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Antenatal detection of fetal growth restriction and risk of stillbirth: population-based case–control study

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KEYWORDS: antenatal detection; fetal growth restriction; stillbirth

CONTRIBUTION

What are the novel findings of this work?
This population-based study reports a smaller protective effect against stillbirth of detection of fetal growth restriction (FGR) than previous studies, with over 40% of stillbirths among small-for-gestational-age (SGA) fetuses occurring despite detection of FGR.

What are the clinical implications of this work?
In the context of universal ultrasound screening, these findings raise the possibility that routine examination may be less efficacious than is sonography indicated based on risk-factor criteria. They call into question focusing solely on improving detection of FGR without addressing management post-detection. Preventive strategies targeting all stillbirths may ultimately have a larger impact on the risks of SGA-related as well as other stillbirths.

ABSTRACT

Objectives *Antenatal surveillance of intrauterine growth aims to detect growth-restricted fetuses (FGR), which face increased risk of stillbirth. Improving their detection could be an effective strategy for prevention of stillbirth. The French REPERE study was conducted to estimate the association between antenatal detection of FGR and risk of stillbirth.*

Methods *REPERE is a case–control study performed in three French districts with a combined total of approximately 30 000 births annually. Cases were singleton small-for-gestational-age (SGA) stillbirths ≥ 24 weeks' gestation and without severe congenital anomaly, between 2012 and 2014, identified using a population-based stillbirth registry; controls were live births fulfilling the same inclusion criteria over a 9-week period from 7 April to 8 June 2014. Data were extracted by trained investigators from medical records and ultrasound reports. SGA was defined as birth weight < 10th percentile of French customized standards. FGR was defined by the presence of at least one of seven predefined parameters (suspected FGR mentioned in medical records or in ultrasound report, suspected faltering growth mentioned in an ultrasound report, documented abdominal circumference or estimated fetal weight < 10th percentile, referral for additional ultrasound examination to monitor growth or abnormal umbilical artery Doppler). We used logistic regression to estimate crude and adjusted odds ratios (ORs) for the association between detection of FGR and risk of stillbirth. Included covariables were parity, maternal medical history, vascular complications during pregnancy and birth-weight percentile, which are known to be associated with risk of detection of FGR and of stillbirth.*

Results *During the study period, there were 92 182 births ≥ 22 weeks' gestation, including 669 stillbirths, of which 79 were singleton SGA stillbirths ≥ 24 weeks and without severe congenital anomaly. Of these cases, 44.3% (35/79) had FGR detected, compared with a detection rate of 36.2% in controls (154/426). The crude OR expressing the association between detection of FGR and risk of stillbirth was 1.4 (95% CI, 0.9–2.3) and the OR adjusted for parity, presence of risk factors for FGR, presence of vascular disorder and birth-weight percentile was 0.6 (95% CI, 0.3–1.0). Among deliveries ≥ 28 weeks, detection rates were 38.3% vs 36.0% for cases and controls, with an adjusted OR of 0.5 (95% CI, 0.2–1.0).*

Conclusion *Antenatal detection of FGR was protective against stillbirth, but over 40% of stillbirths among SGA*

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fetuses occurred despite detection of FGR, pointing to the need to improve management following detection.

INTRODUCTION

Prevention of stillbirth is one of the main challenges in obstetrics; while stillbirth rates have declined in many countries, these declines are less marked than those in infant mortality[1]. Recent international initiatives have called to attention the health burden associated with stillbirth, the consequences for parents and the need for research into effective preventive strategies[2–4].

One focus of attempts to improve prevention of stillbirth is better detection of fetal growth restriction (FGR)[5]. Having a low birth weight for gestational age increases the risk of stillbirth by a factor of between three and four[6]. Consequently, fetal-growth monitoring is a cornerstone of antenatal surveillance and is endorsed by national obstetric societies[7–11]. Guidelines recommend screening for small-for-gestational age (SGA) fetus, most commonly defined by an estimated fetal weight $< 10^{th}$ percentile of growth references, using risk-factor assessment, fundal-height measurement and either risk-based or routine ultrasound examination[7–11]. Further monitoring of fetuses identified as SGA makes it possible to identify those with FGR, defined as faltering growth, and to induce delivery in order to avoid severe fetal compromise and death[12,13]. Despite the general consensus on the importance of screening, current practices are heterogeneous[14] and identify only between 10% and 36% of infants with birth weight $< 10^{th}$ percentile detected during pregnancy[15–20].

Perinatal audits frequently identify inadequate recognition of FGR as a substandard care factor involved in stillbirth[21,22]. Several population-based studies have shown that fetuses with SGA that goes undetected compared with those in which SGA is detected have a higher risk of stillbirth[19,23–25]. Low prenatal detection rates of around 12% among singleton SGA stillbirths $\geq$ 28 weeks, and of 18% and 23% among those stillborn $\geq$ 24 weeks, were reported in New Zealand, England and Sweden, respectively, compared with corresponding SGA live-birth rates of 32%, 31% and 53%, respectively[23–25]. Furthermore, a study in England and Wales over the period 2007–2012 concluded that implementing training and accreditation programs in customized fetal growth assessment, with promotion of evidence-based protocols and best-practice guidelines, was associated with a downward trend in stillbirth rates in high-uptake areas[26].

We therefore sought to estimate the impact of antenatal detection of FGR on risk of stillbirth in a French population and to assess the potential for reducing the rate of stillbirth through improved detection. The French context is of interest as routine second- and third-trimester ultrasound examinations are included in standard antenatal care.

METHODS

Study design

The REPERE Study is a clinical trial ('Repérage du Retard de Croissance Intra-Utérin (RCIU): Bénéfice sur la Mortinatalité et Facteurs Associés', NCT01995968, registered 27 November 2013) which uses a case–control design nested in a population-based stillbirth register, the Registry of Childhood Handicaps and Perinatal Observatory (RHEOP). This register includes all stillbirths to residents in three of the eight districts of the Auvergne-Rhône-Alpes region, with approximately 30 000 births per year[27], and uses the World Health Organization[28] threshold of 500 g or 22 or more completed gestational weeks for registering stillbirths. The register includes stillbirths recorded in 19 public and private maternity hospitals located in the three districts as well as a university referral center located in a neighboring district. Data for inclusion in the register are extracted from medical records by trained nurses, midwives or physicians.

For inclusion in our study group we identified using RHEOP all SGA singleton non-anomalous fetal deaths $\geq$ 24 weeks' gestation between 2012 and 2014. SGA was defined as birth weight $< 10^{th}$ percentile of French references customized for sex, maternal height and weight and parity[29,30]. Terminations of pregnancy, multiple pregnancies and fetuses with severe congenital anomalies were excluded, as their detection and management strategies are different. Information additional to that obtained from the stillbirth registry was collected from medical records and ultrasound reports.

For our control group, from the birth registry of each maternity unit, we identified all singleton non-anomalous live births $\geq$ 24 gestational weeks, with birth weight $< 10^{th}$ percentile of customized references[30], that were delivered to mothers residing in the same three RHEOP districts over a period of 9 consecutive weeks (7 April–8 June 2014) during the recruitment period for stillbirths. For this period, in order to allow identification of SGA live births using customized models, obstetric units recorded for all deliveries maternal height, weight at booking and parity.

According to French regulations for observational studies, oral informed consent was obtained from mothers of cases when they were included initially in the stillbirth register. Mothers of live births were informed prospectively during their hospital stay or the information form was sent after their discharge from hospital. The study protocol was registered (NCT01995968) and authorization was obtained from the French data protection authority, Commission on Information Technology and Liberties (DR-2013-149), and the regional ethics committee, CECIC Auvergne-Rhône-Alpes (IRB 5891).

Data collection

For both cases and controls, the following data were extracted from medical records by trained midwives:

maternal age, profession, medical and obstetric history, maternal height and prepregnancy weight (at booking), pregnancy complications, mode of onset of labor and delivery, gestational age at delivery and birth weight, gestational age at death, findings from placental examination and fetal autopsy for stillbirths and neonatal transfer and in-hospital mortality data for live births.

In France, gestational age is based on the date of the last menstrual period and measurement of crown–rump length at the first-trimester scan[31]. Three routine ultrasound examinations are recommended, at 11–13 weeks for pregnancy dating, 20–25 weeks for detection of fetal anomalies and at 30–35 weeks for growth monitoring[32]. Umbilical artery Doppler is indicated every 3 weeks for SGA fetuses[31]. Data collected from ultrasound reports included gestational age at examination, indication (routine examination or additional exam indicated for growth monitoring or other reason), fetal biometry, estimated fetal weight and corresponding percentiles according to the ultrasound report, umbilical artery Doppler findings, amniotic fluid volume, minor sonographic markers and congenital anomalies, and conclusion of the sonographer (normal growth, or suspicion of FGR/growth faltering).

Detection of FGR was defined, before data collection commenced, as at least one of the following criteria: (1) suspected FGR mentioned in medical charts; (2) suspected FGR mentioned in an ultrasound report; (3) growth faltering mentioned in an ultrasound report; (4) estimated fetal weight (EFW) $< 10^{th}$ centile of the reference curves used by the sonographer documented in the ultrasound report; (5) abdominal circumference (AC) $< 10^{th}$ centile of the reference curves used by the sonographer documented in the ultrasound report; (6) referral for additional growth-monitoring ultrasound examination; or (7) abnormal umbilical artery Doppler documented in the ultrasound report. We used two further definitions for sensitivity analyses: 'confirmed FGR' excluded cases in which detection was followed by a reassuring scan, and 'monitored FGR' was based solely on criterion (6) (referral for additional ultrasound examination for growth monitoring). The time between first detection of FGR and birth was recorded.

Sample size calculation

Based on previous studies[33,34] we hypothesized that 30% of SGA live births would have FGR detected prenatally and that the protective effect of detection on stillbirth risk would correspond to an odds ratio (OR) of 0.4, yielding a required sample size of 88 cases and 264 controls, with three controls per case, a power of 80% and a two-sided risk alpha of 5%. Data collection for cases continued for 3 years to achieve this sample size.

Statistical analysis

To characterize the context of our study, we first computed the stillbirth rate for all births, singleton births, births ≥ 24 weeks and our study sample of non-anomalous, singleton births ≥ 24 weeks. We also computed the prevalence of SGA among singleton stillbirths and live births ≥ 24 weeks in order to estimate the impact of SGA on risk of stillbirth in this population. Total numbers of births were obtained from national-birth-certificate and hospital-discharge data.

Sociodemographic and clinical characteristics of cases and controls were then compared using χ^2 tests and analysis of variance. We described the frequency of ultrasound and Doppler criteria used to identify FGR. The impact of detection of FGR on risk of stillbirth was assessed by crude and adjusted ORs and 95% CIs using logistic regression. Models were adjusted for parity, presence of vascular disorder (gestational hypertension, pre-eclampsia, eclampsia, HELLP syndrome, placental abruption) and a history of medical and obstetric complications that raise the risk of FGR as specified by the French National Health Board recommendations on conditions and risk factors requiring care by an obstetrician, as opposed to a midwife or primary-care physician (chronic hypertension, insulin-dependent diabetes mellitus, maternal renal, cardiac or autoimmune disease, drug abuse, sickle-cell anemia, thrombophilia, previous stillbirth, SGA infant or gestational vascular disorder)[32,34,35]. We also considered birth-weight percentile in the analyses because of the differences between cases and controls.

A final analysis of stillbirths with FGR detected and those with FGR undetected aimed to identify clinical and management profiles which could orient prevention efforts by comparing differences in gestational age at delivery, birth-weight percentile, time between death and last ultrasound examination and gestational age at first detection.

We conducted four sensitivity analyses of our final model. First, we redid the analyses on only third-trimester stillbirths ≥ 28 weeks, as some obstetricians may not initiate active management of FGR in the extremely preterm period[36]. Second, we used alternative definitions for detection of FGR, as described above. Third, we recomputed SGA status under the assumption that death occurred 2 days before delivery. This interval of 2 days has been used in previous studies on SGA stillbirths[23,37]. Finally, we carried out analyses stratified by severity of SGA (birth weight $< 3^{rd}$ percentile *vs* $\geq 3^{rd}$ percentile) and for women with low- *vs* high-risk pregnancy, defined according to presence of risk factors for FGR based on medical or obstetric history and/or complications in the current pregnancy.

$P < 0.05$ was considered statistically significant and statistical analyses were conducted using Intercooled STATA (Version 13, Stata Corp., College Station, TX, USA).

RESULTS

During the 3-year period from 2012 to 2014, there were 92 182 deliveries in the region and 669 stillbirths, of which 57 were in multiple pregnancies and 127 were < 24 weeks

(Figure 1). Rates of singleton stillbirth ≥ 24 weeks varied from 5.1 to 5.2 per 1000 total births during this time. Among the 485 singleton stillbirths ≥ 24 weeks, 121 (24.9%) were SGA. Prior to analysis of detection of FGR, we excluded 25 cases with severe congenital anomaly and 17 which underwent termination of pregnancy. Thus, the final sample included 79 stillbirths ≥ 24 weeks, of which 47 were ≥ 28 weeks. There were 5096 total deliveries during recruitment of the control population; 4927 were singleton live births ≥ 24 weeks, of which 426 (8.6%) were SGA.

Mothers of cases were more often unemployed, nulliparous and of foreign origin, but maternal age distributions between cases and controls were the same (Table S1). About 30% of mothers smoked during pregnancy in both groups. A history of previous FGR was present more often among controls ($P < 0.05$), while a history of diabetes or pregnancy complications (vascular disorder, placental abruption, or PPROM or preterm labor before 28 weeks) was more frequent among cases ($P < 0.01$). Controls were more likely to have had a first-trimester scan ($P < 0.001$) and at least one second-trimester scan ($P < 0.05$). Cases were delivered at earlier gestational ages ($P < 0.001$) and were more likely to have severe SGA ($P < 0.001$). Eight (1.9%) controls had an Apgar score < 7 at 5 min and 17 (5.5%) of the 309 controls with this information had cord blood arterial pH < 7.10. The rate of transfer to a neonatal unit was 16.2% ($n = 69$) and one death associated with a cerebral hemorrhage occurred during neonatal hospitalization at the age of 22 days.

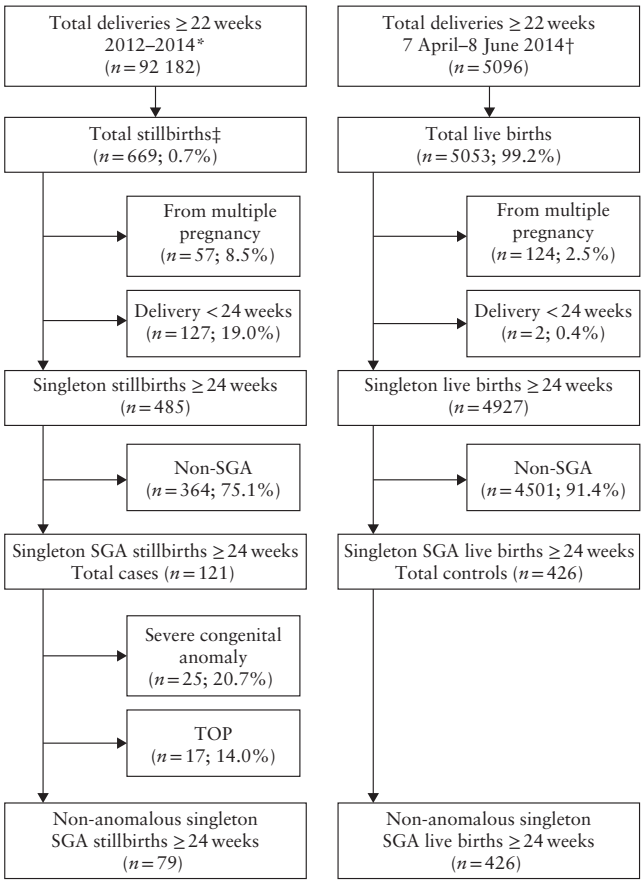

Figure 1 Selection of cases and controls for REPERE study of association between antenatal detection of fetal growth restriction and risk of stillbirth. Total numbers of births obtained from: *national birth certificates (Institut National de la Statistique et des Études Économiques (INSEE), https://insee.fr/fr/accueil), †hospital discharge data and ‡population-based stillbirth register, Registry of Childhood Handicaps and Perinatal Observatory (RHEOP). SGA, small-for-gestational age; TOP, termination of pregnancy.

FGR was detected in 44.3% of cases and 36.2% of controls (Table 1), at a mean ± SD gestational age of 25.7 ± 4.8 and 30.3 ± 5.4 weeks, respectively. Rates of abdominal circumference < 10th centile, abnormal umbilical artery Doppler and growth faltering mentioned in ultrasound reports were significantly higher for cases than controls. The most frequent criterion for antenatal detection of FGR in both groups was mention of suspected FGR in the conclusion of an ultrasound report (in 35.4% of cases and 25.1% of controls). The rate of detection of FGR was higher among early (24–27 weeks) than among late (≥ 28 weeks GA) stillbirths (53.1% vs 38.3%), and detection was based mainly on AC < 10th centile (43.8% of cases stillborn at 24–27 weeks) and abnormal umbilical artery Doppler (21.9% of cases stillborn at 24–27 weeks). Among controls, all obstetric intervention rates were higher in the subgroup in which FGR was detected compared with that in which FGR was not detected ($P < 0.001$, Table S2), including induction of labor (33.8% *vs* 23.5%), Cesarean delivery prelabor (21.4% *vs* 6.3%) and Cesarean delivery overall (37.0% *vs* 18.8%). Mean gestational age at birth in these groups was 37.9 ± 2.8 *vs* 39.7 ± 1.4 weeks ($P < 0.001$).

The unadjusted estimate of the association of detection of FGR with risk of stillbirth (≥ 24 weeks) was > 1 and not significant (OR, 1.4 (95% CI, 0.9–2.3)) (Table 2). After adjustment for parity, risk factors for FGR, vascular disorder and birth-weight percentile, detection of FGR was associated with a decreased risk of stillbirth (OR, 0.6 (95% CI, 0.3–1.0)).

Regarding the four sensitivity analyses, among late stillbirths (≥ 28 weeks), 38.3% of cases had had FGR detected and the adjusted OR in the final model was slightly lower than that obtained for delivery ≥ 24 weeks: 0.5 (95% CI, 0.2–1.0) (Table 2). Confirmed FGR (exclusion of cases with reassuring follow-up ultrasound) rates were lower (36.7% and 32.2%, respectively, for cases and controls) than the rates using the original definition of FGR, and the protective effect was stronger (OR, 0.5 (95% CI, 0.3–0.8)) (Table S3). Monitored FGR (referral for follow-up ultrasound) rates were 30.4% and 23.7%, for cases and controls, respectively, and the adjusted OR was 0.7 (95% CI, 0.4–1.2). Reducing the gestational age at stillbirth by 2 days to account for errors in timing of death did not affect the results (OR, 0.6 (95% CI, 0.3–1.0)). Finally, analyses stratified according to the severity of SGA and the presence of risk factors for FGR confirm the protective effects in all groups, and suggest that the protective effects of detection of FGR may be most acute among cases

Table 1 Antenatal detection of fetal growth restriction (FGR) in cases of singleton small-for-gestational-age stillbirth (SB) and controls liveborn (LB) ≥ 24 weeks

Criterion for diagnosis of FGR	*Cases*			*Controls*	
	SB ≥ 24 weeks	*SB at 24–27 weeks*	*SB ≥ 28 weeks*	*LB ≥ 24 weeks*	P*
n	79	32	47	426	
AC (in mm) < 10th percentile mentioned on US report	20 (25.3)	14 (43.8)	6 (12.8)	60 (14.1)	< 0.05
EFW (in g) < 10th percentile mentioned on US report	20 (25.3)	12 (37.5)	8 (17.0)	78 (18.3)	NS
Abnormal umbilical artery Doppler mentioned on US report	10 (12.7)	7 (21.9)	3 (6.4)	19 (4.5)	< 0.01
Growth faltering mentioned on US report	12 (15.2)	4 (12.5)	8 (17.0)	33 (7.7)	< 0.001
Suspicion of FGR mentioned on US report	28 (35.4)	13 (40.6)	15 (31.9)	107 (25.1)	NS
Additional US indicated for suspicion of FGR	24 (30.4)	11 (34.4)	13 (27.7)	101 (23.7)	NS
Detection of FGR (at least one of above criteria)	35 (44.3)	17 (53.1)	18 (38.3)	154 (36.2)	NS

Data are given as *n* (%). The criterion (suspected growth restriction mentioned in medical charts) did not provide information additional to that obtained from ultrasound reports. *SB ≥ 24 weeks *vs* controls. AC, abdominal circumference; EFW, estimated fetal weight; NS, not significant ($P \geq 0.05$); US, ultrasound.

Table 2 Crude and adjusted odds ratios (OR) for association of detection of fetal growth restriction (FGR) with risk of stillbirth

Covariable	*Stillborn (cases)*	*Liveborn (controls)*	*Crude OR (95% CI)*	*Adjusted OR* (95% CI)*
≥ 24 weeks	*n* = 79	*n* = 426		
Detection of FGR (ref: no)	35 (44.3)	154 (36.2)	1.4 (0.9–2.3)	0.6 (0.3–1.0)
Parity (ref: parous)	49 (62.0)	189 (44.4)	2.0 (1.3–3.4)	1.6 (0.9–2.9)
Presence of risk factors for FGR (ref: no)†	13 (16.5)	108 (25.4)	0.6 (0.3–1.1)	0.6 (0.3–1.2)
Maternal vascular disorder (ref: no)	18 (22.8)	45 (10.6)	2.5 (1.4–4.6)	1.5 (0.8–3.1)
Birth-weight percentile	2.67 ± 2.5	5.64 ± 2.9	0.7 (0.6–0.8)	0.7 (0.6–0.7)
≥ 28 weeks	*n* = 47	*n* = 425		
Detection of FGR (ref: no)	18 (38.3)	153 (36.0)	1.1 (0.6–2.1)	0.5 (0.2–1.0)
Parity (ref: parous)	29 (61.7)	188 (44.2)	2.0 (1.1–3.8)	1.6 (0.8–3.2)
Presence of risk factors for FGR (ref: no)†	6 (12.8)	107 (25.2)	0.4 (0.2–1.1)	0.4 (0.2–1.1)
Maternal vascular disorder (ref: no)	10 (21.3)	43 (10.1)	2.4 (1.1–5.2)	1.5 (0.7–3.6)
Birth-weight percentile	3.04 ± 2.6	5.65 ± 2.9	0.7 (0.6–0.8)	0.7 (0.6–0.8)

Case and control data are given as *n* (%) or mean ± SD. Cases and controls were non-anomalous singleton small-for-gestational-age fetuses; cases underwent stillbirth ≥ 24 weeks and controls were liveborn ≥ 24 weeks. *Adjusted for parity, presence of risk factors for FGR, presence of vascular disorder and birth-weight percentile. †As part of medical or obstetric history (chronic hypertension, insulin-dependent diabetes mellitus, maternal renal, cardiac or autoimmune disease, drug abuse, alcoholism, sickle-cell anemia, uterine malformation, thrombophilia, previous stillbirth, previous small-for-gestational-age infant or gestational vascular disorder). ref, reference.

of severe SGA (birth weight < 3rd centile) and among high-risk women.

Table 3 reveals significant differences between cases of stillbirth in which FGR was detected and those in which it was not. The largest proportion of stillbirths with FGR detected (37%) delivered at 24 to 25 weeks of gestation, while the largest proportion of those which went undetected (32%) delivered at term (≥ 37 weeks) ($P < 0.01$). Stillbirths with FGR detected compared with those which went undetected were much more likely to have birth weight < 5th percentile ($P < 0.001$) and they had more associated complications although this difference was not significant. Among stillbirths with FGR undetected, over 20% had no ultrasounds and more than half occurred 5 weeks or more after the last routine ultrasound examination.

DISCUSSION

We found that 44.3% of singleton non-anomalous SGA stillbirths ≥ 24 weeks' gestation, compared with 36.2% of SGA live births, had FGR detected during pregnancy, leading to a crude estimate of the impact of detection on stillbirth (i.e. OR) of 1.4 (95% CI, 0.9–2.3). Following adjustment for parity, presence of risk factors for FGR, presence of vascular disorder and birth-weight percentile, detection of FGR was protective against stillbirth (adjusted OR, 0.6 (95% CI, 0.3–1.0), confirming previous results[23–25]. However, the magnitude of this effect was smaller than that reported previously, due to higher rates of detection of FGR among SGA stillbirths in our study.

Strengths and limitations

This study's strengths include its population-based design, which allowed us to identify all SGA stillbirths in a population of over 90 000 births. Data were extracted from medical charts and ultrasound reports by trained investigators using a standardized case report form, which made it possible to evaluate detection of FGR using predefined criteria based on clinical and ultrasound parameters and to carry out sensitivity analyses. This study, in the French context, where ultrasound use is

common (in 2010, 98% of pregnant women had at least three ultrasound examinations[38]), adds to the findings of previous reports from countries without routine third-trimester ultrasound[23–25]. Limitations include a lack of information on timing of death, but the sensitivity analysis which assumed death had occurred 2 days prior to the date of delivery yielded similar results. We also lacked information that would have enabled us to consider the reasons for medical teams' decisions after detection.

Table 3 Characteristics of small-for-gestational-age stillbirths ≥ 24 weeks, according to whether fetal growth restriction (FGR) was detected

Characteristic	*FGR detected*	*FGR undetected*	P
n	35	44	
Antenatal care			
Any second-trimester US (20–25 weeks)†	19/22 (86.4)	32/40 (80.0)	NS
Any third-trimester US (30–35 weeks)†	4/4 (100.0)	11/14 (78.6)	NS
Pregnancy complications			
Vascular disorder	10 (28.6)	8 (18.2)	NS
Pre-eclampsia	4 (11.4)	4 (9.1)	NS
Placental abruption	3 (8.6)	2 (4.5)	NS
GH	3 (8.6)	2 (4.5)	NS
PPROM	3 (8.6)	5 (11.4)	NS
GA at detection of FGR			
21–23 weeks	19 (54.3)	N/A	
24–25 weeks	3 (8.6)	N/A	
26–27 weeks	2 (5.7)	N/A	
28–31 weeks	5 (14.3)	N/A	
32–36 weeks	6 (17.1)	N/A	
≥ 37 weeks	0 (0.0)	N/A	
Time between last US and delivery			< 0.001
≤ 1 week	20 (57.1)	3 (6.8)	
2 weeks	11 (31.4)	3 (6.8)	
3–4 weeks	3 (8.6)	7 (15.9)	
≥ 5 weeks*	1 (2.9)	23 (52.3)	
No/missed routine US	0 (0.0)	8 (18.2)	
GA at delivery			< 0.01
24–25 weeks	13 (37.1)	4 (9.1)	
26–27 weeks	4 (11.4)	11 (25.0)	
28–31 weeks	4 (11.4)	8 (18.2)	
32–36 weeks	11 (31.4)	7 (15.9)	
≥ 37 weeks	3 (8.6)	14 (31.8)	
Birth weight			< 0.001
< 1st percentile	28 (80.0)	16 (36.4)	
2nd to < 5th percentile	4 (11.4)	19 (43.2)	
5th to < 10th percentile	3 (8.6)	9 (20.5)	
Presumed cause of death			NS
Chorioamnionitis/ maternofetal infection	1 (2.9)	3 (6.8)	
Maternofetal incompatibility	2 (5.7)	0 (0.0)	
Umbilical cord compression or torsion	1 (2.9)	1 (2.3)	
Vascular disorder	22 (62.9)	22 (50.0)	
FGR	9 (25.7)	18 (40.9)	

Data are given as *n*/*N* (%) or *n* (%). *One FGR case detected at 28 weeks, followed by normal ultrasound examination at 33 weeks, delivered at 38 weeks; 13 cases with undetected FGR with normal second-trimester ultrasound, of which 12 delivered at 28–32 weeks and one at 33–36 weeks; 10 cases with undetected FGR with normal third-trimester ultrasound, delivered at term. †Denominators of survivors ≥ 26 weeks or ≥ 36 weeks. GA, gestational age; GH, gestational hypertension; N/A, not applicable; NS, not significant ($P \geq 0.05$); PPROM, preterm prelabor rupture of membranes; US, ultrasound.

Comparison with previous research

Our FGR detection rate among singleton SGA stillbirths ≥ 24 weeks (44.3%) was over two-fold higher than that reported in both New Zealand[25] (12.3% for stillbirths ≥ 28 weeks) and England[23] and Sweden[24] (17.9% and 23.1%, respectively, for stillbirths ≥ 24 weeks), whereas, for live births, FGR detection rates were more similar (36.2% in our study for live births ≥ 24 weeks *vs* 31.8% in New Zealand at ≥ 28 weeks[25] and 31.0% and 53.3% in England[23] and Sweden[24], respectively, at ≥ 24 weeks). These studies thus found a much higher protective effect of detection, with crude estimates (i.e. ORs) of 0.3–0.5[23–25]. They did not report adjusted effects, but these would have been stronger, given the association of adjustment covariables with the probability of both detection and death. Sensitivity analyses using alternative definitions of antenatal detection of FGR did not explain the discordant results between these studies and ours.

The proportion of singleton stillbirths ≥ 24 weeks that was delivered SGA was lower in our study (24.9%) than found previously in England, Sweden, New Zealand and other high-income countries, with reports ranging from 32.0% to 51.3% (≥ 24 or ≥ 28 weeks GA)[23–25,39], but the impact of SGA on the risk of stillbirth was similar. In our study, 8.6% of live singleton births ≥ 24 weeks were SGA, yielding an estimated stillbirth risk (i.e. crude OR) associated with being SGA of 3.5 (95% CI, 2.8–4.4), consistent with a 2011 meta-analysis in high-income countries[6] (OR, 3.9 (95% CI, 3.0–5.1)). The relatively high socioeconomic status of the study districts likely explains the lower prevalence of SGA births in our study compared with that of France overall (10.8%)[38,40].

Interpretation and relevance for practice and policy

There are several possible explanations regarding our finding of only a modest protective role of FGR detection against stillbirth. First, because almost all women have a third-trimester scan in France[41], there may be less of a socioeconomic gradient associated with detection[6]. Previous French studies of antenatal detection of FGR and of congenital heart defects have shown that sociodemographic factors are not related to detection[42,43]. While cases were more likely to be immigrants and less likely to be employed than were controls, the proportions which received a third-trimester scan were similar and nearly 80% of stillbirths which did not have FGR detected occurred in women who had undergone all three recommended routine scans. In contrast, the England and New Zealand studies[23,25] reported high rates of young and socially disadvantaged mothers with late booking and reduced antenatal-care attendance. Social deprivation might therefore explain the less frequent

antenatal identification of FGR fetuses among stillbirths in those studies, and residual confounding may have contributed to the strong protective effects associated with its detection in those studies.

Another hypothesis is that detection of FGR is less protective in France because of differences in management following detection. It is possible that routine ultrasound examinations impact less on stillbirth than do those requested specifically in order to monitor fetal growth. This explanation would be consistent with the meta-analysis update on routine ultrasound imaging, which did not find an impact on stillbirth rates[44]. Criteria indicating active *vs* expectant management at early gestational ages could also play a role. The comparison of stillbirths with FGR detected *vs* those which went undetected found that a larger proportion of stillbirths with FGR detected delivered at 24–25 weeks of gestation. The protective effect of detection was slightly higher when analyses were restricted to births $\geq$ 28 weeks, consistent with a greater likelihood of active intervention at later gestational ages.

Our results suggest that future research with the aim of reducing SGA stillbirth should focus not only on detection, but also on better management of fetuses identified as having FGR. Our results also support calls to evaluate the risk–benefit balance of universal ultrasound screening and its optimal timing during the third trimester[45]. A policy of later ultrasound screening is likely to improve the sensitivity of detection of SGA infants[46], and would be likely to pick up cases of term stillbirth with FGR undetected that had routine scans at 30–34 weeks. However, such potential benefits must be balanced against the costs of additional ultrasound examinations as well as the iatrogenic consequences of false-positive FGR detection[34,45]. Our study illustrates the relatively small number of fetuses that would be targeted by such policies in the French context. The cost-effectiveness of this strategy may therefore be lower than that of other strategies, including smoking-cessation programs, prevention of maternal overweight and obesity and audits to reduce suboptimal care, that would impact on a broader population[47]. However, further investigation into the impact of detection of FGR on perinatal outcomes not considered in our study[48–50] are needed in order to fully assess the benefits and consequences of detection strategies.

Conclusions

Stillbirths with undetected growth failure constitute tragic events for the parents and are of major concern for health professionals. This population-based study reports a smaller protective effect of FGR detection than previous studies. These findings call into question a focus solely on improving detection without addressing post-detection management, with over 40% of SGA stillbirths occurring despite detection of FGR. They also raise the possibility that routine ultrasound examinations may be less efficacious than are ultrasound exams indicated based on risk-factor criteria. Preventive strategies targeting all stillbirths may ultimately have a larger impact on the risks of SGA-related and other stillbirths.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Comparison of characteristics between cases of small-for-gestational-age stillbirth ≥ 24 weeks and liveborn controls

Table S2 Surveillance and labor and delivery modes among controls liveborn ≥ 24 weeks, according to whether fetal growth restriction had been detected

Table S3 Sensitivity analyses of associations of antenatal detection of fetal growth restriction with risk of stillbirth ≥ 24 weeks