Review

Risk of Thrombosis in Women Undergoing In Vitro Fertilization

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Abstract: This review summarizes the available literature on the association between IVF treatments and thrombosis, focusing on epidemiology and pathophysiology. Thrombosis is a rare IVF-related complication, with an incidence of approximately 0.2%, dramatically increased by ovarian hyperstimulation syndrome (OHSS). Arterial thrombosis, primarily associated with OHSS, is a rare and early event, while venous thrombosis, although more common, remains a rare complication of IVF. Venous thrombosis often affects the upper body. The thrombotic risk is higher during the first trimester of pregnancy obtained through IVF. This review discusses the impact of risk factors such as OHSS, thrombophilia, obesity, smoking, advanced maternal age, and polycystic ovarian syndrome, which predispose women to thromboembolic events during and after IVF stimulation.

Keywords: thrombosis risk; ovarian stimulation; IVF

1. Introduction

In 1978, Robert Edwards and Patrick Steptoe announced the birth of the first baby resulting from in vitro fertilization (IVF). Today, over 8 million babies have been born through IVF [1]. In 2019, the European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE) reported 1,487 clinics offering assisted reproductive technologies (ART) in 40 European countries, with a total of 1,077,813 treatment cycles, including 160,782 IVF cycles [2].

Ovarian stimulation is crucial before IVF treatment to time insemination and obtain multiple oocytes [3]. Controlled ovarian stimulation (COS) for IVF involves administering exogenous gonadotropins [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)] along with

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gonadotropin-releasing hormone (GnRH). Ovarian maturation is triggered by administering human chorionic gonadotropin (hCG) [3]. Excessive response to exogenous gonadotropins can be associated with thrombotic events [4,5].

2. Thrombosis in IVF

Today, ART has become a part of routine care in many countries. With it, the number of risk factors for pregnancy-related thrombosis has significantly increased due to the active introduction of new medical technologies that were not used 30 years ago or whose role in the occurrence of thrombosis could not be studied.

2.1. OHSS and Thrombotic Risk

Severe IVF-related complications are rare [6]. However, the increase in IVF treatments has led to more women experiencing complications. The most common and serious complication is ovarian hyperstimulation syndrome (OHSS) [7], characterized by ovarian enlargement, increased vascular permeability, and intravascular dehydration with fluid accumulation in the third space (Figure 1) [8]. Moderate or severe OHSS occurs in 3-8% of successful IVF cycles and significantly increases the risk of both arterial and venous thrombosis [5]. The incidence of venous thrombosis in IVF cycles is reported as 0.1-0.5% [9–11], while arterial thrombosis is even lower [12,13]. OHSS increases thrombotic risk by about 2% in absolute terms [11,14]. This narrative review focuses on the association between IVF treatments and thrombosis, emphasizing epidemiology and pathophysiology.

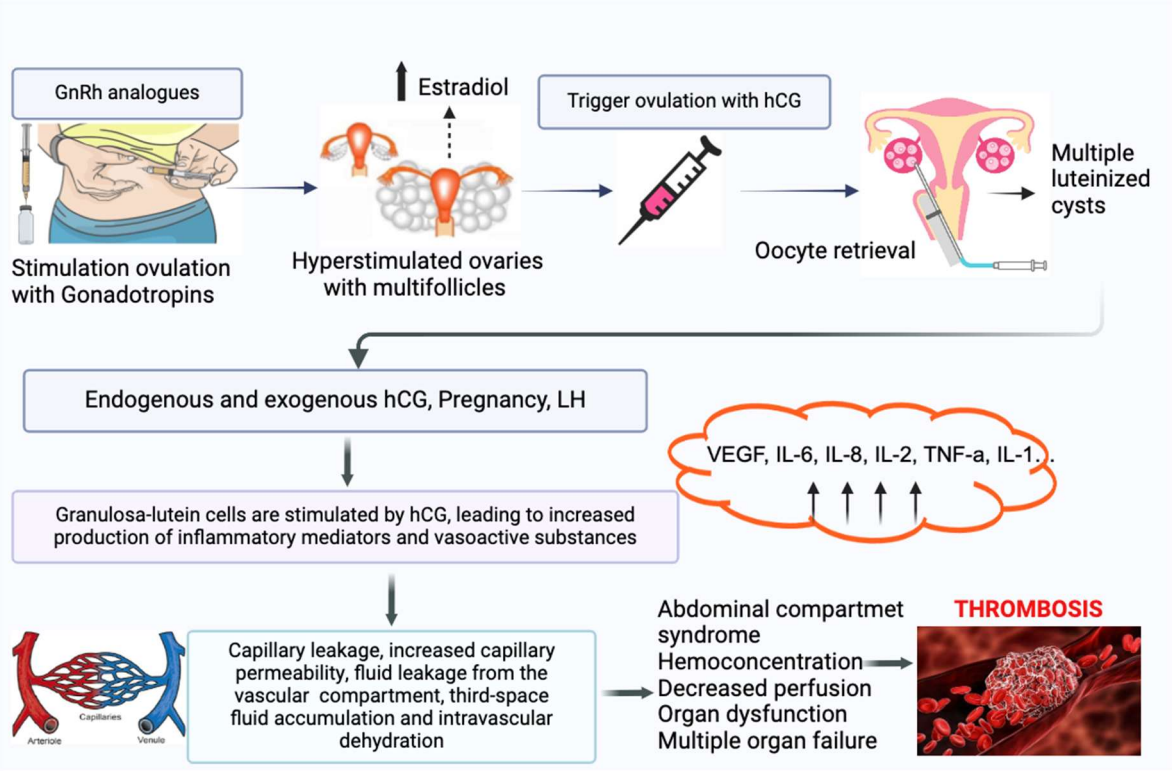

Figure 1. Pathophysiology of OHSS. GnRH – gonadotropin-releasing hormones; hCG – human chorionic gonadotropin; LH – luteinized hormone; VEGF – vascular endothelial growth factor; IL-6 – interleukin-6; IL-8 – interleukin 8; IL-2 – interleukin-2; TNF-a – tumor necrosis factor-alpha; IL-1 – interleukin 1.

2.2. Arterial Thrombosis in IVF Cycles

Arterial thrombotic events (ATE) are rare IVF-associated complications [14–16]. On average, ATE occurs 10 days after the last hCG treatment [15–17] (Table 1). Cohort studies in Denmark, France,

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and Italy have explored the association between ATE and IVF [9,13,18], showing ATE in 1 to 2 ovarian stimulation cycles [9,13,18]. Notably, multiple thromboses can occur in the same cycle; for instance, simultaneous arterial radial and mesenteric vein thromboses were reported in one woman with mild OHSS during her fifth cycle [9]. Several case reports have linked ATE with OHSS [15,17], and Chan WS reported that 95% of ATE occurred with OHSS [19]. However, the relationship between ATE and OHSS has not been explored well. A French cohort study of 2,490 OHSS cases found a 3% prevalence of ATE (n=78) [18], while a Danish cohort study of 30,884 women undergoing 75,141 treatments found no correlation between OHSS and ATE [13]. Women with severe OHSS in this Danish study were treated with low-molecular-weight heparins (LMWH) to reduce VTE risk [13]. Prophylaxis could have impacted both VTE and ATE risks.

Population-based studies suggest that the incidence of arterial thrombosis is not significantly higher in women undergoing ART compared to the general population [13]. Hansen et al. studied 75,141 cycles and observed a 6-month incidence rate of 0.8, which is not significantly different from that in a reference population of young Danish women [reference: 2.5; IRR=0.36, 95% CI: 0.04-1.30] [13].

2.3. Venous Thrombosis in IVF Cycles

Venous thromboembolism (VTE), defined as deep vein thrombosis with or without pulmonary embolism, is more frequently reported than arterial thrombosis (Table 1) but remains a rare IVF-related complication. The estimated prevalence is 0.5%, corresponding to 1.6 per 100,000 cycles/woman [9]. VTE often occurs 26.6 days after hCG administration for ovulation induction cycles (Table 1) [16]. A prospective French cohort study showed a higher risk of VTE in both unsuccessful and successful fertility treatment cycles [18]. VTE was observed in 75 out of 705,186 unsuccessful cycles and 207 out of 82,821 successful cycles. Conventional ovarian stimulation, but not clomiphene citrate-induced ovarian induction, was associated with an age-adjusted IRR of 1.74, 95% CI: 1.30–2.34 [18]. However, discrepancies exist regarding the significant VTE risk associated with IVF cycles [13]. An Italian cohort study reported VTE events in 2/1518 (1.3‰) unsuccessful cycles compared to 3/318 (9.4‰) successful cycles (Two-tailed Fisher exact test, p = 0.04, OR 0.14, 95% CI: 0.02-1.02) [20]. Conversely, Hansen et al. found no increased VTE risk in 30,884 Danish women within 6 and 12 months after ART (IRR: 0.95, 95% CI: 0.38-1.95 and IRR: 1.27, 95% CI: 0.69-2.12, respectively) [13].

2.4. Anatomical Localization

Many studies report that stroke is the most frequent arterial thrombotic event [17] (Table 1), with an unfavorable prognosis, especially in women developing stroke following OHSS-induced hormonal treatment [21–24]. VTE has been reported at unusual sites (Table 1), such as the upper limbs, neck [14,16,25–27], and cerebral veins [28–31]. Isolated pulmonary embolism is more frequently associated with IVF than other conditions [10,18,20,31–34]. The reason for the prevalence of thrombosis in unusual sites is not known. It has been hypothesized that hemostatic changes during controlled ovarian stimulation increase peritoneal fluid, drained through the thoracic duct into the subclavian veins [35], leading to a local environment with an increased VTE risk in the upper body [36]. hCG, previously used for final oocyte maturation and ovulation, contributes to hemostatic modifications by decreasing anticoagulants like protein C, protein S, and antithrombin and increasing endothelial markers of vascular damage such as thrombomodulin [37].

Branchial cysts near the jugular or subclavian veins may also increase VTE risk, particularly during OHSS when these cysts are fluid-filled and impair blood circulation [27].

Table 1. Available data on incidence, anatomical localization and timing of arterial and venous thrombotic events.

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	f		y design	F population (n)	les (n)	(n)	nce AT per cycle (n)	E localization	g of ATE (mean days after hCG)	(n)	ence VTE per cycle (n)	localization	g of VTE (mean days after hCG)
1993	[30]	Delvigne A	Case-control	384	na	0	0%	na	na	1	0,01%	brain	na
1995	[29]	Kodama H	Case-series	23	1316	0	0%	na	na	1	0,08%	brain	11
1998	[34]	Abramov Y	Case-control	163	163	0	0%	na	na	4	2,50%	lung	na
1998	[14]	Serour GI	Case-control	2924	3500	2	0,05%	brain	na	4	0,12%	upper extremit	na
1998	[28]	Aboulghar MA	Case reports	2	2	0	0%	na	na	2	100%	brain	5
2002	[31]	Dulitzky M	Cohort	61	na	1	na	brain	na	2	na	lung	na
2004	[9]	Grandone E	Case-control	305	747	3	0,40%	brain, upper extremity	na	2	0,30%	brain; gu	na
2006	[44]	Yinon Y	Cohort	24	73	0	0%	na	na	0	0%	na	na
2006	[25]	Chan WS	Review case series	37	2500	0	0%	na	na	37	1,48%	upper extremit; neck	28
2007	[15]	Girolami A	Review case series	34	na	34	na	brain, neck,	13,7	0	0%	na	na

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								heart, extremities					
2009	[27]	Salomon O	Case-series	5	na	0	0%	na	na	5	na	upper extremity; neck	16
2009	[16]	Chan WS	Review case series	96	na	35	na	brain, neck, heart, extremities	10.7	61	na	upper extremity; neck	26.6
2011	[38]	Ricci G	Cohort	480	1105	0	0%	na	na	0	0%	na	na
2012	[11]	Rova K	Cohort	1919 4	na	0	0%	na	na	32	na	na	45
2012	[13]	Hansen AT	Cohort	30884	75141	2	0,003%	na	na	7	0,009 %	na	na
2012	[26]	Fleming T	Case-series	2	2	0	0%	na	na	2	100%	neck	39.5
2013	[10]	Henriksson P	Cohort	23498	na	0	0%	na	na	99	na	lung; other not specified sites	na
2014	[40]	Hansen AT	Cohort	18787	na	0	0%	na	na	36	na	lung; other not specified sites	na

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2015	[41]	Villani M	Cohort	234	684	0	0%	na	na	6	0,88%	lung; lower extremit	na
2017	[17]	Yang S	Case-series	38	na	29	na	brain, neck	8	9	na	brain	8.33
2018	[20]	Villani M	Cohort	661	1836	0	0%	na	na	5	0,27%	lung; lower extremit	na
2018	[32]	Grandone E	Cohort	41	ns	0	0%	na	na	41	na	lung; lower and upper extremit	na
2019	[18]	Filipovic-Pierrucci A	Cohort	27791 3	788007	78	0,01%	na	na	282	0,04%	lung; lower extremit	na
2020	[33]	Olausson N	Cohort	30328	na	0	0%	na	na	161	na	lower extremit, gut	na

IVF: In Vitro Fertilization. ATE: Arterial Thrombosis. VTE: Venous Thromboembolism. hCG: human Chorionic Gonadotropins. na: not available.

2.5. Thrombophilia

Case reports and series suggest that IVF, especially with OHSS, creates a hypercoagulable state, triggering thrombosis [16,32]. Individual VTE risk can increase with inherited or acquired thrombophilia, as shown by Dulitzky et al., who reported an 85% prevalence of thrombophilia in women with severe OHSS, indicating a role for thrombophilia in VTE post-OHSS [31]. However, a prospective observational study did not confirm severe OHSS cases among carriers of common inherited thrombophilia (factor V Leiden and prothrombin gene G20210A mutation) [38]. Similarly, Grandone et al. did not find a role for inherited thrombophilia in IVF-associated thrombosis [9,32,39] in low-risk women. An observational study of 305 women undergoing ovarian stimulation found that increased homocysteine levels were significantly associated with VTE (OR: 15.2, 95% CI: 2.0-115.0) but not other thrombophilia [9]. Data from the RIETE registry comparing IVF-related VTE to other VTEs in childbearing-aged women also did not show an increased VTE risk in those with thrombophilia [32].

2.6. Other Maternal Risk Factors

Maternal age can affect ATE and VTE risk. Age above 35 years significantly increases the risk of ATE and VTE in women undergoing IVF [9,11]. A large population-based study showed a two-fold higher VTE risk in women aged 40 years (OR: 2.1; 95% CI: 1.3-3.7) compared to younger women [11].

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However, a Danish cohort study did not confirm this [40]. Hansen et al. found maternal age did not affect VTE risk during pregnancy, although VTE risk was highest in women over 35 during the postpartum period (RR: 2.4, 95% CI: 0.8-7.7) [40]. A Body Mass Index (BMI) >30 kg/m2 also increases individual VTE risk, with ORs ranging from 1.23 (95% CI: 1.01-1.49) to 3.2 (95% CI: 2.2-4.6) [9,11]. It is speculated that estrogen levels in obese women may increase coagulation factors, raising thrombosis risk [10]. There are no systematic data on the impact of smoking on VTE and ATE risk during and after IVF.

2.6. Risk of VTE in Pregnancy after IVF

Robust data indicate that VTE risk in pregnancies following IVF is significantly higher than in natural conceptions [10,40,41]. Many risk factors predispose women to thromboembolic events during pregnancies following successful IVF (Figure 2). Thrombophilia, obesity, smoking, advanced maternal age, and immobilization are known VTE pregnancy-associated risk factors [25,42]. IVF procedures increase this risk three- to four-fold compared to natural conception [40,41,43]. Women with polycystic ovarian syndrome (PCOS) seem particularly prone to thrombotic complications during IVF pregnancies [40,43]. A Danish cohort study found a five-fold increased VTE risk in women with PCOS [40]. OHSS remains the main factor associated with VTE, with a 100-fold increased risk in pregnancies following successful stimulation [10,11,16,40,41]. The risk persists from one-week post-embryo transfer until the end of the first trimester and can last several weeks after OHSS resolution [16,44]. Thus, guidelines recommend LMWH prophylaxis for three months post-OHSS resolution in women with severe OHSS (ACCP guideline) [45,46]. Estradiol increase during IVF has been associated with fibrinolysis downregulation, leading to higher thrombotic risk [47,48]. Increased estradiol levels correlate with increased factor VIII, von Willebrand factor antigen and activity, and decreased ADAMTS13 antigen and activity, further raising thrombotic risk [49]. Pregnancy with a frozen-thawed embryo, not preceded by ovulation induction and estrogen increase, seems to have no different VTE risk than natural conception. A Swedish study found no increased VTE risk with frozen-thawed embryo transfer [11]. A recent cohort study in Sweden showed that frozen-thawed embryo transfer reduces first-trimester VTE risk [33]. The study indicated that VTE incidence after fresh embryo transfer was more than eight-fold higher than in natural conception but did not increase with frozen-thawed embryo transfer [33]. This suggests that frozen-thawed embryo transfer could reduce maternal VTE risk post-IVF.

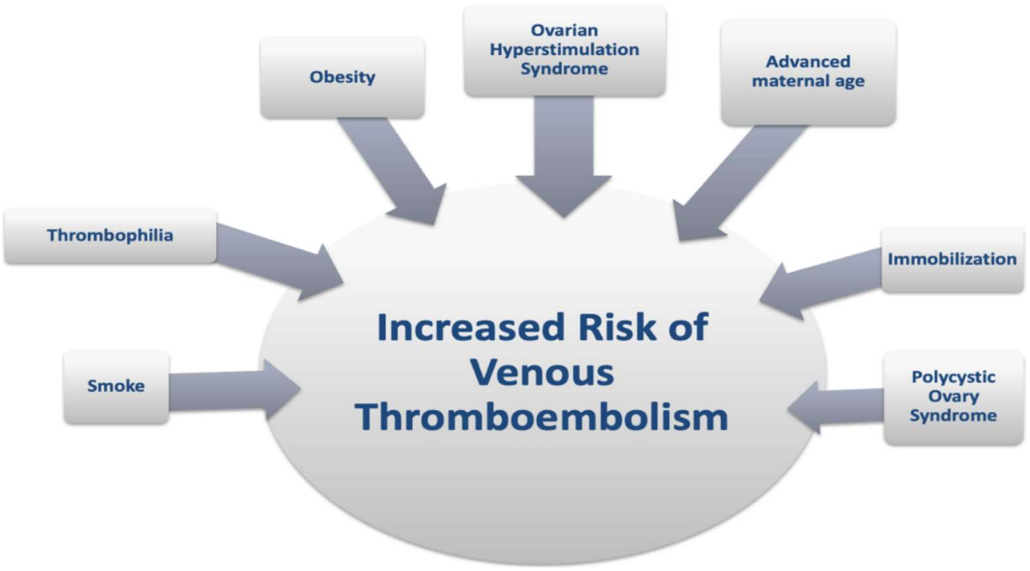

Figure 2. Risk factors predisposing to thromboembolic events during In Vitro Fertilization.

4. Conclusions

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Thromboembolism is a rare IVF complication, with arterial events being less frequent than VTE. OHSS is the main thromboembolism risk factor, warranting current guidelines' recommendations for thromboprophylaxis. More data are needed on the impact of thrombophilia, especially in women with multiple VTE risk factors. Frozen-thawed embryo transfer may reduce thromboembolic risk, but further research is necessary.

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