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Risk of thrombosis in women undergoing in vitro fertilization: a narrative review.

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ABSTRACT

Summary:

Infertility is defined as the inability to conceive after more than 12 months of regular, unprotected sexual intercourse.

Thromboembolism is defined as a condition in which a thrombosis in a vein or artery, usually forming in the deep veins of the legs or pelvis, can travel to the pulmonary arteries,
resulting in a pulmonary embolism.

The association between medically assisted reproductive techniques and thromboembolic complications has been widely reported in numerous published studies. Although venous thromboembolism is not thought to be a common complication, it is associated with a high morbidity and is often preventable. As we continue to see an increase in the total number of cycles of medical treatments for reproduction, particularly in women over 40 years of age, coupled with a continued increase in the number of cycles of fertility preservation for both medical and social reasons, we are likely to see an increase in the absolute number of thromboembolic complications.

The aim of this review is to provide information on thromboembolic risk factors, thrombosis risk scoring, and best practice recommendations on risk reduction strategies for at-risk individuals undergoing ovarian stimulation and embryo transfer cycles.

Keywords: Thrombosis risk, ovarian motility, in vitro fertilization

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Introduction

Infertility is defined as the inability to achieve pregnancy after more than 12 months of regular, unprotected sexual intercourse [1]. It is estimated that infertility affects approximately 8–15% of couples of reproductive ages worldwide [2]. Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) with or without pulmonary embolism (PE), is a condition in which a thrombus forms within the venous system, most commonly in the deep veins of the lower extremities or pelvis, and may subsequently embolize to the pulmonary arteries, resulting in pulmonary embolism [3]. Although the incidence of VTE increases with advancing age, it remains an important cause of morbidity and one of the leading causes of maternal mortality among women of reproductive age [4]. Although VTE is considered an uncommon complication of in vitro fertilization (IVF), its true incidence remains uncertain. The estimated prevalence is approximately 0.5%, corresponding to 1.6 cases per 100,000 IVF treatment cycles [5]. Nevertheless, pregnancies achieved through IVF are associated with a significantly higher risk of venous thromboembolism compared with spontaneous conceptions [6]. Routine screening for inherited thrombophilia is not recommended in women undergoing IVF who have no personal or family history of venous thromboembolism [7]. Overall, women receiving IVF treatment have a two- to three-fold greater risk of developing venous thromboembolism than women with spontaneous pregnancies [8]. The most commonly used treatment in assisted reproduction is IVF with either fresh or frozen embryo transfer. Controlled ovarian stimulation, typically achieved with exogenous gonadotropins, results in supraphysiological endogenous estradiol concentrations. In hormone replacement treatment (HRT) cycles for frozen embryo transfer (FET), exogenous estrogens are administered to prepare the endometrium for implantation. The association between IVF and venous thromboembolic complications has been extensively documented, both in women who develop ovarian hyperstimulation syndrome (OHSS) and, importantly, in those who do not [9].

Although arterial thrombosis is an uncommon complication of fertility treatment, it is associated with substantial morbidity and mortality and is frequently preventable [10]. Arterial thrombotic events are rare but may occur as early as 10 days after administration of human chorionic gonadotropin (hCG) for final oocyte maturation [9].

This narrative review summarizes the current evidence regarding the epidemiology, pathophysiology, risk factors, and clinical implications of thromboembolic events associated with IVF. Particular emphasis is placed on thrombosis risk assessment and evidence-based strategies for preventing venous thromboembolism in women undergoing ovarian stimulation and embryo transfer.

Methodology

This narrative review examines the association between in vitro fertilization (IVF) treatment modalities and thrombotic complications. We reviewed relevant studies published in reputable journals, focusing on the epidemiology, pathophysiology, and clinical outcomes of thrombotic events in women undergoing IVF. Particular emphasis was placed on ovarian hyperstimulation syndrome (OHSS) as a key complication associated with an increased risk of both arterial and venous thrombotic events.

Data were extracted from cohort studies, case reports, and review articles. The incidence of thrombotic events among IVF-treated populations was evaluated and analyzed.

Pre-cycle Treatment and the Risk of Thromboembolism

To initiate an in vitro fertilization (IVF) cycle, oral contraceptive pills (OCPs) or progesterone may be used during the preceding menstrual cycle. These medications are administered either before controlled ovarian stimulation or before estrogen administration for endometrial preparation in frozen embryo transfer (FET) cycles. However, no studies have specifically evaluated the short-term risk of venous thromboembolism (VTE) associated with these pre-cycle treatment protocols [10].

The risk of venous thromboembolism among oral contraceptive users is highest during the first three months after initiation of therapy. The thromboembolic risk associated with combined oral contraceptives is dose-dependent, being influenced by the estrogen dose and the type of progestin component.

Ovulation Suppression and the Risk of Thromboembolism

To prevent premature ovulation during controlled ovarian stimulation, medications such as gonadotropin-releasing hormone (GnRH) antagonists or GnRH agonists are commonly used. Currently, no specific data have been identified regarding the risk of venous thromboembolism (VTE) associated with the use of GnRH agonists or antagonists during ovarian stimulation cycles.

Ovarian Stimulation and the Risk of Thromboembolism

The association between ovarian stimulation and thrombus formation was first reported in 1965 in The Lancet among women undergoing ovulation induction therapy. Ovarian stimulation results in supraphysiological endogenous estradiol levels; although these levels do not reach those observed

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during pregnancy, peak estradiol concentrations may exceed 20-fold higher than baseline levels.
The stimulation phase during in vitro fertilization (IVF) treatment appears to exert effects on the coagulation system similar to those observed during pregnancy, oral contraceptive use, and hormone replacement therapy.

Human Chorionic Gonadotropin for Final Oocyte Maturation and the Risk of Thromboembolism

Human chorionic gonadotropin (hCG) is commonly administered to induce final oocyte maturation. This hormone may further enhance the prothrombotic changes that occur during ovarian stimulation. In fact, thromboembolic events are rare before ovulation triggering. Following administration of hCG, increases in fibrinogen levels and changes in the coagulation system with activation of fibrinolytic pathways have been observed. These alterations occur within two days after hCG administration, with peak changes in coagulation factors II, V, VII, VIII, and IX occurring on day 8. These factors may remain elevated until day 10, even in the absence of ovarian hyperstimulation syndrome (OHSS). The duration of these hemostatic changes and their clinical significance in the absence of a subsequent pregnancy remain unknown. No data have been identified regarding the risk of venous thromboembolism associated with the administration of a GnRH agonist bolus used as an alternative trigger for final oocyte maturation to prevent premature ovulation.

Oocyte Retrieval and the Risk of Venous Thromboembolism

Prolonged surgery, reduced mobility, and dehydration are recognized risk factors for thromboembolism. Oocyte retrieval, whether performed through a transvaginal or transabdominal approach, is a short-duration surgical procedure. Patients are placed in the lithotomy or semi-lithotomy position, which itself is associated with a lower risk of thrombosis compared with the supine position [11]. The risk of venous thromboembolism (VTE) can be reduced by using graduated elastic compression stockings (class I, mild compression with a pressure of 14–17 mmHg) or intermittent pneumatic compression devices if the procedure is expected to last more than 30 minutes. Routine use of these preventive measures is not required for patients with a low baseline risk of venous thromboembolism.

Luteal Phase Support in In Vitro Fertilization and the Risk of Venous Thromboembolism

For luteal phase support, medications such as progesterone, dydrogesterone, and less commonly human chorionic gonadotropin (hCG) are used. The prothrombotic changes that have already been initiated by ovarian stimulation and hCG triggering may potentially be further enhanced by these hormones. We did not identify any studies providing evidence regarding an association between luteal phase support medications and the risk of venous thromboembolism (VTE). Recent studies evaluating dydrogesterone have been reassuring [12].

Pregnancies Following In Vitro Fertilization and the Risk of Thromboembolism

Pregnancy is a hypercoagulable state, and in vitro fertilization (IVF) is a recognized additional risk factor for thromboembolic events. A meta-analysis demonstrated that pregnancies following IVF with fresh embryo transfer are associated with a two-fold increased risk of venous thromboembolism (VTE) [2]. The incidence of VTE during the first trimester of pregnancy following IVF cycles with embryo transfer is increased approximately tenfold compared with the background population. However, this increased risk does not appear to persist beyond the first trimester [13]. Multiple pregnancies, regardless of the method of conception, are a well-established risk factor for venous thromboembolism compared with singleton pregnancies [14].

Frozen Embryo Transfer and the Risk of Thromboembolism

Frozen embryos can be transferred during either natural cycles or medicated cycles. In the latter approach, exogenous estrogen is used for endometrial preparation prior to embryo transfer, often following pituitary downregulation. Estradiol valerate and estradiol hemihydrate are commonly used in medicated cycles, with exogenous natural progesterone added for luteal phase support. Data regarding the risk of venous thromboembolism (VTE) following a frozen embryo transfer (FET) cycle are limited and inconsistent. Most evidence regarding estrogen-related thromboembolic risk has been derived from postmenopausal women receiving hormone replacement therapy, demonstrating a dose-dependent increase in relative risk [15]. In this population, oral estradiol appears to be associated with a higher thromboembolic risk compared with transdermal estrogen, possibly due to estradiol metabolites generated through the hepatic first-pass effect. Data regarding thromboembolic risk during frozen embryo transfer cycles remain limited [16].

Duration of the Hypercoagulable State in the Absence of Pregnancy

In the absence of pregnancy following embryo transfer, the duration of the hypercoagulable state after an unsuccessful IVF cycle remains unknown. A Danish cohort study did not demonstrate an increased risk of venous thromboembolism (VTE) following an unsuccessful IVF cycle [17]. The onset of menstrual bleeding after discontinuation of luteal phase support, following confirmation of a negative pregnancy test, marks the end of an unsuccessful IVF cycle. This

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usually indicates that estradiol levels have returned to baseline. However, alterations in the coagulation system have been detected 10 days after the final dose of hCG administered for oocyte maturation, and the duration of persistence of these changes remains unclear [18]. A study among oral contraceptive users demonstrated that fibrinogen levels returned to baseline approximately one month after discontinuation, whereas factor X concentrations required eight weeks to return to baseline levels.

Ovarian Hyperstimulation Syndrome and the Risk of Venous Thromboembolism

Ovarian hyperstimulation syndrome (OHSS) is characterized by ovarian enlargement and the shift of a large volume of fluid from the intravascular space, resulting in ascites, pleural effusion, and hemoconcentration. The association between OHSS and thromboembolic disorders, both in the presence and absence of pregnancy, is well established [17]. This association is multifactorial and involves hemoconcentration, activation of the coagulation cascade, increased thrombin–antithrombin III and plasmin–antiplasmin complexes, and an increase in platelet count. The incidence of thrombosis in patients with OHSS ranges from 0% to 11% [19]. Thrombotic events are predominantly venous (67–75%), although they may involve unusual sites such as the upper extremities and neck veins. Venous thromboembolism (VTE) most commonly occurs during the onset of OHSS; however, the risk may persist for 1–2 months after resolution of hyperstimulation symptoms [20]. It remains unclear whether these "late" venous thrombotic events are primarily related to pregnancy or whether the risk remains elevated even in the absence of pregnancy. Thrombotic markers remain elevated for more than three weeks after the onset of OHSS in pregnant patients, and coagulation abnormalities may persist even after clinical resolution of OHSS. The risk of VTE among women who achieved pregnancy following an IVF cycle and required hospitalization due to OHSS was 1.7% during the first trimester, compared with 0.017% among non-IVF pregnancies, representing an approximately 100-fold increase in risk [13]. Prevention of OHSS is a crucial strategy for reducing thrombotic risk. However, when OHSS occurs, the use of low-molecular-weight heparin (LMWH) is recommended for thromboprophylaxis.

Additional Risk Factors for Thromboembolism

Many underlying medical conditions can increase an individual's risk of developing venous thromboembolism (VTE). Some comorbidities are associated with a high risk of VTE, whereas others confer moderate or lower levels of risk. Risk factors are cumulative and should not be considered in isolation. Underlying medical conditions should be optimized prior to pregnancy planning or fertility preservation procedures to minimize thromboembolic risk.

Assessment of Thromboembolic Risk Factors

Risk factors for thromboembolism can be assessed using the scoring system provided in the following table. Points are assigned according to the presence of specific clinical conditions and risk factors. A score greater than 4 is considered high risk. A score of 3 indicates moderate risk, whereas a score below 3 represents low risk, for which no specific intervention is generally required. Management should be individualized, and treatment decisions should be personalized based on the patient's overall clinical profile. Multiple factors, including baseline risk, type of assisted reproductive treatment, presence of ovarian hyperstimulation syndrome, pregnancy status, and additional medical comorbidities, should be taken into consideration.

Previous Malignancy in the Patient

Oocyte or embryo cryopreservation for fertility preservation is an established option for individuals undergoing medical or surgical treatments that may result in infertility due to premature ovarian failure, as well as for transgender men, typically before initiation of hormone therapy. The estimated incidence of venous thromboembolism (VTE) in patients with cancer is up to 10 times higher than that in the general population [21]. Approximately 20% of cancer patients are at risk of developing deep vein thrombosis; however, this risk varies depending on the type, location, and size of the tumor, as well as the chemotherapeutic agents used. Among cancer patients who choose oocyte or embryo cryopreservation, breast cancer is the most common malignancy. Compared with other malignancies, breast cancer is associated with one of the lowest incidences of VTE [22]. Gastrointestinal malignancies have the highest reported rates of VTE, ranging from 2.7% to 14%. Hematologic malignancies, including leukemia and lymphoma, have reported VTE incidences of 1.8–7.4% and 3.7%, respectively [23]. Chemotherapy can usually be initiated a few days after oocyte retrieval. Therefore, menstruation occurring at the end of a fertility preservation cycle may coincide with chemotherapy-induced thrombocytopenia, depending on the agents used. If thromboprophylaxis is initiated during this period, the risk of heavy menstrual bleeding should be considered.

Oocyte/Embryo Cryopreservation in Patients with Pre-existing Non-malignant Conditions

An increasing number of non-malignant conditions are treated with hematopoietic stem cell transplantation, including sickle cell disease, transfusion-dependent thalassemia, and multiple sclerosis. Recipients of stem cell transplantation undergo gonadotoxic conditioning regimens, including alkylating agents such as

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cyclophosphamide and busulfan, as well as total body irradiation. These treatments are associated with up to an 80% risk of premature ovarian insufficiency (POI) [24]. An increasing number of these patients are undergoing oocyte or embryo cryopreservation prior to receiving conditioning therapies to preserve fertility. Furthermore, oncologists may wish to consider the risk of venous thromboembolism (VTE) when chemotherapy is initiated immediately after an ovarian stimulation cycle, particularly in patients with malignancies or receiving chemotherapeutic agents associated with a higher risk of VTE.

Modifiable Risk Factors

Some risk factors for venous thromboembolism (VTE) are modifiable. All women planning pregnancy should be advised to achieve a normal body mass index (BMI), or to reduce their weight as much as possible toward a normal BMI, and to discontinue smoking. Smoking cessation can often be achieved within a few weeks with appropriate support and intervention. However, for individuals who are overweight or living with obesity, achieving sufficient weight reduction to meaningfully improve the VTE risk profile may require an unacceptably long period of time. This consideration may be particularly important for individuals of advanced reproductive age, in whom significant delays in treatment may negatively affect live birth rates, or for those undergoing fertility preservation procedures, where treatment is often time-sensitive and cannot be postponed.

Adaptation of In Vitro Fertilization Protocols to Reduce the Risk of Thromboembolism

Currently, there are no universally accepted guidelines regarding the optimal in vitro fertilization (IVF) protocol for individuals at increased risk of venous thromboembolism (VTE).

Antagonist Cycle with GnRH Agonist Trigger

The use of a GnRH antagonist protocol with a GnRH agonist trigger may reduce the risk of venous thromboembolism (VTE). Using a GnRH agonist trigger instead of human chorionic gonadotropin (hCG) is an appropriate strategy to reduce the risk of ovarian hyperstimulation syndrome (OHSS), particularly in patients with a high ovarian response [25].

Freeze-All Strategy with Natural Cycle Frozen Embryo Transfer

In individuals at increased risk of ovarian hyperstimulation syndrome (OHSS), the use of a GnRH antagonist protocol followed by a freeze-all strategy and subsequent frozen embryo transfer (FET) can be beneficial.

Mild Stimulation

Mild stimulation refers to protocols designed to promote the development of a limited number of follicles and the retrieval of fewer oocytes compared with conventional ovarian stimulation protocols [26]. This approach is used in young women who are at increased risk of ovarian hyperstimulation syndrome (OHSS). Although there is no universally accepted definition of mild stimulation, it is generally agreed that the dose of gonadotropins used does not exceed 225 IU per day, depending on the patient's ovarian reserve [27].

Modified Natural Cycle

A modified natural cycle refers to oocyte retrieval during a natural menstrual cycle with the addition of agents to delay the premature luteinizing hormone (LH) surge, such as indomethacin [28]. This approach prevents supraphysiological elevations of estradiol levels.

Modified natural cycles may also include the use of human chorionic gonadotropin (hCG) for final oocyte maturation. Typically, only a single oocyte is retrieved, which is associated with a relatively low live birth rate.

Adjunctive Aromatase Inhibitors

Aromatase inhibitors are used in combination with gonadotropins in patients with hormone-sensitive breast cancer undergoing fertility preservation to maintain lower estradiol concentrations [29]. Studies evaluating venous thrombosis in breast cancer patients receiving tamoxifen or aromatase inhibitors have demonstrated that the risk of venous thromboembolism is higher with tamoxifen compared with aromatase inhibitors [30].

Pharmacological Thromboprophylaxis

The use of pharmacological prophylaxis or treatment should involve a careful balance between the benefits of thrombosis prevention and the risk of bleeding at the time of oocyte retrieval. It should also be considered that estradiol levels are continuously rising and reach their peak on the day of oocyte retrieval, and that an hCG trigger may further increase the risk of venous thromboembolism (VTE) in this hyperestrogenic state. Long-acting medications, including aspirin, should be avoided because of the potential increased risk of bleeding during oocyte retrieval. Low-molecular-weight heparin (LMWH) is the anticoagulant of choice for perioperative prophylaxis and treatment in most surgical settings. It is generally administered subcutaneously in most patients unless there is severe renal impairment. LMWH has a relatively short half-life of approximately 3–7 hours. The last dose of enoxaparin should be discontinued 24 hours before oocyte retrieval, and anticoagulation can generally be restarted 6–12 hours (up to 24 hours) after oocyte

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retrieval, depending on the patient's bleeding risk and clinical circumstances.

Management of Patients at High Risk for Venous Thromboembolism

In cases where a risk factor for venous thromboembolism (VTE) is identified, modification of the standard ovarian stimulation or frozen embryo transfer protocol should be considered to a regimen that may be associated with a lower thrombotic risk. For patients with identified VTE risk factors, adequate hydration should be ensured during and/or after oocyte retrieval. If an increased risk of VTE is recognized, single embryo transfer should be recommended to reduce the risk associated with multiple pregnancy. In individuals with a low risk of VTE, pharmacological thromboprophylaxis is not routinely required unless ovarian hyperstimulation syndrome (OHSS) develops. In individuals with a moderate risk of VTE, initiation of low-molecular-weight heparin (LMWH) should be considered 6–12 hours after oocyte retrieval, based on the individual bleeding risk. Initiation should not be delayed beyond 24 hours after the procedure. During frozen embryo transfer (FET) cycles using hormone replacement protocols, LMWH prophylaxis should be initiated from the start of potentially thrombogenic pretreatment or from the initiation of estrogen therapy, whichever occurs first.

Management of Patients at High Risk for Venous Thromboembolism

Before initiating any fertility treatment, referral to an appropriate specialist, such as a cardiologist or other relevant specialist, should be considered. Any patient who is receiving therapeutic-dose low-molecular-weight heparin (LMWH) due to an underlying medical condition should have an individualized management plan developed by a specialist. This plan should include a specific peri-procedural anticoagulation strategy for oocyte retrieval. Modification of the standard IVF protocol to an approach that may be associated with a lower risk of venous thromboembolism (VTE) should be considered. Elimination of progesterone and/or estrogen pretreatment should be considered whenever possible. If discontinuation of such pretreatment is not feasible, LMWH prophylaxis should be initiated concurrently with the start of potentially thrombogenic hormonal therapy. LMWH should be initiated with ovarian stimulation unless it has already been started during pretreatment. To reduce the risk of bleeding during oocyte retrieval, LMWH should be withheld before the procedure. The last dose (according to the patient's bridging plan, such as prophylactic dosing or, when appropriate, half-dose therapeutic anticoagulation) should be administered at least 24 hours before oocyte retrieval. Depending on the bleeding risk assessed by the treating physician, LMWH should be restarted 6–12 hours after the procedure, but no later than 24 hours after oocyte retrieval. The dose should follow the individualized bridging plan. Whenever possible, natural-cycle frozen embryo transfer (FET) should be preferred over hormone replacement cycles. LMWH should be initiated upon confirmation of pregnancy or as soon as possible thereafter. If hormonal therapy is used for frozen embryo transfer cycles, LMWH should be started at the beginning of potentially thrombogenic pretreatment or at the initiation of estrogen therapy, whichever occurs first.

Contraindications and Precautions for the Use of Low-Molecular-Weight Heparin (LMWH)

- Active bleeding or severe thrombocytopenia (platelet count $<50 \times 10^9$/L).
- Uncontrolled severe hypertension (systolic/diastolic blood pressure ≥230/120 mmHg).
- Recent ischemic or hemorrhagic stroke.
- Known bleeding disorder requiring formal hematologic evaluation before initiating anticoagulation.
- Previous heparin-induced thrombocytopenia (HIT) or documented hypersensitivity to LMWH or unfractionated heparin.
- Bleeding during pregnancy or the presence of a subchorionic hematoma (SCH); LMWH should be used with caution, and the risks and benefits should be assessed individually.
- In the absence of pregnancy following an IVF cycle or embryo transfer cycle without OHSS, discontinuation of LMWH may be considered 2–4 weeks after the onset of menstruation, which indicates the end of the cycle.
- After an unsuccessful frozen embryo transfer cycle, discontinuation of LMWH may be considered 2–4 weeks after cessation of all hormonal support.

If OHSS occurs in the absence of embryo transfer or pregnancy, continuation of thromboprophylaxis should be considered for 4 weeks after resolution of symptoms. If pregnancy does not occur after an uncomplicated oocyte or embryo cryopreservation cycle without OHSS, or after a frozen embryo transfer cycle, LMWH prophylaxis can be discontinued with the onset of menstruation, indicating the end of the cycle. If OHSS occurs in the absence of embryo transfer or pregnancy, discontinuation of thromboprophylaxis should be considered either at the onset of menstruation, indicating the end of the cycle, or after resolution of OHSS symptoms—whichever occurs later.

Discussion

Venous thromboembolism (VTE) is a well-recognized complication of in vitro fertilization (IVF). Although relatively uncommon, it is a potentially preventable

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condition associated with significant morbidity and mortality if left untreated. Therefore, patient education aimed at reducing modifiable risk factors is an essential component of IVF care. Ovarian hyperstimulation syndrome (OHSS) remains the most important risk factor for thromboembolic events during assisted reproductive treatment. Women who develop OHSS are at substantially increased risk of both venous and arterial thrombosis. Consequently, current clinical guidelines emphasize thromboprophylaxis, particularly in patients with severe OHSS. At present, there is no universally accepted consensus regarding routine thromboprophylaxis in women undergoing IVF, and the available evidence is insufficient to support universal pharmacologic prophylaxis. Instead, an individualized risk assessment approach is recommended to identify patients who are most likely to benefit from preventive anticoagulation while minimizing unnecessary treatment and bleeding risk. Given the limited high-quality evidence in this field, current recommendations for risk assessment, thromboprophylaxis, and risk-reduction strategies are largely based on observational studies, expert consensus, and extrapolation from thrombosis prevention guidelines in pregnancy and other high-risk populations. Further prospective studies are needed to establish evidence-based protocols for thromboprophylaxis in women undergoing assisted reproductive technologies.

Ethical Issue

This review does not involve ethical considerations.

Conflict of Interests

There was no conflict of interest in this study.

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