

# Fetal Growth in Twin Pregnancies and the Choice of Growth Chart

Nir Melamed<sup>1,\*</sup>, Liran Hiersch<sup>2</sup>

## Background

Twin gestations are associated with an increased risk of pregnancy complications such as preterm birth, hypertensive disorders of pregnancy (HDP), and fetal growth restriction (FGR).<sup>1–5</sup> Twin pregnancies are characterized by a slower fetal growth compared to singletons during the third trimester. The mechanisms underlying this phenomenon and whether it represents a pathological FGR or a harmless physiologic adaptation are currently unclear.<sup>6</sup> One important implication of these questions relates to the growth charts that should be used by care providers to monitor growth of twins. If the slower growth represents a pathology, then singleton growth charts should be used to identify the small twin fetus which may be at an increased risk of mortality and morbidity. If, however, the slower growth of twins reflects a benign adaptation, then twin-based charts may be preferable to avoid overdiagnosis of FGR in twin gestations.<sup>7,8</sup>

## Differences in fetal growth between twin and singleton fetuses

A large number of studies have compared the growth of twin fetuses with that of singletons.<sup>9–31</sup> The 50<sup>th</sup> centile curves of some of these charts are compared in Figure 1 along with a representative singleton chart as a reference. Twin fetuses demonstrate reduced growth rate starting at approximately 26–28 weeks based on either birthweight-based or ultrasound-based charts (Fig. 1). Because of these differences, the use of singleton charts in twin pregnancies may result in a relatively large proportion of twin fetuses suspected to be growth restricted due to either ‘falling off the curve’ or being small for gestational age (SGA, defined as weight <10<sup>th</sup> centile for gestational age).<sup>7,12,17,31</sup>

## The slower growth of twin fetuses - pathology or physiology?

The most intuitive explanation for the slower growth of twins is the failure of the uteroplacental unit to meet the nutritional demands of two fetuses.<sup>32–35</sup> However, some have argued against this explanation based on the observation that twins experience slower growth already early in the third trimester, at a time where nutrient supply by the placenta is unlikely to be a limiting factor.<sup>30,36,37</sup>

In addition, placentas of SGA twins are less likely to demonstrate histopathological evidence of placental insufficiency compared with SGA singletons.<sup>38–40</sup> Others suggested that the slower growth of twins is the result of the physical constraint imposed by the uterine size,<sup>32,33</sup> or due to placental crowding.<sup>33</sup>

However, more recent evidence suggests that the slower growth of twins is a physiologic phenomenon that is the result of fetal programming early in pregnancy<sup>41,42</sup> through hormonal<sup>43,44</sup> and epigenetic mechanisms.<sup>45–47</sup>

This hypothesis is supported by evidence that twins may downregulate their growth rate early in gestation,<sup>36,48</sup> as well as by studies on fetal reduction.<sup>34,49</sup>

## Predictive value of twin compared with singleton-based charts

Ultimately, the decision on whether to use singleton or twin charts should be based on the diagnostic accuracy of the two types of charts for adverse perinatal outcomes. Several studies compared the outcomes of twin fetuses diagnosed as SGA using singleton *vs.* twin charts. In a study of 7673 women with a twin pregnancy, the association of SGA with the neonatal morbidity was stronger when SGA was diagnosed using a twin chart compared with a singleton chart.<sup>7</sup> In another retrospective of 730 dichorionic twin pregnancies, it was found that the use of twin-based charts can decrease the proportion of SGA by approximately 50% and improve the prediction of perinatal complications.<sup>50</sup> In another recent study,<sup>51</sup> the use of twin charts to diagnose SGA in twins reduced the rate of SGA without affecting the predictive accuracy of SGA for stillbirth. In another recent study, Proctor *et al.* compared the association between SGA and HDP in twin pregnancies.<sup>8</sup> No association between SGA and HDP was found when a singleton chart was used to diagnose SGA. In contrast, the diagnosis of SGA using a twin-based chart was associated with an increased risk of HDP and the magnitude of this association was similar to that seen in singletons, suggesting that the diagnosis of SGA in twins is more likely to be equivalent to the diagnosis of SGA in singletons when a twin-based chart (rather than a singleton-based chart) is used to diagnose SGA in twins. Finally, in a large population-based study of singleton and twin infants born at 36–42 weeks,<sup>52</sup> the authors identified

<sup>1</sup> Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre, Toronto M5N 3M5, ON, Canada; <sup>2</sup> Department of Obstetrics and Gynaecology, Lis Maternity Hospital, Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6423906, Israel.

\* Corresponding author: Nir Melamed, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynaecology, Sunnybrook Health Sciences Center, Toronto M5N 3M5, ON, Canada. E-mail: nir.melamed@sunnybrook.ca  
Copyright © 2022 The Chinese Medical Association, published by Wolters Kluwer Health, Inc.

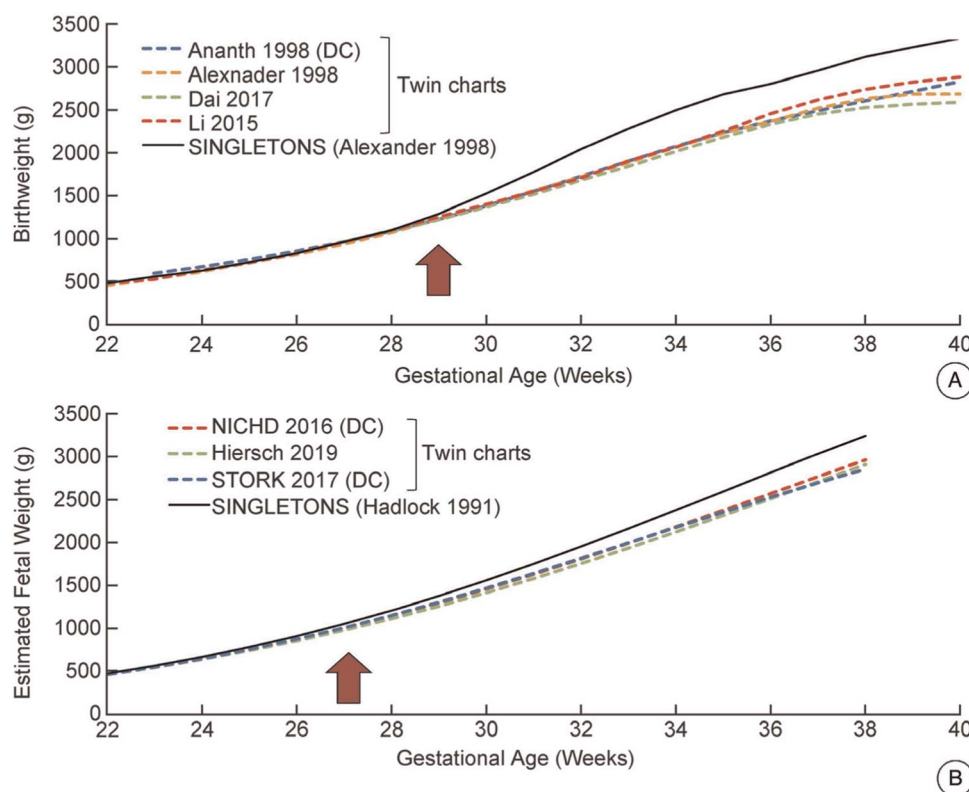
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Maternal-Fetal Medicine (2022) 4:4

Received: 5 July 2021 / Accepted: 28 September 2021

First online publication: 22 October 2021

<http://dx.doi.org/10.1097/FM9.0000000000000131>



**Figure 1.** Comparison of twin-based fetal growth charts. The 50<sup>th</sup> centile curves are presented for several birthweight-based (A) and ultrasound-based (B) twin chart. Representative birthweight and ultrasound singletons charts (Alexander 1998<sup>15</sup> and Hadlock 1991<sup>62</sup>, respectively) are shown for comparison (black lines). The arrow points to the point where the 50<sup>th</sup> centile curves of twin and singleton fetuses starts to diverge (approximately 28–30 weeks for birthweight charts and 26–28 weeks for ultrasound charts). DC: Dichorionic; NICHD: National Institute of Child Health and Human Development; STORK: Southwest Thames Obstetric Research Collaborative.

the range of absolute birthweight at each gestational week that was associated with the lowest risk of neonatal mortality and morbidity. The lower threshold of this optimal range of birthweight was lower by approximately 150 g for twins compared with singletons across all gestational weeks, suggesting that the relative smallness of twins is not associated with an increased risk of mortality and morbidity.

Taken together, these findings provide support to the hypothesis that the relative smallness of twins represents a physiologic adaptation, and that the use of twin charts can avoid over diagnosis of FGR and may result in a diagnosis of FGR that is more clinically relevant.

## Discussion

The question of whether twin-specific charts should be used in twin pregnancies is important from both clinical and research perspectives and can have a considerable impact on the use of resources, unnecessary interventions, and patient anxiety. There is a growing body of evidence suggesting that the use of twin charts can reduce the rate of SGA without compromising the detection of twin fetuses at risk of adverse outcome due to placental insufficiency. In addition, given that twin fetuses are screened with serial ultrasound growth scans,<sup>53–57</sup> it is likely that twin fetuses that are truly growth restricted will be detected by serial ultrasound exams irrespective of which chart is used. Finally, measures such as umbilical and fetal Doppler and intertwin size discordance<sup>53,55,58–60</sup> are likely to further contribute to the detection of growth restricted twin fetuses irrespective of which chart is being used.<sup>61</sup>

Still, it should be kept in mind that most of the available data described above are observational in nature, and are further limited by the fact that twin fetuses are usually being followed more closely than singletons and are delivered by 37–38 weeks of gestation. Therefore, adequately-powered trials are likely needed to confirm that the use of twin charts can decrease the rate of SGA without compromising outcomes in twin pregnancies. Finally, further studies are needed to provide better understanding of the mechanisms responsible for the slower growth in twins through correlation with biochemical and angio-genic biomarkers, placental markers of hypoxia, eigenetic markers in the placenta and the fetus, and through correlation with long-term neonatal outcomes.

## Funding

None.

## Conflicts of Interest

None.

## References

- [1] Hirsch L, Berger H, Okby R, et al. Incidence and risk factors for gestational diabetes mellitus in twin versus singleton pregnancies. *Arch Gynecol Obstet* 2018;298(3):579–587. doi: 10.1007/s00404-018-4847-9.
- [2] Salem SY, Kibel M, Asztalos E, et al. Neonatal outcomes of low-risk, late-preterm twins compared with late-preterm singletons. *Obstet Gynecol* 2017;130(3):582–590. doi: 10.1097/AOG.0000000000002187.
- [3] Laine K, Murzakanova G, Sole KB, et al. Prevalence and risk of preeclampsia and gestational hypertension in twin pregnancies: a population-based register study. *BMJ Open* 2019;9(7):e029908. doi: 10.1136/bmjopen-2019-029908.

- [4] Fuchs F, Senat MV. Multiple gestations and preterm birth. *Semin Fetal Neonatal Med* 2016;21(2):113–120. doi: 10.1016/j.siny.2015.12.010.
- [5] Simchen MJ, Okrent Smolar AL, Dulitzky M, et al. Neonatal morbidities and need for intervention in twins and singletons born at 34–35 weeks of gestation. *J Perinat Med* 2016;44(8):887–892. doi: 10.1515/jpm-2015-0113.
- [6] Research Committee SMFM, Grantz KL, Kawakita T, et al. SMFM special statement: state of the science on multifetal gestations: unique considerations and importance. *Am J Obstet Gynecol* 2019;221(2): B2–B12. doi: 10.1016/j.ajog.2019.04.013.
- [7] Mendez-Figueroa H, Truong V, Pedroza C, et al. Growth among twins: use of singleton versus twin-specific growth nomograms. *Am J Perinatol* 2018;35(2):184–191. doi: 10.1055/s-0037-1606381.
- [8] Proctor LK, Kfoury J, Hirsch L, et al. Association between hypertensive disorders and fetal growth restriction in twin compared with singleton gestations. *Am J Obstet Gynecol* 2019;221(3):251.e1–251.e8. doi: 10.1016/j.ajog.2019.04.022.
- [9] Doom EC, Delbaere I, Martens G, et al. Birth weight for gestational age among Flemish twin population. *Facts Views Vis Obgyn* 2012; 4(1):42–49.
- [10] Dollberg S, Haklai Z, Mimouni FB, et al. Birth weight standards in the live-born population in Israel. *Isr Med Assoc J* 2005;7(5):311–314.
- [11] Min SJ, Luke B, Gillespie B, et al. Birth weight references for twins. *Am J Obstet Gynecol* 2000;182(5):1250–1257. doi: 10.1067/mob.2000.104923.
- [12] Grantz KL, Grewal J, Albert PS, et al. Dichorionic twin trajectories: the NICHD fetal growth studies. *Am J Obstet Gynecol* 2016;215(2): 221.e1–221.e16. doi: 10.1016/j.ajog.2016.04.044.
- [13] Hirsch L, Okby R, Freeman H, et al. Differences in fetal growth patterns between twins and singletons. *J Matern Fetal Neonatal Med* 2020;33(15):2546–2555. doi: 10.1080/14767058.2018.1555705.
- [14] Ong S, Lim MN, Fitzmaurice A, et al. The creation of twin centile curves for size. *BJOG* 2002;109(7):753–758. doi: 10.1111/j.1471-0528.2002.01361.x.
- [15] Alexander GR, Kogan M, Martin J, et al. What are the fetal growth patterns of singletons, twins, and triplets in the United States? *Clin Obstet Gynecol* 1998; 41(1):114–125. doi: 10.1097/00003081-199803000-00017.
- [16] Ananth CV, Vintzileos AM, Shen-Schwarz S, et al. Standards of birth weight in twin gestations stratified by placental chorionicity. *Obstet Gynecol* 1998;91(6):917–924. doi: 10.1016/s0029-7844(98) 00052-0.
- [17] Gielen M, Lindsey PJ, Derom C, et al. Twin-specific intrauterine 'growth' charts based on cross-sectional birthweight data. *Twin Res Hum Genet* 2008;11(2):224–235. doi: 10.1375/twin.11.2.224.
- [18] Li Z, Umstad MP, Hilder L, et al. Australian national birthweight percentiles by sex and gestational age for twins, 2001–2010. *BMC Pediatr* 2015;15:148. doi: 10.1186/s12887-015-0464-y.
- [19] Bricelj K, Blickstein I, Brzan-Simenc G, et al. Growth curves for twins in Slovenia. *J Matern Fetal Neonatal Med* 2017;30(4):479–481. doi: 10.1080/14767058.2016.1175425.
- [20] Dai L, Deng C, Li Y, et al. Population-based birth weight reference percentiles for Chinese twins. *Ann Med* 2017;49(6):470–478. doi: 10.1080/07853890.2017.1294258.
- [21] Horst N, Dera-Szymanowska A, Breborowicz GH, et al. Outcome dependent twin growth curves based on birth weight percentiles for Polish population. *J Matern Fetal Neonatal Med* 2020;1–6. doi: 10.1080/14767058.2020.1786810. Online ahead of print.
- [22] Araujo Júnior E, Ruano R, Javadian P, et al. Reference charts for fetal biometric parameters in twin pregnancies according to chorionicity. *Prenat Diagn* 2014;34(4):382–388. doi: 10.1002/pd.4318.
- [23] Shivkumar S, Himes KP, Hutcheon JA, et al. An ultrasound-based fetal weight reference for twins. *Am J Obstet Gynecol* 2015;213(2): 224.e1–224.e9. doi: 10.1016/j.ajog.2015.04.015.
- [24] Stirrup OT, Khalil A, D'Antonio F, et al. Patterns of second- and third-trimester growth and discordance in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Fetal Diagn Ther* 2017;41(2):100–107. doi: 10.1159/000447489.
- [25] Gabbay-Benziv R, Crimmins S, Contag SA. Reference values for sonographically estimated fetal weight in twin gestations stratified by chorionicity: a single center study. *J Ultrasound Med* 2017;36(4): 793–798. doi: 10.7863/ultra.16.02049.
- [26] Wilkof Segev R, Gelman M, Maor-Sagie E, et al. New reference values for biometrical measurements and sonographic estimated fetal weight in twin gestations and comparison to previous normograms. *J Perinat Med* 2019;47(7):757–764. doi: 10.1515/jpm-2019-0207.
- [27] Sekiguchi M, Mikami M, Nakagawa C, et al. An ultrasonographic estimated fetal weight reference for Japanese twin pregnancies. *J Med Ultrason* 2001 2019;46(2):209–215. doi: 10.1007/s10396-018-0921-y.
- [28] Savirón-Cornudella R, Esteban LM, Aznar-Gimeno R, et al. A cohort study of fetal growth in twin pregnancies by chorionicity: comparison with European and American standards. *Eur J Obstet Gynecol Reprod Biol* 2020;253:238–248. doi: 10.1016/j.ejogrb.2020.08.044.
- [29] Stirrup OT, Khalil A, D'Antonio F, et al. Fetal growth reference ranges in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2015;45(3):301–307. doi: 10.1002/uog.14640.
- [30] Ghi T, Prefumo F, Fichera A, et al. Development of customized fetal growth charts in twins. *Am J Obstet Gynecol* 2017;216(5):514.e1–514.e17. doi: 10.1016/j.ajog.2016.12.176.
- [31] Odibo AO, Cahill AG, Goetzinger KR, et al. Customized growth charts for twin gestations to optimize identification of small-for-gestational age fetuses at risk of intrauterine fetal death. *Ultrasound Obstet Gynecol* 2013;41(6):637–642. doi: 10.1002/uog.12404.
- [32] Blickstein I. Is it normal for multiples to be smaller than singletons? *Best Pract Res Clin Obstet Gynaecol* 2004;18(4):613–623. doi: 10.1016/j.bpobgyn.2004.04.008.
- [33] Bleker OP, Wolf H, Oosting J. The placental cause of fetal growth retardation in twin gestations. *Acta Genet Med Gemellol (Roma)* 1995;44(2):103–106. doi: 10.1017/s000156600001768.
- [34] Vamick I, Schoknecht PA, Darrigrand R, et al. Growth and metabolism of the placenta after unilateral fetectomy in twin pregnant ewes. *J Dev Physiol* 1991;15(6):351–356.
- [35] Liao AW, Brizot Mde L, Kang HJ, et al. Longitudinal reference ranges for fetal ultrasound biometry in twin pregnancies. *Clinics (Sao Paulo)* 2012;67(5):451–455. doi: 10.6061/clinics/2012(05)08.
- [36] Leveno KJ, Santos-Ramos R, Duenhoehter JH, et al. Sonar cephalometry in twins: a table of biparietal diameters for normal twin fetuses and a comparison with singletons. *Am J Obstet Gynecol* 1979;135(6): 727–730. doi: 10.1016/0002-9378(79)90382-x.
- [37] Iffy L, Lavenhar MA, Jakobovits A, et al. The rate of early intrauterine growth in twin gestation. *Am J Obstet Gynecol* 1983; 146(8):970–972. doi: 10.1016/0002-9378(83)90976-6.
- [38] Kibel M, Kahn M, Sherman C, et al. Placental abnormalities differ between small for gestational age fetuses in dichorionic twin and singleton pregnancies. *Placenta* 2017;60:28–35. doi: 10.1016/j.placenta.2017.10.002.
- [39] Barber E, Weiner E, Feldstein O, et al. The differences in placental pathology and neonatal outcome in singleton vs. twin gestation complicated by small for gestational age. *Arch Gynecol Obstet* 2018;298(6):1107–1114. doi: 10.1007/s00404-018-4921-3.
- [40] Matthews KC, Fox NS, Rebarber A. The association between placental histopathology, fetal growth restriction, and preeclampsia in twin pregnancies. *Am J Perinatol* 2021;38(8):784–790. doi: 10.1055/s-0039-3402716.
- [41] Muhlhauser BS, Hancock SN, Bloomfield FH, et al. Are twins growth restricted? *Pediatr Res* 2011;70(2):117–122. doi: 10.1203/PDR.0b013e31821f6cfd.
- [42] Phillips DI, Davies MJ, Robinson JS. Fetal growth and the fetal origins hypothesis in twins-problems and perspectives. *Twin Res* 2001;4(5):327–331. doi: 10.1375/1369052012669.
- [43] Rumball CW, Harding JE, Oliver MH, et al. Effects of twin pregnancy and periconceptional undernutrition on maternal metabolism, fetal growth and glucose-insulin axis function in ovine pregnancy. *J Physiol* 2008;586(5):1399–1411. doi: 10.1113/jphysiol.2007.144071.
- [44] Rumball CW, Oliver MH, Thorstensen EB, et al. Effects of twinning and periconceptional undernutrition on late-gestation hypothalamic-pituitary-adrenal axis function in ovine pregnancy. *Endocrinology* 2008;149(3):1163–1172. doi: 10.1210/en.2007-1306.
- [45] Begum G, Stevens A, Smith EB, et al. Epigenetic changes in fetal hypothalamic energy regulating pathways are associated with maternal undernutrition and twinning. *FASEB J* 2012;26(4):1694–1703. doi: 10.1096/fj.11-198762.
- [46] Tsai PC, Van Dongen J, Tan Q, et al. DNA methylation changes in the IGF1R gene in birth weight discordant adult monozygotic twins. *Twin Res Hum Genet* 2015;18(6):635–646. doi: 10.1017/thg.2015.76.
- [47] Williams-Wyss O, Zhang S, MacLaughlin SM, et al. Embryo number and periconceptional undernutrition in the sheep have differential effects on adrenal epigenotype, growth, and development. *Am J Physiol Endocrinol Metab* 2014;307(2):E141–E150. doi: 10.1152/ajpendo.00051.2012.
- [48] Divers WA Jr, Hemsell DL. The use of ultrasound in multiple gestations. *Obstet Gynecol* 1979;53(4):500–504.
- [49] Alexander JM, Hammond KR, Steinkampf MP. Multifetal reduction of high-order multiple pregnancy: comparison of obstetrical outcome with nonreduced twin gestations. *Fertil Steril* 1995;64(6):1201–1203. doi: 10.1016/s0015-0282(16)57985-0.

- [50] Shea SK, Likins BJ, Boan AD, et al. Dichorionic twin-specific vs singleton growth references for diagnosis of fetal growth restriction. *Am J Obstet Gynecol* 2021;224(6):603.e1-603.e9. doi: 10.1016/j.ajog.2021.03.022.
- [51] Kalafat E, Sebghati M, Thilaganathan B, et al. Predictive accuracy of Southwest Thames Obstetric Research Collaborative (STORK) chorionicity-specific twin growth charts for stillbirth: a validation study. *Ultrasound Obstet Gynecol* 2019;53(2):193–199. doi: 10.1002/uog.19069.
- [52] Joseph KS, Fahey J, Platt RW, et al. An outcome-based approach for the creation of fetal growth standards: do singletons and twins need separate standards? *Am J Epidemiol* 2009;169(5):616–624. doi: 10.1093/aje/kwn374.
- [53] ACOG Practice Bulletin No. 144: Multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol* 2014;123(5):1118–1132. doi: 10.1097/01.AOG.0000446856.51061.3e.
- [54] Committee on Practice Bulletins—Obstetrics; Society for Maternal-Fetal Medicine. Practice Bulletin No. 169: multifetal gestations: twin, triplet, and higher-order multifetal pregnancies. *Obstet Gynecol* 2016;128(4):e131–e146. doi: 10.1097/AOG.0000000000001709.
- [55] Khalil A, Rodgers M, Baschat A, et al. ISUOG practice guidelines: role of ultrasound in twin pregnancy [published correction appears in *Ultrasound Obstet Gynecol*. 2018 Jul;52(1):140]. *Ultrasound Obstet Gynecol* 2016;47(2):247–263. doi: 10.1002/uog.15821.
- [56] FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Role of ultrasound in the management of twin pregnancy. *Int J Gynaecol Obstet* 2019;144(3):338–339. doi: 10.1002/ijgo.12743.
- [57] Morin L, Lim K. No. 260-ultrasound in twin pregnancies. *J Obstet Gynaecol Can* 2017;39(10):e398–e411. doi: 10.1016/j.jogc.2017.08.014.
- [58] NICE Guideline [NG137]: Twin and triplet pregnancy. 2019. Available from: <https://www.nice.org.uk/guidance/ng137>. Accessed September 5, 2021.
- [59] Morin L, Lim K. Diagnostic Imaging Committee; Special Contributor; Genetics Committee; Maternal Fetal Medicine Committee. Ultrasound in twin pregnancies. *J Obstet Gynaecol Can* 2011;33(6):643–656. doi: 10.1016/S1701-2163(16)34916-7.
- [60] Hirsch L, Barrett J, Aviram A, et al. Patterns of discordant growth and adverse neonatal outcomes in twins. *Am J Obstet Gynecol* 2021; 225(2):187.e1–187.e14. doi: 10.1016/j.ajog.2021.01.018.
- [61] Melamed N, Baschat A, Yinon Y, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet* 2021;152(Suppl 1):3–57. doi: 10.1002/ijgo.13522.
- [62] Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991;181(1):129–133. doi: 10.1148/radiology.181.1.1887021.

Edited By Yang Pan

---

**How to cite this article:** Melamed N, Hirsch L. Fetal Growth in Twin Pregnancies and the Choice of Growth Chart. *Maternal Fetal Med* 2022;4(4):234–237. doi: 10.1097/FM9.000000000000131.