in these patients.

The association of ovarian stimulation, OHSS and pregnancy with COVID-19 infection would be potentially serious, so all efforts should be directed towards avoiding this combination of events. Even applying the prophylactic measures mentioned, attention should still be paid to the luteal phase of these women, given that studies have shown that haemodynamic and other aspects related to the hypercoagulability status of these patients would dramatically increase their risk in the situation of COVID-19 infection.

Finally, another interesting aspect to address in the current situation is endometrial preparation for frozen-thawed embryo transfer (FET). Over the last decade, the proportion of FET has substantially increased, so there is a large number of infertile patients in whom endometrial preparation with hormonal therapy replacement (HRT) is performed. In this sense, and based on studies conducted in menopausal women undergoing HRT, there is evidence that the risk of VTE is closely related to the route of administration, with a four times greater threat from the oral versus the transdermal route (*Olie et al.,*

2010). Thus, it is suggested that the transdermal route should be used, since in the current situation in which the number of visits to reproduction centres should be minimized, endometrial preparation in the natural cycle should be avoided. In cases of suspected or confirmed COVID-19 infection after FET, thromboprophylaxis with LMWH should also be given. Furthermore, due to the increased thrombotic risk in case of twin pregnancies, we suggest single-embryo transfer during the pandemic period.

In conclusion, in the current situation of uncertainty and risk, specialists in the reproductive field should maximize prophylactic measures in order to minimize thrombotic risk. Based on previous knowledge about thrombogenic risk in the context of assisted reproduction and recent knowledge on COVID-19 infection, unexpected clinical scenarios could otherwise be encountered.

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