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Stillbirth and Fetal Growth Restriction

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Abstract: The association between stillbirth and fetal growth restriction is strong and supported by a large body of evidence and clinically employed for the stillbirth prediction. However, although assessment of fetal growth is a basis of clinical practice, it is not trivial. Essentially, fetal growth is a result of the genetic growth potential of the fetus and placental function. The growth potential is the driving force of fetal growth, whereas the placenta as the sole source of nutrients and oxygen might become the rate limiting element of fetal growth if its function is impaired. Thus, placental dysfunction may prevent the fetus from reaching its full genetically determined growth potential. In this sense fetal growth and its aberration provides an insight into placental function. Fetal growth is a proxy for the test of the effectiveness of placenta, whose function is otherwise obscured during pregnancy.
Key words: fetal growth restriction, stillbirth, intrauterine growth restriction

Stillbirth is strongly associated with fetal growth restriction (Fig. 1). The risk factors and potential causes of stillbirth and fetal growth restriction largely overlap. Fetal growth restriction is associated with a number of maternal, fetal, and placental risk factors. Maternal smoking, low educational level, advanced maternal age, nulliparity, and black race are associated with increased risk of fetal growth restriction and stillbirth. Also maternal hypertensive disorders, including chronic hypertension, preeclampsia, HELLP syndrome and eclampsia, pre and gestational diabetes, systemic lupus erythematosus, chronic renal disease, and thyroid disorders are associated with increased rate of both fetal growth restriction and stillbirth.[2] The strong relationship between

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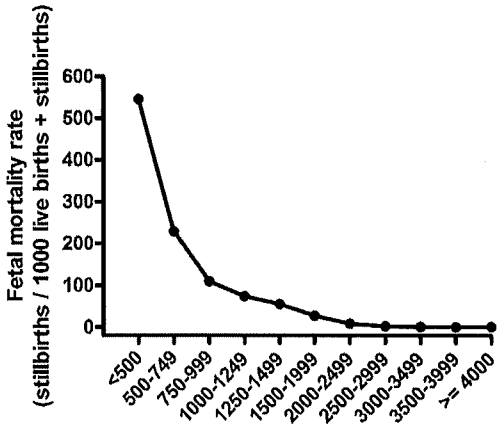

FIGURE 1. Fetal mortality rate as a function of birth weight. Fetal mortality rate expressed as a number of stillbirths per 1000 live birth and stillbirth in each birth weight category. Stillbirth is defined as fetal death at or after 20 weeks of gestation. Data from 2005 US national statistics.[1]

fetal growth restriction and stillbirth is emphasized by the observations that prior delivery of a growth restricted infant is among the strongest risk factors for stillbirth, comparable to the history of prior stillbirth.[2] Fetal risk factors, multifetal gestation, fetal congenital structural and chromosomal abnormalities, and fetal infections are also associated with both fetal growth restriction and with stillbirth.[2] Moreover, the same is also observed among placental risk factors for fetal growth restriction. Placental abruption and perhaps confined placental mosaicism are associated with increased rates of fetal growth restriction and stillbirth.[3,4]

The placental function is critical in the causation of stillbirth and studies of various aspects of placental function support its important role. Patterns of high resistance flow on fetal and maternal sides of the placenta, maternal concentrations of placental hormones, and placental pathologic changes are associated with both stillbirth and fetal growth restriction. During uncomplicated pregnancy on the maternal side of placental circulation, high resistance patterns of flow in the first half of pregnancy are replaced with low resistance circulation in the later half. This conversion results from invasion of maternal spiral arteries by extravillous trophoblast and can be assessed by uterine artery Doppler velocimetry. An unsuccessful invasion of the spiral arteries results in persistence of high resistance circulation on the maternal side of the placenta and is associated with increased risk of fetal growth restriction and stillbirth.[5,6] The high resistance flow on the fetal side of placental circulation is also associated with fetal growth restriction and stillbirth.[7,8] These high resistance flow patterns of the fetal side of placental circulation have been seen to be associated with maldevelopment of villi and their circulation.[9]

The importance of placental function in the causation of stillbirth is not confined to placental circulation. The placenta is a powerful source of hormones and other placenta-derived proteins, which can be measured in the maternal circulation. Elevated maternal concentrations of α-fetoprotein (AFP) and human chorionic gonadotropin (hCG) in the second trimester of pregnancy are associated with both growth restriction and stillbirth.[10] Maternal AFP concentrations above the 95th percentile were associated with almost 3 fold increase in the risk of stillbirth (odds ratio 2.8, 95% CI 2.1-3.7) whereas hCG concentrations above the 95th percentile with a 2-fold increase risk of stillbirth (odds ratio 1.9, 95% CI 1.4-2.7). Moreover, elevated maternal concentrations of AFP were even more strongly associated with unexplained stillbirths with fetal growth restriction.[10]

Moreover, placenta-derived proteins Pregnancy Associated Plasma Protein A (PAPP-A) and soluble fms-like tyrosine kinase-1 (sFlt-1) measured in early pregnancy between 10 and 14 weeks are also associated with stillbirth and fetal growth restriction. These associations show the importance of placental function and its proxy fetal growth restriction in stillbirth causation and prediction, respectively. They also show early pregnancy origins of stillbirth. Women with PAPP-A concentration < fifth percentile in the first trimester had a 4-fold increased risk of stillbirth (odds ratio 3.9, 95% CI 1.3-11.7).[3] Furthermore, these women had a 40 to 50-fold increased risk of stillbirth related to fetal growth restriction or placental abruption.[3] The risk of stillbirth is also increased in women with lower maternal first trimester concentrations of sFlt-1, a potent placenta-derived antiangiogenic factor. One decile increase in the concentration of sFlt-1 was associated with an over 20% reduction in the risk of stillbirth associated with placental abruption or fetal growth restriction (odds ratio 0.77, 95% CI 0.61-0.95).[11]

Specific placental pathologic changes have also been associated with stillbirth.

Placentae of unexplained stillbirth, thus unrelated to known risk factors, with fetal growth restriction show changes consistent with chronic placental dysfunction.[12] Conversely, unexplained stillbirths without fetal growth restriction are associated with placental changes suggestive of acute placental dysfunction.[12] The foregoing, clearly indicates that placental function is a crucial element in the causative path leading to a large proportion of stillbirths. It also shows that in stillbirths, abnormal placental function, measured either by aberration of placental blood flow resistance or production of placenta-derived proteins, is strongly associated with fetal growth restriction. Thus, this supports the role of fetal growth restriction as a proxy for abnormal placental function and as a predictor of stillbirth.

However, the effectiveness of fetal growth monitoring in prediction of stillbirth depends strongly on accuracy of fetal growth assessment. The accurate assessment of fetal growth is important in clinical practice and in research on stillbirth prediction and prevention. The latter is challenging and the results are often affected by the accuracy of gestational age estimates, by the effect of the time interval between time of fetal death and time of delivery, by the effects of genetically determined individual characteristics on fetal growth and by the definition of what is considered aberrant fetal growth.

As fetal growth is an exponential function of gestational age, the accuracy of the gestational age estimate is critical in estimating if the growth is adequate. The estimates are based either on menstrual or early ultrasound criteria. However, menstrual dating is associated with a systematic error that overestimates the rate of preterm birth.[13,14] Comparing with early ultrasound dating, menstrual estimates of gestational age misclassify approximately 25% of term pregnancies as preterm.[14] Such underestimation of gestational age by menstrual dating results also in underestimation of the rate of fetal growth restriction, as a lower gestational age is assigned for a given birth weight. This misclassification of gestational age in preterm is of a special significance for stillbirth, because the vast majority of stillbirths occur before term.[1]

In the case of stillbirth, gestational age estimate and thus the rate of fetal growth restriction are additionally affected by the time interval between time of death and time of delivery. Ideally, gestational age at the time of death should be used to determine gestational age used for assessment of fetal growth, however, time of death is rarely precisely known. The studies that address the time interval between fetal death and time of delivery show that, although median interval is quite short, approximately 30 hours, the range is quite wide and skewed toward longer intervals.[15] It has been shown that in approximately 20% of stillbirths the time interval between time of death and time of delivery exceeds 2 weeks.[15] Such large differences in gestational age estimates would result in overestimation of the rate of fetal growth restriction, when much more advanced gestational age at birth is used for estimation of fetal growth.

Even when gestational age is precisely known, the estimate of gestational age is affected by what is defined as normal growth. Conventionally, birth weight is assessed by comparison to population or ultrasound norms. The population norms include all pregnancies in a population and assign percentiles based on distribution of birth weight for each gestational age. Thus, population norms include pregnancies with pathologic conditions potentially affecting fetal growth and birth weight[16] and hence erroneously "widen" the norms. This systematic error of population norms results in underestimation of the rate of fetal growth restriction. The ultrasound norms are based on serial ultrasound estimations of fetal

weight in uncomplicated pregnancies. They assign percentiles based on distribution of estimated fetal weights for each gestational age. The ultrasound norms are usually developed in populations of uncomplicated pregnancies, thus are not subject to the same limitation affecting population norms. However, by averaging individual trajectories of fetal growth, the ultrasound norms remove physiologic variability, undermining individualization of growth.[17–22]

Customized norms predict optimal term birth weight for each pregnancy based on 4 maternal characteristics maternal weight, height, parity, race, and infant's sex. This term optimal weight is extrapolated to earlier gestational ages to allow calculation of birth weight percentiles for gestational ages from 20 weeks to term. Customized norms were shown to better detect aberrations of fetal growth than population norms.[23–26] However, their accuracy in comparison to ultrasound norms is uncertain.[27] Many factors known to affect birth weight are not considered by customized norms.[28] They also do not account for factors with dual physiologic and pathologic effect on birth weight and for early variation in fetal growth.[29,30] Consequently, their accuracy in defining normal birth weight variability and ability to individualize fetal growth norms is limited.[31]

Traditional norms of fetal growth, population, ultrasound, and customized norms, systematically underestimate the fetal growth. In a normal population, birth weight distribution for each gestational age is expected to follow a Gaussian distribution. In a study comparing those norms in a carefully selected population of normal pregnancies, without complications or adverse outcomes of pregnancy, all those norms classified less than expected normal pregnancies above 90th percentile and more than expected below the 10th percentile.[31] This is likely owing to earlier mentioned "widening" of population norms owing to inclusion of complicated pregnancies with abnormalities of fetal growth in the norms and insufficient adjustment of norms for individual characteristics that affect fetal growth in ultrasound based and customized norms.

We recently developed individualized norms of optimal fetal growth-fetal growth potential norms, which do not have those limitations. The growth potential norms classified above the 90th or below the 10th percentile more complicated pregnancies than either population, ultrasound, or customized norms.[31] In pregnancies resulting in neonatal morbidity, growth potential norms classified 33.3% of those fetuses as abnormally grown, 11%, 34%, and 69% more than customized, ultrasound, and population-based norms, respectively.[31] In the same study unpublished data showed that fetal growth potential classified more stillbirths as growth restricted than population norms. In fact, pregnancies identified as growth restricted by population norms only did not have increase risk of stillbirth compared with pregnancies identified as normally grown by both population and growth potential norms (Fig. 2).

Thus, accurate estimation of fetal growth could potentially be a good measure of placental function and thus a good predictor of stillbirth. This could be achieved if accurate estimates of gestational age, time of death, and the effect of individual characteristics affecting fetal growth could be implemented. However, a good prediction method is insufficient for successful prevention of stillbirth. Prevention is a net result of accurate prediction of a group at increased risk of stillbirth and an effective intervention. To date there are no effective methods of stillbirth prevention.[2] This state of the matter might reflect either inadequate identification of groups at risk or ineffectiveness of interventions in the prevention trials. Interventions are unlikely to be effective in all patients across diverse

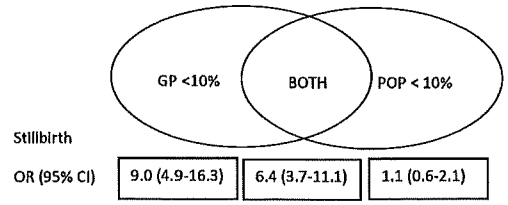

FIGURE 2. Risk of stillbirth in relation to fetal growth restriction defined by growth potential and population norms. Stillbirth, defined as fetal death at or after 20 weeks 0 days of pregnancy; OR (95% CI), odds ratio and 95% CI of stillbirth among pregnancies with birth weight below 10th percentile by growth potential norms only (GP < 10%), population norms only (POP < 10%) and with birth weight below 10th percentile by both norms (Both); reference 4 unpublished data.

patient characteristics and phenotype variations. Thus an intervention effectively preventing stillbirth in a group at high risk may seem ineffective when applied to unselected population. This inadequate selection of the population at risk seems to inflict many of the trials of fetal monitoring during pregnancy to prevent stillbirth.

The main purpose of the management of fetal growth restriction is prevention of stillbirth. However, achieving of this objective is difficult owing to several limitations of techniques and concepts employed in this management today. First, the diagnosis of fetal growth restriction is very inaccurate. Traditionally fetal growth restriction is identified using small for gestational age fetus or infant as a proxy. However, it is estimated that approximately 30% of small for gestational age infants are not growth restricted. Second, there are to date no effective methods of stillbirth prediction or prevention.[2] On account of these limitations, current management of fetal growth restriction, aimed at prevention of stillbirth, can only be based on 3 evidence-supported concepts. These concepts are more accurate identification of fetal growth restriction, use of umbilical artery Doppler velocimetry as a pivotal test in management and on the decision to deliver the fetus identified as growth restricted based on results of fetal heart rate monitoring and possibly ductus venosus Doppler velocimetry.

The accuracy of the diagnosis of fetal growth restriction can be increased by serial ultrasound estimates of fetal weight. This is because serial estimates allow assessment of rate of growth or trend of declining growth and concept of regression to the mean. The latter shows that although all measurements are subject to random error and form a distribution around the true value, the subsequent measurements are more likely than not to be closer to the mean of this distribution, thus closer to the true value. The accuracy of the fetal growth restriction diagnosis can be also increased by using individualized norms of fetal growth.[31] Those norms identify stillbirth risk better than population norms because they adjust for the confounding effects of maternal and pregnancy characteristics that affect fetal growth. For example, smaller mothers have smaller children that are not growth restricted but rather constitutionally small. Finally, the accuracy of fetal growth restriction diagnosis can be increased by using additional other measurements such as amniotic fluid index and genetic ultrasound and testing. A small for gestational age fetus identified during ultrasound examination with oligohydramnios is much more likely to be growth restricted than one with normal amount of amniotic fluid.[32] Similarly, a fetus with congenital malformations or fetus with chromosomal abnormalities is more likely to be growth restricted than 1 without those findings during genetic ultrasound examination or genetic testing, respectively.[33]

The only fetal monitoring method that has been associated with a decrease in perinatal mortality in systematic review

and metaanalysis is umbilical artery Doppler velocimetry in high-risk pregnancies including fetal growth restriction.[8,34] In this systematic review of 16 studies and 10,225 babies, use of umbilical artery Doppler for management of pregnancy was associated with 30% reduction in perinatal mortality from 1.7% to 1.2% (Relative risk, 95% CI; 0.71, 0.52-0.98). Tumber of umbilical artery Doppler examinations needed to prevent one perinatal death (number needed to treat, 95% CI) was 203 (103-4352). Use of umbilical artery Doppler velocimetry was also associated with a significant reduction in obstetrical interventions, induction of labor (relative risk, 95% CI; 0.89, 0.80-0.99) and cesarean delivery (relative risk, 95% CI; 0.90, 0.84-0.97). Thus the evidence of reduction in perinatal mortality and obstetrical interventions supports the use of umbilical artery Doppler velocimetry as a pivotal test in the management of fetal growth restriction. In this capacity normal umbilical artery Doppler velocimetry could be managed with serial estimates of fetal growth and umbilical artery velocimetry to identify potential worsening of placental function. Increase in the indices of placental resistance would warrant weekly or twice weekly fetal heart rate or biophysical profile testing and evaluation of amniotic fluid index to identify fetuses at increased risk of distress. Absence or reversal of end-diastolic flow in the umbilical artery would indicate daily or continuous fetal monitoring to determine the optimal time of delivery. Determination of the optimal time of delivery is difficult because umbilical artery Doppler velocimetry is not well suited for this purpose and fetal heart rate testing and fetal vessel Doppler velocimetry were not found to improve perinatal mortality or were not sufficiently studied in randomized interventional trials. However, it could be argued that the risk of stillbirth to neonatal death ratio in pregnancies at term would favor delivery when there is absence or reversal of the end-diastolic flow in the umbilical artery, regardless of fetal heart rate, or fetal ductus venosus Doppler testing. In preterm pregnancies the optimal time of delivery can be determined by using a combination of fetal heart rate and ductus venosus testing and gestational age estimate. It is important that the suggested approach is general and specific situations may require its modification and that, with possible exception of umbilical artery Doppler velocimetry, it is not based on high-quality evidence.

The future studies should focus first on prediction methods in large prospective cohorts to identify accurate methods of assessment of fetal growth and thus accurate prediction of stillbirth. The interventions should then be studied in population of pregnancies with accurately identified fetal growth restriction, thus at high risk of stillbirth. The common intervention in stillbirth prevention is delivery of the fetus at risk before stillbirth occurs. In such case the outcome of the prevention trials should be perinatal mortality, stillbirth and neonatal death, as preterm delivery to avert stillbirth may result in neonatal death.

References

1. MacDorman MF, Kirmeyer S. Fetal and perinatal mortality, United States, 2005. *Natl Vital Stat Rep.* 2009;57:1–19.
2. Smith GC, Fretts RC. Stillbirth. *Lancet.* 2007;370:1715–1725.
3. Smith GC, Crossley JA, Aitken DA, et al. First-trimester placentation and the risk of antepartum stillbirth. *JAMA.* 2004; 292:2249–2254.
4. Reddy UM, Goldenberg R, Silver R, et al. Stillbirth classification—developing an international consensus for research: executive summary of a National Institute of Child Health and Human Development workshop. *Obstet Gynecol.* 2009; 114:901–914.
5. Lees C, Parra M, Missfelder-Lobos H, et al. Individualized risk assessment for adverse pregnancy outcome by uterine

artery Doppler at 23 weeks. *Obstet Gynecol.* 2001;98:369–373.
6. Smith GC, Yu CK, Papageorghiou AT, et al. Maternal uterine artery Doppler flow velocimetry and the risk of stillbirth. *Obstet Gynecol.* 2007;109:144–151.
7. Baschat AA, Gembruch U, Weiner CP, et al. Qualitative venous Doppler waveform analysis improves prediction of critical perinatal outcomes in premature growth-restricted fetuses. *Ultrasound Obstet Gynecol.* 2003;22:240–245.
8. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database Syst Rev.* 2010;1:CD007529.
9. Krebs C, Macara LM, Leiser R, et al. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol.* 1996; 175:1534–1542.
10. Smith GC, Shah I, White IR, et al. Maternal and biochemical predictors of antepartum stillbirth among nulliparous women in relation to gestational age of fetal death. *BJOG.* 2007;114:705–714.
11. Smith GC, Crossley JA, Aitken DA, et al. Circulating angiogenic factors in early pregnancy and the risk of preeclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth. *Obstet Gynecol.* 2007;109:1316–1324.
12. Stallmach T, Hebisch G, Meier K, et al. Rescue by birth: defective placental maturation and late fetal mortality. *Obstet Gynecol.* 2001;97:505–509.
13. Joseph KS, Huang L, Liu S, et al. Reconciling the high rates of preterm and postterm birth in the United States. *Obstet Gynecol.* 2007;109:813–822.
14. Kramer MS, McLean FH, Boyd ME, et al. The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. *JAMA.* 1988;260:3306–3308.
15. Genest DR, Williams MA, Greene MF. Estimating the time of death in stillborn fetuses: I. Histologic evaluation of fetal organs; an autopsy study of 150 stillborns. *Obstet Gynecol.* 1992;80: 575–584.
16. Alexander GR, Himes JH, Kaufman RB, et al. A United States national reference for fetal growth. *Obstet Gynecol.* 1996;87: 163–168.
17. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology.* 1991;181:129–133.
18. Gallivan S, Robson SC, Chang TC, et al. An investigation of fetal growth using serial ultrasound data. *Ultrasound Obstet Gynecol.* 1993;3:109–114.
19. Jeanty P, Cantraine F, Romero R, et al. A longitudinal study of fetal weight growth. *J Ultrasound Med.* 1984;3:321–328.
20. Marsal K, Persson PH, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr.* 1996;85:843–848.
21. Schwarzler P, Bland JM, Holden D, et al. Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15-40 weeks of gestation. *Ultrasound Obstet Gynecol.* 2004;23:23–29.
22. Johnsen SL, Rasmussen S, Wilsgaard T, et al. Longitudinal reference ranges for estimated fetal weight. *Acta Obstet Gynecol Scand.* 2006;85:286–297.
23. Gardosi J, Chang A, Kalyan B, et al. Customised antenatal growth charts. *Lancet.* 1992;339:283–287.
24. Clausson B, Gardosi J, Francis A, et al. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. *BJOG.* 2001;108: 830–834.
25. Ego A, Subtil D, Grange G, et al. Customized versus population-based birth weight standards for identifying growth restricted infants: a French multicenter study. *Am J Obstet Gynecol.* 2006;194: 1042–1049.
26. Efkarpidis S, Alexopoulos E, Kean L, et al. Case-control study of factors associated with intrauterine fetal deaths. *MedGenMed.* 2004;6:53.
27. Owen P, Ogah J, Bachmann LM, et al. Prediction of intrauterine growth restriction with customised estimated fetal weight centiles. *BJOG.* 2003;110:411–415.
28. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics.* 1987;80:502–511.

29. Smith GC, Smith MF, McNay MB, et al. First-trimester growth and the risk of low birth weight. *N Engl J Med.* 1998;339: 1817–1822.
30. 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.
31. Bukowski R, Uchida T, Smith GC, et al. Individualized norms of optimal fetal growth: fetal growth potential. *Obstet Gynecol.* 2008;111:1065–1076.
32. Banks EH, Miller DA. Perinatal risks associated with borderline amniotic fluid index. *Am J Obstet Gynecol.* 1999;180 (6 Pt 1):1461–1463.
33. Snijders RJ, Sherrod C, Gosden CM, et al. Fetal growth retardation: associated malformations and chromosomal abnormalities. *Am J Obstet Gynecol.* 1993; 168:547–555.
34. Grivell RM, Alfirevic Z, Gyte GM, et al. Antenatal cardiotocography for fetal assessment. *Cochrane Database Syst Rev.* 2010;1:CD007863.