UpToDate® Official reprint from UpToDate®
www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

# Diagnosis and outcome of first-trimester growth delay

**AUTHOR:** Joan M Mastrobattista, MD
**SECTION EDITOR:** Lynn L Simpson, MD
**DEPUTY EDITOR:** Vanessa A Barss, MD, FACOG

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Jun 23, 2023.**

## INTRODUCTION

Prior to the widespread use of ultrasound in early pregnancy, first-trimester fetal growth was thought to be uniform and under genetic control. Differences in fetal growth rates were believed to not manifest until the second half of pregnancy. However, these beliefs were challenged when data from thousands of first-trimester ultrasound examinations documented early delay in fetal growth in pregnancies with precise gestational age dating [1-5]. Early growth delay is noteworthy because it is predictive of an increased risk for adverse perinatal outcomes, such as aneuploidy, growth restriction, and preterm birth.

This topic will discuss the diagnosis and potential consequences of first-trimester growth delay. Fetal growth restriction later in pregnancy is reviewed separately. (See "Fetal growth restriction: Screening and diagnosis" and "Fetal growth restriction: Evaluation".)

## TERMINOLOGY

The first trimester extends to 13+6 weeks of gestation. The biological term for human life up to 10 weeks of gestation is "embryo," and the biological term for human life in utero thereafter (11 weeks of gestation to birth) is "fetus." In this discussion, the term "fetus" will be used when the topic spans the age/size ranges of embryo/fetus. When the topic is only referring to pregnancies up to 10 weeks, the term "embryo" will be used.

These gestational ages are based on the first day of the last menstrual period and are sometimes called the "menstrual age" in the first trimester. The "fertilization age" or "conceptional age" is two weeks less.

## DIAGNOSIS

First-trimester growth delay should be suspected when the crown-rump length (CRL) on a first-trimester ultrasound indicates a gestational age that is >5 to 7 days less than expected. Making the diagnosis depends on the clinical setting:

- **Gestational age established by history and an early ultrasound examination –** The diagnosis of growth delay is made when the CRL on a subsequent first-trimester ultrasound examination performed at least one to two weeks later indicates a gestational age that is >5 to 7 days less than expected by the initial ultrasound examination [6].

- **Gestational age established by the embryo transfer date (in vitro fertilization) –** The diagnosis of growth delay is made when the CRL on any first-trimester ultrasound indicates a gestational age that is >5 to 7 days less than expected.

Precise determination of gestational age early in pregnancy is essential for accurately determining the expected size of the fetus and enabling a valid comparison of this size with the observed size. Gestational age assessment is reviewed in detail separately. (See "Prenatal assessment of gestational age, date of delivery, and fetal weight".)

**Pitfalls in making the diagnosis —** In the absence of an embryo transfer, most national guidelines recommend using ultrasound-based dating if the initial CRL-based gestational age differs by more than 5 to 7 days from that calculated using the last menstrual period (LMP). Thus, correction of the LMP-based gestational age is routinely performed when discordant with the initial CRL-based gestational age ( table 1). Although routinely adjusting the gestational age in these cases almost always results in a more accurate estimation of gestational age and estimated date of delivery, it prevents (or may delay) diagnosis of first-trimester growth delay unless the patient has two CRL measurements in the first trimester and the second shows a slower than expected increase in CRL, as described above. This sometimes occurs when the patient has an early ultrasound examination at 6 to 9 weeks and then a later one at 11 to 14 weeks.

Ideally, revisions of gestational age based on an LMP-CRL discordancy on an initial ultrasound should be confirmed by documenting normal fetal growth on a follow-up ultrasound examination in two weeks. A lag in CRL growth between examinations suggests first-trimester growth delay rather than incorrect LMP-based assessment of gestational age. In a study that performed weekly CRL measurements in over 200 singleton pregnancies to assess normal first-trimester fetal growth, the mean absolute growth rate was constant at approximately 1 mm/day from 6 to 9 weeks of gestation [7]. Growth then accelerated to a constant mean relative growth rate of 4.1 percent per day in spontaneously conceived

pregnancies and 3.9 percent per day in pregnancies conceived by IVF. Three CRL measurements were made per time point per pregnancy and averaged, and the measurements were made using three-dimensional holograms, which have a high degree of precision and reliability [8].

## POSSIBLE ETIOLOGIES

**Aneuploidy** — A small crown-rump length (CRL) measurement is associated with some aneuploidies. In a meta-analysis performed to define the risk of chromosomal aberrations in pregnancies with small versus normal first-trimester CRLs (two studies, 403 fetuses with small CRLs and 4047 control pregnancies), a small first-trimester CRL was associated with a more than fivefold increase in risk of fetal chromosomal abnormalities (odds ratio 5.54, 95% CI 1.2-26.1) [9]. Review of these and 10 additional studies suggested that pregnancies with abnormal chromosomal composition, such as trisomy 18 and triploidy, are associated with a slower rate of first-trimester fetal growth, whereas trisomy 21 and sex chromosomal aneuploidy are not. However, available data are limited by the small number of cases of each aneuploidy in the available studies.

**Congenital anomalies** — Anencephaly and other anomalies that affect the CRL can result in a smaller than expected CRL. The anencephalic fetus can be definitively identified by the $12^{th}$ postmenstrual week by transvaginal ultrasound, and in some cases, this diagnosis has been made as early as 9 to 10 postmenstrual weeks (see "Neural tube defects: Prenatal sonographic diagnosis", section on 'Exencephaly-anencephaly sequence'). Other anomalies potentially affecting CRL may be missed in the first trimester but are usually identifiable in the second trimester.

Three-dimensional (3D) ultrasound can measure embryonic volume. Low embryonic volume may perform better than small CRL for prediction of congenital anomalies; however, volume measurements are rarely performed and data on the clinical utility of the information are limited [10,11].

**Suboptimal uterine environment** — A suboptimal intrauterine environment, such as from a defect in early pregnancy placentation, has been suggested as a possible cause of early growth delay [2,12,13]. This hypothesis is supported by the observation that low first-trimester circulating maternal concentrations of pregnancy-associated plasma protein A (PAPP-A, accepted threshold <0.4 multiples of the median or $5^{th}$ percentile [14]) have been associated with subsequent growth restriction [2,14,15]. PAPP-A is a trophoblast-derived positive regulator of insulin-like growth factors that is one of the components measured in the first trimester combined screening test for Down syndrome. (See "First-trimester combined test and integrated tests for screening for Down syndrome and trisomy 18", section on 'Timing of blood sample and ultrasound'.)

**Constitutional factors —** Biologic variation in embryo size is minimal at six to nine weeks; normal biologic variation in fetal size is usually observed in the late second and third trimesters. However, an association between first-trimester fetal growth and size at birth suggests that constitutional factors may affect fetal growth as early as the first trimester [7,16].

## POSTDIAGNOSTIC EVALUATION

- **Genetic screening/diagnostic testing –** While offering all pregnant people fetal aneuploidy screening or diagnostic testing is a routine part of prenatal care, diagnosis of first-trimester growth delay is an additional factor for individuals to consider when deciding whether to undergo genetic screening or diagnostic testing for fetal chromosomal abnormalities. (See "Prenatal care: Initial assessment", section on 'Discussion of screening and diagnostic testing for genetic and anatomic abnormalities'.)

- **Late first-trimester anatomic survey –** Early growth delay is an indication for an early survey of fetal anatomy. Although the first-trimester anatomic survey is limited by the small size and immature developmental stage of organ systems, many abnormalities can be detected [17-21]. Multidisciplinary guidelines for the detailed diagnostic obstetric ultrasound examination between 12+0 to 13+6 weeks (American Institute of Ultrasound in Medicine [AIUM]) and 11+0 to 14+0 weeks (International Society of Ultrasound in Obstetrics and Gynecology [ISUOG]) describe the types of high-risk assessments that can be interpreted by experienced sonologists [22,23].

- **18- to 20-week anatomic survey –** A follow-up fetal anatomic survey should be performed at 18 to 20 weeks, and possibly earlier depending on the gestational age, findings at the initial ultrasound examination (eg, degree of uncertainty of suspected diagnosis, type of anomaly, amniotic fluid volume), and relevant clinical information (eg, personal or family history of a specific anomaly).

## PREGNANCY OUTCOME (SINGLETON PREGNANCY)

Information on pregnancy and childhood outcome is very limited. In particular, accurate information on the frequency and severity of abnormal outcomes and the likelihood of a normal outcome is not available, thus recommendations for modifications of routine prenatal care in singleton pregnancy are not possible.

- A crown-rump length deficit below that expected for gestational age, especially if it exceeds two standard deviations, is associated with an increased risk of miscarriage

[24-29]. Possible etiologies include aneuploidy and placental dysfunction.

- In ongoing pregnancies, first-trimester growth delay is associated with an increased frequency of delivery of a low birth weight, preterm, or small for gestational age newborn [4,5,30-33].

- Impaired fetal growth documented in the first trimester has been associated with an adverse cardiovascular risk profile in school-age children [34].

- Postnatal growth after early growth delay has not been studied extensively, but one large study reported compensatory postnatal growth acceleration until age two years [33].

## TWIN PREGNANCIES

**Adverse pregnancy outcome —** Discordance in crown-rump length (CRL) is a factor predictive of a variety of adverse outcomes in twin pregnancy, but the use of different thresholds of discordance and different exclusion criteria (eg, anomalous twins, aneuploid twins, monochorionic [MC] twins) among studies has made meta-analysis of published data difficult [35].

- A study of dichorionic (DC), monochorionic diamniotic (MCDA), and monochorionic monoamniotic (MCMA) twin pregnancies with two live fetuses at 11 to 13 weeks of gestation, no anatomic or chromosomal anomalies, and known pregnancy outcome provides informative data, although the findings should be interpreted with caution since the absolute number of cases with CRL discordance was small [36].

  - In the DC twin pregnancies, the overall rate of fetal loss at <24 weeks of gestation was 2.8 percent, but in the subgroup with CRL discordance of ≥15 percent (94 in 4896 [1.9 percent]), the fetal loss rate was 9.6 percent (9 in 94).

  - In the MCDA twin pregnancies, the overall rate of fetal loss <24 weeks was 9 percent, but in the subgroup with CRL discordance of ≥15 percent (35 in 1274 [2.7 percent]), the fetal loss rate was 37.1 percent (13 in 35). CRL discordance was also associated with increased risks for preterm birth at <32 and <37 weeks, birth of at least one small for gestational age ($^{<5^{th}}$ percentile) neonate, birth-weight discordance ≥20 percent and ≥25 percent, and in MCDA pregnancies, development of twin-twin transfusion syndrome (TTTS) and/or selective fetal growth restriction (sFGR) requiring endoscopic laser surgery.

- In another study, CRL discordance at 11 to 14 weeks in DC twins was associated with an increased risk of preeclampsia, especially early-onset preeclampsia [37]. However, the

predictive performance of CRL discordance for any adverse pregnancy outcome was poor, thus it is not a good screening test.

- A study assessing the role of first-trimester and early second-trimester markers to predict twin-twin transfusion syndrome (TTTS) in MC twin gestations found that MC twin gestations with an intertwin nuchal translucency discrepancy, nuchal translucency >95$^{th}$ percentile in at least one twin, intertwin CRL discrepancy >10 percent, or abnormal ductus venosus flow on first-trimester sonography were at increased risk to develop TTTS [38]. (See "Twin-twin transfusion syndrome: Screening, prevalence, pathophysiology, and diagnosis".)

Since detecting CRL discordance at 11 to 14 weeks is associated with increased adverse pregnancy outcomes but has low predictive accuracy, this finding does not warrant a major change in the usual close monitoring of twin pregnancies, but we suggest heightened awareness for the above pregnancy complications. In our ultrasound unit, if the CRL measurement lags menstrual dating by more than 7 days in a well-dated first-trimester pregnancy (earlier ultrasound, assisted reproductive technology), we use the larger twin's CRL to date the pregnancy and repeat the ultrasound evaluation in two weeks. If the growth lag continues into the second trimester and is unexplained, we suggest interval growth ultrasounds at three- to four-week intervals (see "Twin pregnancy: Routine prenatal care", section on 'Screening for fetal growth restriction and discordance' and "Twin pregnancy: Management of pregnancy complications", section on 'Growth restriction and discordance'). MCDA twins are monitored for TTTS and sFGR. (See "Selective fetal growth restriction in monochorionic twin pregnancies", section on 'Presentation' and "Twin-twin transfusion syndrome: Screening, prevalence, pathophysiology, and diagnosis", section on 'Our approach to monitoring'.)

**Aneuploidy —** There is minimal information about first-trimester CRL discordance in twins and risk for aneuploidy.

- In one study of 182 twin pregnancies, a 17 mm difference in CRL was associated with trisomy 18 in one twin pair, and a 16 mm difference was associated with triploidy in another twin pair [39]. The difference in CRL in these two pregnancies was above the 90$^{th}$ centile (8 mm). Of the remaining 18 twin pairs with CRL discordance ≥8 mm, 11 had a normal outcome, 5 delivered preterm at 29 to 36 weeks, and 1 underwent pregnancy termination for cystic fibrosis.

## SUMMARY AND RECOMMENDATIONS

- **Diagnosis**

- If the gestational age has been established by history and an early ultrasound examination, then the diagnosis of growth delay is made when the crown-rump length (CRL) on a subsequent first-trimester ultrasound examination performed at least one to two weeks later indicates a gestational age that is >5 to 7 days less than expected by the initial ultrasound examination. In pregnancies conceived by in vitro fertilization, growth delay should be suspected when the CRL on any first-trimester ultrasound indicates a gestational age that is >5 to 7 days less than expected. (See 'Diagnosis' above.)

- Ideally, revisions in gestational age based on a last menstrual period (LMP)-CRL discordancy ( table 1) should be confirmed by documenting normal fetal growth on a follow-up ultrasound examination in one to two weeks. A lag in CRL growth between examinations suggests first-trimester growth delay rather than incorrect LMP-based assessment of gestational age. (See 'Pitfalls in making the diagnosis' above.)

- **Etiology and evaluation –** First-trimester growth delay has been associated with aneuploidy, some congenital anomalies (eg, anencephaly), and a suboptimal intrauterine environment for fetal growth, but it may also be associated with a normal constitutionally small fetus. Because of these risks, fetal aneuploidy screening or diagnostic testing and first- and second-trimester fetal anatomic surveys are reasonable in affected pregnancies. (See 'Possible etiologies' above and 'Postdiagnostic evaluation' above.)

- **Prognosis –** Adverse pregnancy outcomes that have been associated with first-trimester growth delay include delivery of a low birth weight, preterm, or small for gestational age infant and fetal demise, but the frequency and severity of these outcomes have not been well-defined. (See 'Pregnancy outcome (singleton pregnancy)' above.)

  In twin pregnancies, CRL discordance at 11 to 14 weeks is associated with adverse pregnancy outcomes but alone has low accuracy to predict outcomes, such as fetal loss ≥24 weeks, perinatal loss, preterm delivery <34 weeks, or birth weight discordance. CRL discrepancy >10 percent in monochorionic twins may be associated with an increased risk of developing twin-twin transfusion syndrome. (See 'Twin pregnancies' above.)

Use of UpToDate is subject to the Terms of Use.

**REFERENCES**

1. Salomon LJ, Bernard JP, Duyme M, et al. Revisiting first-trimester fetal biometry.

Ultrasound Obstet Gynecol 2003; 22:63.

2. Smith GC. First trimester origins of fetal growth impairment. Semin Perinatol 2004; 28:41.
3. Deter RL, Buster JE, Casson PR, Carson SA. Individual growth patterns in the first trimester: evidence for difference in embryonic and fetal growth rates. Ultrasound Obstet Gynecol 1999; 13:90.
4. Smith GC, Smith MF, McNay MB, Fleming JE. First-trimester growth and the risk of low birth weight. N Engl J Med 1998; 339:1817.
5. Bukowski R, Smith GC, Malone FD, et al. Fetal growth in early pregnancy and risk of delivering low birth weight infant: prospective cohort study. BMJ 2007; 334:836.
6. Committee on Practice Bulletins—Obstetrics and the American Institute of Ultrasound in Medicine. Practice Bulletin No. 175: Ultrasound in Pregnancy. Obstet Gynecol 2016; 128:e241. Reaffirmed 2022.
7. van Uitert EM, Exalto N, Burton GJ, et al. Human embryonic growth trajectories and associations with fetal growth and birthweight. Hum Reprod 2013; 28:1753.
8. Verwoerd-Dikkeboom CM, Koning AH, Hop WC, et al. Reliability of three-dimensional sonographic measurements in early pregnancy using virtual reality. Ultrasound Obstet Gynecol 2008; 32:910.
9. Sagi-Dain L, Peleg A, Sagi S. First-Trimester Crown-Rump Length and Risk of Chromosomal Aberrations-A Systematic Review and Meta-analysis. Obstet Gynecol Surv 2017; 72:603.
10. Baken L, Benoit B, Koning AHJ, et al. First-Trimester Crown-Rump Length and Embryonic Volume of Fetuses with Structural Congenital Abnormalities Measured in Virtual Reality: An Observational Study. Biomed Res Int 2017; 2017:1953076.
11. Falcon O, Peralta CF, Cavoretto P, et al. Fetal trunk and head volume in chromosomally abnormal fetuses at 11+0 to 13+6 weeks of gestation. Ultrasound Obstet Gynecol 2005; 26:517.
12. Morin I, Morin L, Zhang X, et al. Determinants and consequences of discrepancies in menstrual and ultrasonographic gestational age estimates. BJOG 2005; 112:145.
13. Smith GC, Stenhouse EJ, Crossley JA, et al. Early-pregnancy origins of low birth weight. Nature 2002; 417:916.
14. Bilagi A, Burke DL, Riley RD, et al. Association of maternal serum PAPP-A levels, nuchal translucency and crown-rump length in first trimester with adverse pregnancy outcomes: retrospective cohort study. Prenat Diagn 2017; 37:705.
15. He B, Hu C, Zhou Y. First-trimester screening for fetal growth restriction using Doppler color flow analysis of the uterine artery and serum PAPP-A levels in unselected

pregnancies. J Matern Fetal Neonatal Med 2021; 34:3857.

16. Dickey RP, Gasser RF. Ultrasound evidence for variability in the size and development of normal human embryos before the tenth post-insemination week after assisted reproductive technologies. Hum Reprod 1993; 8:331.
17. Karim JN, Roberts NW, Salomon LJ, Papageorghiou AT. Systematic review of first-trimester ultrasound screening for detection of fetal structural anomalies and factors that affect screening performance. Ultrasound Obstet Gynecol 2017; 50:429.
18. Rossi AC, Prefumo F. Accuracy of ultrasonography at 11-14 weeks of gestation for detection of fetal structural anomalies: a systematic review. Obstet Gynecol 2013; 122:1160.
19. Tekesin I. The Value of Detailed First-Trimester Ultrasound Anomaly Scan for the Detection of Chromosomal Abnormalities. Ultraschall Med 2019; 40:743.
20. Edwards L, Hui L. First and second trimester screening for fetal structural anomalies. Semin Fetal Neonatal Med 2018; 23:102.
21. Syngelaki A, Hammami A, Bower S, et al. Diagnosis of fetal non-chromosomal abnormalities on routine ultrasound examination at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2019; 54:468.
22. AIUM Practice Parameter for the Performance of Detailed Diagnostic Obstetric Ultrasound Examinations Between 12 Weeks 0 Days and 13 Weeks 6 Days. J Ultrasound Med 2021; 40:E1.
23. International Society of Ultrasound in Obstetrics and Gynecology, Bilardo CM, Chaoui R, et al. ISUOG Practice Guidelines (updated): performance of 11-14-week ultrasound scan. Ultrasound Obstet Gynecol 2023; 61:127.
24. Papaioannou GI, Syngelaki A, Maiz N, et al. Ultrasonographic prediction of early miscarriage. Hum Reprod 2011; 26:1685.
25. Reljic M. The significance of crown-rump length measurement for predicting adverse pregnancy outcome of threatened abortion. Ultrasound Obstet Gynecol 2001; 17:510.
26. Choong S, Rombauts L, Ugoni A, Meagher S. Ultrasound prediction of risk of spontaneous miscarriage in live embryos from assisted conceptions. Ultrasound Obstet Gynecol 2003; 22:571.
27. Mukri F, Bourne T, Bottomley C, et al. Evidence of early first-trimester growth restriction in pregnancies that subsequently end in miscarriage. BJOG 2008; 115:1273.
28. Abuelghar WM, Fathi HM, Ellaithy MI, Anwar MA. Can a smaller than expected crown-rump length reliably predict the occurrence of subsequent miscarriage in a viable first trimester pregnancy? J Obstet Gynaecol Res 2013; 39:1449.

29. Mantoni M, Pedersen JF. Fetal growth delay in threatened abortion: an ultrasound study. Br J Obstet Gynaecol 1982; 89:525.
30. Leung TY, Sahota DS, Chan LW, et al. Prediction of birth weight by fetal crown-rump length and maternal serum levels of pregnancy-associated plasma protein-A in the first trimester. Ultrasound Obstet Gynecol 2008; 31:10.
31. Mercer BM, Merlino AA, Milluzzi CJ, Moore JJ. Small fetal size before 20 weeks' gestation: associations with maternal tobacco use, early preterm birth, and low birthweight. Am J Obstet Gynecol 2008; 198:673.e1.
32. Thorsell M, Kaijser M, Almström H, Andolf E. Expected day of delivery from ultrasound dating versus last menstrual period--obstetric outcome when dates mismatch. BJOG 2008; 115:585.
33. Mook-Kanamori DO, Steegers EA, Eilers PH, et al. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA 2010; 303:527.
34. Jaddoe VW, de Jonge LL, Hofman A, et al. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. BMJ 2014; 348:g14.
35. D'Antonio F, Khalil A, Pagani G, et al. Crown-rump length discordance and adverse perinatal outcome in twin pregnancies: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2014; 44:138.
36. Litwinska E, Syngelaki A, Cimpoca B, et al. Intertwin discordance in fetal size at 11-13 weeks' gestation and pregnancy outcome. Ultrasound Obstet Gynecol 2020; 55:189.
37. Zhu J, Zhang J, Wu Y, et al. Intertwin growth discordance throughout gestation and hypertensive disorders of pregnancy. Am J Obstet Gynecol 2023; 228:730.e1.
38. Stagnati V, Zanardini C, Fichera A, et al. Early prediction of twin-to-twin transfusion syndrome: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2017; 49:573.
39. Salomon LJ, Cavicchioni O, Bernard JP, et al. Growth discrepancy in twins in the first trimester of pregnancy. Ultrasound Obstet Gynecol 2005; 26:512.

Topic 410 Version 35.0

## GRAPHICS

### First trimester fetal size smaller than expected

| Gestational age range based on LMP | Biometric parameter(s) for ultrasound dating | Discrepancy between ultrasound dating and LMP dating that supports redating |
|---|---|---|
| ≤$13^{6/7}$ weeks of gestation | CRL | |
| ▪ ≤$8^{6/7}$ weeks of gestation | | ▪ More than five days |
| ▪ $9^{0/7}$ to $13^{6/7}$ weeks of gestation | | ▪ More than seven days |

LMP: last menstrual period; CRL: crown rump length.

---

*Modified from: Committee on Obstetric Practice, American Institute of Ultrasound in Medicine, Society for Maternal-Fetal Medicine. Method for estimating due date. Obstet Gynecol 2014; 124:863.*

---

Graphic 105010 Version 1.0

## Contributor Disclosures

**Joan M Mastrobattista, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Lynn L Simpson, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Vanessa A Barss, MD, FACOG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy