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Association of fetal growth restriction and stillbirth in twin compared with singleton pregnancies

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CONTRIBUTION

What are the novel findings of this work?

Fetal growth restriction (FGR) and small for gestational age (SGA) are significantly associated with the risk of stillbirth in both twin and singleton pregnancies. In singleton pregnancies, SGA, and particularly FGR, were associated with an increased likelihood of stillbirth, across all gestational ages. For twin pregnancies, when twin-specific charts were used, SGA and in particular FGR were associated with a significantly increased risk of stillbirth, across all gestational ages at delivery.

What are the clinical implications of this work?

It is essential to identify fetuses with growth restriction in both singleton and twin pregnancies, given that they are at increased risk of stillbirth. In singleton pregnancies, growth restriction was associated with stillbirth with increasing odds as gestation advances. A diagnosis of SGA or FGR on twin-specific charts was strongly associated with stillbirth in twin pregnancies, and therefore these findings support the use of twin-specific charts.

ABSTRACT

Objective: Twin pregnancies are at an increased risk of stillbirth compared to singletons. Fetal growth restriction (FGR) is a leading cause of perinatal mortality and morbidity, in both singleton and multiple pregnancies. Whether the contribution of FGR to stillbirth in twin pregnancies differs from that in singletons is yet to be determined. The main aim of this study was to determine the association between FGR and stillbirth in twin compared to singleton pregnancies. The secondary objectives include an assessment of the contribution of FGR to stillbirths, stratified by gestational age at delivery. Furthermore, we aimed to compare the association between FGR and stillbirth in twin pregnancies using the twin-specific versus singleton birthweight charts, stratified by chorionicity.

Methods: This was a cross-sectional study including pregnancies receiving obstetric care and birth at St George's Hospital, London. The exclusion criteria included triplet and higher order pregnancies, those resulting in miscarriage or livebirths at or prior to 23^{+6} weeks, or had a termination of pregnancy, or with missing data on the gestational age at birth. FGR and small for gestational age (SGA) were defined as birthweight <5^{th} and <10^{th} centile, respectively. While standard logistic regression was used for singleton pregnancies, the association of FGR and SGA designation with stillbirth in twin pregnancies was investigated with mixed-effects logistic regression models. For twin pregnancies, intercepts were allowed to vary for twin pairs to account for inter-twin dependency. Analyses were stratified by gestational age at delivery and chorionicity.

Results: The study included 95,342 singleton and 3,576 twin pregnancies. There were 494 (0.52%) stillbirths in singleton and 41 (1.15%) stillbirths in twin pregnancies (17 dichorionic and 24 monochorionic). FGR and SGA were significantly associated with stillbirth in singleton pregnancies, across all gestational ages at delivery (before 32 weeks- SGA: OR 2.36; 95% CI 1.78-3.13, p<0.001 and FGR: OR 2.67; 95% CI 2.02- 3.55, p<0.001; between 32-36 weeks- SGA: OR 2.70; 95% CI 1.71-4.31, p<0.001 and FGR: OR 2.82; 95% CI 1.78- 4.47, p<0.001; above 36 weeks- SGA: OR 3.85; 95% CI 2.83 – 5.21, p<0.001 and FGR: OR 4.43; 95% CI 3.16 – 6.12, p<0.001)

A greater proportion of fetuses from twin pregnancies were diagnosed as SGA and FGR when singleton compared to the twin-specific chart was used (48.43% vs. 9.12%, and 36.73% vs. 6.23%, respectively).

When stratified by gestational age at delivery, both SGA and FGR determined by the twin-specific charts were associated with significantly increased odds of having a stillbirth for those delivered before 32 weeks (SGA: OR 3.87; 95% CI 1.56-9.50, p=0.003 and FGR: OR 5.26;

95% CI 2.11-13.01, p<0.001), those delivered between 32-36 weeks (SGA: OR 6.67; 95% CI 2.11-20.41, p=0.001 and FGR: OR 9.54; 95% CI 3.01-29.40, p<0.001) and those delivered beyond 36 weeks (SGA: OR 12.68 95% CI 2.47-58,15, p=0.001 and FGR: OR 23.84; 95% CI 4.62-110.25, p<0.001), whereas the association of stillbirth with either SGA or FGR was inconsistent when analysed using singleton charts (before 32 weeks- SGA: p=0.014 and FGR: p=0.005; between 32-36 weeks- SGA: p=0.036 and FGR: p=0.008; above 36 weeks- SGA: p=0.080 and FGR: p=0.063). For dichorionic twins delivered before 32 weeks, the odds of an SGA or FGR fetus having a stillbirth was increased when analysed using twin-specific charts. In contrast, monochorionic twins delivered before 32 weeks showed lower and non-significant associations with stillbirth for both SGA and FGR cases using either twin-specific or singleton charts.

In dichorionic twin pregnancies delivered between 32-36 weeks, the OR for stillbirth of SGA using twin birthweight chart was 6.70 (95% CI 0.80-56.46, p=0.059), and using singleton chart was 0.92 (95% CI 0.11-7.71, p=0.934) and statistically non-significant. Similarly, the OR for stillbirth of FGR using twin birthweight chart and singleton chart was 9.59 (95% CI 1.14-81.06, p=0.025), and 1.40 (95% CI 0.17-11.76, p=0.735), respectively.

On the other hand, in monochorionic twin pregnancies delivered between 32-36 weeks, the OR for stillbirth of SGA and FGR using twin birthweight chart was 9.37 (95% CI 2.20- 37.72, p=0.001), and 13.55 (95% CI 3.12 – 55.94 p < 0.001) respectively.

Conclusions: Our study demonstrates a significant association between SGA, particularly for FGR, with increased odds of stillbirths in singleton pregnancies across all gestational ages. For twin pregnancies, when twin-specific charts were used, SGA and in particular FGR were associated with a significantly increased risk of stillbirth, across all gestational ages at delivery.

INTRODUCTION

Prediction and prevention of stillbirth remain a challenge for both clinicians and researchers[1-4]. Despite improvements in maternity care, stillbirth continues to represent a significant burden of adverse pregnancy outcomes[5,6]. In 2019, 2 million babies were stillborn at 28 weeks or more of gestation worldwide, and the global stillbirth rate was 13.9 per 1000 total births[4]. Stillbirth rates in 2019 differed among regions, ranging from 22.8 per 1000 total births in West and Central Africa to 3.0 in North America and 2.9 in Western Europe[4]. In the United States, stillbirth affects 1 in 160 births[5], and approximately 21,000 fetal deaths at 20 weeks or greater of gestation were reported in 2020[6].

Stillbirth is defined as the delivery of a fetus showing no signs of life as indicated by the absence of pulsation of the umbilical cord, heartbeats, breathing, or movements of voluntary muscles[4,7,8]. There is a lack of uniformity among countries regarding the gestational age (GA) that defines stillbirth[4]. Whereas fetal death at 24 weeks and beyond qualifies in the UK[9] , in the United States the definition specifies 20 weeks of gestation or more[6].

Twin gestations are at increased risk of antenatal complications and stillbirth than singleton pregnancies[10,11]. Previous studies have reported that fetal growth restriction (FGR) complicates 25-47% of twin and 8% of singleton pregnancies[12-16]. Noticeably, FGR is a leading cause of stillbirth worldwide[17-25]. Nonetheless, data are scarce regarding the contribution of FGR to stillbirth in multiple compared to singleton pregnancies. This study aims to establish the association between FGR and stillbirth in twins compared to singleton pregnancies. The secondary aims include an assessment of contribution of FGR to stillbirths, stratified by gestational age at delivery. Furthermore, we aimed to compare the association between FGR and stillbirth in twin pregnancies using the twin-specific versus singleton birthweight charts, stratified by chorionicity.

METHODS

Study design, participants, and data sources

This cross-sectional study was carried out among all pregnant individuals receiving obstetric care and giving birth at St George's Hospital, London between January 1999 and December 2022. January 1999 was selected as the study initiation point as the ultrasound data was systematically recorded since this period. The exclusion criteria included triplet and higher order pregnancies, those resulting in miscarriage or livebirths at or prior to 23^{+6} weeks' gestation, or had a termination of pregnancy, or with missing data on the GA at birth or birth weight. Data on maternal and pregnancy data variables, as well as study outcomes, were obtained using the electronic maternity (Euroking E3 maternity information system) and ultrasound (ViewPoint 5.6.8.428, ViewPoint Bildverarbeitung GmbH, Weßling, Germany software) databases, while neonatal outcomes were obtained from the online neonatal electronic (Badgernet) database.

Study variables

Data on the number of fetuses in the pregnancy, chorionicity and amnionicity in twin pregnancies, GA at birth or diagnosis of stillbirth, birthweight, and stillbirth were collected and assessed. In twin pregnancies, chorionicity was ascertained by the number of placentae and the presence or absence of the lambda sign at the junction of the intertwin membrane to the placenta, and the intertwin membrane thickness at the site of placental insertion in the chorion at 11–14 weeks of gestation[26]. Chorionicity was also determined by the number of placentae, thickness of the inter-twin membrane and fetal gender if the first ultrasound scan was performed above 14 weeks of gestation[26].

GA was determined in the first trimester by assessing the crown–rump length of the larger fetus in pregnancies with natural conception. In gestations conceived by *in-vitro* fertilization (IVF), GA was calculated according to the oocyte retrieval date or the embryonic age from fertilization[27]. After 14 weeks' gestation in non-IVF pregnancies, GA was determined using the head circumference of the larger fetus[28] .

Stillbirth was defined as a recorded birth of a stillborn baby of at least 24^{+0} weeks of gestation[29].

FGR and small for gestational age (SGA) were defined as birth weight below the 5th and 10th centile for gestational age, respectively, according to Fetal Medicine Foundation weight charts[30]. FGR and SGA in twin pregnancies were additionally defined as birthweight below the 5th and 10th centile for gestational age, respectively, according to the twin chorionicity-specific charts[31].

The Index of Multiple Deprivation (IMD) was used as a measure of socioeconomic status[32]. The IMD provides a measure of deprivation for small areas or neighborhoods in England, and is derived from information regarding income, education, employment, crime, and the living environment. Women were categorized into five socioeconomic groups according to the level of deprivation of their neighborhood relative to that of other areas (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019). The first quintile contains the most deprived areas, whereas the fifth quintile contains the least deprived. The postcode of each pregnant individual was used to ascertain their IMD.

Statistical analysis

Continuous data were described as median and interquartile range (IQR), while categorical data variables were described as numbers and proportions. Comparisons between the characteristics of the study groups were performed using Student's t-test or Mann-Whitney U test for continuous variables and Fisher's exact testing for categorical variables. While standard logistic regression was used for singleton pregnancies, the association of FGR and SGA designation with stillbirth in twin pregnancies was investigated with mixed-effects logistic regression models. For twin pregnancies, intercepts were allowed to vary for twin pairs to account for inter-twin dependency. Analyses were stratified by gestational age at delivery and chorionicity. Results are reported as odds ratios with 95% confidence intervals. Statistical significance was set at a p-value of 0.001.R version 4.0.3 (The R Foundation for Statistical Computing) was used for statistical analysis.

RESULTS

After applying the exclusion criteria, 95,342 singleton and 3,576 twin pregnancies (2722 dichorionic and 854 monochorionic) were included in the analysis. Stillbirth was reported in 494 (0.52%) singleton and 41 (1.15%) twin pregnancies. Of stillbirths in twin pregnancies, 17 were dichorionic and 24 were monochorionic. Data on maternal demographics and pregnancy characteristics of the study population are shown in Table 1. Compared to singleton pregnancies, women with twin pregnancies were significantly older (32.0 vs 34.0 years, p<0.001), had higher maternal BMI (24.1 vs 25.0 kg/m^2, p<0.001), more likely to be nulliparous (50.5% vs 55.4%, p<0.001), less likely to be a smoker (6.3% vs 4.7%, p<0.001) or consume alcohol in pregnancy (5.5% vs 1.4%, p<0.001). Additionally, compared to pregnant patients with singleton pregnancies, women with twins were more likely to have White (52.6% vs 60.8%, p<0.001) or Black (12.4% vs 15.8%, p<0.001) ethnic background, and less likely to have Asian (19.2% vs 12.7%, p<0.001) or mixed (15.7% vs 10.6%, p<0.001) ethnic background. They were more likely to live in the least deprived area (13.9% vs. 18.3%, p<0.001). They were less likely to have had a spontaneous conception (50.5% vs. 93.8%, p<0.001). The median GA at birth was significantly lower in twin compared to singleton pregnancies (37.0 vs 40.0 weeks, p<0.001).

Data on maternal demographics and pregnancy characteristics of singleton and twin pregnancies complicated by stillbirth are shown in Tables S1 and S2, respectively.

Association of FGR and SGA and stillbirth

i) Singleton pregnancies stratified by gestational age at delivery.

We stratified the singleton pregnancies by gestational age at delivery into three groups: those delivered up to 32 weeks, between 32-36 weeks, and beyond 36 weeks (Table 2). Among pregnancies delivered before 32 weeks, 24.1% (146/607) of SGA resulted in stillbirth (OR 2.36, 95% CI 1.78-3.13, p<0.001), while 26.1% (138/528) of FGR cases ended in stillbirth (OR 2.67, 95% CI 2.02-3.55, p<0.001). In the group delivered between 32-36 weeks, the proportion of SGA and FGR fetuses which resulted in stillbirth was 4.8% (43/889, OR 2.70, 95% CI 1.71-4.31, p<0.001), and 5.3% (38/718, OR 2.82, 95% CI 1.78-4.47, p<0.001), respectively. For those delivered beyond 36 weeks, 0.5% (67/12599) of SGA fetuses and 0.7% (49/7344) of FGR fetuses had a stillbirth with an OR of 3.85 (95% CI 2.83-5.21, p<0.001), and OR of 4.43 (95% CI 3.16-6.12, p<0.001), respectively.

ii) Twin pregnancies stratified by gestational age at delivery and chorionicity.

Next, we analysed the association of SGA and FGR with stillbirth in twin pregnancies, stratified by gestational age at delivery, chorionicity and use of singleton/twin-specific charts.

For all twin pregnancies delivered up to 32 weeks, both SGA and FGR determined by the twin-specific charts was associated with a significantly increased odds of having a stillbirth with an OR of 3.87 (95% CI 1.56-9.50, p=0.003) and OR of 5.26 (95% CI 2.11-13.01, p<0.001), respectively. When assessed using singleton charts, the association of stillbirth with either FGR or SGA was statistically non-significant, with OR of 3.81 (95% CI 1.55-10.24, p=0.005) and OR of 3.35 (95% CI 1.33-9.54, p=0.014), respectively.

These associations were more pronounced in dichorionic twin pregnancies. In dichorionic twin pregnancies, the OR for stillbirth of SGA and FGR using twin birthweight chart was 7.52 (95% CI 2.41-25.79, p=0.001), and 10.72 (95% CI 3.40-37.16, p<0.001), respectively. On the other hand, when classified using singleton charts, the OR for stillbirth associated with SGA and FGR was 5.38 (95% CI 1.61-24.40, p=0.012) and 8.25 (95% CI 2.45-37.50, p=0.002), respectively and did not attain statistical significance.

In contrast, monochorionic twins showed lower and non-significant associations with stillbirths for both SGA and FGR cases using both charts. In monochorionic twin pregnancies, the OR for stillbirth associated with SGA using twin birthweight chart was 1.18 (95% CI 0.17-5.42, p=0.846), and using singleton chart was 1.53 (95% CI 0.36-7.67, p=0.573) (Table 3a). Similarly, the OR for stillbirth of FGR using twin birthweight chart and singleton birthweight chart was 1.48 (95% CI 0.21-6.87, p=0.643), and 1.16 (95% CI 0.26-5.08, p=0.840), respectively.

For all twin pregnancies delivered between 32-36 weeks, both SGA and FGR determined by the twin-specific charts were associated with a significantly increased odds of having a stillbirth with an OR of 6.67 (95% CI 2.11-20.41, p=0.001) and OR of 9.54 (95% CI 3.01-29.40, p<0.001), respectively. When assessed using singleton charts, the association of stillbirth with either FGR or SGA was statistically non-significant, with OR of 7.75 (95% CI 2.07-50.27, p=0.008) and OR of 5.04 (95% CI 1.34-32.68, p=0.036), respectively.

In dichorionic twin pregnancies delivered between 32-36 weeks, the OR for stillbirth associated with SGA using twin birthweight chart was 6.70 (95% CI 0.80-56.46, p=0.059), and using singleton chart was 0.92 (95% CI 0.11-7.71, p=0.934) (Table 3b). Similarly, the OR for stillbirth associated with FGR using twin birthweight chart and singleton chart was 9.59 (95% CI 1.14-81.06, p=0.025), and 1.40 (95% CI 0.17-11.76, p=0.735), respectively. In monochorionic twin pregnancies delivered between 32-36 weeks, the OR for stillbirth associated with SGA and FGR using twin birthweight chart was 9.37 (95% CI 2.20- 37.72, p=0.001), and 13.55 (95% CI 3.12-55.94, p <0.001), respectively (Table 3b).

For all twin pregnancies delivered beyond 36 weeks, 2.5% of SGA cases resulted in a stillbirth with an OR of 12.68 (95% CI 2.47-58.15, p=0.001), while 4.4% of FGR cases suffered

a stillbirth, with an OR of 23.84 (95% CI 4.62-110.25, p<0.001). When analyzed using the singleton chart, the association of both SGA and FGR with stillbirth was statistically non-significant with OR of 6.65 (1.13-125.64, p=0.080) and 4.75 (1.02-33.21, p=0.063), respectively (Table 3c).

For dichorionic twins delivered beyond 36 weeks, 1.9% of SGA cases based on the twin charts had a stillbirth rate with an OR of 15.55 (95% CI 1.85-130.67, p=0.006), while 3.4% of FGR cases resulted in stillbirths with an OR of 30.04 (95% CI 3.55-254.02, p=0.001). When classified by singleton charts, both SGA (OR 3.41, 95% CI 0.44-68.92, p=0.289) and FGR (OR 5.79, 95% CI 0.74-117.24, p=0.129), demonstrated non-significant associations with stillbirths. For monochorionic twins delivered beyond 36 weeks, when classified by twin-specific charts, 6.7% of SGA and 10.0% of FGR resulted in stillbirth, with an OR of 13.54 (95% CI 0.61-149.72, p=0.038) and an OR of 21.33 (95% CI 0.94-243.74, p=0.016), respectively. When classified using the singleton charts, 1.5% and 1.4% of SGA and FGR cases, resulted in stillbirth, however the odds could not be computed.

DISCUSSION

Summary of the key findings

In this large retrospective cohort, we have performed a comprehensive analysis of the association between SGA and FGR with stillbirths in singleton and twin pregnancies, stratified by gestational age at delivery and, for twins, further by chorionicity and the use of singleton/twin-specific charts. In singleton pregnancies, both SGA and FGR were associated with a consistent significant increase in the odds for stillbirths, when stratified by gestational age at delivery. The twin pregnancies revealed a more complex pattern. Overall, twin-specific charts generally showed a higher odd for stillbirths compared to singleton charts for both SGA and FGR cases, across all gestational ages at delivery. The association was especially pronounced in dichorionic twins delivered before 32 weeks where the odds for stillbirths were notably higher than in monochorionic twins, indicating a potentially different mechanism influencing stillbirth risks.

Interpretation of study findings and comparison with published literature

In this study, we report that in singleton pregnancies SGA, and particularly FGR, were associated with an increased likelihood of stillbirths, with advancing gestation. This reiterates the findings from other population-based studies[33-35]. In a large US based population of 3,399,816 non-anomalous singleton pregnancies, Pillod et al reported that the risk of stillbirth increases with gestational age and is inversely related to the birthweight percentile, particularly marked in the lowest percentile cohort (less than 3rd percentile)[33]. Similar findings were reported by Hong et al[34]. This is not surprising given that the mechanism for fetal demise in FGR at term is primarily an interplay of mismatched demand-supply of a fetus with poor reserves and fragile compensatory mechanisms, of a senescent placenta[36-38].

Our study has shown that a diagnosis of SGA or FGR using twin-specific charts is strongly associated with stillbirths than when diagnosed by singleton charts, across all gestational ages. Growth trajectories of singletons and twin pregnancies are different, especially in the third trimester[39-41]. Whether this is physiological or represents a pathological lag, the mechanism is still not well defined. Furthermore, other researchers have shown that SGA twins are less likely to have an adverse perinatal outcome than SGA singletons[42]. Thus, a growing body of evidence supports the use of twin charts over singleton charts to monitor fetal growth in twin pregnancies [22, 43-45] .

Lastly, this study shows that growth restriction, either SGA or FGR, is associated with an increased likelihood of stillbirth in dichorionic compared to monochorionic twins, before 32

weeks of gestation. Overall, monochorionic twins have up to a 5-fold higher risk of demise compared to dichorionic twins[46] , which is largely attributable to monochorionic-specific complications like twin-to-twin transfusion syndrome (TTTS)[47,48]. In our study, monochorionic twins who had a stillbirth before 32 weeks, 69% (9/13) of cases had factors other than growth restriction, as an etiology for stillbirth and more than half of these cases were affected by twin-to-twin transfusion syndrome. Growth restriction is usually a marker of placental dysfunction with increasing gestational age[49-52]. Interestingly, the prospective risk of stillbirth in singleton and dichorionic twins increases with gestation, concurrent with placental senescence, while the prospective risk of stillbirth in monochorionic twins is highest before 28 weeks of gestation[53]. These observed differences point towards different magnitudes or effects of the role of SGA and FGR in the causation of stillbirth in these pregnancies. The absolute number of stillbirth cases was small for gestational ages beyond 32 weeks, when stratified by chorionicity, therefore although the odds observed were raised, statistical significance could not be achieved. Nonetheless, it is important to note that in the overall population of twin pregnancies, severe smallness on twin-specific charts were more likely to be associated with stillbirths than those twins classified small by singleton charts.

Clinical and research implications

The findings underscore the nuanced interplay of smallness, chorionicity, and gestational age, highlighting the importance of tailored risk assessments and the consideration of specific growth charts in understanding the risks associated with stillbirths in both singleton and twin pregnancies. FGR is a known risk factor for stillbirth[3,17-20,22-25,33]. Both FGR and perinatal loss are higher in twin compared to singleton pregnancies[54-56]. However, data are scant regarding the contribution of growth restriction to stillbirth in multiple compared to singleton pregnancies.

The study underscores the importance of using appropriate growth charts for twins, suggesting that twin-specific charts provide a more accurate risk assessment compared to singleton charts. The management of FGR in twin pregnancies differs according to the chorionicity. In monochorionic twin pregnancies complicated by sFGR, the demise of the smaller twin is associated with an increased risk of demise or neurological impairment of the larger twin[26,57,58]. Similarly, there is limited evidence on the ideal gestation to deliver in dichorionic twin pregnancies complicated by FGR[59]. Further research is needed to elucidate the mechanisms behind the varying stillbirth risks in dichorionic versus monochorionic twins and across gestational ages. It's crucial to develop and validate twin-specific growth charts that account for chorionicity, enhancing predictive accuracy. Moreover, evaluating interventions for preventing stillbirth in high-risk pregnancies, especially those with SGA or FGR, including delivery timing and methods, as well as antenatal surveillance, is essential.

Strengths and limitations

The main strengths of this study include the large cohort size and cross-sectional design which enabled us to examine the occurrence of a clinically significant but relatively rare outcome of stillbirth, stratified by timing. Additionally, the contribution of growth restriction to stillbirth in twin pregnancies has been addressed using singleton and twin-specific growth charts and has been stratified by chorionicity. There are some limitations to our study. Birthweight instead of EFW has been used to identify smallness as EFW data were not readily available for both twin and singleton pregnancies. Secondly, in the United Kingdom, obstetric care, especially for twin pregnancies, has changed and evolved over time with the implementation of the National Institute for Health and Care Excellence (NICE) guideline on the antenatal care of uncomplicated twin and triplet pregnancies. This was concurrent with the decline in stillbirth rates in twin pregnancies as reported by the UK MBRRACE 2016[60,61] . Thirdly, Gestational age at delivery has been used as a surrogate for the time of stillbirth in singleton pregnancies. Fetal growth restriction itself can be associated with both spontaneous and iatrogenic preterm delivery, thereby affecting stratification by gestational age at delivery[62,63]. Another consideration is that the growth velocity of SGA/FGR fetuses may change with advancing gestation. These dynamic changes in fetal growth profiles have been eloquently described by Deter et al[64-66.]

Lastly, a notable limitation is the small sample size in the subgroup of twins delivered beyond 36 weeks. As most twin pregnancies are delivered by 36-37 weeks, the number of cases available for analysis in this late gestational period was small, potentially affecting the statistical power and the conclusiveness of the findings for this specific subgroup.

Conclusions

In conclusion, our study demonstrates a significant association between SGA, particularly for FGR, with increased odds of stillbirths in singleton across all gestational ages. For twin pregnancies, when twin-specific charts were used, SGA and in particular FGR were associated with a significantly increased risk of stillbirth, across all gestational ages at delivery. When stratified by chorionicity, this association was significant in dichorionic twins delivered before 32 weeks and in monochorionic twins between 32-36 weeks when using twin-specific charts, suggesting chorionicity-specific stillbirth risks. These findings highlight the importance of tailored monitoring strategies based on gestational age and chorionicity and support the

practice of using twin-specific charts, to effectively manage and mitigate stillbirth risks in twin pregnancies complicated by SGA and FGR.

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Table 1. Comparison of the demographic characteristics and pregnancy outcomes of the two study groups: twin and singleton pregnancies

	Twin pregnancies (n=3,576)	**Singleton pregnancies (n=95,342)**	**P value**
Maternal age in years, median (IQR)	34.0 (30.0 – 37.0)	32.0 (28.0 – 35.0)	< 0.001
Maternal age > 35 years, n (%)	1280 (42.2)	27902 (29.3)	< 0.001
Maternal age > 40 years, n (%)	296 (9.8)	5342 (5.6)	< 0.001
Maternal age > 45 years, n (%)	36 (1.2)	346 (0.4)	< 0.001
Maternal ethnic group, n (%)			
White	1986 (60.8)	18044 (52.6)	< 0.001
Black	516 (15.8)	4246 (12.4)	< 0.001
Asian	416 (12.7)	6588 (19.2)	< 0.001
Mixed	346 (10.6)	5396 (15.7)	< 0.001
Body mass index >25 kg/m^2	1354 (48.7)	39036 (44.8)	< 0.001
Body mass index >30 kg/m^2	514 (18.5)	14453 (16.6)	0.009
Body mass index >35 kg/m^2	186 (6.7)	4965 (5.7)	0.027
Body mass index >40 kg/m^2	56 (2.0)	1618 (1.9)	0.550
Index of Multiple Deprivation. 1st quintile (most deprived), n (%)	120 (7.7)	8017 (8.5)	0.245
Index of Multiple Deprivation. 2nd quintile, n (%)	392 (25.0)	25747 (27.3)	0.050
Index of Multiple Deprivation. 3rd quintile, n (%)	480 (30.7)	31246 (33.1)	0.043
Index of Multiple Deprivation. 4th quintile, n (%)	288 (18.4)	16322 (17.3)	0.249
Index of Multiple Deprivation. 5th quintile (least deprived), n (%)	286 (18.3)	13123 (13.9)	< 0.001

Nulliparous, n (%)	1980 (55.4)	48143 (50.5)	< 0.001
Spontaneous conception, n (%)	938 (50.5)	19951 (93.8)	<0.001
Monochorionic, n (%)	854 (23.9)	NA	
Maternal smoking during pregnancy, n (%)	164 (4.7)	5971 (6.3)	< 0.001
Alcohol consumption during pregnancy, n (%)	22 (1.4)	5282 (5.5)	< 0.001
Gestational age at birth in weeks, median (IQR)	37.0 (35.0 – 37.0)	40.0 (39.0 – 40.9)	< 0.001
Preterm birth (< 37 weeks), n (%)	2020 (56.5)	5977 (6.3)	< 0.001
Preterm birth (< 32 weeks), n (%)	420 (11.7)	1372 (1.4)	< 0.001
Preterm birth (< 28 weeks), n (%)	164 (4.6)	615 (0.6)	< 0.001
Birthweight in grams, median (IQR)	2380 (1980 – 2699)	3360 (3025 – 3690)	< 0.001

Data are presented as median (interquartile range) or n (%).

Not applicable (NA).

Table 2. Association of fetal growth restriction (FGR) or small for gestational age (SGA) with stillbirth in singleton pregnancies, stratified by gestational age at delivery.

GA at delivery up to 32 weeks	**Livebirth**	**Stillbirth**	**OR (95% CI)**	**P value**
SGA (n=607)	461 (75.9)	146 (24.1)	2.36 (1.78-3.13)	<0.001
FGR (n=528)	390 (73.9)	138 (26.1)	2.67 (2.02-3.55)	<0.001
GA at delivery between 32 to 36 weeks				
SGA (n=889)	846 (95.2)	43 (4.8)	2.70 (1.71-4.31)	<0.001
FGR (n=718)	680 (94.7)	38 (5.3)	2.82 (1.78-4.47)	<0.001
GA at delivery above 36 weeks				
SGA (n=12599)	12532 (99.5)	67 (0.5)	3.85 (2.83-5.21)	<0.001
FGR (n=7344)	7295 (99.3)	49 (0.7)	4.43 (3.16-6.12)	<0.001

GA: gestational age; OR: odds ratio; CI: confidence interval

Data are presented as n (%)

Table 3. Association of fetal growth restriction (FGR) or small for gestational age (SGA) with stillbirth in twin pregnancies, results from a mixed effects logistic regression model stratified by chorionicity and gestational ages (GA) at delivery: a) GA at delivery up to 32 weeks, b) GA at delivery between 32-36 weeks, and c) GA at delivery beyond 36 weeks

a)

GA at delivery up to 32 weeks	**n**	**Livebirth**	**Stillbirth**	**OR (95% CI)***	**P value**
• **All twins**					
SGA (Twin chart)	90	80 (88.9)	10 (11.1)	3.87 (1.56-9.50,)	0.003
FGR (Twin chart)	72	62 (86.1)	10 (13.9)	5.26 (2.11-13.01)	0.001
SGA (Singleton chart)	195	180 (92.3)	15 (7.7)	3.35 (1.33-9.54)	0.014
FGR (Singleton chart)	159	145 (91.2)	14 (8.8)	3.81 (1.55-10.24)	0.005
• ***DC twins***					
SGA (Twin chart)	58	50 (86.2)	8 (13.8)	7.52 (2.41-25.79)	0.001
FGR (Twin chart)	45	37 (82.2)	8 (17.8)	10.72 (3.40-37.16)	<0.001
SGA (Singleton chart)	119	109 (91.6)	10 (8.4)	5.38 (1.61-24.40)	0.012
FGR (Singleton chart)	92	82 (89.1)	10 (10.9)	8.25 (2.45-37.50)	0.002
• ***MC twins***					
SGA (Twin chart)	32	30 (93.8)	2 (6.2)	1.18 (0.17-5.42)	0.846
FGR (Twin chart)	27	25 (92.6)	2 (7.4)	1.48 (0.21-6.87)	0.643

SGA (Singleton chart)	76	71 (93.4)	5 (6.6)	1.53 (0.36-7.67)	0.573
FGR (Singleton chart)	67	63 (94.0)	4 (6.0)	1.16 (0.26-5.08)	0.840

OR: odds ratio; CI: confidence interval; MC: monochorionic; DC: dichorionic

*Multilevel logistic regression with random intercepts for twin pairs

b)

GA at delivery between 32 to 36 weeks	n	Livebirth	Stillbirth	OR (95% CI)*	P value
• **All twins**					
SGA (Twin chart)	118	112 (94.9)	6 (5.1)	6.67 (2.11-20.41)	0.001
FGR (Twin chart)	87	81 (93.1)	6 (6.9)	9.54 (3.01-29.40)	<0.001
SGA (Singleton chart)	524	513 (97.9)	11 (2.1)	5.04 (1.34-32.68)	0.036
FGR (Singleton chart)	419	408 (97.4)	11 (2.6)	7.75 (2.07-50.27)	0.008
• ***DC twins***					
SGA (Twin chart)	90	88 (97.8)	2 (2.2)	6.70 (0.80-56.46)	0.059
FGR (Twin chart)	66	64 (97.0)	2 (3.0)	9.59 (1.14-81.06)	0.025
SGA (Singleton chart)	355	353 (99.4)	2 (0.6)	0.92 (0.11-7.71)	0.934
FGR (Singleton chart)	284	282 (99.3)	2 (0.7)	1.40 (0.17-11.76)	0.735
• ***MC twins***					
SGA (Twin chart)	28	24 (85.7)	4 (14.3)	9.37 (2.20-37.72)	0.001
FGR (Twin chart)	11	17 (81.0)	4 (19.0)	13.55 (3.12-55.94)	<0.001
SGA (Singleton chart)	169	160 (94.7)	9 (5.3)	NE	
FGR (Singleton chart)	135	126 (93.3)	9 (6.7)	NE	

OR: odds ratio; CI: confidence interval; MC: monochorionic; DC: dichorionic, NE: not estimable

*Multilevel logistic regression with random intercepts for twin pairs

c)

GA at delivery above 36 weeks	n	Livebirth	Stillbirth	OR (95% CI, P value)*	P value
• ***All twins***					
SGA (Twin chart)	122	119 (97.5)	3 (2.5)	12.68 (2.47-58.15)	0.001
FGR (Twin chart)	68	65 (95.6)	3 (4.4)	23.84 (4.62-110.25)	<0.001
SGA (Singleton chart)	1017	1011 (99.4)	6 (0.6)	6.65 (1.13-125.64)	0.080
FGR (Singleton chart)	740	735 (99.3)	5 (0.7)	4.75 (1.02-33.21)	0.063
• ***DC twins***					
SGA (Twin chart)	107	105 (98.1)	2 (1.9)	15.55 (1.85-130.67)	0.006
FGR (Twin chart)	58	56 (96.6)	2 (3.4)	30.04 (3.55-254.02)	0.001
SGA (Singleton chart)	817	814 (99.6)	3 (0.4)	3.41 (0.44-68.92)	0.289
FGR (Singleton chart)	596	593 (99.5)	3 (0.5)	5.79 (0.74-117.24)	0.129
• ***MC twins***					
SGA (Twin chart)	15	14 (93.3)	1 (6.7)	13.54 (0.61-149.72)	0.038
FGR (Twin chart)	10	9 (90.0)	1 (10.0)	21.33 (0.94-243.74)	0.016
SGA (Singleton chart)	200	197 (98.5)	3 (1.5)	NE	
FGR (Singleton chart)	144	142 (98.6)	2 (1.4)	3.54 (0.34-76.47)	0.304

OR: odds ratio; CI: confidence interval; MC: monochorionic; DC: dichorionic, NE: not estimable

*Multilevel logistic regression with random intercepts for twin pairs