

SYSTEMATIC REVIEW

Cardiovascular Complications of Pregnancy

Understanding changes in echocardiographic parameters at different ages following fetal growth restriction: a systematic review and meta-analysis

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Abstract

Fetal growth restriction (FGR) increases cardiovascular risk by cardiac remodeling and programming. This systematic review and meta-analysis across species examines the use of echocardiography in FGR offspring at different ages. PubMed and Embase.com were searched for animal and human studies reporting on echocardiographic parameters in placental insufficiency-induced FGR offspring. We included six animal and 49 human studies. Although unable to perform a meta-analysis of animal studies because of insufficient number of studies per individual outcome, all studies showed left ventricular dysfunction. Our meta-analyses of human studies revealed a reduced left ventricular mass, interventricular septum thickness, mitral annular peak velocity, and mitral lateral early diastolic velocity at neonatal age. No echocardiographic differences during childhood were observed, although the small age range and number of studies limited these analyses. Only two studies at adult age were performed. Meta-regression on other influential factors was not possible due to underreporting. The few studies on myocardial strain analysis showed small changes in global longitudinal strain in FGR offspring. The quality of the human studies was considered low and the risk of bias in animal studies was mostly unclear. Echocardiography may offer a noninvasive tool to detect early signs of cardiovascular predisposition following FGR. Clinical implementation yet faces multiple challenges including identification of the most optimal timing and the exact relation to long-term cardiovascular function in which echocardiography alone might be limited to reflect a child’s vascular status. Future research should focus on myocardial strain analysis and the combination of other (non)imaging techniques for an improved risk estimation.

echocardiography; fetal growth restriction; meta-analysis; small for gestational age

INTRODUCTION

Cardiovascular disease remains the leading cause of mortality in adults worldwide (1). Although the cardiovascular burden clearly manifests during adulthood, the predisposition of cardiovascular disease starts already during fetal development (2, 3). Cardiac remodeling and programming in utero can be negatively influenced by exposure to adverse early life events (2, 4). The exposure to other unhealthy behavioral (e.g., smoking) or biological factors (e.g., untreated hypertension) throughout the life span add to the cardiovascular risk profile, whereby sub-clinical changes might progress into cardiovascular disease in adulthood (5).

Fetal growth restriction (FGR) is one of these adverse early life events that has been associated with increased susceptibility to cardiovascular disease by fetal programming (2). This common complication of pregnancies arises from placental insufficiency in which a reduced supply of nutrients and oxygen hampers the fetus from reaching its intrinsic growth potential (6, 7). Chronic hypoxia initiates endothelial dysfunction and fetal hemodynamic redistribution. In addition, the increased placental resistance results in persistent volume/pressure overload in the fetal heart (8). Cardiac remodeling occurs with the purpose of maintaining output in which the phenotype depends on the severity (8). Increasing evidence shows cardiac remodeling on both macroscopic and microscopic levels in growth-restricted fetuses



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that persists after birth (4, 8–10). This fetal cardiac remodeling and adverse programming may underlie the observed increased cardiovascular risk in the FGR population.

Early identification of high-risk patients provides the opportunity to prevent or minimize the cardiovascular health burden from the start of life. Acknowledgment of this window of opportunity led to a shift in approach toward prevention as a key strategy in cardiovascular health management over the life span (11). Longitudinal follow-up of cardiac remodeling after birth provides insight into the progression from subclinical to clinical signs of cardiovascular disease secondary to fetal growth restriction. This gradual process is currently insufficiently understood and depends on several factors including sex and severity of FGR. In addition, the dynamic aspects make the moment of measurement essential when researching this topic. For instance, hypertrophic remodeling has been observed more frequently in early-onset FGR while late-onset FGR mostly shows less severe cardiac remodeling (8). A better understanding of effect modifiers allows identification of the subgroups most at risk and simultaneously who will benefit most from perinatal interventions or early screening programs. However, longitudinal assessment of cardiovascular health in the pediatric population remains a relatively uncharted territory.

Echocardiography is the golden standard for evaluating cardiac development and function at different ages in a non-invasive way. Novel ultrasound techniques such as speckle-tracking have recently augmented the potential of conventional ultrasound to detect subclinical changes in structure and function as an early biomarker for cardiovascular predisposition (12–14). Both clinical and animal studies have shown differences in cardiac development following FGR (8). Although cardiac ultrasound presents a unique opportunity to improve cardiovascular outcomes in growing numbers of children and adolescents at risk, a current overview of (sub)clinical progression over the life span and effect modifiers is lacking.

This systematic review and meta-analysis across species examine the use of cardiac ultrasound in fetal growth-restricted offspring as a consequence of placental insufficiency. We aim to understand echocardiographic changes during different ages following FGR. An improved understanding of the role of echocardiography could eventually contribute to the ongoing development of cardiovascular screening programs in FGR offspring.

METHODS

Study Protocol

This systematic review was conducted according to a protocol preregistered on PROSPERO (CRD42022330269) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table S1; all Supplemental Material is available at <https://doi.org/10.6084/m9.figshare.25479805.v2>) (15).

Literature Search

We searched PubMed and Embase.com from inception up to March 4, 2024, to identify animal and human

studies reporting on cardiac ultrasound measurements in fetal growth-restricted offspring. The search string is provided in the supplemental data (Supplemental Table S2). No publication dates or language restrictions were applied.

Inclusion and Exclusion Criteria

Two independent researchers (MvdM and SJ) screened articles for inclusion using predefined inclusion and exclusion criteria using Rayyan (<https://rayyan.ai/cite>). Discrepancies were resolved by discussion and in case of no consensus by a third investigator (FT).

We included echocardiographic studies in fetal growth-restricted offspring after exposure to placental insufficiency or chronic hypoxia in singleton pregnant mammals. FGR in human studies was defined as an estimated fetal weight (EFW) or abdominal circumference below the 10th percentile or deviating growth of two time points with a minimal of at least 2 wk. Of note, this definition of FGR was formulated by a Delphi procedure in 2016, and we did not want to exclude human studies published before 2016. We therefore broadened the definition of the human study population to include small for gestational age (SGA), which is defined as birth weight below the 10th percentile for gestational age. Studies including low birth weight without correction for gestational age were excluded as this population is either prematurity or a combination of prematurity and SGA wherefore the solitary effect of FGR could not be investigated. Induction methods of FGR in animals included surgical ligation of uterine vessels, chronic hypoxia exposure, and genetic predisposition [i.e., Dahl salt-sensitive (SS) rats (16) or spontaneous hypertension and heart failure (SHHF) (17) rats (18)].

Studies on FGR caused by diet restriction or genetic modeling were excluded as the induction of these models lacks the exposure of chronic hypoxia and thereby the pathophysiological sequela of hemodynamic redistribution and cardiac remodeling (6, 7). Other exclusion criteria were lack of a control group and lack of original data (e.g., narrative review). For human studies, we included observational cohort studies, randomized controlled trials (RCT), or case-control trials.

Data Extraction

Two researchers (MvdM and KN) independently extracted data. Discrepancies were resolved by discussion in case of no consensus by a third investigator (FT). All echocardiographic data and information on study design were extracted including birth weight, sex of offspring, age, and conditions during measurements. In addition for animal studies, we extracted data on species, strain, animal model, and litter size, and for human studies also ethnicity, BMI, and coexistence of other hypertensive disorders of pregnancy. Per primary outcome, we noted for all echocardiographic measurements including speckle-tracking measurements: means (SD) and number of subjects per group. Secondary outcomes included other cardiovascular parameters, for example, blood pressure and heart rate. The corresponding authors were contacted once by email in case of missing data.

Assessment of Risk of Bias and Study Quality

The risk of bias was assessed by two independent researchers (MvM and KN). Discrepancies were resolved by discussion and by a third investigator (FT or KW). For animal studies, we used the risk of bias tools from Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) (19) and the Newcastle-Ottawa Scale for human cohort studies (20). Adjustments to the tools are described in the supplement (Supplemental Method). Studies were not excluded based on poor study quality.

Meta-Analysis

Meta-analyses across species were performed for each echocardiographic outcome reported in more than five studies in a similar age group (these age categories are defined below). The pooled effect size estimates were presented as standardized mean difference (SMD) with their 95% confidence intervals (95%CI). First, we explored the potential difference in the pooled effect size caused by species to decide whether pooling of data was justified. We applied a random effects model because of potential heterogeneity in animal studies with various species and strains, FGR induction methods, and different units of measurement reported. We used nesting if multiple cohorts from one study were included. In case of multiple measurements at different ages as part of a follow-up study, we used only the latest measurement within the same age category for the meta-analysis.

Meta-regression analysis allows exploring the impact of certain study characteristics on the observed effect size, e.g., determining sources of heterogeneity. We only performed meta-regression when at least two of the subgroups contained at least 10 studies per age category. The following groups were predefined; species (human vs. rat vs. mice), severity of FGR (in percentiles [p]: <p3 vs. p3–p10), method of FGR induction (surgical vs. hypoxic chamber), sex (male vs. female), and age at cardiac ultrasound assessment (neonate vs. child vs. young adult). Definition of these age categories included neonates from birth until 28 days after birth, children from 29 days after birth until 17 yr old, and adults as 18 yr and older.

Statistical analyses were performed using R software (v. 4.2.3, Auckland, New Zealand, Metafor package). A two-sided P value < 0.05 was considered significant. For outcomes reported in at least 20 studies, we produced funnel plots and Egger's regression test to assess publication bias. Heterogeneity (I^2) among studies of 25% was considered low, 25–50% as moderate, 50–75% as high, and 75–100% as very high, in accordance with the Cochrane Handbook of Systematic Reviews of Interventions (21).

RESULTS

Study Selection

Our search retrieved 7,926 records (Supplemental Fig. S1). Screening resulted in a total of 55 included studies in this systematic review and meta-analysis. A complete list of exclusion criteria is reported in the supplemental data (Supplemental Table S3). Exclusion of studies was mostly

based on the lack of the correct study groups (both FGR or control group), followed by missing an outcome of interest. Because of the very limited amount of animal study data available in the various age groups, the suitability of pooling animal and human data could not be assessed. Consequently, to avoid inappropriate pooling across species, only human data were included in our meta-analysis. Therefore, and according to our predefined protocol, we analyzed and presented the results separately for humans (Table 1) and animals (Table 2).

Human Studies

Study characteristics of human studies.

All studies were either prospective cohort studies or case-control studies. Almost all studies defined the study population as SGA with birth weight below the 10th percentile for gestational age or minus two standard deviations corrected for gestational age, and only eight studies defined FGR more accurately with EFW and abnormal prenatal doppler measurements (36, 37, 47, 50, 55, 65–67). None of the studies reported the measurements per sex to assess sex-specific differences. The majority of cardiac ultrasounds occurred during the neonatal phase, with a range of 2.8 h after birth until 41 yr old. Only three studies stratified results based on severity of FGR (31, 32, 43) and one study stratified per sex (57). The gestational age at birth was mostly at term.

Effect of FGR on conventional echocardiographic parameters in human studies.

An overview of the echocardiographic outcomes is shown in Table 3, and the full data extraction is available in Supplemental Table S4. According to our predefined protocol, we were unable to perform a meta-analysis on all reported outcomes because of lack of more than five studies reporting on the same outcome at the similar age. The performed meta-analyses in human studies will be discussed below per age group.

Meta-analysis of echocardiographic data in neonates.

Ultrasound measurement on cardiac morphology showed a smaller left ventricular mass with a SMD of -0.97 ($[-1.73; -0.22]$, $P = 0.03$) in FGR neonates compared with controls (Supplemental Fig. S2A). However, note that the lower limit of the CI is very close to 0, and a very high between-study heterogeneity is present ($I^2 = 93%$). Some of these studies also reported ventricular mass index to correct for body weight, which did not reveal a significant difference (Supplemental Fig. S2B). The left ventricular posterior wall thickness and end-diastolic dimension of the left ventricle were similar between groups (Supplemental Fig. S2, C and D). The interventricular septal thickness (IVS) during diastole was smaller in FGR than in controls with an SMD of -0.74 ($[-1.25; -0.24]$, $P = 0.00$), and a very high between-study heterogeneity of $I^2 = 91%$ (Supplemental Fig. S2E).

Echocardiographic systolic function measurements showed a reduced mitral annular systolic peak velocity in FGR of -0.85 SMD ($[-1.27; -0.44]$, $P = 0.01$, $I^2 = 68%$) compared with controls (Supplemental Fig. S3A). However, left ventricular cardiac output index, left ventricular ejection fraction,

Table 1. Overview of the main study characteristics and results of included human studies

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Aburawi (2011) (22)	BW > -2 SD	17	15	1 wk	Cardiac morphology: LVMi increased in FGR. Coronary flow: Basal and peak flow velocity increased in FGR.	Cardiac morphology: LV end-diastolic dimension, LVM. Systolic function: Cardiac output, mitral peak early wave, fractional shortening. Cardiac morphology: LV posterior wall, RWT, LVMi. Systolic function: fractional shortening, left cardiac output index, tricuspid lateral s', global circumferential strain. Diastolic function: mitral E wave, mitral A wave, mitral E/A ratio, tricuspid E wave, tricuspid A wave, tricuspid E/A ratio, mitral E deceleration time, tricuspid e', E/e' (LV lateral), E/e' (septal), E/e' (RV), MPI.
Akazawa (2016) (23)	BW < p10	38	30	1 wk	Cardiac morphology: LV diastolic dimensions decreased in SGA. Systolic function: stroke volume, left cardiac output, septal s' peak velocity, mitral lateral s' increased in SGA, global longitudinal strain decreased in SGA. Diastolic function: mitral annular early diastolic velocity decreased in SGA, isovolumetric relaxation time increased in severe SGA.	Cardiac morphology: LVM. Systolic function: left cardiac output index, Septal S' peak velocity. Diastolic function: mitral E wave, mitral A wave, mitral E/A ratio, mitral E deceleration time, mitral septal E' tissue Doppler velocity.
Akazawa (2018) (24)	BW < p10	31	27	1 wk	Cardiac morphology: LV diastolic dimension decreased in SGA, LV mass index increased in SGA. Systolic function: fractional shortening increased in SGA, stroke volume, left cardiac output, mitral lateral annular systolic (S') decreased in SGA. Diastolic function: left isovolumic relaxation time increased in SGA, mitral early diastolic lateral (E') tissue Doppler velocity decreased in SGA.	Cardiac morphology: LVM. Systolic function: left cardiac output index, Septal S' peak velocity. Diastolic function: mitral E wave, mitral A wave, mitral E/A ratio, mitral E deceleration time, mitral septal E' tissue Doppler velocity.
Altin (2012) (25)	BW > -2 SD	30	30	72 h postpartum	Cardiac morphology: IVSd, LVPWTd, LVEDd, LVESd, and LVOTd decreased in SGA. LVEDdl increased in SGA. Systolic function: LV stroke volume, LV cardiac output, LV myocardial systolic peak velocity, RV myocardial systolic peak velocity, IVS myocardial peak velocity decreased in SGA. LV cardiac index increased in SGA. Diastolic function: LV E/A increased. LV Em/Am, RV Am decreased.	Systolic function: EF, fractional shortening, LV stroke index. Diastolic function: LV E, LV A, RV E, RV A, RV E/A, LV Em, LV Am, LV E/Em, RV Em, RV Em/Am, RV E/Em, IVS Em, IVS Am, IVS Em/Am.
				3 mo	Cardiac morphology: LVPWTd, LVEDd, LVESd, LVOTd decreased in SGA. LVEDdl increased in SGA. Systolic function: LV stroke volume, LV cardiac output decreased in SGA. LV cardiac index increased in SGA.	Cardiac morphology: IVSd. Systolic function: LVEF, fractional shortening, LV stroke index, LV myocardial systolic peak velocity, RV myocardial systolic peak velocity, IVS myocardial peak velocity. Diastolic function: LV E, LV A, LV E/A, RV E, RV A, RV E/A, LV Em, LV Am, LV Em/Am, LV E/Em, RV Em, RV Em/Am, RV E/Em, IVS Em, IVS Am, IVS Em/Am.
				6 mo	Cardiac morphology: LVEDdl and increased in SGA. Systolic function: LV stroke volume decreased in SGA. LV cardiac index increased in SGA.	Cardiac morphology: IVSd, LVPWTd, LVEDd, LVOTd. Systolic function: EF, fractional shortening, LV stroke index, LV cardiac output, LV myocardial systolic peak velocity, RV myocardial systolic peak velocity. Diastolic function: LV E, LV A, LV E/A, RV E, RV A, RV E/A, LV Em, LV Am, LV Em/Am, LV E/Em, RV Em, RV Em/Am, RV E/Em, IVS Em, IVS Am, IVS Em/Am.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Ánhagen (2022) (12)	BW > -2.5 SD or 22% lower fetal weight than predicted for GA and/or 10% or greater drop in fetal growth velocity based on the weight that would be predicted from the most recent ultrasound examination	19	35	12–72-h postpartum	Left ventricle: LVEDd, IVSd, LVPWtd, LV mass, LV mass index, VL septum systole, VL septum diastole, sphericity index increased. Right ventricle: DL septum, VL septum systole, DL free wall, VL free wall systole, VL free wall diastole increased. Left ventricle: LV mass index increased. DL septum, VL septum diastole, VL septum systole, DL lateral wall, VL lateral wall systole, VL lateral wall diastole, average four segment SL, average SL septal wall, average SL lateral wall, sphericity index decreased. Right ventricle: DL septum, VL septum diastole decreased.	Left ventricle: RWT, DL septum, DL lateral wall, VL lateral wall systole, VL lateral wall diastole, average four segment SL, average SL septal wall, average SL lateral wall. Right ventricle: VL septum diastole.
Arnott (2015) (26)	BW < p10	157	627	3–4 mo 34–49 yr	Cardiac morphology (indexed for BSA): LVEDD, LVESD, LV basal diameter, RV base-to-apex increased. Systolic function (adjusted for age, sex, blood pressure, physical activity levels, and socioeconomic status); LV stroke volume decreased.	Cardiac morphology (indexed for BSA): Left atrial area, left atrial volume, right atrial area, right atrial volume, LV end-systolic volume, LV end-diastolic volume, LVM, RV basal diameter, RV end-systolic volume, RV end-diastolic volume. Systolic function (adjusted for age, sex, blood pressure, physical activity levels, and socioeconomic status); LV S' lateral, LV stroke volume, EF, LV cardiac output, LV fractional area change, RV fractional area change. Diastolic function (adjusted for age, sex, blood pressure, physical activity levels, and socioeconomic status): LV E wave, LV A wave, LV E' medial, LV E' lateral, LV E/E', LV deceleration time.
Bjarnegård (2013) (27)	BW > -2.5 SD (symmetric)	19	18	23 yr	Cardiac morphology: LVEDd decreased in FGR.	Cardiac morphology: Left atrium, IVSd, LVPWd, LVMI.
Castagno (2019) (28)	BW < p10	20	20	2 yr	Cardiac morphology: LVEDd, LVESd, LV area, LV volume decreased in SGA. LVPW, RWT increased in SGA. Systolic function: LV stroke volume, TAPSE decreased in SGA. Diastolic function: Mitral lateral E' velocity decreased in SGA.	Cardiac morphology: IVSd, LVM, LVMI. Systolic function: Fractional shortening, LVEF, LV output. Diastolic function: Mitral E peak, mitral A peak, E/A ratio, E/E' ratio.
Cinar (2013) (29)	BW < p10, ponderal index > 2.25 (symmetric) BW < p10, ponderal index < 2.25 (asymmetric)	39 62	50 50	48–72-h postpartum 48–72-h postpartum	Cardiac morphology: LVEDd, LVPWd, LVWPDs, RWT, LVM, LVMI decreased in FGR. Cardiac morphology: LVEDd, LVESd, LVPWd, LVPWs, RWT, LVM, LVMI decreased in FGR.	Cardiac morphology: IVSd, IVSs, LVESd, LVPWs. Systolic function: LVEF, fractional shortening. Cardiac morphology: IVSd, IVSs. Systolic function: LVEF, fractional shortening.

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Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Cohen (2017) (30)	EFW < p10 and/or fetal growth plus abnormal Doppler	24	23 preterm 19 term	24 h 1 mo	Cardiac morphology: 3-D sphericity index increased in FGR. Cardiac morphology: 2-D sphericity index decreased in FGR. 3-D sphericity index increased in FGR. Diastolic function: Medial and lateral E/e' ratio decreased in FGR. No significant differences.	Cardiac morphology: 2-D sphericity index, LVPWd, RWT. Diastolic function: Lateral E/e' ratio, medial E/e' ratio. Cardiac morphology: LVPWd, RWT.
Crispi (2010) (31)	BW < p10 with normal PI UA	40	120	5 yr	Cardiac morphology: Base-to-apex length LV decreased in FGR. Basal diameter LV and RV, sphericity index LV and RV increased in FGR. Systolic function: Mitral septal S', E/E' (lateral), E/E' (septal) decreased in FGR. Left cardiac output increased in FGR. Diastolic function: Mitral E deceleration time, tricuspid E deceleration time increased in FGR. Cardiac morphology: Basal diameter LV, sphericity index LV, and RV increased in FGR. Systolic function: Left stroke volume, mitral lateral S', mitral septal S', tricuspid S' decreased in FGR. Diastolic function: Mitral E deceleration time, tricuspid E deceleration time E/E' (lateral), E/E' (septal) increased in FGR. Mitral lateral E', mitral septal E', tricuspid E' decreased in FGR.	Cardiac morphology: 2-D sphericity index, 3-D sphericity index, LVPWd, RWT. Diastolic function: Lateral E/e' ratio, medial E/e' ratio. Cardiac morphology: IVSd, LVPWd, RWT. Systolic function: Left stroke volume, LVEF, mitral lateral S', tricuspid S'. Diastolic function: Mitral E wave, mitral A wave, mitral E/A ratio, tricuspid E wave, tricuspid A wave, tricuspid E/A ratio, left isovolumic relaxation time, tricuspid E deceleration time, mitral lateral E', mitral septal E', tricuspid E', E/E' (lateral), E/E' (septal). Cardiac morphology: IVSd, LVPWd, RWT. Systolic function: LVEF. Diastolic function: Mitral E wave, mitral A wave, mitral E/A ratio, tricuspid A wave, tricuspid E/A ratio, left isovolumic relaxation time.
Crispi (2012) (32)	BW p3–p10 with normal CPR BW < p3 or abnormal CPR	25 25	100 100	5 yr 4 yr	Cardiac morphology: left sphericity index decreased in FGR. Systolic function: normalized left stroke volume, MAPSE decreased in FGR. Normalized left cardiac output, left ventricular thickening increased in FGR. Diastolic function: Mitral isovolumic relaxation time'. Cardiac morphology: left and right sphericity index decreased in FGR. Systolic function: normalized left stroke volume, tricuspid S', MAPSE decreased in FGR. Normalized left cardiac output, left ventricular thickening increased in FGR. Diastolic function: mitral E deceleration time, mitral E'/A' decreased in FGR.	Cardiac morphology: Right sphericity index, RWT. Systolic function: LVEF, mitral S', TAPSE, tricuspid S'. Diastolic function: Mitral E deceleration time, mitral E/A ratio, mitral E', mitral E'/A', left isovolumic relaxation time, E/E', tricuspid E deceleration time, tricuspid E/A ratio, tricuspid E', tricuspid A', tricuspid isovolumic relaxation time'. Cardiac morphology: RWT. Systolic function: LVEF. Diastolic function: Mitral E/A ratio, mitral E', mitral E'/A', left isovolumic relaxation time, mitral isovolumic relaxation time', E/E', tricuspid E/A ratio, tricuspid E', tricuspid A', tricuspid isovolumic relaxation time'.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Cruz-Lemini (2015) (10)	EFW and BW < p10	80	80	6.5 mo	Cardiac morphology: Left atrial area IVS increased in FGR. Left sphericity index decreased in FGR. Systolic function: right cardiac output, TAPSE, MAPSE, Tricuspid S' decreased in FGR. Diastolic function: Left isovolumetric relaxation time, mitral E deceleration time, mitral A duration, tricuspid E deceleration time, tricuspid A duration increased in FGR. Mitral lateral E', mitral lateral A', tricuspid E/A ratio, tricuspid E', tricuspid A' decreased in FGR.	Systolic function: LVEF, left stroke volume, right stroke volume, left cardiac output. Diastolic function: Mitral E/A ratio.
Czernik (2013) (33)	BW < p3	19	21	2 days	Cardiac morphology: LVPWd, LVEDd, LVM, mitral valve increased in FGR. Systolic function: fractional shortening decreased in FGR. Cardiac morphology: Mitral valve increased in FGR.	Cardiac morphology: IVSd. Systolic function: left ventricular output.
Elmakaty (2023) (34)	BW < p10	114	414	2–3 days	Cardiac morphology: IVSd, IVSs, LVIDd, LVIDs, LVPWd, LVPWs, LVM, LVMI decreased. Systolic function: LV fractional shortening decreased. Systolic function: TAPSE decreased in FGR. LVEF, LV and RV Tei index increased in FGR. Diastolic function: E/e' ratio decreased in FGR. Left and right E/A ratio increased in FGR.	No nonsignificant differences.
Faienza (2016) (35)	BW and/or length < p3	27	25	10 yr	Cardiac morphology: IVSd, LVIDd, LVPWd, LA, RWT decreased in FGR. IVSd/LVPWd ratio increased in FGR. Systolic function: LV stroke volume, LV cardiac output, LV and RV IVCT' increased in FGR. Mitral lateral S', tricuspid lateral S' decreased in FGR. Diastolic function: Mitral E', mitral E'/A' ratio, tricuspid E', tricuspid A', tricuspid E'/A' ratio decreased in FGR. LV IVRT, RV IVRT, LV E/E' ratio, RV E/E' ratio increased in FGR.	No nonsignificant differences.
Fouzaz (2014) (36)	BW < p10 who suffered IUGR documented by fetal ultrasound biometry and umbilical artery Doppler	30	30	2 days	Cardiac morphology: IVSd, LVIDd, LVPWd, LA, RWT decreased in FGR. IVSd/LVPWd ratio increased in FGR. Systolic function: LV stroke volume, mitral lateral S', tricuspid lateral S' decreased in FGR. LV IVCT' increased in FGR. Diastolic function: Mitral E', mitral E'/A' ratio, tricuspid E', tricuspid A', tricuspid E'/A' ratio, RV IVRT, LV E/E' ratio, RV E/E' ratio increased in FGR.	Systolic function: LV fractional shortening, LVEF. Diastolic function: Mitral E wave, mitral A wave, mitral E/A ratio, tricuspid E wave, tricuspid A wave, tricuspid E/A ratio, mitral A', tricuspid A', tricuspid E'/A'.
				5 days	Cardiac morphology: IVSd, LVPWd, LA, RWT decreased in FGR. IVSd/LVPWd ratio increased in FGR. Systolic function: LV stroke volume, mitral lateral S', tricuspid lateral S' decreased in FGR. LV IVCT' increased in FGR. Diastolic function: Mitral E', mitral E'/A' ratio, tricuspid E', tricuspid A', tricuspid E'/A' ratio, RV IVRT, LV E/E' ratio, RV E/E' ratio increased in FGR.	Cardiac morphology: LVIDd. Systolic function: LV fractional shortening, LVEF, LV cardiac output index, RV isovolumic contraction time'. Diastolic function: Mitral E wave, mitral A wave, mitral E/A ratio, tricuspid E wave, tricuspid A wave, tricuspid E/A ratio, mitral A', tricuspid A', tricuspid E'/A'.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Fouzaz (2014) (37)	BW < p10 who suffered IUGR documented by fetal ultrasound biometry and umbilical artery Doppler	25	25	2 days	Cardiac morphology: IVSd, LVPWd, RWT decreased in FGR. IVSd/LVPWd increased in FGR. Systolic function: LV ICT and RV ICT increased in FGR. Diastolic function: Mitral E', tricuspid E' decreased in FGR. Mitral E/E', tricuspid E/E', LV IRT', RV IRT' increased in FGR.	Cardiac morphology: LVIDd.
Garofoli (2012) (38) Guajardo (1994) (39)	BW < p10	43 15	35 15	5 days 3, 30 days 1 day	Cardiac morphology: LVPWd, RWT decreased in FGR. IVSd/LVPWd increased in FGR. Systolic function: LV ICT', RV ICT' increased in FGR. Diastolic function: Mitral E', tricuspid E' decreased in FGR. Mitral E/E' tricuspid E/E', LV IRT', RV IRT' increased in FGR. No absolute values provided. Systolic function: cardiac output increased in FGR.	Cardiac morphology: LVIDd.
Gürses (2013) (40)	Ponderal index < 10%	20	20	5 days 5 days	No significant differences. Cardiac morphology: LVPWd, LVEDd, IVSd, RVEDd, LA, LVM decreased in FGR.	No nonsignificant differences. Systolic function: cardiac output. Systolic function: LVEF, fractional shortening.
Harada (1998) (41)	BW < 2SD	13	29	1 mo 3 mo 4–6 days	Cardiac morphology: LVEDd, RVEDd, LA, LVM decreased in FGR. Cardiac morphology: LVM decreased in FGR.	Cardiac morphology: LVPWd, IVSd. Systolic function: LVEF, fractional shortening. Cardiac morphology: LVPWd, LVEDd, IVSd, RVEDd, LA. Systolic function: LVEF, fractional shortening. Diastolic function: Velocity time integral of A wave, velocity time integral of E/A.
Ishii (2013) (42)	BW < p10 with a head circumference within + 2SD	30	57	3–6 h 12 h 24 h 48 h 72 h	Diastolic function: Peak E wave, peak A wave, peak E/A wave, velocity time integral of E wave, first third filling fraction, peak filling rate normalized to stroke volume, deceleration time decreased in FGR. Systolic function: LVEF, LV cardiac output decreased in FGR. No significant differences.	Diastolic function: E/e'. Systolic function: LVEF, LV cardiac output. Diastolic function: E/e'.
Ivanov (2019) (43)	BW p3–p10, > 2 SDs, symmetric BW p3–p10, > 2 SDs, asymmetric	15 47	62 62	2–5 days, 6, 12 mo 2–5 days, 6, 12 mo	Systolic function: LVEF, LV cardiac output decreased in FGR. Systolic function: LVEF, LV cardiac output decreased in FGR. Systolic function: LVEF, LV cardiac output decreased in FGR. No P values of statistical tests provided. No P values of statistical tests provided.	Diastolic function: E/e'. Diastolic function: E/e'.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Karagol (2019) (44)	BW < p10	55	200	1 mo	Left and right coronary artery diameters decreased in FGR.	No nonsignificant differences.
Kumar (2019) (45)	BW < 2SDs	35	35	Day 1	Left and right coronary artery diameters decreased in FGR. Cardiac morphology: LVIDD and LVIDs index increased in FGR. Diastolic function: TV E wave deceleration time decreased in FGR.	No nonsignificant differences. Systolic function: Fractional shortening, LVEF. Diastolic function: MV E, MV A, MV E/A, TV E, TV A, TV E/A, MV E wave deceleration time.
Levent (2009) (46)	BW < p10	32	31	8.8 yr	Cardiac morphology: LVIDD, LVIDs increased in FGR. Diastolic function: MV E, MV A, TV A decreased in FGR.	Systolic function: Fractional shortening, LVEF. Diastolic function: MV E/A, TV E, TV E/A, MV E wave deceleration time, TV E wave deceleration time.
Mäkkilä (2016) (47)	BW < p10 and/or an UA PI > 2 SD	60	52	1 wk	Cardiac morphology: LVIDD and LVIDs index increased in FGR.	Systolic function: Fractional shortening, LVEF. Diastolic function: MV E, MV A, MV E/A, TV A, TV E/A, MV E wave deceleration time, TV E wave deceleration time.
Mikkola (2007) (48)	BW < 2 SDs	22	25	5 yr	No significant differences.	Cardiac morphology: LVEDd, IVSd, LVPWd, LVM, LVMI. Systolic function: LVEF, fractional shortening.
Miyamoto (2013) (49)	BW < p10	14	23	2.8 h	No results of statistical tests between FGR and controls shown (only over time difference provided within group). No results of statistical tests between FGR and controls shown (only over time difference provided within group).	Cardiac morphology: IVSd, LVEDd, LV systolic diameter, LVPWd. Systolic function: Fractional shortening, LVEF, left ventricle stroke index, left ventricle cardiac index s. Systolic function: Fractional shortening, LVEF. Diastolic function: Transmittal E, transmittal A, transmittal E/A, Ew, Aw, Ew/Aw, E/Ew.
Montaldo (2022) (50)	BW < p10 with FGR defined as EFw < p3 or < p10 combined with abnormal MCA, UA or uterine artery doppler arteries and/or abnormal CPR	105	105	6 h	Cardiac morphology: LVPWs decreased in FGR.	Systolic function: RV cardiac output.
Morsing (2014) (51)	BW z-score < 2, being delivered on fetal indication by cesarean section	32	32	72 h 7 yr	Systolic function: LV cardiac output decreased in FGR. Systolic function: LV cardiac output decreased in FGR. No significant differences.	Systolic function: RV cardiac output. Systolic function: LV cardiac output, RV cardiac output.
Niewiadomska-Jarosik (2016) (52)	BW < p10 with IUGR features	77	30	7.6 yr	No significant differences. No significant differences.	Systolic function: RV cardiac output. Cardiac morphology: LVMI, IVSd, LVPWd, LVEDd. Systolic function: Fractional shortening, LVEF. Diastolic function: Mitral E/A ratio, mitral velocity time interval, E wave deceleration time.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Olander (2022) (53)	BW < 2 SD, < p3	23	48	5.8 yr	Diastolic function: Mitral E wave, A wave, septal E/E' increased in FGR. Systolic function: MAPSE, TAPSE decreased in FGR.	Cardiac morphology: LV basal sphericity index, LV midpapillary sphericity index, RV base sphericity index, RV midcavity sphericity index. Diastolic function: Mitral E/A ratio, septal E' wave peak velocity, septal E/E' ratio. Systolic function: LVEF.
Olander (2020) (54)	BW < 2 SDs	39	90	34 h (AGA), 56 h (SGA)	Cardiac morphology: IVS increased in SGA. RV midcavity dimension decreased in SGA. Diastolic function: E wave, E/E' decreased in SGA.	Cardiac morphology: Left atrial area, LV basal dimension, LVEDd, LVPWd, LV area, LVM, LV volume, right atrial area, RV basal dimension, RV area, LV basal sphericity index, LV midcavity sphericity index, RV basal sphericity index, RV midcavity sphericity index. Systolic function: LVEF. Diastolic function: MV lateral E' wave peak velocity.
Patey (2019) (55)	EFW < p10 with Doppler evidence of placental dysfunction	33	54	0.5 days	Cardiac morphology: LVEDd decreased in FGR. RV/LVEDd ratio, IVS increased in FGR. Systolic function: RV cardiac output, IVS-S', LV IVCT', RV IVCT' increased in FGR. Diastolic function: LV E/A, RV E/A, LV E'/A', IVS E'/A' decreased in FGR. LV IVRT', RV IVRT' increased in FGR.	Cardiac morphology: RV EDD. Systolic function: RV cardiac output, RV S'. Diastolic function: LV-E/E'.
Rodriguez-Guerineau (2018) (56)	BW < p10	25	25	3.5	Cardiac morphology: LV sphericity index, LV base-to-apex length, RV sphericity index, RV base-to-apex length, IVS, LVPWT, LVM decreased in FGR. Systolic function: LV stroke volume increased in FGR. MAPSE, lateral mitral annulus s', septal mitral annulus s', TAPSE, tricuspid annulus IVCT' decreased in FGR. Diastolic function: Septal mitral annulus e', tricuspid annulus e', tricuspid annulus IVRT' decreased in FGR.	Cardiac morphology: LV basal diameter, RV basal diameter, RWT. Systolic function: LV cardiac output, fractional shortening, RV stroke volume, RV cardiac output, tricuspid annulus s', septal mitral annulus IVCT', lateral mitral annulus IVCT', lateral mitral annulus ET', tricuspid annulus ET', septal mitral annulus ET'. Diastolic function: Lateral mitral annulus e', lateral mitral annulus a', septal mitral annulus a', LV E/A ratio, E mitral deceleration time, tricuspid annulus a', RV E/A ratio, E tricuspid deceleration time, lateral mitral annulus IVRT', septal mitral annulus IVRT'.
Rodriguez-Lopez (2023) (57) Male	BW < p10	108	142	26–36 yr	Cardiac morphology: LV basal diameter increased. Systolic function: LV MAPSE decreased.	Cardiac morphology: LV base-to-apex length, LV sphericity index, LV RWT, LA area, RV basal diameter, RV base-to-apex length, RV sphericity index, RV area. Systolic function: LVEF, LV cardiac output, mitral lateral annular peak systolic velocity, LV global longitudinal strain, fractional area change, TAPSE; tricuspid annular peak systolic velocity. Diastolic function: Mitral E/A, isovolumic relaxation time, tricuspid E/A.
Rodriguez-Lopez (2023) (57) Female	BW < p10	153	120	26–36 yr	Cardiac morphology: LV basal diameter, LV base-to-apex length, RV base-to-apex length increased. Systolic function: LVEF, MAPSE, mitral lateral annular peak systolic velocity, tricuspid annular peak systolic velocity decreased.	Cardiac morphology: LV sphericity index, LV RWT, LV area, RV basal diameter, RV sphericity index, RV area. Systolic function: LV cardiac output, LV global longitudinal strain, fractional area change, TAPSE; Diastolic function: Mitral E/A, isovolumic relaxation time, tricuspid E/A.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Sarvari (2017) (58)	BW < p10	58	96	10.75 yr	Cardiac morphology: LV and RV base to apex length, LV and RV sphericity index decreased in FGR. LV basal diameter increased in FGR. Systolic function: Mitral s', LV global longitudinal strain decreased in FGR. Diastolic function: LV IVRT, RV IVRT increased in FGR.	Cardiac morphology: RWT, RV basal diameter, left atrial area, right atrial area. Systolic function: LV cardiac output, LVEF, tricuspid s'. Diastolic function: Mitral e', tricuspid E/A ratio, tricuspid e'.
Sehgal (2018) (59)	BW or EFW < p10	20	20	10.4 days	No results of statistical tests between FGR and controls shown (only correlations between arterial mechanics and cardiac function parameters).	
Sehgal (2017) (60)	BW < p10	20	20	10.4 days	Systolic function: MAPSE decreased in FGR. Diastolic function: E wave, A wave, TDI mitral E', TDI mitral A' decreased in FGR. E/A ratio, TDI E'/A', E/E' increased in FGR.	Cardiac morphology: RWT. Systolic function: Fractional shortening. Diastolic function: TDI E'/A'
Sehgal (2013) (61)	BW < p3	20	20	76.5 h	Systolic function: Fractional shortening, LV cardiac output index decreased in SGA. Diastolic function: E wave, A wave, IVRT increased in SGA. E/A ratio, E deceleration time, IVRT increased in FGR.	No nonsignificant differences.
Sehgal (2013) (14)	BW < p3	20	20	76.5 h	Systolic function: Left ventricular global longitudinal strain, basal septal strain, basal septal SR, middle septal SR, apical septal strain, apical septal SR, basal lateral strain, basal lateral SR, middle lateral strain, middle lateral SR, apical lateral strain, apical lateral SR decreased in SGA.	No nonsignificant differences.
Sehgal (2022) (62)	BW < p10 with absent/reversed antenatal umbilical artery Doppler	28	26	10.1 days	Cardiac morphology: LVEDd, LVPWd, LVM increased in FGR. Diastolic function: Transmitral E/A increased in FGR.	Systolic function: Fractional shortening, LV cardiac output.
Suciu (2022) (63)	EFW < p10	18	18	1 day	Systolic function: RV cardiac output, TAPSE decreased in SGA. LVEF increased in SGA. Diastolic function: Tricuspid E/A decreased, mitral E, mitral A in SGA. IVRT increased in SGA.	Systolic function: Fractional shortening, LVEF, LV cardiac output. Diastolic function: Tricuspid E, tricuspid A.
				2 days	Systolic function: RV cardiac output, TAPSE decreased in SGA. LVEF increased in SGA. Diastolic function: Tricuspid E/A decreased, mitral E, mitral A in SGA. IVRT increased in SGA.	Systolic function: Fractional shortening, LVEF, LV cardiac output. Diastolic function: Tricuspid E, tricuspid A.

Continued

Table 1.— Continued

Author (Year)	FGR Definition	FGR, n	Control, n	Age	Significant Differences	Nonsignificant Results
Vats (2021) (64)	BW < p10	100	100	53 h	Cardiac morphology: IVSs decreased in SGA. Systolic function: LV ET and RV ET decreased in SGA. RV IVCT increased in SGA. Diastolic function: RV IVRT increased in SGA.	Cardiac morphology: IVSd, LVIDd, LVIDs, LVPWd, LVPWs. Systolic function: LV IVCT. Diastolic function: E wave, A wave, E/A ratio, LV IVRT.
Verma (2023) (65)	BW < p3, or BW < p10 with FGR defined plus abnormal Doppler	24	30	24–48 h	Systolic function: TAPSE decreased in FGR.	Systolic function: Fractional shortening, LVEF, LV output, RV output.
Yiallourou (2017) (66)	EFW < p10 plus absent or reversed EDF of UA	18	15	48 h 9 yr	Systolic function: Fractional shortening, LV EF, TAPSE, RV cardiac output decreased in FGR. No significant differences.	Systolic function: LV output.
Zaharie (2019) (67)	EFW < p10 abnormal Doppler of the UA or/and MCA	40	21	1 and 6 mo	No results of statistical tests between FGR and controls shown (only over time difference provided within FGR group).	Cardiac morphology: LVIDd, LVIDs, LVPWd, sphericity index, RWT, left atrium. Systolic function: Stroke volume, cardiac output, LVEF, fractional shortening. Diastolic function: Mitral E wave velocity, mitral A wave velocity, mitral E/A ratio, left IVRT.

A, diastolic late peak velocity; AGA, appropriate for gestational age; BW, birth weight; MCA, middle cerebral artery; con, control; E, diastolic early peak velocity; EDL, end-diastolic length; EF, ejection fraction; EFW, estimated fetal weight; Em, early myocardial peak velocity; ET, ejection time; FGR, fetal growth restriction; GA, gestational age; IVCT, isovolumetric contraction time; IVS, interventricular septum thickness; IVRT, isovolumetric relaxation time; LV, left ventricle; LVEDd, left ventricular end-diastolic diameter; LVEDs, left ventricular end-systolic diameter; LVEDdi, left ventricular end-diastolic diameter index; LVIDd, left ventricular internal diameter during diastole; LVIDs, left ventricular internal diameter during systole; LVM, left ventricular mass; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall thickness at end diastole; LVPWs, left ventricular posterior wall thickness at end systole; MAPSE, mitral annular plane systolic excursion; MV, mitral valve; p, percentile; RV, right ventricle; RVEDd, right ventricular end-diastolic diameter; RWT, relative wall thickness; SGA, small for gestational age; SL, strain longitudinal; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue doppler imaging; UA, umbilical artery; VL, velocity longitudinal.

Table 2. Overview of the main study characteristics and results of included animal studies

Author (Year)	Species (Strain)	FGR Model	FGR, n	Con, n	Age	Significant Differences	Nonsignificant Results
Alsaid (2017) (68)	Mice (C57BL/6J)	Uterine artery ligation	12	12	12 wk	Cardiac morphology: LVIDs increased in FGR. Systolic function: Fractional shortening, LV EF decreased in FGR.	Cardiac morphology: IVSd, IVSs, LVPWd, LVPWs, LVIDd, LV mass.
Coats (2021) (69)	Rat (SD)	Reduced uterine pressure perfusion	4	4	24 wk	Cardiac morphology: LVIDs increased in FGR. Systolic function: Fractional shortening, LV EF decreased in FGR.	Cardiac morphology: IVSd, IVSs, LVPWd, LVPWs, LVIDd, LV mass.
Kumar (2020) (70)	Rat (SD)	Hypoxic chamber	—	—	Day 1	Cardiac morphology: LVIDs increased in FGR. Systolic function: Stroke volume decreased in FGR. LV EF, cardiac output decreased in FGR.	Cardiac morphology: IVSd, IVSs, LVPWd, LVIDd, LV mass.
					Day 3	No significant differences.	Cardiac morphology: LV mass. Systolic function: Fractional shortening.
					1 wk	Diastolic function: LV lateral wall E'/A' decreased in FGR.	Cardiac morphology: LVEDd/weight, LVPWd/weight, stroke volume/weight, VCFc. Systolic function: Septal S' velocity, LV LW S' velocity. Diastolic function: MV E velocity, MV A velocity, LV LW E' velocity, LV LW A' velocity, LV LW E'/A' velocity.
					2 wk	Systolic function: Septal S', LV lateral wall increased in FGR ($P < 0.008$). Diastolic function: LV lateral wall E', LV lateral wall A' increased in FGR. Diastolic function: LV lateral wall E'/A' decreased in FGR.	Cardiac morphology: LVEDd/weight, LVPWd/weight, stroke volume/weight, VCFc. Systolic function: Septal S' velocity, LV LW S' velocity. Diastolic function: MV E velocity, MV A velocity, LV LW E' velocity, LV LW A' velocity.
					4 wk	Systolic function: LV lateral wall S' increased in FGR. Diastolic function: MV E, LV lateral wall E'/A' decreased in FGR. LV lateral wall A' increased in FGR.	Cardiac morphology: LVEDd/weight, LVPWd/weight, stroke volume/weight, VCFc. Systolic function: Septal S' velocity, LV LW S' velocity. Diastolic function: MV E velocity, MV A velocity, LV LW E' velocity, LV LW A' velocity.
Rueda-Clausen (2008) (71)	Rat, male (SD)	Hypoxic chamber	12	14	4 mo	No significant differences.	Cardiac morphology: RV diameter in diastole, IVSd, IVSs, LVIDd, LVIDs, LVPWtd, LVPWts, M-mode trace LV end-diastolic volume. Systolic function: CO/weight, LV shortening fraction, LVEF. Diastolic function: Mitral E maximum velocity, Mitral A maximum velocity, Mitral E/A index, mitral deceleration time, MPI, Mitral IVRT, Mitral IVCT.

Continued

Table 2.— Continued

Author (Year)	Species (Strain)	FGR Model	FGR, n	Con, n	Age	Significant Differences	Nonsignificant Results
Shah (2017) (72)	Rat, female(SD)	Hypoxic chamber	13	12	4 mo	Cardiac morphology: RV diameter in diastole increased in FGR. IVSs, LVPWTs decreased in FGR. Diastolic function: Mitral E/A index, mitral IVRT increased in FGR. Mitral A maximum velocity, mitral E deceleration time decreased in FGR. No significant differences.	Cardiac morphology: IVSd, LVEDd, M-mode trace LV end-diastolic volume. Systolic function: CO/weight, LV shortening fraction, LVEF. Diastolic function: Mitral A maximum velocity, Mitral IVCT.
	Rat, male(SD)	Hypoxic chamber	—	—	13 wk	Diastolic function: Mitral A maximum velocity, mitral E deceleration time decreased in FGR. Mitral E/A index, mitral IVRT increased in FGR. No significant differences.	Cardiac morphology: IVSd, LVEDd, LVPWTd, M-mode trace LV end-diastolic volume. Systolic function: CO/weight, LV shortening fraction, LVEF. Diastolic function: Mitral E maximum velocity, Mitral IVCT.
	Rat, female(SD)	Hypoxic chamber	—	—	13 wk	Diastolic function: Mitral A max velocity decreased in FGR. Mitral E deceleration time increased in FGR.	Cardiac morphology: LVAWd, LVAWs, LVPWTd, LVIDd, LVIDs, LVEDV, LVEVS. Systolic function: LVEF, fractional shortening. Diastolic function: Mitral E max velocity, Mitral E/A index, Mitral deceleration time, IVRT, Tei index, Mitral annular E' velocity, Mitral annular A' velocity, E/E' ratio.
Thompson, 2018 (42)	Guinea pig, male	Hypoxic chamber	9	9	3 mo	Systolic function: Stroke volume, cardiac output, LV EF, fractional shortening decreased in FGR.	Cardiac morphology: LV diameter in diastole, LV diameter in systole, LVPWTd, LVPWTs, IVSd, IVSs. Systolic function: Stroke volume, CO, LVEF, fractional shortening.
	Guinea pig, female	Hypoxic chamber	9	9	3 mo	No significant differences.	Cardiac morphology: LV diameter in diastole, LV diameter in systole, LVPWTd, LVPWTs, IVSd, IVSs. Systolic function: Stroke volume, CO, LVEF, fractional shortening.

A, diastolic late peak velocity; con, control; E, diastolic early peak velocity; EF, ejection fraction; FGR, fetal growth restriction; IVRT, isovolumetric relaxation time; IVS, interventricular septum thickness; LV, left ventricle; LVIDd, left ventricle internal diameter during diastole; LVIDs, left ventricle internal diameter during systole; LVPWd, left ventricular posterior wall thickness at end diastole; LVPWs, left ventricular posterior wall thickness at end systole; NA, not applicable; MV, mitral valve; RV, right ventricle; SD, Sprague–Dawley, VCF, circumferential shortening velocity.

Table 3. Summary overall effect derived from the forest plots per age category in human FGR versus control

	Neonate	Child
<i>Primary outcome measures</i>		
Cardiac morphology		
Left ventricular mass	↓	=
Left ventricular mass index	=	NA
Left ventricle end-diastolic dimension	=	=
Left ventricular posterior wall thickness in diastole	=	=
Interventricular septum thickness in diastole	↓	=
Systolic function		
Mitral annular systolic peak velocity	↓	=
Tricuspid annular systolic peak velocity	NA	=
Left ventricle cardiac output index	=	NA
Left ventricular ejection fraction	=	=
Fractional shortening	=	=
Diastolic function		
E/A ratio mitral valve	=	=
E/A ratio tricuspid valve	NA	=
Mitral lateral e	↓	=
<i>Secondary outcome measures</i>		
Heart rate	↑	=
Systolic blood pressure	↑	=
Diastolic blood pressure	↑	=

An upward pointing arrow (↑) represents a significant increase in FGR offspring, a downward pointing arrow (↓) represents a significant decrease in FGR offspring, and an equal to sign (=) represents no significant difference in outcome. A, late diastole; E, early diastole; NA, not applicable.

and fractional shortening were similar between groups (Supplemental Fig. S3, B–D).

Echocardiographic diastolic function measurements showed a reduced mitral lateral velocity during early diastole (e) in FGR compared with controls (SMD -0.66 [-0.98; -0.33], $P < 0.01$, $I^2 = 39%$, Supplemental Fig. S4A), but no difference in E/A ratio of the mitral valve was observed (Supplemental Fig. S4B).

Meta-analysis of secondary outcomes showed an increase in both systolic (SMD 0.83 [0.20; 1.45], $P = 0.01$) and diastolic blood pressure in FGR neonates (SMD 0.65 [0.21; 1.08], $P < 0.01$) compared with control neonates (Supplemental Fig. S5, A and B). Both meta-analyses showed very high between-study heterogeneity of $I^2 = 92%$ and $I^2 = 84%$, respectively. Heart rate did not differ between the groups (Supplemental Fig. S5C).

Meta-analysis of echocardiographic data in children.

A total of 23 studies reported echocardiographic data in children, with ages ranging between 30 days and 10.1 yr old. Ultrasound measurements of cardiac morphology (Supplemental Fig. S6), systolic function (Supplemental Fig. S7), and diastolic function (Supplemental Fig. S8) were all similar between FGR and control.

In contrast to the neonatal data, meta-analysis on secondary outcomes, including systolic and diastolic blood pressure and heart rate, showed no differences between the groups (Supplemental Fig. S9).

Echocardiographic data in adults.

As only two studies were performed in the adult age category (age range, 20–49 yr old), we were not able to perform a meta-analysis on this data (26, 57). These two studies showed subtle changes in echocardiographic parameters and regarding cardiac morphology in particular (i.e., the

heart of FGR offspring was slightly enlarged) (Table 1). One of these studies determined echocardiographic parameters for male and female offspring separately and showed that female offspring was more affected (57).

Effect of FGR on myocardial strain analysis using speckle tracking in humans: subtle (preclinical) changes of the heart.

Four studies investigated subclinical cardiac changes with the use of speckle-tracking ultrasound and three found impaired global longitudinal strain (12, 14, 23). One of these studies investigated longitudinal changes and reported no differences directly at birth between FGR and control, yet over a short time of aging of 3 to 4 mo, an impaired cardiac development was observed in FGR offspring compared with control offspring in left ventricular longitudinal strain (12). Another study showed that the severity of decrease of global longitudinal strain depended on the severity of FGR as measured at the age of 1 wk (23). Lastly, one study performed strain analysis in males and females separately, but no significant differences were observed in global longitudinal strain in both male and female offspring (57).

Risk of bias in human studies.

Quality assessment demonstrated a relatively low study quality, especially in the representativeness of the FGR group, because of restricted use of prenatal biometry and Doppler measurements to define FGR, but also in the outcome assessment because of missing reporting on blinding, and unclear reporting on loss of follow-up of participants in the cohort (Supplemental Fig. S10A and Supplemental Table S5). Funnel plots were not created according to protocol (<20 studies per outcome).

Animal Studies

Study characteristics of animal studies.

All five animal studies included rodents with species varying from rats ($n = 4$) (70–72), mice ($n = 1$) (68), to guinea pigs ($n = 1$) (73) (Table 2). Surgical induction by uterine artery ligation was applied in the mice study and by reduced uterine perfusion pressure in one rat study while the other studies induced FGR by use of a hypoxic chamber. Three of the studies assessed sex-specific differences (71–73). Age ranged from 1 day old until 12 mo old. Three of the studies repeated the cardiac ultrasound parameters at multiple time points (68, 70, 71).

Effect of FGR on conventional echocardiographic parameters in animal studies.

An overview of the echocardiographic outcomes is shown in Table 2, and the full data extraction is available in Supplemental Table S4. Considering the restricted overlap in reported echocardiographic parameters, we were unable to perform a meta-analysis.

All five animal studies showed either systolic or diastolic dysfunction of the left ventricle (68, 70–73). Signs of systolic dysfunction included decreased ejection fraction and fractional shortening (68, 70, 73), while signs of diastolic dysfunction included reduced early and late peak velocity over the mitral valve and increased isovolumetric relaxation time (70–72). Cardiac morphological changes were observed with an increase in inner diameter of the left ventricle and decrease in

septal thickness (68, 71). Two studies showed either persistence or progression of cardiac dysfunction over time (68, 70). Sex-specific differences were reported to the prejudice of male offspring in two studies (71, 73), however, another study only observed effects on outcome in female offspring (72).

Secondary outcomes reported in these six animal studies showed conflicting effects with no difference or decreased stroke volume (70, 73), no difference or transient decreased heart rate after birth (70, 71), and no difference or an increase in blood pressure in FGR offspring (71, 73). The included studies reporting on pulse wave velocity as a marker for aortic stiffness appeared persistently increased over time in the FGR group with the largest difference compared with control offspring direct after birth (70).

Risk of bias assessment in animal studies.

Quality assessment of animal studies revealed poor or absence of reporting of essential information, and consequently, we designated the risk of most types of bias largely as unclear (Supplemental Fig. S10B and Supplemental Table S6).

DISCUSSION

Our meta-analysis revealed small differences in echocardiographic parameters between human FGR and control offspring in the neonatal period only, namely, a reduced left ventricular mass and interventricular septum thickness, reduced mitral annular peak velocity, and mitral lateral early diastolic velocity. The few clinical studies on myocardial strain analysis using speckle tracking unanimously showed small preclinical changes in longitudinal global strain FGR offspring. The limited number of animal studies per individual outcome prevented us from performing a meta-analysis.

Age-Dependent Influence of FGR on Conventional Echocardiographic Parameters in Human Studies

Our meta-analysis of human studies revealed only differences in the neonatal population and not during childhood. Potential explanations are related to the small group sizes and the selection of studies as the age range of children in the included studies is skewed with most studies until 8 yr old, only one study at 11 yr old, and only two studies in the (young) adult age category. The limited number of studies in the adult age group showed subtle changes in echocardiographic parameters. Nevertheless, as the onset of some cardiovascular deteriorations (e.g., atherogenesis) occurs later during childhood, an effect of FGR would possibly be more apparent if more studies were performed within this age category (74).

Alternatively, the discrepancy between the neonatal and childhood comparison might reflect cardiac plasticity. The increased workload of the fetal heart as a response to hemodynamic redistribution during pregnancy possibly recovers since the birth of the neonate and thereby discontinued exposure to an adverse hypoxic environment allows rehabilitation. The observed difference in the neonatal study population might more purely reflect the FGR impact since the exposure to other factors has not occurred yet. Therefore, the diagnosis of FGR might just be as valuable to predict long-term outcomes as the neonatal echocardiographic parameters. Besides

the natural ongoing maturation and growth of the heart as part of aging, other factors at older age such as catch-up growth, genetic resilience, or second hits unavoidably play a more significant role in cardiovascular risk development (4, 8, 75); these factors might outweigh the effect of FGR itself later in life.

Nevertheless, at all ages, the echocardiographic differences in FGR offspring could be considered an early sign of susceptibility to develop cardiovascular disease. Specifically, studies on myocardial strain analysis using speckle tracking showed impaired global strain in the left ventricle in FGR, which suggests preclinical left ventricular dysfunction. However, the relation to relevant long-term consequences remains to be elucidated. The same applies to the most optimal time frame to perform cardiac ultrasound to detect patients with FGR at risk.

Echocardiographic Parameters in Animal Models of FGR: A Small Number of Studies and Use of Small Animals Only

Our systematic review identified a limited number of studies on the effect of FGR on echocardiographic parameters in animals. This may be because ultrasound is noninvasive in humans, while in rodents it requires anesthesia, making humans the preferred study population. In animals, anesthesia can affect echocardiographic measurements, which may explain the conflicting observations on some parameters (76). Our systematic review mostly included studies using a hypoxic chamber to induce FGR, while the surgical induction by uterine artery ligations appears to be more suitable to study cardiac function in FGR (77). Currently, none of the studies used larger animals such as pigs or sheep. The use of large animal models of FGR could increase the translational value (78) as they are anatomically closer to humans, and cardiac ultrasound can be performed in these animals without anesthesia.

The few studies that have been performed in animal models all showed some differences in systolic or diastolic function in the FGR group. In contrast to human studies, the effect seems to either persist or become greater at older age. This might be explained by the accelerated aging observed in animals while the human studies only included young adults as long-term follow-up remains challenging in human trials. On the other hand, the included animal studies were of poor quality, which is associated with an overestimation of intervention effects.

Strengths and Limitations

Our systematic review and meta-analysis are the first to provide an overview of all the cardiac ultrasound measurements available (no restrictions applied on species or specific measurements) in FGR offspring in both human and animal studies, which allows for evaluation of modifying factors and highlights the need of uniformization of study design and improvement of study quality. With that, we aimed to create awareness of the limitations of included studies among researchers in the field and the results of this study could be used to optimize future study designs on this topic.

Although intended, our meta-analysis is limited to being unable to study the influence of several potential factors

because of underreporting and small group sizes. Sex is believed to be of great influence from the developmental origin of disease perspective and has also been described in a few animal studies (71–73), thereupon it is unfortunate that the exact impact of sex remains unclear as we were unable to perform meta-regression. Only one human study investigated sex-specific differences in echocardiographic parameters including myocardial strain in which female SGA offspring appeared to be more susceptible to cardiac dysfunction (57). In addition, interobserver and intraobserver differences are a well-known limitation of ultrasound. Although we are aware that this hampers reproducibility, we were unable to take this into account and therefore unable to distinguish the influence on heterogeneity of our data. In general, there were too limited data to perform subgroup analyses, leaving considerable levels of between-study heterogeneity unexplained for a number of outcomes. In addition, the interdependence of multiple ultrasound outcomes increases the statistical chance of false-positive findings. We acknowledge that this poses interpretive challenges to the results of our meta-analyses, and further research is needed to elucidate the sources of heterogeneity in these analyses. Of note, the poor reporting of key quality indicators and measures to reduce bias in both human and animal studies reduces the confidence we can have in their findings and should be taken into account when interpreting the results of our data synthesis. The reader should also be aware that the limited number of studies included in our meta-analyses prevented us from assessing publication bias, and we can therefore not rule out an influence of publication bias on our meta-analysis. Finally, our meta-analysis focused on cardiac ultrasound measurements, rather than potential adverse arterioventricular interactions in the FGR group. FGR has an established negative impact on vascular development and maturation, which can increase cardiac afterload (79). This can trigger a cascade of adverse arterioventricular interactions that ultimately lead to cardiac dysfunction (80). It is tempting to speculate that the age-dependent influence of FGR on cardiac parameters is explained by normalization of the cardiac afterload during childhood. The interaction between the vascular system and cardiac performance was not the focus of this meta-analysis, however. Further studies are needed to elucidate mechanisms underlying the normalization of cardiac parameters in FGR children during childhood.

Future Perspectives

Although cardiac ultrasound offers a noninvasive manner to detect or monitor early signs of cardiovascular predisposition in FGR offspring, the clinical value of echocardiography alone to reflect a child's vascular status appears limited and hampers further implementation in clinical practice. The largest challenges include identification of optimal timing and the exact relation to long-term cardiovascular function. Besides, most likely one specific ultrasound measurement will not form a good predictor, but rather the combination of multiple promising echocardiographic or the combination of other parameters could contribute to the estimation of an individual cardiovascular risk profile. Regarding echocardiographic parameters, we would recommend focusing more on

myocardial strain analysis and include an older human study population or larger animal models of FGR. Other imaging parameters that hold promise involve cardiac MRI to evaluate cardiac remodeling in FGR (81), while nonimaging parameters such as arterial stiffness measured with carotid distensibility coefficient or pulse wave velocity might offer a better risk estimation (23). As the best prevention of cardiovascular disease so far concerns hypertensive treatment, conventional blood pressure measurements over time to start early therapy in FGR offspring might provide the most gainful approach (82).

DATA AVAILABILITY

All data are provided within the article or supplemental data.

SUPPLEMENTAL DATA

Tables S1–S6 and Supplemental Figs. S1–S10: <https://doi.org/10.6084/m9.figshare.25479805.v2>.

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DISCLOSURES

None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

M.v.d.M., S.C.A.J., K.E.W., A.T.L., and F.T. conceived and designed research; M.v.d.M. and F.T. analyzed data; M.v.d.M., K.T.N., S.C.A.J., J.K., H.S.S., K.E.W., A.T.L., and F.T. interpreted results of experiments; M.v.d.M. and F.T. prepared figures; M.v.d.M. and F.T. drafted manuscript; M.v.d.M., K.T.N., J.K., H.S.S., K.E.W., A.T.L., and F.T. edited and revised manuscript; F.T. approved final version of manuscript.

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