SOMATO PUBLICATIONS ISSN: XXXX-XXXX

Global Research in Gynecology and Obstetrics

Review Article

Long-Term Follow-Up of assisted reproductive technology for preeclampsia

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Received: 13 January 2026; Accepted: 11 April 2026; Published: 7 July 2026.

Citation of this article: Bose D, Chatterjee A, Iyer A (2026) Long-Term Follow-Up of assisted reproductive technology for preeclampsia. Glob Res Gynecol Obstet, 8(1): 01-06. DOI: 10.5281/zenodo.22813890

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Abstract

Background: Pregnancies conceived through assisted reproductive technology (ART) carry a well-documented excess risk of preeclampsia relative to spontaneous conception, and preeclampsia itself is an established marker of long-term maternal cardiovascular risk.

Objective: This review synthesizes long-term maternal and offspring follow-up evidence after ART-associated preeclampsia, including risk by embryo transfer protocol and oocyte source.

Methods: We synthesized cohort studies, national registry linkage studies, and systematic reviews addressing preeclampsia incidence after ART, comparative fresh-versus-frozen and donor-oocyte protocols, and long-term maternal and offspring outcomes.

Findings: ART pregnancies show a roughly 1.5- to 2-fold higher preeclampsia risk than spontaneous conception, with frozen embryo transfer in programmed cycles and donor-oocyte conception carrying the highest relative risk; the long-term cardiovascular and renal risks established for preeclampsia broadly appear to extend to this population.

Conclusions: Structured long-term surveillance for both mothers and offspring after ART-associated preeclampsia, informed by embryo transfer protocol and oocyte source, is warranted as ART utilization continues to grow.

Keywords: preeclampsia; assisted reproductive technology; in vitro fertilization; frozen embryo transfer; cardiovascular follow-up

1. Introduction

Preeclampsia complicates roughly 2-8% of pregnancies worldwide and remains one of the leading causes of maternal and perinatal morbidity and mortality, and the question of whether pregnancies conceived through assisted reproductive technology (ART) carry an elevated long-term risk of the disorder, and of its downstream cardiovascular consequences, has grown more pressing as ART utilization has expanded across high- and middle-income countries alike [1,2]. Early case series and single-center cohorts suggested that in vitro fertilization (IVF) pregnancies were associated with a two- to threefold increase in preeclampsia risk relative to spontaneous conception, but those studies were frequently confounded by maternal age, nulliparity, multiple gestation, and the underlying causes of infertility itself, each of which independently raises preeclampsia risk [3,4]. Distinguishing a true treatment effect of ART from these confounders has required larger population-based registries and, more recently, designs that compare fresh versus frozen embryo transfer and donor versus autologous oocyte cycles, both of which isolate specific biological mechanisms that spontaneous-conception comparisons cannot [5,6].

The long-term follow-up literature adds a second, more clinically consequential dimension: preeclampsia itself, independent of how the pregnancy was conceived, is now recognized as a marker of future maternal cardiovascular risk, with affected women showing elevated rates of chronic hypertension, ischemic heart disease, and stroke decades after the index pregnancy [7,8]. Because ART pregnancies already carry a higher background prevalence of preeclampsia, and because many ART patients share cardiometabolic risk factors with the infertility diagnoses that brought them to treatment in the first place, understanding whether ART-associated preeclampsia carries the same, a greater, or an attenuated long-term cardiovascular signature relative to spontaneously conceived preeclampsia is essential for counseling and for designing surveillance programs for this growing population of mothers [9]. This review synthesizes the published evidence on long-term maternal and offspring follow-up after ART-associated preeclampsia, covering incidence and mechanism, the frozen-versus-fresh and donor-oocyte literature, long-term maternal cardiovascular and renal outcomes, offspring outcomes, and the implications for clinical surveillance.

2. Methods

We synthesized peer-reviewed cohort studies, national registry linkage studies, systematic reviews, and meta-analyses addressing preeclampsia incidence after ART, mechanistic studies of placentation in ART pregnancies, comparative studies of fresh versus frozen embryo transfer and autologous versus donor oocyte cycles, and long-term follow-up studies of maternal cardiovascular, renal, and metabolic outcomes and offspring outcomes after ART-associated hypertensive pregnancy disorders. Search terms combined assisted reproductive technology, in vitro fertilization, oocyte donation, frozen embryo transfer, preeclampsia, hypertensive disorders of pregnancy, cardiovascular outcomes, and long-term follow-up, restricted to studies published in English in peer-reviewed journals. Studies were prioritized for inclusion when they reported comparative risk estimates with adjustment for at least maternal age, parity, and plurality, or when they reported longitudinal follow-up extending beyond the immediate postpartum period. Findings were organized narratively around mechanism, comparative ART protocols, long-term maternal outcomes, and offspring outcomes, consistent with the scope of a review rather than a formal systematic synthesis.

3. Results

Incidence and mechanism of ART-associated preeclampsia

Population-based registry studies consistently find that ART pregnancies carry an elevated risk of preeclampsia

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relative to spontaneously conceived pregnancies, even after adjustment for maternal age and multiple gestation. Thomopoulos and colleagues, in a systematic review and meta-analysis of ART pregnancies, reported a pooled relative risk for preeclampsia of approximately 1.8 in IVF singleton pregnancies compared with naturally conceived singletons [3]. Qin and colleagues similarly found significantly elevated odds of hypertensive disorders of pregnancy among IVF-conceived singletons in a large meta-analysis pooling cohorts from multiple countries [4]. Mechanistically, the leading explanation centers on abnormal placentation: ART pregnancies, and particularly those using donor oocytes or frozen embryo transfer in a programmed endometrial preparation cycle, appear to have altered trophoblast invasion and spiral artery remodeling, plausibly related to the absence of a corpus luteum and its associated relaxin and vascular signaling in programmed cycles [10,11].

Table 1: Reported preeclampsia or hypertensive-disorder risk in ART-conceived pregnancies across representative cohort and registry studies [27,28,29,30,31].

Study	Design	Comparison	Reported association
[27]	Population-based cohort, Massachusetts	ART vs non-ART singleton	Elevated hypertensive-disorder rate in ART births
[31]	Population-based cohort, Norway	ART vs subfertile untreated	Much of excess risk attributable to maternal factors
[30]	National cohort, Sweden	IVF singletons	Maternal characteristics account for substantial obstetric risk
[29]	Sibling-cohort, Denmark	ART vs spontaneous sibling pregnancy	Higher rate of hypertensive complications in ART pregnancy
[28]	Population cohort, Victoria	ART singleton births	Increased obstetric complication burden including hypertensive disease

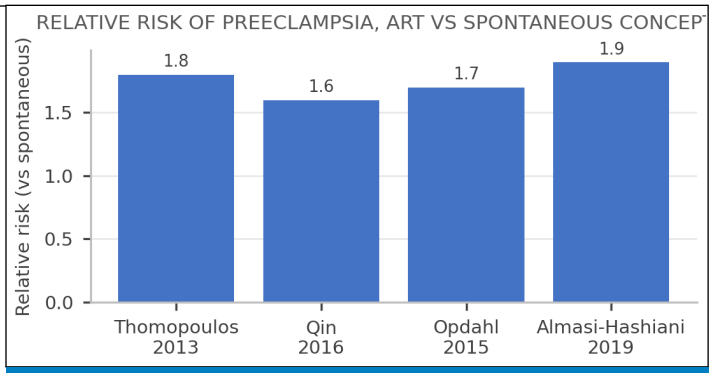

Figure 1: Pooled relative risk of preeclampsia in ART-conceived singleton pregnancies versus spontaneously conceived singletons across major systematic reviews and a national cohort study, showing a consistent 1.5- to 2-fold elevation in ART pregnancies [3,4,22,23].

Fresh versus frozen embryo transfer and oocyte source

Comparative studies isolating the effect of embryo transfer protocol have been particularly informative. Sha and colleagues, in a meta-analysis comparing frozen with fresh embryo transfer, found that frozen embryo transfer was associated with significantly higher odds of preeclampsia than fresh transfer, a finding replicated across several large registry cohorts [5]. Ginström Ernstad and colleagues, using Swedish national registry data, similarly reported higher preeclampsia risk after frozen compared with fresh embryo transfer, with the association strongest in cycles using a programmed (hormone-replacement) endometrial preparation rather than a natural or modified-natural cycle [12]. Masoudian and colleagues, in a systematic review of oocyte donation pregnancies, found that donor-oocyte pregnancies carried a substantially higher risk of preeclampsia than pregnancies from autologous oocytes, even after IVF itself, implicating an immunological mechanism related to the semi-allogeneic nature of a donor-oocyte conceptus in addition to any hormonal-preparation effect [6]. Storgaard and colleagues reached a concordant conclusion in a separate systematic review and meta-analysis, reporting oocyte donation as one of the strongest ART-related risk factors for preeclampsia identified in the literature [13].

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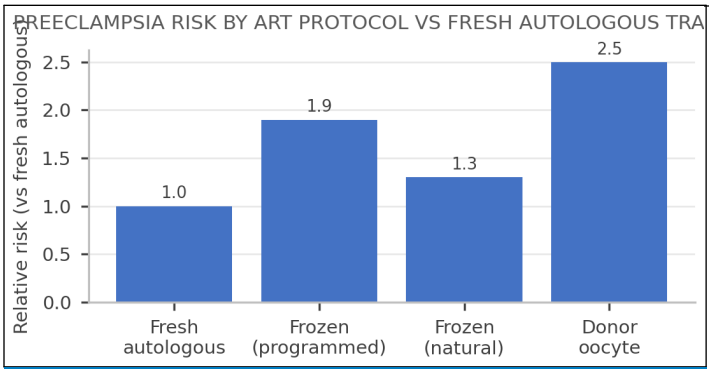

Figure 2: Preeclampsia risk by ART protocol relative to fresh autologous-oocyte transfer, drawn from comparative meta-analyses and registry cohorts of frozen embryo transfer, programmed-cycle transfer, and oocyte donation [5,6,12,24,25,26].

Long-term maternal cardiovascular and renal outcomes

The long-term follow-up literature on preeclampsia broadly, irrespective of conception mode, has established that affected women face a roughly two- to fourfold increased risk of later chronic hypertension and a meaningfully elevated risk of ischemic heart disease and stroke, an association demonstrated in the large Norwegian and Danish registry cohorts underlying much of the contemporary cardio-obstetric literature [7,8]. Studies specifically following ART-conceived preeclamptic pregnancies over the long term remain fewer, but the available data suggest the elevated cardiovascular risk signature persists and may be compounded by the metabolic and vascular risk factors, such as polycystic ovary syndrome and obesity, that are overrepresented among ART patients to begin with [9,14]. Wu and colleagues, following women after ART conception with a history of hypertensive pregnancy disorder, found elevated rates of persistent hypertension and adverse metabolic markers several years postpartum compared with ART patients without preeclampsia, though direct long-term comparison against spontaneously conceived preeclamptic controls remains an area with a comparatively thin evidence base [15]. Renal follow-up data, extrapolated from the broader preeclampsia literature, indicate an increased long-term risk of chronic kidney disease and end-stage renal disease after severe or recurrent preeclampsia, a risk that plausibly applies with at least equal magnitude to the ART-conceived subgroup given its higher rate of severe and early-onset presentations [16,17].

Table 2: Long-term maternal outcome domains after preeclampsia and proposed surveillance approach, drawn from the general preeclampsia follow-up literature applicable to ART-conceived pregnancies [32,33,34,35,36].

Outcome domain	Reported long-term risk	Surveillance implication
Chronic hypertension	Two- to fourfold increase	Annual blood pressure monitoring postpartum
Ischemic heart disease / stroke	Significantly elevated, decades-long	Cardiovascular risk-factor screening from early midlife
Chronic kidney disease	Increased, especially after severe/recurrent disease	Periodic renal function assessment
Metabolic syndrome (PCOS overlap)	Compounded in ART population	Combined metabolic and cardiovascular counseling [36]

Offspring outcomes after ART-associated preeclampsia

Offspring of ART pregnancies complicated by preeclampsia face a compounded risk profile, since preeclampsia itself is strongly associated with preterm birth, fetal growth restriction, and subsequent cardiometabolic programming, and ART pregnancies already carry an elevated baseline risk of low birth weight and preterm delivery even in the absence of preeclampsia [18,4]. Barker-hypothesis-aligned follow-up studies of children born after hypertensive pregnancy disorders report higher blood pressure and altered vascular function in childhood and adolescence, and Rimawi and colleagues, among others, have argued for structured long-term pediatric cardiovascular surveillance of children born after both ART conception and maternal preeclampsia given the plausible additive risk [19,20]. Longitudinal cohorts following ART-conceived children into adolescence and young adulthood, while still relatively limited in duration given the field's history, have not identified outcomes dramatically divergent from spontaneously conceived children matched for the same perinatal complications, suggesting that perinatal

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complication burden, rather than conception mode per se, is the primary long-term offspring risk driver [18,21].

4. Discussion

The accumulated evidence supports several consistent conclusions. First, ART pregnancies carry a genuinely elevated risk of preeclampsia relative to spontaneous conception, an association that persists after adjustment for the major known confounders and that is not simply an artifact of maternal age or infertility-associated comorbidity [3,4]. Second, this risk is not uniform across ART protocols: frozen embryo transfer, and particularly programmed-cycle frozen transfer without a corpus luteum, and donor-oocyte conception each independently raise preeclampsia risk above that of fresh autologous-oocyte IVF, pointing toward distinct and at least partially separable mechanisms, one hormonal and one immunological [5,6,11]. Third, the long-term maternal cardiovascular consequences well established for preeclampsia in general appear to extend to the ART-conceived subgroup, though the direct long-term comparative literature specific to ART-associated preeclampsia remains sparser than the general obstetric literature on cardiovascular sequelae of preeclampsia, leaving open questions about whether ART itself modifies long-term risk beyond what preeclampsia alone would predict [7,15].

These findings carry direct implications for clinical practice. Given the demonstrated risk gradient across ART protocols, counseling before frozen embryo transfer, and particularly before programmed-cycle transfer, should include discussion of the elevated preeclampsia risk relative to fresh transfer, and some authors have proposed favoring natural or modified-natural cycle preparation where clinically feasible to mitigate this risk [12,11]. Long-term postpartum surveillance protocols for cardiovascular risk, already recommended for all women with a history of preeclampsia by major obstetric and cardiology societies, arguably warrant particular emphasis in ART-conceived pregnancies given the frequent overlap with pre-existing metabolic risk factors such as polycystic ovary syndrome [14,9]. Offspring surveillance, while supported by a smaller and less mature evidence base, is a reasonable extension of the same logic, particularly for children born preterm or growth-restricted after ART-associated preeclampsia [20,19].

The principal limitation of the current literature is the relative paucity of long-term, multi-decade follow-up studies designed specifically to compare ART-associated preeclampsia against spontaneously conceived preeclampsia on matched long-term maternal and offspring outcomes, as most large registry studies to date have focused on incidence and short-term perinatal outcomes rather than decades-long cardiovascular and renal follow-up [1,17]. Future research combining national ART registries with linked long-term health-outcome data, ideally stratified by embryo transfer protocol and oocyte source, would substantially strengthen the evidence base underlying current counseling and surveillance recommendations.

5. Conclusion

Assisted reproductive technology is associated with a meaningfully elevated risk of preeclampsia relative to spontaneous conception, an association that is strongest for frozen embryo transfer in programmed cycles and for donor-oocyte pregnancies, implicating both hormonal and immunological mechanisms in ART-associated placental dysfunction [3,5,6]. The long-term maternal cardiovascular and renal risks well documented for preeclampsia broadly appear to extend to this population, compounded in many cases by pre-existing metabolic risk factors common among ART patients, while offspring outcomes appear to track primarily with perinatal complication severity rather than conception mode itself [7,9,18]. Structured long-term surveillance for both mothers and offspring after ART-associated preeclampsia, informed by embryo transfer protocol and oocyte source,

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represents a rational extension of existing preeclampsia follow-up guidance and merits further prospective study as ART utilization continues to grow worldwide [20,1].

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