Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-020-05747-4

MATERNAL-FETAL MEDICINE

Identification of the optimal growth chart and threshold for the prediction of antepartum stillbirth

Liran Hiersch[1,2,3] · Hayley Lipworth[1] · John Kingdom[2,4] · Jon Barrett[1,2] · Nir Melamed[1,2]

Received: 19 July 2020 / Accepted: 10 August 2020

Abstract

Purpose To evaluate the effect of the choice growth chart and threshold used to define small for gestational age (SGA) on the predictive value of SGA for placenta-related or unexplained antepartum stillbirth.

Methods A retrospective cohort study of all women with a singleton pregnancy who gave birth > 24 week gestation in a single center (2000–2016). The exposure of interest was SGA, defined as birth weight < 10th or < 25th centile according to three fetal growth charts (Hadlock et al., Radiology 181:129–133, 1991; intergrowth-21st (IG21), WHO 2017, and a Canadian birthweight-based reference—Kramer et al., Pediatrics 108:E35, 2001). The outcome of interest was antepartum stillbirth due to placental dysfunction or unknown etiology. Cases of stillbirth attributed to other specific etiologies were excluded.

Results A total of 49,458 women were included in the cohort. There were 103 (0.21%) cases of stillbirth due to placental dysfunction or unknown etiology. For cases in the early stillbirth cluster (≤ 30 weeks), the detection rate was high and was similar for the three ultrasound-based fetal growth charts of Hadlock, IG21, and WHO (range 83.3–87.0%). In contrast, the detection rate of SGA for cases in the late stillbirth cluster (> 30 weeks) was low, being highest for WHO and Hadlock (36.7% and 34.7%, respectively), and lowest for IG21 (18.4%). Using a threshold of the 25th centile increased the detection rate for stillbirth by approximately 15–20% compared with that achieved by the 10th centile cutoff.

Conclusion At > 30 week gestation, the Hadlock or WHO fetal growth charts provided the best balance between detection rate and false positive rate for stillbirth.

Keywords Growth charts · Small for gestational age · Stillbirth · Detection · Prediction

Introduction

Fetal growth restriction (FGR) is an important cause of stillbirth and neonatal mortality and morbidity [1–3]. FGR is defined as a failure of a fetus to meet its genetic growth potential due to an underlying pathological factor, most commonly uteroplacental dysfunction [4]. In clinical practice, however, the detection of small for gestational age (SGA) fetuses (defined by a sonographic fetal weight estimation < 10th percentile for gestational age) is commonly used to screen for FGR [5, 6]. A major challenge with this approach is that the proportion of fetuses classified as SGA, as well as the predictive accuracy of SGA for FGR and perinatal mortality and morbidity associated with FGR, are highly dependent upon the choice of growth chart used to define SGA [7, 8].

Considerable controversy exists regarding the optimal type of growth chart to be used for the detection of an SGA fetus. This controversy has further intensified over the last

This study was presented as a poster presentation at the 2020 annual meeting of the Society for Maternal–Fetal Medicine (Dallas, TX, Feb 3–8, 2020).

✉ Liran Hiersch
lirhir@gmail.com

1 Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N3M5, Canada

2 Department of Obstetrics and Gynecology, University of Toronto, Toronto, ON M5G 1X8, Canada

3 Lis Hospital for Women, Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

4 Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai Hospital, 600 University Avenue, Toronto, ON M5G 1X5, Canada

Published online: 14 August 2020

several years when, in addition to commonly used birthweight-based reference charts (e.g., Alexander [9], Williams [10]) and ultrasound-based charts (e.g., Hadlock [11]), several new well-designed ultrasound-based standards became available [12–14].

One approach to identify the optimal chart is through the comparison of the correlation of different charts with adverse perinatal outcome [15–20]. However, the interpretation of available studies that used this approach is limited by the choice of the outcomes used to evaluate the performance of the charts. The use of neonatal outcomes for that purpose is limited by the lack of gold standard postnatal diagnosis of FGR and by the fact that many of these adverse perinatal events are not specific to FGR, and may be the result of other factors such as prematurity [21, 22]. Other studies have compared the ability of various charts to predict stillbirth, with its avoidance being the primary goal of screening [17, 19, 20]. However, most studies used population-based vital statistics data where information on the etiology and timing of stillbirth are limited. This limitation may result in the inclusion of cases of stillbirth that are unrelated to placental dysfunction, thereby underestimating the association between SGA and placenta-related stillbirth. Such population-based studies also lack information on the timing of stillbirth and on the stillbirth-to-delivery interval, which may result in overestimation of the rate of FGR among stillborn due to the effects of fetal maceration on birthweight [17, 23].

A final consideration is that while the 10th centile is the most commonly used threshold to suspect FGR, a higher threshold (up to the 25th centile) may provide a better balance between the detection rate and false positive rate of SGA for stillbirth, since FGR-related stillbirth rates progressively rise below the 25th centile [20].

The objective of the current study was, therefore, to identify the optimal growth chart and the optimal centile threshold used to define SGA in our population based on the prediction accuracy for placenta-related (or unexplained) stillbirth.

Methods

Study population

A retrospective cohort study was conducted comprising all women with a singleton pregnancy who gave birth at a single tertiary referral center in Toronto, ON, Canada between Jan 2000 and Dec 2016. The following cases were excluded: fetal genetic or structural anomalies, cases of stillbirth attributed to etiologies other placental dysfunction or unknown etiology, cases where the best estimate of the stillbirth-to-delivery interval was > 10 days, cases of intrapartum stillbirth, or gestational age at birth < 24 weeks. The study was approved by the Sunnybrook Health Sciences Center Research Ethics Board (#353–2014). Due to the retrospective design of the study, informed consent from each participant was not required.

Data collection

Women were identified though the institutional perinatal database. The medical charts of all cases complicated by stillbirth were reviewed in detail for demographic characteristics, medical and obstetric history, gestational age at delivery, ultrasound reports, results of the investigation that was performed, most likely etiology of stillbirth, and the best estimate of the timing of stillbirth and stillbirth-to-delivery interval.

The following investigation is offered in cases of stillbirth based on the institutional protocol: autopsy, placental pathology, genetic testing, screening for fetal infection through maternal serology and cultures from the fetus and placenta, and screening for fetomaternal hemorrhage.

Exposure and outcomes

The primary exposure of interest was small for gestational age (SGA), defined as birth weight < 10th centile for gestational age according to three ultrasound-based charts (Hadlock 1991 [11], intergrowth-21st (IG21) [14], World Health Organization (WHO) 2017 [12] and one Canadian Querybirthweight-based reference (Kramer 2001) [24]. We also explored a secondary exposure of birthweight < 25th centile for gestational age according to each of the four charts since FGR-related stillbirth rates have been shown to progressively rise below the 25th centile[20].

The outcome of interest was stillbirth due to placental dysfunction or unknown etiology. Placental dysfunction was suspected on either clinical grounds (abnormal antenatal Doppler studies of the umbilical, uterine or middle cerebral arteries, associated hypertensive complications, or clinical evidence of placental abruption) placental histopathological findings [25, 26].

Statistical analysis

The baseline characteristics were compared between the stillbirth and livebirth groups. The 10th centile lines and, the proportion of cases diagnosed as SGA, and the distribution of cases of stillbirth by gestational age and weight centile at the time of diagnosis, were compared between the four growth charts. The predictive value of SGA according to each of the charts for stillbirth was described using the following measures: detection rate (sensitivity), false positive rate (1-specificity), positive and negative predictive value, and positive and negative likelihood ratio.

Data were analyzed using SPSS statistical software Version 24.0 (Armonk, NY: IBM Corp.). Significance was set to a two-sided p value of < 0.05.

Results

Characteristics of the study cohort

A total of 49,458 singleton pregnancies met the study criteria, of which 103 were complicated by stillbirth due to placental dysfunction ($n = 51$) or an unknown etiology ($n = 52$), resulting in an incidence of 2.08 cases per 1000 non-anomalous singleton births at ≥ 24 week's gestation (Fig. 1). Women with stillbirth were more likely to be nulliparous, to have hypertensive complications, to give birth at an earlier gestational age, and to have a female fetus (Table 1).

Rate of SGA < 10th centile by growth chart

The 10th centile line of each of the four growth charts are compared in Fig. 2. The Hadlock and WHO charts were very similar and were shifted upwards compared with the other charts. The birthweight-based chart of Kramer was similar to the Hadlock and WHO charts at term, but was considerably shifted downwards compared with these charts before 37 weeks. The IG21 chart was shifted downwards compared with all other charts from 34 weeks beyond; prior to 34 weeks it was shifted upwards compared with the

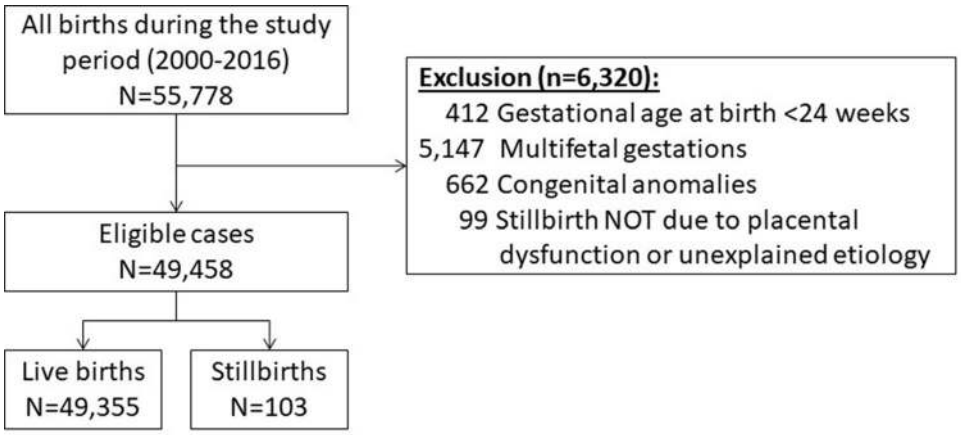

Fig. 1 Selection of the study group

Table 1 Baseline characteristics of the live birth and stillbirth groups

Characteristic	Live birth ($n = 49,355$)	Stillbirth ($n = 103$)	p value
Maternal age (years)	32.8 ± 5.0	33.5 ± 5.5	0.162
> 35 years	14,568 (29.5%)	39 (37.9%)	0.064
Nulliparity	24,999 (50.7%)	67 (65.0%)	**0.004**
Gestational age at birth (weeks)	38.5 ± 2.6	30.8 ± 5.4	**< 0.001**
≤ 30 weeks	1693 (3.4%)	54 (52.4%)	**< 0.001**
> 30 weeks	47,765 (96.6%)	49 (47.6%)	**< 0.001**
Chronic hypertension	397 (0.8%)	4 (3.9%)	**< 0.001**
Pregestational diabetes	402 (0.8%)	1 (1.0%)	0.860
Gestational hypertension	1681 (3.4%)	6 (5.8%)	0.177
Preeclampsia	630 (1.8%)	8 (7.8%)	**< 0.001**
Gestational diabetes	1557 (3.2%)	4 (3.9%)	0.673
Fetal female sex	23,909 (48.4%)	54 (52.4%)	**< 0.001**
Birthweight < 10th%			
Hadlock chart	3886 (7.9%)	63 (61.2%)	**< 0.001**
IG21 chart	1626 (3.3%)	54 (52.4%)	**< 0.001**
WHO chart	4934 (10.0%)	65 (63.1%)	**< 0.001**
Kramer chart	3711 (7.5%)	50 (48.5%)	**< 0.001**

Significant associations are emphasized in bold

WHO World Health Organization, *IG21* intergrowth-21st. Data are presented as n (%) or mean ± SD

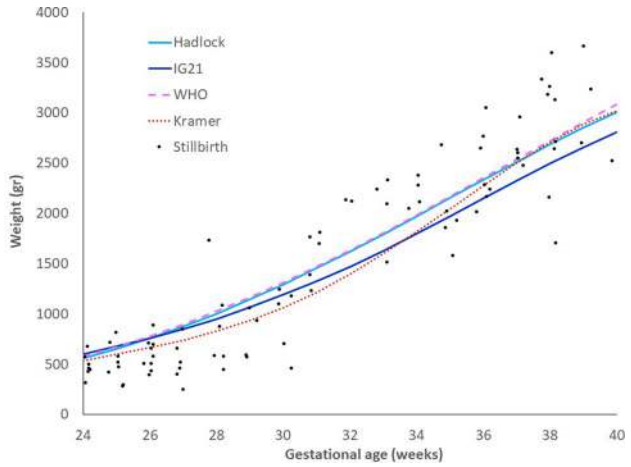

Fig. 2 Distribution of cases of stillbirth by gestational age and weight centile in relation to the 10th centile of the different growth charts. The 10th centile lines are presented for the charts of Hadlock (solid light blue line), intergrowth-21st (solid dark blue line), World Health Organization (dashed pink line), and Kramer (dotted red line). The black dots represent cases of stillbirth ($n=103$) by gestational age and birthweight at diagnosis

birthweight-based chart of Kramer but remained below the Hadlock and WHO charts (Fig. 2). The rate of SGA < 10th centile varied by growth chart, being highest for the WHO chart (10.0%) and lowest for the IG21 chart (3.3%) (Table 1).

Distribution of cases of stillbirth by gestational age and weight centile

The distribution of cases of stillbirth by gestational age and weight centile is presented in Fig. 2. We identified two clusters of stillbirth cases based on gestational age at diagnosis of ≤ 30 and > 30 weeks' gestation. While the majority of cases of stillbirth in the early stillbirth cluster (≤ 30 weeks) were SGA < 10th centile for gestational age according to all four charts, most cases in the late stillbirth cluster (> 30 weeks) had a weight > 10th centile for gestational age (Fig. 2).

To describe better the distribution of weight centiles of cases of stillbirth diagnosed at > 30 weeks, we superimposed the cases of stillbirth on the different centile lines (10th, 25th, 50th, and 90th centile lines) of each growth

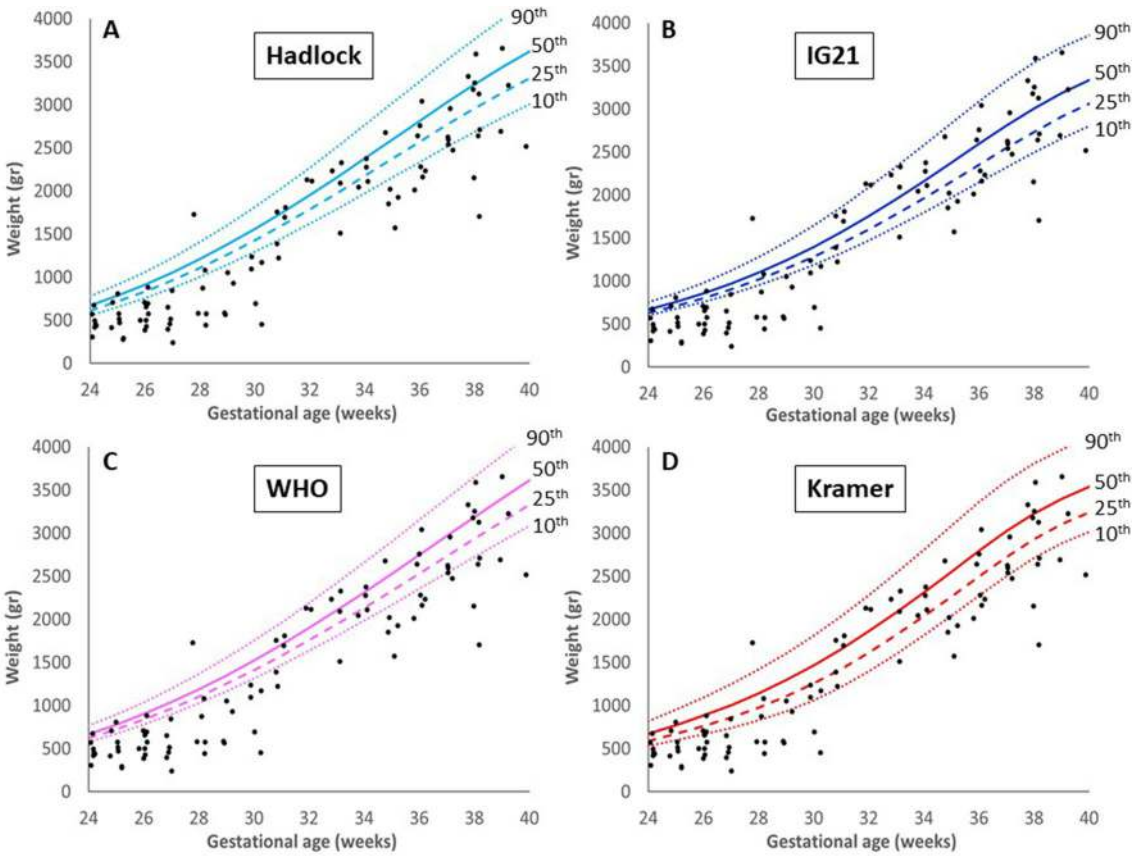

Fig. 3 Distribution of cases of stillbirth by gestational age and weight centile in relation to various centiles of the different growth charts. The black dots represent cases of stillbirth ($n=103$) by gestational age and birthweight at diagnosis and are superimposed on the growth charts of Hadlock (**a**), intergrowth-21st (**b**), World Health Organization (**c**), and Kramer (**d**). For each growth chart, the following 4 centile lines are displayed: 10th and 90th centile (dotted lines), 25th centile (dashed line), and 50th centile (solid line)

chart (Fig. 3). This figure illustrates that at > 30 week gestation, the use of a threshold higher than the 10th centile (e.g., 25th centile) may improve the detection rate of stillbirth, especially for charts that are shifted downwards such as the IG21 chart (Fig. 3b).

Predictive accuracy of 10th centile for stillbirth

We next calculated the predictive accuracy of SGA < 10th centile for stillbirth based on each of the four growth charts (Table 2 and Fig. 4). The detection rate of SGA < 10th centile for stillbirth in the overall cohort was highest for the Hadlock and WHO charts (61.2% and 63.1%, respectively), and lowest for the IG21 and Kramer charts (52.4% and 48.5%, respectively). For cases in the early stillbirth cluster (≤ 30 weeks), the detection rate was higher than in the overall cohort and was similar for all charts (83.3–87.0%) with the exception of the chart of Kramer (66.7%). In contrast, the detection rate of SGA for cases in the late stillbirth cluster (> 30 weeks) was low, being highest for WHO and Hadlock (36.7% and 34.7%, respectively) and lowest for IG21 (18.4%) (Table 2 and Fig. 4).

The opposite pattern was observed for the false positive rate (which essentially reflects the proportion of fetuses diagnosed as SGA using each chart) which was lowest for the IG21 chart and highest for the Hadlock and WHO charts (Table 2). To facilitate the comparison of the predictive accuracy of the four growth charts, the detection rate and false positive rate of the four charts are presented graphically in Fig. 4.

Predictive accuracy of 25th centile for stillbirth

Given the low detection rate of SGA < 10th centile for late stillbirth (> 30 weeks), we explored the performance of a higher threshold, 25th centile, in predicting stillbirth at this gestational age window (Table 3 and Fig. 4). The detection rate of SGA < 25th centile for stillbirth at > 30 weeks was in the range of 38.8–51.0%, reflecting an increase of approximately 15–20% compared with the detection rate achieved

Table 2 Predictive accuracy of SGA < 10th centile for stillbirth by growth chart

Growth chart	Detection rate (%, [95% CI])	False positive rate (%, [95% CI])	PPV (%, [95% CI])	NPV (%, [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	Overall accuracy (%, [95% CI])
Overall cohort							
Hadlock	61.2 (60.7–61.6)	7.9 (7.6–8.1)	1.6 (1.5–1.7)	99.9 (99.9–99.9)	7.77 (7.61–7.93)	0.42 (0.18–0.66)	92.1 (91.8–92.3)
IG21	52.4 (52.0–52.9)	3.3 (3.1–3.5)	3.2 (3.1–3.4)	99.9 (99.9–99.9)	15.91 (15.72–16.10)	0.49 (0.29–0.69)	96.6 (96.5–96.8)
WHO	63.1 (62.7–63.5)	10.0 (9.7–10.3)	1.3 (1.2–1.4)	99.9 (99.9–99.9)	6.31 (6.16–6.46)	0.41 (0.16–0.66)	89.9 (89.7–90.2)
Kramer	48.5 (48.1–49.0)	7.5 (7.3–7.8)	1.3 (1.2–1.4)	99.9 (99.9–99.9)	6.46 (6.25–6.66)	0.56 (0.37–0.74)	92.4 (92.2–92.6)
Births ≤ 30 weeks							
Hadlock	85.2 (83.5–86.9)	25.6 (23.5–27.7)	9.9 (8.5–11.3)	99.3 (99.0–99.7)	3.32 (3.19–3.46)	0.20 (− 0.44–0.84)	74.7 (72.6–76.8)
IG21	83.3 (81.6–85.1)	22.3 (20.3–24.3)	10.9 (9.5–12.4)	99.3 (98.9–99.7)	3.73 (3.58–3.88)	0.21 (− 0.38–0.81)	77.8 (75.9–79.8)
WHO	87.0 (85.4–88.6)	29.9 (27.7–32.1)	8.8 (7.4–10.1)	99.4 (99.0–99.8)	2.91 (2.78–3.04)	0.18 (− 0.51–0.88)	70.6 (68.5–72.8)
Kramer	66.7 (64.4–68.9)	9.4 (8.0–10.8)	18.9 (17.1–20.8)	98.8 (98.3–99.3)	7.10 (6.85–7.34)	0.37 (− 0.01–0.75)	89.8 (88.4–91.3)
Births > 30 weeks							
Hadlock	34.7 (34.3–35.1)	7.3 (7.0–7.5)	0.5 (0.4–0.6)	99.9 (99.9–100.0)	4.78 (4.39–5.16)	0.70 (0.50–0.91)	92.7 (92.4–92.9)
IG21	18.4 (18.0–18.7)	2.6 (2.5–2.8)	0.7 (0.6–0.8)	99.9 (99.9–99.9)	6.96 (6.36–7.55)	0.84 (0.71–0.97)	97.3 (97.1–97.4)
WHO	36.7 (36.3–37.2)	9.3 (9.1–9.6)	0.4 (0.3–0.5)	99.9 (99.9–100.0)	3.94 (3.58–4.31)	0.70 (0.48–0.91)	90.6 (90.4–90.9)
Kramer	28.6 (28.2–29.0)	7.5 (7.2–7.7)	0.4 (0.3–0.4)	99.9 (99.9–99.9)	3.83 (3.39–4.28)	0.77 (0.59–0.95)	92.5 (92.2–92.7)

PPV, positive predictive value; *NPV*, negative predictive value; *LR*, likelihood ratio; *CI*, confidence interval; *WHO*, World Health Organization; *IG21*, intergrowth-21st; *SGA*, small for gestational age

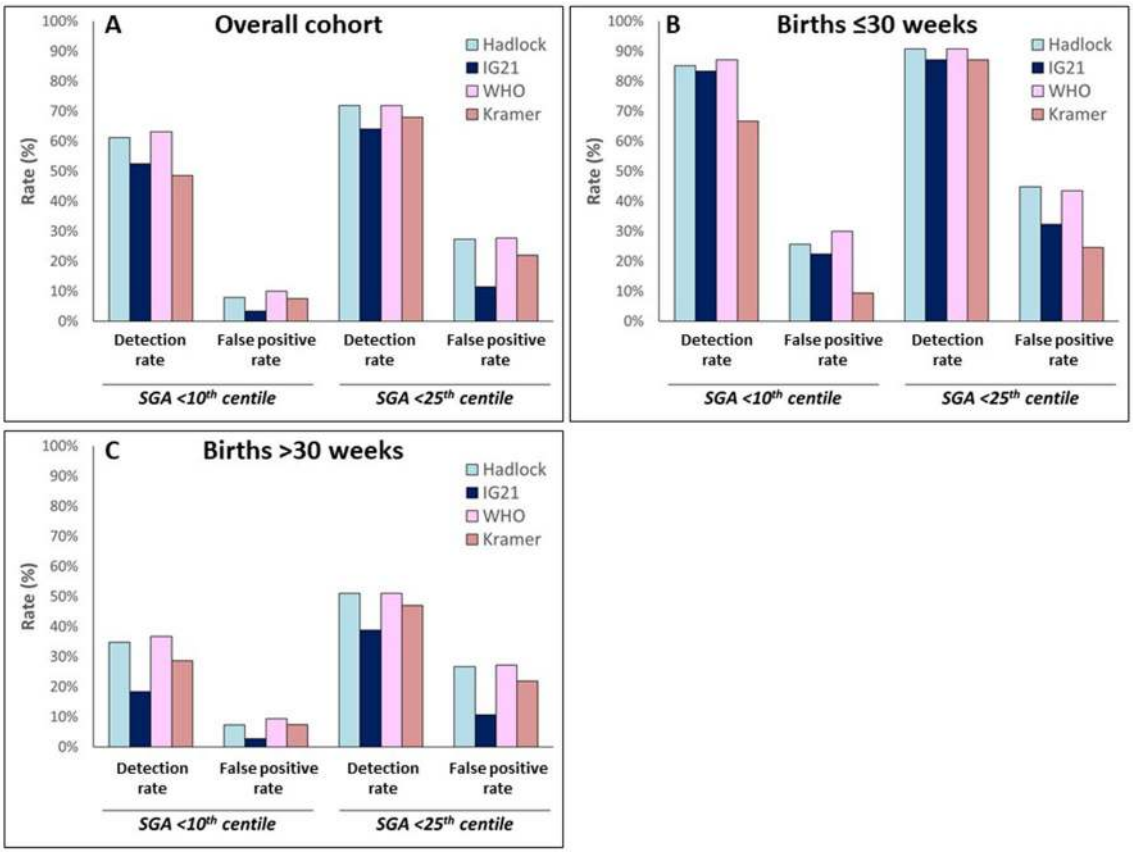

Fig. 4 Detection rate and false positive rate of the different growth charts for stillbirth. The detection rate and false positive rate of SGA for stillbirth is presented for the overall cohort (**a**), and for the subgroup births occurring at ≤ 30 weeks (**b**) and at > 30 weeks (**c**). Data are stratified by the choice of growth chart and the threshold (10th or 25th centile) used to define SGA. *SGA* small for gestational age

with the 10th centile threshold (18.4–36.7%, Table 2). However, this was associated with a considerable increase in false positive rate (10.7–27.1% for the 25th centile threshold compared with 2.6–9.3% for the 10th) (Table 3). This is illustrated graphically in Fig. 4c.

For cases in the early stillbirth cluster (≤ 30 weeks), with the exception of the birthweight-based chart of Kramer, increasing the threshold from 10 to 25th centile had little effect on the detection rate of stillbirth (range 87.0–90.7% compared with 83.3–87.0% when using the 10th centile), while it resulted in a considerable increase in the false positive rate (Table 3 and Fig. 4b).

Discussion

Principal findings

The objective of the current study was to evaluate the effect of the choice growth chart and the centile threshold used to define SGA on the predictive value of SGA for placenta-related or unexplained stillbirth. Our main findings are as follows: (1) we identified two clusters of stillbirth, distinguished by gestational age at diagnosis of ≤ 30 and > 30 weeks, respectively; (2) in the early stillbirth cluster (≤ 30 weeks), the use of the 10th centile to define SGA had a high detection rate for stillbirth irrespective of the growth chart used, with the exception of the birthweight-based chart of Kramer which had a considerably lower detection rate compared with the three ultrasound-based charts; (3) in the late stillbirth cluster (> 30 weeks), the ultrasound-based charts of Hadlock and WHO provided the best balance between detection rate and false positive rate for stillbirth, while the IG21 has a low detection rate for stillbirth in this cluster. In this cluster (> 30 weeks), the use of the 10th centile threshold was associated with an overall low detection rates for stillbirth; the use of the higher threshold of the 25th centile to define SGA in this cluster improved the detection rate for stillbirth, but was associated with a concomitant increase in the false positive rate.

Table 3 Predictive accuracy of SGA < 25th centile for stillbirth by growth chart

Growth chart	Detection rate (%, [95% CI])	False positive rate (%, [95% CI])	PPV (%, [95% CI])	NPV (%, [95% CI])	Positive LR (95% CI)	Negative LR (95% CI)	Overall accuracy (%, [95% CI])
Overall cohort							
Hadlock	71.8 (71.4–72.2)	27.3 (26.9–27.7)	0.5 (0.5–0.6)	99.9 (99.9–99.9)	2.63 (2.51–2.75)	0.39 (0.08–0.70)	72.7 (72.3–73.1)
IG21	64.1 (63.7–64.5)	11.4 (11.1–11.7)	1.2 (1.1–1.3)	99.9 (99.9–99.9)	5.62 (5.48–5.77)	0.41 (0.15–0.66)	88.6 (88.3–88.8)
WHO	71.8 (71.4–72.2)	27.7 (27.3–28.1)	0.5 (0.5–0.6)	99.9 (99.9–99.9)	2.60 (2.47–2.72)	0.39 (0.08–0.70)	72.3 (71.9–72.7)
Kramer	68.0 (67.5–68.4)	21.9 (21.6–22.3)	0.6 (0.6–0.7)	99.9 (99.9–99.9)	3.10 (2.96–3.23)	0.41 (0.13–0.69)	78.0 (77.7–78.4)
Births ≤ 30 weeks							
Hadlock	90.7 (89.4–92.1)	44.7 (42.4–47.1)	6.3 (5.1–7.4)	99.5 (99.1–99.8)	2.03 (1.93–2.13)	0.17 (− 0.67–1.00)	56.4 (54.0–58.8)
IG21	87.0 (85.4–88.6)	32.2 (30.0–34.4)	8.2 (6.9–9.5)	99.4 (99.0–99.7)	2.70 (2.58–2.83)	0.19 (− 0.50–0.88)	68.4 (66.2–70.6)
WHO	90.7 (89.4–92.1)	43.4 (41.1–45.8)	6.4 (5.3–7.6)	99.5 (99.1–99.8)	2.09 (1.99–2.19)	0.16 (− 0.67–1.00)	57.6 (55.3–60.0)
Kramer	87.0 (85.4–88.6)	24.5 (22.5–26.6)	10.5 (9.0–11.9)	99.4 (99.1–99.8)	3.55 (3.42–3.68)	0.17 (− 0.52–0.86)	75.8 (73.8–77.9)
Births > 30 weeks							
Hadlock	51.0 (50.6–51.5)	26.7 (26.3–27.1)	0.2 (0.2–0.2)	99.9 (99.9–100.0)	1.91 (1.64–2.19)	0.67 (0.38–0.95)	73.3 (72.9–73.7)
IG21	38.8 (38.3–39.2)	10.7 (10.4–11.0)	0.4 (0.3–0.4)	99.9 (99.9–100.0)	3.63 (3.28–3.98)	0.69 (0.46–0.91)	89.3 (89.0–89.5)
WHO	51.0 (50.6–51.5)	27.1 (26.7–27.5)	0.2 (0.2–0.2)	99.9 (99.9–100.0)	1.88 (1.61–2.16)	0.67 (0.39–0.96)	72.8 (72.4–73.2)
Kramer	46.9 (46.5–47.4)	21.9 (21.5–22.2)	0.2 (0.2–0.3)	99.9 (99.9–100.0)	2.15 (1.85–2.45)	0.68 (0.42–0.94)	78.1 (77.7–78.5)

PPV, positive predictive value; *NPV*, negative predictive value; *LR*, likelihood ratio; *CI*, confidence interval; *WHO*, World Health Organization; *IG21*, intergrowths21st; *SGA*, small for gestational age

Results of the study in the context of other observations

The incidence of stillbirth in our cohort (2.08 per 1000 births) was lower than previously reported (6.25 per 1000 births) [27], most likely due to the fact that our study was limited to cases of stillbirth related to placental dysfunction or of unknown etiology which accounts for approximately 40% of cases of stillbirth [28, 29]. Our findings regarding the two clusters of stillbirth across gestation is in agreement with prior reports [30, 31] and in concordance with data presented in a recently published obstetric care consensus by the American College of Obstetrician and Gynecologists (ACOG) and Society for Maternal–Fetal Medicine (SMFM) addressing the management of stillbirth [27].

We found that at > 30 weeks of gestation, IG21 had a low detection rate for stillbirth compared to the other growth charts, which is in agreement with prior studies comparing IG21 to other growth charts for the identification of fetuses at risk for morbidity and mortality [15]. Anderson et al. reported that at > 33 weeks of gestation, the use of customized centiles identified more SGA infants at risk of perinatal mortality and morbidity compared with the IG21 standard [16]. Other studies comparing customized [15, 17, 18] or non-customized [15] charts with the IG21 standard reached similar conclusions. In contrast, others reported that the IG21, WHO and other charts had a similar predictive accuracy for the prediction of adverse perinatal outcome at term, although the relatively small sample size may limit the interpretation of this finding [32].

We also found that at > 30 weeks, the use of the 10th centile as the threshold to define SGA had a low detection rate for stillbirth. In a recent study by Iliodromiti et al. [20], it was found that the risk of stillbirth at term started to increase once birthweight fell below the 25th centile. Based on that the authors recommended that the threshold used to predict adverse perinatal outcome, and to trigger increased fetal monitoring and consideration of delivery near term should be increased to the 25th centile. Our data demonstrate that increasing the threshold from 10 to 25th

centile at > 30 weeks resulted in a considerable increase in the detection rate of SGA for stillbirth at the cost of a concomitant increase in the false positive rate. Therefore, the use of a higher centile threshold should likely be used in combination with additional biomarkers that are specific for FGR, thereby decreasing the false positive rate associated with a higher centile threshold. Gaccioli et al. [33] reported that the combining the diagnosis of SGA with the angiogenic markers soluble fms-like tyrosine kinase receptor 1 (sFLT1) and placental growth factor (PlGF) improved the prediction of perinatal complications compared to the use of SGA alone. More recently, maternal serum metabolite ratio was found to further improve the discrimination ability for term FGR [34]. Other biomarkers that may decrease the false positive rate include measures of fetal growth velocity [35], and Doppler studies such as the cerebro-placental ratio (CPR) [36, 37] and uterine artery Dopplers [38].

The low detection rate of the 10th centile threshold for stillbirth at > 30 weeks in consistent with the findings from recent studies where the association of placental abnormalities with stillbirth at late gestation was less likely to be mediated by poor fetal growth [39, 40]. Placental lesions such as maternal and fetal circulatory disorders and maternal inflammatory response were associated with stillbirth irrespective of whether the fetus was SGA [40]. These findings suggest that the pathophysiologic mechanisms underlying stillbirth late in gestation differ from that of early stillbirth [41], and that the phenotype of placental dysfunction late in gestation may involve abnormal gas exchange or acute placental complications with relatively subtle effects of fetal growth [31, 41]. This scenario is in contrast to early-onset placental dysfunction where poor fetal growth is a dominant phenotype of placental dysfunction.

Our finding that the birth weight-based chart of Kramer had a poor detection rate for early stillbirth (< 30 weeks) highlights the well-established limitations of using birth weight-based charts to diagnose fetal growth restriction in early gestation. These limitations are attributed to the fact that infants born prematurely are more likely to be affected by placental dysfunction and growth restriction, such that their inclusion in a growth chart lowers the expected normal fetal growth prior to 37 weeks. Consequently, the fetus with true growth restriction is more likely to be undetected, if a birthweight-based chart is employed [42–48].

Strengths and limitations

The main strengths of the current study include the use of data from a single-tertiary center with a standardized protocol for evaluating cases of stillbirth which, in contrast to population-based studies, allowed us to focus on the outcome that is most relevant for the detection of fetal growth restriction, which is placenta-mediated and unexplained stillbirth. Despite being from one center, our catchment area is located within a diverse city, such that our conclusions are likely to be generalizable to other diverse populations. Finally, our conclusions are robust as they are based on a full exploration of all contemporary fetal growth chart methods [16, 17, 19, 49–51].

One limitation of the current study is the use of birthweight rather than sonographic fetal weight estimation. This is especially relevant to stillbirth cases, which may lose up to 10% of body weight through intrauterine maceration before birth [23, 41]. Still, this limitation, which may result in overestimation of the proportion of SGA fetuses in cases of stillbirth, is unlikely to confound our conclusions at > 30 weeks, where the majority of stillbirths were not SGA < 10th centile. Another limitation is the relatively small sample size as compared to prior registry-based studies [19, 52], although, the number of stillbirths in our cohort was relatively similar [30]. Finally, we lacked information on certain risk factors such maternal smoking and maternal body mass index.

Conclusions

The choice of optimal growth chart and the threshold centile to suspected fetal growth restriction depend on the optimal balance between detection rate and false positive rate for adverse perinatal outcome, which should be determined by clinical practice guidelines. The findings of the current study seem to support the use of the fetal ultrasound-based Hadlock or WHO charts, especially at > 30 weeks, due to their better detection rate for stillbirth at a relatively small cost of increased proportion of fetuses diagnoses as SGA. The use of the 10th centile of birthweight to define SGA resulted in an unacceptably low detection rate for stillbirth at > 30 weeks, while a more liberal 25th centile threshold of fetal size to suspect fetal growth restriction significantly increased the detection rate. To establish an acceptable level of screening test precision, an optimal assessment of fetal growth must be combined with other biomarkers for FGR, such biochemical markers, fetal cerebral Doppler, or a subsequent assessment of fetal size in 2–3 weeks to determine fetal growth velocity.

Author contributions LH: project development, data analysis, and manuscript writing. HL: data collection and manuscript writing. JK: manuscript writing. JB: data analysis and manuscript writing. NM: project development, data analysis, and manuscript writing.

Funding Dr. Melamed holds the Waugh Family Chair in Twin Fetal Medicine Research at the Sunnybrook Health Sciences Center and the University of Toronto.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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