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AOGS SYSTEMATIC REVIEW

Thromboembolism and in vitro fertilization – a systematic review

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Key words
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Abstract

Introduction. There is no accepted consensus on thromboprophylaxis in relation to in vitro fertilization (IVF). We aimed to study the frequency of thromboembolism and to assess thromboprophylaxis in relation to IVF. *Material and methods.* We performed a systematic review. All study designs were accepted except single case reports. Language of included articles was restricted to English. *Results.* Of 338 articles, 21 relevant articles (nine cohort studies, six case–control studies, three case series, and three reviews of case series) were identified. The antepartum risk of venous thromboembolism (VTE) after IVF is doubled (odds ratio 2.18, 95% CI 1.63–2.92), compared with the background pregnant population. This is due to a 5- to 10-fold increased risk during the first trimester in IVF pregnancies, in turn related to a very high risk of VTE after ovarian hyperstimulation syndrome (OHSS), i.e. up to a 100-fold increase, or an absolute risk of 1.7%. The interval from embryo transfer to VTE was 3–112 days and the interval from embryo transfer to arterial thromboembolism was 3–28 days. No robust study on thromboprophylaxis was found. *Conclusions.* The antepartum risk of VTE after IVF is doubled, compared with the background pregnant population, and is in turn related to a very high risk of VTE after OHSS in the first trimester. We recommend that IVF patients with OHSS be prescribed low-molecular-weight heparin during the first trimester, whereas other IVF patients should be given thromboprophylaxis based on the same risk factors as other pregnant women.

Abbreviations: ART, assisted reproductive techniques; ATE, arterial thromboembolism; ET, embryo transfer; IVF, in vitro fertilization; LMWH, low-molecular-weight heparin; OHSS, ovarian hyperstimulation syndrome; TE, thromboembolism; VTE, venous thromboembolism.

Introduction

Infertility affects 10–15% of couples trying to conceive. In 1978, Robert Edwards announced the birth of the first test tube baby (1). In vitro fertilization (IVF) has been rapidly growing as the treatment of choice all around the world. Today, approximately 5 million babies are born

Key Message

There is a very high risk of thromboembolism in in vitro fertilization complicated by ovarian hyperstimulation syndrome. Thromboprophylaxis is warranted in the first trimester when ovarian hyperstimulation syndrome occurs.

after IVF. Sweden contributes to this number with around 19 000 IVF treatments per year, resulting in 3000 deliveries, corresponding to 3% of all neonates (2). Postponed childbearing, new medical treatment options for serious illness and a growing demand for fertility preservation in women with malignant disease contribute to a steady increase in the demand for assisted reproductive techniques (ART). Safety aspects of treatment are central and preconception risk assessments include obstetric considerations, for example in the case of older women who wish to conceive by egg donation. Cross-border reproductive travelers seek treatment options not available or allowed in their own countries, and ART-related complications and complicated pregnancies are thus brought home.

Severe complications in IVF are rare but the increasing number of treatments will increase the absolute number of women affected. Ovarian hyperstimulation syndrome (OHSS) is the most common and serious of these complications (3,4). In its severe forms, it is associated with an increase in the risk of thromboembolism (TE), which may be fatal. Data on the incidence of venous thromboembolism (VTE) and arterial thromboembolism (ATE) related to OHSS are limited, and are dominated by case reports in the literature.

IVF is reported to double the risk of TE in pregnancy, but the absolute risk is presumed to be low (5). The literature provides scarce data concerning the true incidence of TE and IVF and there is no generally accepted consensus on thromboprophylaxis in relation to IVF.

The aim of this systematic review was to create a basis for a Swedish guideline on thromboprophylaxis in women undergoing IVF. Primary outcome was the frequency of TE including venous and arterial complications after IVF with or without OHSS. Secondary outcomes were timing of TE onset related to IVF and reported regimes of thromboprophylaxis.

Material and methods

The Swedish Society of Obstetrics and Gynecology (SFOG) asked Hem-ARG, a working and reference group for hemostatic disorders in obstetrics and gynecology, to create an evidence-based guideline for thromboprophylaxis related to IVF. The literature was searched for relevant articles on IVF and TE. The following electronic databases were searched: MEDLINE, PubMed, Clinical Queries PubMed, and Wiley Interscience Cochrane Library.

The search lines were established with professional help from a librarian at the Karolinska University Hospital. A MEDLINE search was performed with the following MeSH-terms:(((((((Reproductive Techniques, Assisted)) OR (ivf)) OR (egg donation))) AND (((thrombo prophylaxis)) OR ("Thrombosis"[Mesh] OR thrombos* OR dvt OR vte)))) OR ((((((Reproductive Techniques, Assisted)) OR (ivf)) OR (egg donation))) AND (((thrombophilia)) OR (coagulation disorder))). The search covered the period 1 January 1966 to 31 December 2016. Additional searches were made in Clinical Queries PubMed with the search term "fertilization in vitro AND thrombosis," as well as in the Cochrane Database of Systemic Reviews and in the Cochrane Central Register of Controlled Trials with the search terms "fertilization in vitro" and "thromboembolism."

All study designs were accepted except single case reports. Review articles of case series were included to avoid missing studies. Cross-references were read and additional articles were found and included. The language of included papers was restricted to English.

Exclusion criteria were: animal studies, biochemical studies, articles not addressing the subject, articles without patient data, and reviews consisting of already included articles.

A first selection was made by three of the authors (R.H., E.N., M.S.), who all undertook an overview of all titles and abstracts and selected the articles identified as relevant for this systematic overview. All articles were then read, tabulated and evaluated (Table 1). Only studies with valid control group were used for calculations of frequency of TE and the risk of VTE during the first trimester. Meta-analysis was done with REVIEW MANAGER 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

A total of 338 articles were identified. After the first selection, 60 articles (17 reviews and 43 others) were considered relevant for further exploration, and were carefully studied by the group. A total of 19 articles from database searches were eligible. Two articles, relevant for the subject, were found in cross-references after the initial search and a total of 21 articles were thus finally included in this systematic review (Figure 1) (6,7). We considered the overlap between reviews of case-series when results were presented, in order not to present data more than once. Details of included studies are presented in Table 1.

Risk of TE in relation to IVF

The frequency of TE during pregnancy in patients after IVF, with or without OHSS varies between 0.8 and 25/1000, compared with 0.17–2.5/1000 in the background pregnant population (Table 1) (5,6,8–14). The study by Dulitzky et al. (15) and Ricci et al. (16) included only

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Table 1. Studies included, incidence and type of thromboembolism.

Year	Ref	Author	Study design	Aim	Population (*n*)	OHSS (*n*)	Cycles (*n*)	Control population (*n*)	Incidence TE pc/ppreg (*n*)	Thromboembolic events (*n*)
1993	22	Delvigne A	Case-con	Prediction of OHSS	128	128/118 sev	na	256	na	VTE 1/128 (1 UBVTE)
1995	8	Kodama H	Case ser	Hemostasis in OHSS	23	23	1316	None	0.08%*	1 UBATE
1998	9	Abramov Y	Case-con	Severe OHSS	163	163	163	None	2.5%*	4 VTE (4 PE)
1998	6	Serour GI	Case-con	IVF	2924	222	3500	None	0.17%*	6 TE (4 VTE + 2 ATE)
1998	19	Aboulghar MA	Case- con	OHSS with CVT	2	2	na	None	na	2 ATE
2002	15	Dulitzky M	Cohort	Thrombophilia in OHSS	20	20	na	41	na	3 VTE (2 PE and 1UBVTE) 17/20 thorombophilia
2004	10	Grandone E	Case-con	Prevalence TE	305	na	747	None	0.5%*	3 TE (1 ATE + 2 [ATE + VTE])
2006	7	Yinon Y	Cohort	Thromboprophylaxis	24	na	74	None	0	0 VTE 0 ATE
2006	12	Chan WS	R-case ser	UBVTE in IVF	2	na	2500	None	0.08%*	2 VTE + 32 cases reviewed
2007	20	Girolami A	R-case ser	Risk of ATE	34	na	na	None	na	34 ATE (19 UBATE)
2008	21	Jacobsen AF	Case-con	Assessment of risk factors for VTE	ap = 268 pp = 291	na	na	1229	na	ap 20/268 vs. 23/1229 OR = 4.3 pp 8/291 vs. 23/1229 OR = 2.6
2009	24	Salomon O	Case ser	Explain UBVTE	5	na	na	None	na	5 UBVTE
2009	17	Chan WS	R-case ser	Risk of ATE and VTE	96	79	na	None	na	35 ATE (90% OHSS), 61 VTE (78% OHSS)
2011	16	Ricci G	Cohort	Thrombophilia in OHSS	480	na	1105	490	0*	0 VTE 0 ATE
2011	26	Gbaguidi X	Cohort	Risk for UBVTE	1948	na	na	None	na	5 OHSS (17.2%) UBVTE
2012	5	Rova K	Cohort	VTE in IVF (giving birth)	19 194 IVF	1291	na	935 338 0.017%	0.17% 1st trim 1.7% OHSS 1st trim**	VTE 32/19194 IVF OR = 9.8 VTE/1113 OHSS OR = 100
2012	18	Hansen AT	Cohort	VTE in IVF(not pregnant)	30 884	na	75 141	None†	0.009% VTE 0.003% ATE*	7 VTE, 2 ATE
2012	23	Fleming T	Case ser	UBVTE with OHSS	2	na	na	None	na	2 VTE OHSS
2013	13	Henriksson P	Cohort	VTE (giving birth)	23 498 IVF	na	na	116 960	0.42% 0.25% control**	99 VTE, control 291 VTE 1st trim 0.15%, 0.03% control
2014	14	Hansen AT	Cohort	VTE in IVF (giving birth)	16 191 women 18 787 preg	549	na	None†	0.29%**	36 VTE, ap 0.29% HR = 3.0, 12 VTE pp 0.28% HR = 1.2 1st trim HR 5,9, 2nd trim HR 2.4
2015	11	Villani M	Cohort	Incidence of VTE in IVF (giving birth)	234	10	684	3339 0.18%	0.85% VTE** 0% OHSS	2 VTE case, 6 VTE control

ap, antepartum; ATE, arterial thromboembolism; Case-con, case–control; Case ser, case series; HR, hazard ratio; na, not applicable; OHSS, ovarian hyperstimulation syndrome; OR, Odds ratio; pc, per cycle (marked *); PE, pulmonary embolism; pp, postpartum; ppreg, per pregancy (marked **); preg, pregnancies; R-case ser, review case series; ref, reference number; sev, severe; trim, trimester; UBATE, upper body ATE; UBVTE, upper body VTE; VTE, venous thromboembolism.

†Assumption of prevalence in background population of the authors.

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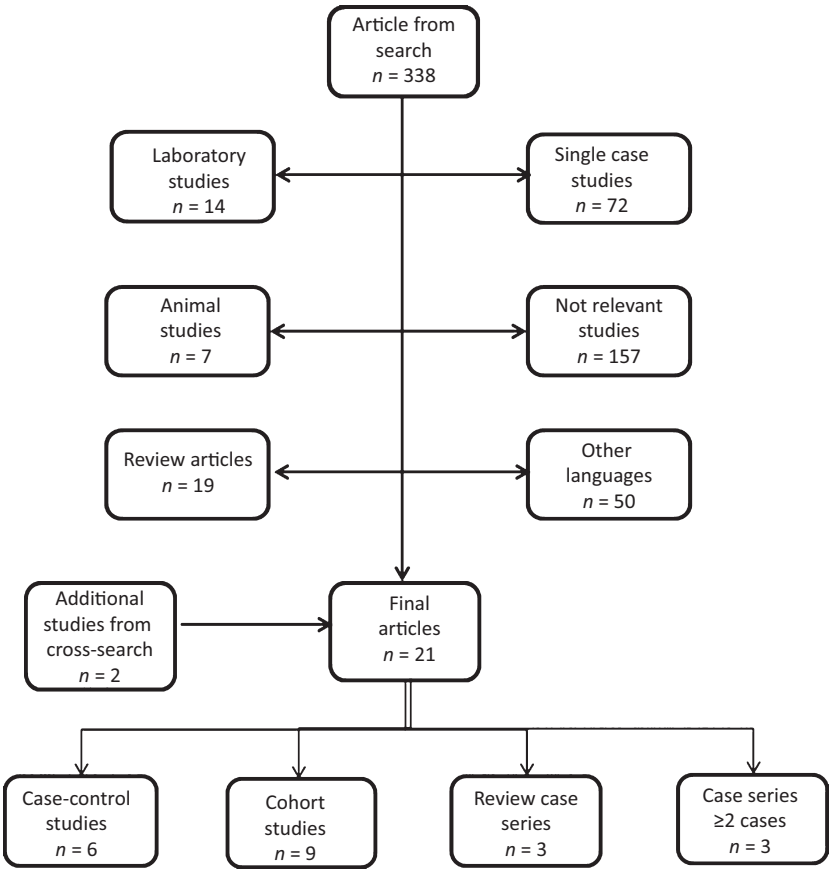

Figure 1. Flow chart of articles identified in searches.

women with thrombophilia and were therefore not included in these figures. In studies assessing the risk of antepartum VTE, the reported risk was approximately doubled, odds ratio (OR) 2.2 (95% CI 1.6–2.9) (Figure 2) (5,11,13,14,17) and the reported risk of first-trimester VTE was increased 5- to 10-fold (OR 6.4, 95% CI 4.0–10.1) (Figure 3) (5,13,14). The risk of VTE after IVF failing to lead to conception was not increased compared with a reference population (18). ATE was rare and a high propensity for ATE in relation to OHSS was reported (Table 1) (6,10,12,17,19,20). Data regarding postpartum VTE were diverse (13,14,21).

Risk of TE in relation to IVF complicated by OHSS

Ten articles concerning TE in connection with OHSS presented TE results as either the primary or secondary outcome (Tables 1 and 2) (5,6,8,9,11,14,15,17,19,22). In the study by Rova et al., the subgroup of women conceiving after fresh IVF and hospitalized due to OHSS had a 1.7% risk of VTE in the first trimester, compared with a 0.017% risk in the background non-IVF population, a 100-fold increase (5). The corresponding result published by Hansen et al. was a 14-fold increased risk, after exclusion of high-risk cases (14). Hansen et al. also reported that women with polycystic ovary syndrome (PCOS), the major risk factor for OHSS, had a similarly increased risk (14).

Timing of TE in relation to IVF

The reported interval from embryo transfer (ET) to VTE was 3–112 days (5,11,12,17,23,24). In the review by Chan (12), this interval from ET to VTE was shorter (mean 18 days, range 3–49 days) in the group contracting OHSS than in the group without OHSS (mean 57 days, range 14–105 days) (Table 2). The reported interval from ET to ATE was between 3 and 28 days (8,17,19,20).

Thromboprophylaxis

Thromboprophylaxis was reported on in three studies, but only one study including 24 women had this as the primary aim (Table 3) (7,11,23). The two case series by Chan (12,17) are not included since the treatments varies to a large extent within the report. Low-molecular-weight

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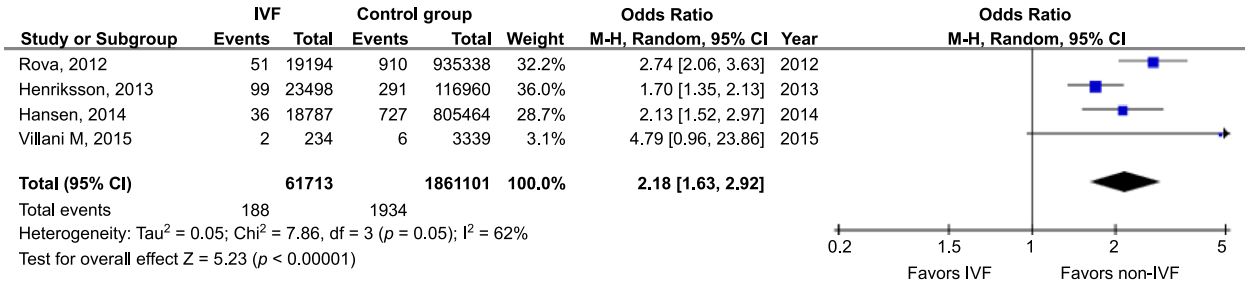

Figure 2. Meta-analysis of frequency of antepartum VTE in IVF pregnancies. [Color figure can be viewed at wileyonlinelibrary.com].

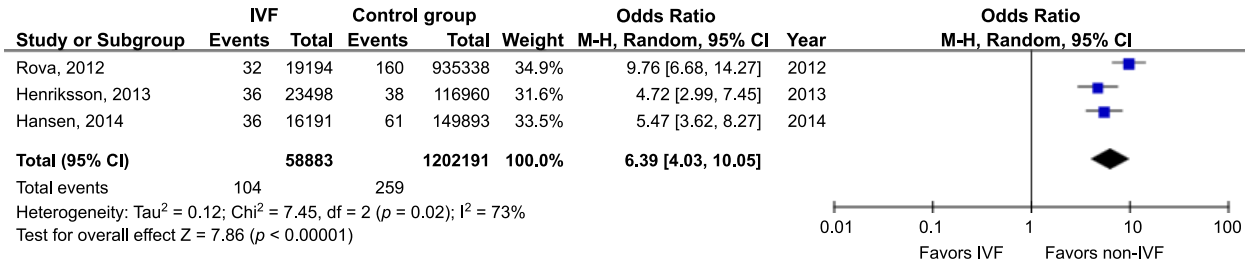

Figure 3. Meta-analysis of risk of first trimester VTE in IVF pregnancies. [Color figure can be viewed at wileyonlinelibrary.com].

Table 2. Time from embryo transfer (ET) to thromboembolism.

			Venous thromboembolism (VTE)			Arterial thromboembolism (ATE)		
Year (ref)	Author	Study design	*n*	Days after ET	OHSS *n*/total *n*	*n*	Days after ET	OHSS *n*/total *n*
1995 (8)	Kodama H	Case ser	0	na	na	1	11	1/1
1998 (19)	Aboulghar MA	Case ser	0	0	0	2	7 and 9	2/2
2006 (12)	Chan WS	R-case ser	10	Mean 57 (14–105)	0	0	na	na
			24	Mean 24 (3–49) OHSS	24	0	na	na
2007 (20)	Girolami A	R-case ser	0	na	na	10	Mean 9 (3–28)	na
2009 (24)	Salomon O	Case ser	5	49–63	5/5	0	na	na
2009 (17)	Chan WS	R-case ser	61†	Mean 42	47/60	35	Mean 11	27/31
2012 (5)	Rova K	Cohort	32	Mean 60 (OHSS)/mean 68 (no OHSS)	19/32	na	na	na
2012 (23)	Fleming T	Case ser	2	8 and 35	2/2	0	na	na
2015 (11)	Villani M	Case-con	1*	112	0	0	na	na

case ser, case series; ET, embryo transfer; na, not applicable; R-case ser, review case series; ref, reference number.
OHSS *n*/total *n* = number of OHSS related VTE/IVF as compared with total number VTE/IVF.
*One pulmonary embolism, time of PE not reported.
†2 VTE in the same patient.

heparin (LMWH) with or without aspirin was administered in all reported studies, but mostly the type and dose were not stated. Despite administered prophylaxis, the number of TE cases was higher than expected in a normal pregnant population. There were no robust investigations regarding bleeding complications, efficacy or osteoporosis in relation to thromboprophylaxis and IVF. Allergic reactions were reported in about 2% of patients (25).

Discussion

We conclude that the antepartum risk of VTE after IVF is approximately doubled, mainly due to a 5- to 10-fold increased risk during the first trimester, in turn primarily due to a very high risk in the subgroup complicated by OHSS (5,14). Thrombosis connected to IVF has been shown to have a propensity to occur in the upper

Table 3. Thromboprophylaxis and in vitro fertilization.

Year	Author	Study design	Prophylaxis (*n*)	VTE (*n*)	ATE (*n*)	TE (*n*)	Type of prophylaxis	Start-duration
2006	Yinon Y	Cohort	24	0	0	0 TE	LMWH* (*n* = 19) LMWH* + ASA (*n* = 5)	OI – 6–12 weeks pp
2012	Fleming T	Case ser	2	2	0	2 UBVTE	LMWH	(1) 8 days after ET, (2) Before OI
2015	Villani M	Case-con	23 (3 OHSS)	0	0	0 TE	LMWH or LMWH + ASA[†]	na[‡]

case-con, case–control; case ser, case series; LMWH, low-molecular-weight heparin; na, not appliccable; OHSS, ovarian hyperstimulation syndrome; OI, ovarian induction; pp, postpartum; TE, thrombotic event; UBVTE, upper body VTE.
*LMWH 0.6–1 mg/kg.
[†]LMWH + ASA doses not specified.
[‡]Unknown start of thromboprophylaxis.

extremities (8,12,15,20,22,24,26). A suggested explanation for the increased risk of upper-extremity TE is the result of inflammatory peritoneal fluid draining through the thoracic ducts (27). ATE was reported more often in subgroups of patients with OHSS, but as most reports are case studies, the degree of the upper-body propensity and the strength of the relation between ATE and OHSS are as yet unknown. Thus, large studies are needed.

Biological explanations for the increased incidence of TE associated with IVF may comprise normal physiological changes in pregnancy, resulting in a hypercoagulable state with increased risk of VTE (28–30). Increased estrogen levels may impact the state of hypercoagulability (31). Studies during ovarian stimulation, before and after ovulation induction, show activated coagulation (32–34). Patients developing OHSS were found to have increased levels of hemostatic markers compared with those who did not contract OHSS, as well as in comparison with a control group of healthy women (35).

Most studies are small and many of them have not reported confounders in the control group. There is a risk of bias concerning age of women, body mass index, and obstetric complications. Another weakness of this review is the risk for selection bias due to the inclusion of case series (8,12,17,20,23,24). However, we only included larger studies in meta-analysis in order to compare robust data. Furthermore, case series may increase the risk for publication bias (12,17,20,23,24,36). Regarding postpartum VTE, a Norwegian hospital-based, case–control study found a fourfold increased risk for VTE antepartum in pregnancies after IVF (OR 3.8, 95% CI 1.8–8), but the postpartum TE risk was not increased (21). The results of two Swedish studies (5,13) were contradictory; however, the one reporting increased postpartum risk had included cases long before the modern thromboprophylaxis algorithm was implemented in Sweden (37).

The studies, albeit mostly small, are fairly consistent regarding timing of VTE onset after IVF, ranging from 3 to 112 days after ET (5,12,17,23,24). Thus, the risk period was longer than has previously been perceived and the increased risk persisted throughout the whole first trimester. The small studies did not allow comparison of the time intervals ET to ATE and ET to VTE.

The proper dosage and the duration of LMWH administration in relation to IVF are uncertain as they cannot be determined from the literature. The Royal College of Obstetricians and Gynecologists states that LMWH should be given on an individualized basis in cases of OHSS (38). Thromboprophylaxis with LMWH during pregnancy is related to a relative risk-reduction of up to 88% at appropriate doses of LMWH (25,39–41). However, LMHW in pregnancy has been reported to be related to a low (2%) but increased risk of bleeding, postpartum hemorrhage and hematomas (25,39,42). The occurrence of osteoporosis in relation to LMWH thromboprophylaxis seems to be substantially lower than with unfractionated heparin (43–45).

In Sweden, thromboprophylaxis is recommended to all pregnant women at an estimated risk of VTE at least similar to the antepartum risk of women with one prior VTE (i.e. ≈5% absolute risk during all three trimesters, or 1.7% per trimester) (39). The risk of VTE related to OHSS in the first trimester is 1.7% (5) Therefore, in the absence of additional risk factors for VTE, LMWH is recommended to be administered to OHSS patients during the whole first trimester, but not thereafter (5,39,46).

In conclusion, the antepartum risk of VTE in pregnancies after IVF is doubled that in the background pregnant population, mainly due to a 5- to 10-fold increased risk during the first trimester. This risk is related to a very high risk of VTE during the entire first trimester after OHSS. The recommendation from our group of authors and clinical experts (an expert opinion) is that IVF patients with OHSS should be prescribed LMWH during the first trimester. Other IVF patients should be given

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thromboprophylaxis based on the same risk factors as other pregnant women.

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