ISSN: 3152-8686

Vol3; Issue3, Aug. 2026

JOURNAL OF
TAZEEZ FOR PUBLIC HEALTH

AN OFFICIAL JOURNAL OF SAUDI HEALTH PROMOTION AND EDUCATION ASSOCIATION

Systematic review

Fetal growth restriction in IVF pregnancies: outcomes and risk factors: a systematic review

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Published: 1st August, 2026

https://doi.org/10.65759/k4c8pq27

ISSN: 3152-8686

Abstract

Background: Fetal growth restriction (FGR) in *in vitro* fertilization pregnancies is a clinically important concern because assisted conception linked with altered placentation, singleton low birth weight, small-for-gestational-age birth, hypertensive disorders, and medically indicated preterm delivery. **Objective:** This systematic review evaluated outcomes and risk factors for FGR or related small-for-gestational-age birth in singleton pregnancies conceived through in vitro fertilization or intracytoplasmic sperm injection. **Methods:** A PRISMA-guided systematic review designed using PubMed, Scopus, Web of Science, and Cochrane Library searches. Eligible studies were original human studies evaluating FGR, small-for-gestational-age birth, birthweight percentile, or fetal growth trajectory after in vitro fertilization or intracytoplasmic sperm injection. Data synthesized qualitatively because exposure definitions, embryo-transfer protocols, comparator groups, and outcome definitions differed across studies. **Results:** Ten original studies were included in the results synthesis. Data linked fetal growth impairment with fresh embryo transfer, supraphysiologic estradiol, higher total gonadotrophin dose, vanishing twin syndrome, multiple embryo transfer, female infertility factors, and thin endometrium. Frozen embryo transfer was generally associated with higher birthweight and lower small-for-gestational-age frequency than fresh transfer, although it was linked with larger infants and hypertensive disorders in wider literature. **Conclusion:** FGR risk in *in vitro* fertilization pregnancies appears multifactorial. Clinical surveillance needs individualized attention to infertility background, stimulation intensity, embryo-transfer strategy, early multifetal loss, placental disease, and maternal vascular risk.

Keywords

Fetal growth restriction; *in vitro* fertilization; intracytoplasmic sperm injection; small for gestational age; frozen embryo transfer

Introduction

Fetal growth restriction (FGR) is commonly defined as failure of the fetus to reach its biological growth, with international consensus emphasizing estimated fetal weight, abdominal circumference, growth velocity, and Doppler evidence of placental dysfunction rather than birthweight alone (1). Small-for-gestational-age birth and FGR overlap, although small size alone does not prove pathological placental insufficiency. This distinction is important in *in vitro* fertilization pregnancies because neonatal small-for-gestational-age status is used as a practical outcome when antenatal Doppler-defined FGR is unavailable in registry studies (2).

Assisted conception linked with higher risks of adverse outcomes in singletons, including preterm birth, low birthweight, and small-for-gestational-age birth (3). A systematic review of singleton IVF/ICSI pregnancies found increased obstetric and perinatal complications compared with spontaneous conception, showing that singleton status does not fully remove excess risk after assisted reproduction (4). Another systematic review concluded that subfertility contributes to poorer perinatal outcomes in ART singletons, and treatment-related factors were relevant through ovarian stimulation, laboratory handling, embryo culture, and embryo-transfer context (5).

Frozen-thawed embryo transfer has been associated with different fetal growth patterns compared with fresh transfer (6). Clinical reviews describe IVF pregnancies as successful, although they show higher burdens of hypertensive disorders, preterm delivery, low birthweight, and placental complications than unassisted

pregnancies (7). A prospective cohort comparing IVF, subfertile, and fertile singleton pregnancies reported that adverse obstetric outcomes reflected contributions from both infertility and IVF treatment, reinforcing the need to separate parental background from procedure-related exposure (8). This systematic review aimed to evaluate the outcomes and risk factors associated with FGR and small-for-gestational-age birth in singleton pregnancies conceived through *in vitro* fertilization or intracytoplasmic sperm injection.

Methods

This systematic review was conducted according to PRISMA principles for transparent identification, eligibility assessment, extraction, and synthesis. The review question was structured using the population, exposure, comparator, outcome, and study-design format. The population consisted of singleton pregnancies conceived through IVF or ICSI. The exposure covered IVF/ICSI treatment, fresh embryo transfer, frozen embryo transfer (FET), stimulation intensity, estradiol exposure, embryo number, vanishing twin syndrome, infertility factor, endometrial status, and maternal risk profile. Comparators included spontaneous conception, fertile controls, subfertile controls, fresh transfer versus frozen transfer, natural-cycle IVF, and different stimulation categories.

PubMed, Scopus, Web of Science, and Cochrane Library were searched for records from database inception to Jan 2026. Search terms combined controlled vocabulary and free-text terms for “in vitro fertilization,” “intracytoplasmic sperm injection,” “assisted reproductive technology,” “FGR,” “intrauterine growth restriction,” “small for gestational age,” “birthweight,” “frozen embryo transfer,” “fresh embryo transfer,” “ovarian stimulation,” “estradiol,” and “vanishing twin.” Reference lists of relevant reviews and included studies were checked for additional eligible original articles.

Studies were eligible when they are original human studies, registry studies, cohort studies, comparison studies, or clinical datasets reporting FGR, SGA, birthweight percentile, intrauterine growth trajectory, low birthweight, or related neonatal size outcomes after IVF/ICSI. Reviews, editorials, animal studies, case reports, conference abstracts without full data, and studies focused only on multiple gestations were excluded from the results synthesis. Multiple gestation studies were excluded.

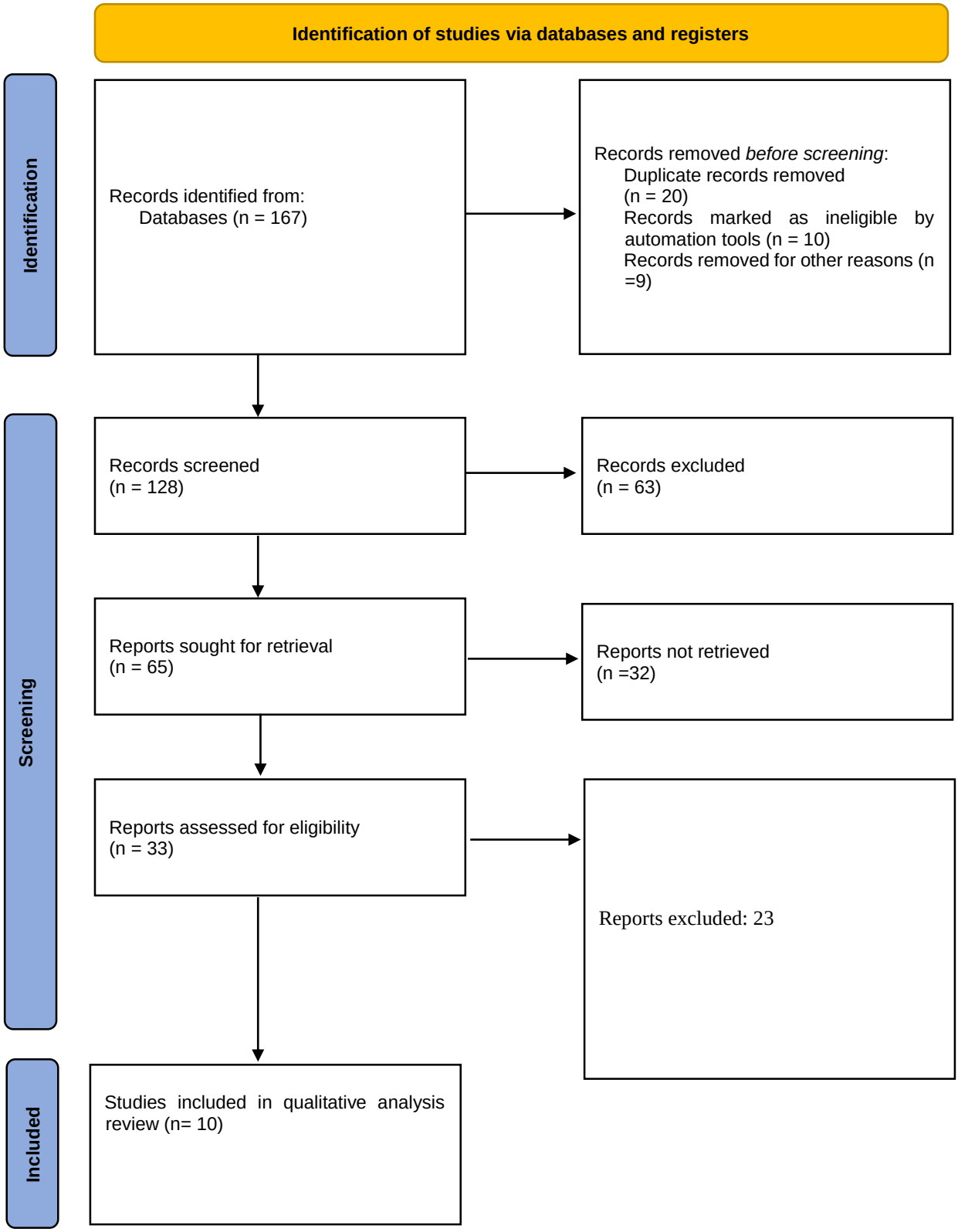
Two-stage screening was planned using title and abstract review followed by full-text assessment. Extracted variables included country, design, sample size, conception mode, embryo-transfer type, comparator group, fetal growth endpoint, risk factors, adjustment variables, and key estimates. Risk of bias was assessed in selection, exposure definition, outcome ascertainment, confounding control, missing data, and reporting domains. Meta-analysis was not undertaken because of heterogeneity in outcome definitions, fetal growth metrics, transfer protocols, and comparator groups. A qualitative synthesis grouped evidence into IVF risk, infertility background, fresh versus frozen transfer, ovarian stimulation exposure, vanishing twin syndrome, endometrial factors, and maternal-placental risk.

01/08/2026

Table 1: Risk of bias assessment using Newcastle–Ottawa Scale cohort version

Study	Selection /4	Comparability /2	Outcome /3	Total /9	Quality
Koudstaal et al., 2000	3	1	2	6	Moderate
Schieve et al., 2002	4	1	3	8	High
Zhu et al., 2007	4	2	3	9	High
Pinborg et al., 2007	4	1	3	8	High
Cooper et al., 2011	3	2	2	7	High
Wennerholm et al., 2013	4	1	3	8	High
Schwartz et al., 2019	3	1	3	7	High
Shinohara et al., 2020	3	2	2	7	High
Wu et al., 2022	3	2	2	7	High
Slavov et al., 2022	2	1	2	5	Moderate

Fig 1: PRISMA flow chart



Results

Ten original studies were included in the synthesis, and most used retrospective cohort or registry-linked designs with singleton pregnancies as the analytic focus. Earlier matched and population-based studies showed higher rates of SGA, low birthweight, smaller fetal size after IVF, and infertility treatment compared with fertile or spontaneous-conception groups. Large registry and cohort findings indicated that fetal growth outcomes after IVF reflect treatment exposures and underlying subfertility more than a single procedural mechanism (9, 10).

A Danish cohort found that infertility was associated with FGR (11). A Danish IVF study reported that vanishing co-twin status increased SGA risk in IVF singletons, when the co-twin disappeared later in gestation (12). A US cohort reported smaller first-trimester fetal size and lower neonatal weight in infertile women (13). Fresh versus frozen transfer produced one of the clearest patterns in the included studies (14). A cohort study found lower SGA odds after frozen-thawed embryo transfer compared with fresh IVF/ICSI, with a rise in large-for-gestational-age and macrosomia outcomes after frozen transfer (14). IVF-focused studies linked SGA risk with gonadotrophin stimulation, high estradiol exposure, high total gonadotrophin dose, fresh transfer, multiple embryo transfer, vanishing twin syndrome, and female infertility factors (15–18).

Table 2. Characteristics of the studies included

Study	Country	Design	Exposure and comparator	Growth outcome
Koudstaal et al. (9)	Netherlands	Matched control study of singleton IVF pregnancies	IVF versus matched controls	SGA, preterm birth, obstetric outcome
Schieve et al. (10)	United States	National ART-related analysis of infants	ART versus reference births	Low birthweight and very low birthweight
Zhu et al. (11)	Denmark	National birth cohort	Infertility with or without treatment	FGR, perinatal outcome
Pinborg et al. (12)	Denmark	Multicenter IVF singleton cohort	Vanishing twin versus primary singleton	SGA and term low birthweight
Cooper et al. (13)	United States	Retrospective observational cohort	Infertile versus fertile women	First-trimester size, birthweight
Wennerholm et al. (14)	Nordic countries	Population-based CoNARTaS cohort	FET versus fresh IVF/ICSI	SGA, LGA, macrosomia, PTB, LBW
Schwartz et al. (15)	Switzerland	Cohort comparing stimulated IVF and natural-cycle IVF	High estradiol and stimulation exposure	SGA and birthweight percentile
Shinohara et al. (16)	Japan	Retrospective cohort with multilevel growth modeling	Infertility treatment groups	Intrauterine growth trajectory and birthweight
Wu et al. (17)	China	Retrospective cohort of singleton fresh transfers	Gonadotrophin dose categories	SGA after fresh embryo transfer

Study	Country	Design	Exposure and comparator	Growth outcome
Slavov et al. (18)	Bulgaria	Prospective-retrospective singleton IVF study	IVF versus spontaneous conception	SGA and IVF-related risk factors

Table 3. Draft synthesis of outcomes and risk factors

Domain	Main finding	Direction of association	Key studies
IVF singleton outcome	IVF singletons had higher SGA or low-birthweight burden in older matched and registry studies	Higher growth-related risk versus controls	(9,10)
Infertility background	Infertility contributed to FGR and smaller fetal size	Higher risk linked with underlying reproductive pathology	(11,13)
Vanishing twin syndrome	Surviving IVF singletons after early multifetal loss had higher SGA risk	Higher SGA risk versus primary IVF singletons	(12,18)
Frozen versus fresh transfer	FET had lower SGA and LBW than fresh transfer in Nordic data	Lower SGA with FET, higher LGA/macrosomia	(14)
Ovarian stimulation and estradiol	Conventional stimulation and high estradiol were linked with higher SGA	Higher SGA with supraphysiologic exposure	(15)
Gonadotrophin dose	Total gonadotrophin dose above 2500 IU increased SGA risk after fresh transfer	Higher SGA with higher dose	(17)
IVF procedure factors	Multiple embryo transfer, fresh transfer, vanishing twin syndrome, and female infertility factor were linked with SGA	Higher SGA risk in exposed subgroups	(18)
Growth trajectory	FET altered intrauterine growth trajectory from midpregnancy to term	Different growth curve, especially in female fetuses	(16)

Discussion

This systematic review found that FGR and small-for-gestational-age birth in IVF pregnancies are not explained by a single factor, but by overlapping treatment-related, maternal, infertility-related, and placental pathways. Recent national cohort from Taiwan found that embryo-transfer strategy affected singleton neonatal outcomes, with frozen transfer linked to lower SGA and higher LGA frequency compared with fresh transfer (19). A linked national IVF registry found that FET was associated with lower SGA risk and higher LGA risk than fresh transfer in singleton siblings, strengthening inference by reducing family-level confounding (20). These findings align with the Nordic CoNARTaS cohort and indicate that fetal growth after IVF differs by transfer environment rather than conception technology alone (14).

Endometrial characteristics were relevant because thin endometrium after fresh IVF/ICSI embryo transfer has been associated with increased SGA risk (21). Maternal vascular disease also matters because assisted reproductive technology is associated with higher odds of hypertensive disorders and preeclampsia (22). The included studies support a multifactorial model in which fresh transfer and supraphysiologic ovarian stimulation create a less physiologic endometrial environment during implantation (15). High estradiol and high gonadotrophin dose were linked with lower birthweight percentile or higher SGA risk (15,17). Frozen transfer removes the stimulated-cycle endometrium from implantation timing, which explains its lower SGA pattern (14,20,22).

Underlying infertility is a major source of confounding because infertility without IVF was linked with FGR and smaller fetal size in cohort studies (11,13). This finding means that future research needs comparison groups that include fertile spontaneous conception, subfertile spontaneous conception, non-IVF treatment, fresh IVF, frozen IVF, and sibling-paired pregnancies (5,11,13,20). The strongest designs were population registries and sibling comparisons because they addressed maternal background more directly than simple IVF versus spontaneous-conception comparisons (14,20).

Clinical interpretation requires separation of antenatal FGR from neonatal SGA because many registry studies used birthweight percentile rather than Doppler-based FGR criteria (1,2). IVF pregnancies with fresh transfer, high stimulation burden, thin endometrium, vanishing twin syndrome, female-factor infertility, hypertensive disease, or prior placental disease deserve closer growth surveillance in the second and third trimesters (12,17,18,21,22). Future studies need standardized FGR definitions, trimester-specific ultrasound data, placental pathology, embryo-culture details, and protocol-level IVF exposure data to distinguish growth restriction from constitutionally small neonatal size.

Conclusion

FGR and SGA in IVF pregnancies arise from overlapping maternal, infertility-related, placental, and treatment-related pathways. The most consistent risk factors were fresh embryo transfer, intense ovarian stimulation, high estradiol, high gonadotrophin dose, vanishing twin syndrome, multiple embryo transfer, female infertility factors, thin endometrium, and hypertensive disorders. FET showed lower SGA frequency than fresh transfer, while larger fetal size and hypertensive disease remained relevant. IVF pregnancies need individualized fetal growth surveillance rather than uniform classification as high risk.

01/08/2026

List of abbreviations

ART: Assisted reproductive technology
EFW: Estimated fetal weight
ET: Embryo transfer
FET: Frozen embryo transfer
FGR: Fetal growth restriction
HDP: Hypertensive disorders of pregnancy
ICSI: Intracytoplasmic sperm injection
IVF: In vitro fertilization
LBW: Low birthweight
LGA: Large for gestational age
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTB: Preterm birth
SGA: Small for gestational age
VTS: Vanishing twin syndrome

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