At a time when the beginning of assisted reproduction is being recognised as an outstanding contribution to medical science, practitioners have a responsibility to develop its use wisely. Doctors managing infertile couples are no longer entitled to take risks with the health of the next generation.

1 McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JCM, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of data on individual patients in randomised trials. *BMJ* 2010;341:c6945
2 Templeton A, Morris JK. Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization. *N Engl J Med* 1998;339:573-7.
3 Templeton A. Avoiding multiple pregnancies in ART. Replace as many embryos as you like—one at a time. *Hum Reprod* 2000;15:1662.
4 Martikainen H, Tiitinen A, Tomás C, Tapanainen J, Orava M, Tuomivaara L, et al. One versus two embryo transfer after IVF and ICSI: a randomized study. *Hum Reprod* 2001;16:1900-3.
5 Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in vitro fertilization. *N Engl J Med* 2004;351:2392-402.
6 Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Van de Meerssche M, Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod* 1999;14:2581-7.
7 Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EMM, Scheenjes E, et al. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2005;20:702-8.
8 Van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GAJ, et al. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2006;21:338-43.
9 Kjellberg AT, Carlsson P, Bergh C. Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis. *Hum Reprod* 2006;21:210-6.
10 Maheshwari A, Griffiths S, Bhattacharya S. Global variations in the uptake of single embryo transfer. *Hum Reprod Update* 2010; online 15 October; doi:10.1093/humupd/dmq028.

Induction of labour for intrauterine growth restriction at term

May not be necessary in resource rich settings

RESEARCH, p 35

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The suspicion of fetal growth restriction at or close to term is a common clinical scenario, but the management of such pregnancies is controversial. Fetuses with growth restriction have a higher risk of perinatal morbidity and mortality. About 40% of stillbirths have been associated with suboptimal fetal growth,[1] and the risk of stillbirth increases beyond 37 weeks.[2] Consequently, when a suspected growth restricted fetus is detected before birth, obstetricians often induce labour with the aim of reducing the risk of stillbirth. However, induction of labour can be associated with an increase in operative delivery rates, including caesarean section. Thus, other clinicians advocate expectant management, with maternal and fetal monitoring, while awaiting the onset of spontaneous labour.

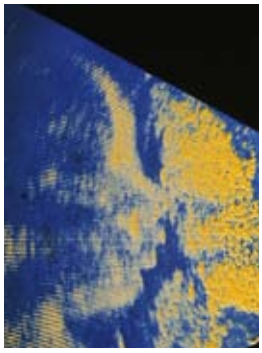
Little evidence is available to inform best practice about the optimum management of the suspected growth restricted fetus near term. The linked randomised controlled study (DIGITAT) by Boers and colleagues compares expectant management with induction of labour.[3] Women with pregnancies complicated by suspected fetal growth restriction after 36 weeks' gestation were randomised to induction of labour or expectant management. The primary outcome was a composite measure of adverse neonatal outcome, and the secondary outcome was operative delivery. No significant difference was found in either outcome between study groups.

This is an important study, and will probably inform clinical care for the foreseeable future. The absence of difference in outcome between the two groups supports a strategy of induction of labour or conservative management, depending on the wishes of the woman. However, several caveats exist. The association between suboptimal growth and stillbirth is well accepted, but a study powered to examine this would require thousands of participants and may not be feasible because recruitment to the DIGITAT trial took four years and involved more than 50 hospitals.

Thus, it is appropriate to counsel women that, in a suspected growth restricted pregnancy beyond 36 weeks, induction of labour may prevent the rare but devastating outcome of stillbirth. Because this strategy does not increase maternal risk, it might be the preferred option for many women. Early induction also reduces the proportion of infants born with a birth weight less than the third population centile, and outcomes at two years from the planned follow-up of this cohort will show whether this translates into improved outcomes in childhood.

Secondly, optimal outcome of expectant management for the fetus with suspected growth restriction depends on a high level of fetal and maternal surveillance. In Boers and colleagues' study, participants allocated to the expectant group were monitored until the onset of spontaneous labour with daily fetal movement counts, together with twice weekly fetal heart rate tracings, ultrasound examination, maternal blood pressure measurement, assessment of proteinuria, laboratory tests of liver and kidney function, and full blood count. Abnormal results prompted earlier intervention, and after randomisation more than half of the women in the expectantly managed group were induced for maternal or fetal indications. This level of fetal monitoring may not be universally available in routine clinical practice, and the findings of this study should not be extrapolated to lower resource settings, where induction of labour may be safer. In view of the findings of equivalent maternal and fetal outcomes in the current study, an economic analysis of the two treatment modalities would also be informative.

A limitation of this study, which the authors acknowledged, is the diagnostic uncertainty surrounding suspected fetal growth restriction and how to define it after birth. This study used population birthweight centiles to define fetal growth restriction. Customised birthweight centiles identify more small babies at high risk of morbidity and mortality than population centiles,[4] and it would have been useful to report customised birthweight centiles in each study arm.



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Babies in the DIGITAT trial born to women who were expectantly managed were 130 g heavier and born 10 days later than those whose mothers were induced. This may indicate that a proportion of babies in this group were still growing and not growth restricted but constitutionally small.

A substantial barrier to conducting a study like DIGITAT is that in routine clinical practice fewer than 30% of infants who are small for gestational age are identified before birth.[5] The National Institute for Health and Clinical Excellence (NICE) recommends screening for fetal growth restriction by performing maternal symphysiofundal height measurements using a tape measure. Antenatal detection of growth restricted infants may be further increased by use of customised fundal height measurements, but even with this tool about half of growth restricted fetuses still remain undetected.[6]

The development of a reliable and valid screening test for fetal growth restriction would enable antenatal care to be matched to clinical need. Identification and surveillance of growth restricted fetuses in the low risk population could prevent 800 stillbirths in the United Kingdom each year. Equally, a test with a high negative predictive value would reduce potentially harmful and expensive antenatal interventions, and considerable cost savings could be made from streamlined healthcare. Future research should focus on the development of accurate predictive tests as well as research into the causes of fetal growth restriction. This would potentially facilitate targeted treatments aimed at preventing fetal growth restriction, which could have a substantial global health, economic, and societal impact.

1 Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ* 2005;331:1113-7.
2 Vashevnik S, Walker S, Permezel M. Stillbirths and neonatal deaths in appropriate, small and large birthweight for gestational age fetuses. *Aust N Z J Obstet Gynaecol* 2007;47:302-6.
3 Boers KE, Scherjon SA, Bloemenkamp KWM, le Cessie S, Rijken M, van Lith JMM, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). *BMJ* 2010;341:c7087.
4 McCowan LM, Harding JE, Stewart AW. Customized birthweight centiles predict SGA pregnancies with perinatal morbidity. *BJOG* 2005;112:1026-33.
5 McCowan LME, Roberts CT, Dekker GA, Taylor RS, Chan EHY, Kenny LC, et al. Risk factors for small for gestational age infants by customized birthweight centiles: data from an international prospective cohort study. *BJOG* 2010; doi:10.1111/j.1471-0528.2010.02737.x.
6 Gardosi J, Francis A. Controlled trial of fundal height measurement plotted on customised antenatal growth charts. *BJOG* 1999;106:309-17.

Transmission of HIV to infants whose mothers seroconvert postnatally

Primary prevention is the key

RESEARCH, p 37

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In November 2009, the World Health Organization published revised guidelines for the prevention of mother to child transmission of HIV in developing countries that will extend antiretroviral prophylaxis throughout the breastfeeding period.[1] If implemented fully, the recommendations promise to reduce vertical transmission rates from 25-48% to 5% or lower.[2 3] This has prompted several prominent international organisations to call for the worldwide eradication of AIDS in children.[4]

In most of the resource poor world, women and children bear a disproportionate share of the AIDS burden. In sub-Saharan Africa, women account for more than 60% of infections, and in the nine countries in southern Africa most affected by HIV, prevalence among women aged 15–24 years is three times higher than that among men of the same age.[5] Pregnant and lactating women are particularly vulnerable to the acquisition of HIV,[6] probably because of immunological and hormonal changes that affect the genital tract, and when they seroconvert, their infants are also at high risk of infection.[7] More than 20% of new HIV infections in sub-Saharan Africa occur in children.[8]

In the linked study, Humphrey and colleagues assess the rates and timing of breastfeeding associated HIV transmission in 351 mothers who seroconverted postnatally.[9] The authors performed a secondary analysis of the ZVITAMBO study, a large Zimbabwean randomised controlled trial evaluating the effects of vitamin A supplementation given immediately postpartum to mothers or their babies (or both) to prevent transmission of HIV.[10] Although the primary study found no role for vitamin A supplements in preventing mother to child transmission, with its 14 110 mother-infant pairs enrolled (4846 of whom already were or became HIV positive), ZVITAMBO is the largest vertical HIV transmission trial ever reported. Its quarterly follow-up and large repository of serum and breast milk specimens have allowed a careful description of both the timing and size of the risk of mother to child transmission in women who became infected in late pregnancy or while breast feeding.

In their primary analysis, the authors found that 8.5% of infants who were born without HIV, but whose mothers were chronically infected, would become infected by 12 months of age. The instantaneous risk of infection among these children was constant over the observation period (2.5×10^{-4} per day of exposure). In contrast, 23.6% of infants whose mothers seroconverted postpartum were infected by 12 months of life, and the instantaneous risk of transmission was highest shortly after acute infection and then declined precipitously. At 70 days after seroconversion, this risk was 18.5×10^{-4} per day of exposure, more than seven times the transmission risk among chronically infected mothers.

Acute HIV infection has similar effects on both vertical and horizontal transmission.[11] In both situations, acute infection results in very high plasma viral loads (often more than 10^6 copies/ml) and consequently high titres within cervicovaginal fluid and breast milk. These high viral concentrations contribute to a high risk of onward transmission, often almost immediately, even before routinely identifiable anti-HIV antibodies have developed.