Clinical review

Recent developments in fetal medicine

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Several advances have been made in the field of fetal medicine since the last *BMJ* review on the subject. This review covers advances in prenatal screening, imaging techniques, management of multiple pregnancies, and fetal therapy

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Advances in fetal imaging, genomics, and minimally invasive techniques, as well as a better understanding of the natural history of many fetal diseases, mainly from animal studies, have over the past few years revolutionised the management of many fetal conditions diagnosed prenatally. Although the challenge in modern obstetrics still remains to a large extent the prevention of preterm labour, pre-eclampsia, and cerebral palsy, many fetal conditions exist for which treatment is possible and gives a good postnatal outcome. For many pregnant patients this is an option that years ago would have been denied them.

The principal purpose of antenatal screening programmes is to identify diseases and then to give the parents the option of termination of pregnancy in the event of an affected fetus. "Wrongful birth" resulting from failed prenatal diagnosis has become a major source of litigation for the NHS and is at least on a par with birth asphyxia and cerebral palsy.

Summary points

- Improved Down's syndrome screening should be available by 2007
- Use of fetal cells or DNA in maternal circulation may render invasive testing obsolete
- Advances in imaging (fetal magnetic resonance imaging and three dimensional ultrasonography) are likely to improve diagnosis of fetal abnormalities
- Advances in prevention of preterm labour and improved minimally invasive techniques may allow safer in utero treatment
- Advances in proteomics, genomics, and stem cell research may allow early in utero treatment for some genetic conditions

Sources and selection criteria

Prenatal screening has also moved on considerably since the last review on this topic in the *BMJ* in 1998.[1] This review will deal with many of the developments that have occurred over the past few years. In preparing this review we did a PubMed literature search to obtain up to date references on recent advances in fetal medicine. In addition, we obtained guidelines pertaining to antenatal care from the National Institute for Clinical Excellence's website (www.nice.org.uk). We obtained information about the ongoing North American spina bifida study from colleagues and fellow members of the International Fetal Medicine and Surgery Society.

Prenatal screening

As more than 90% of structural and chromosomal abnormalities arise in pregnancies without any obvious risk factors, anomaly and aneuploidy screening is offered universally. In some situations screening for specific genetic disorders may be confined to certain ethnic groups.

Although the risk of Down's syndrome is higher in older women, most pregnancies occur in women younger than 35 years, and most cases of Down's syndrome are missed when screening is restricted to women over 35.[2] In England and Wales, prenatal diagnosis of Down's syndrome cases rose from 28% in 1989 to 53% in 1999, and the number of invasive tests done to diagnose each case fell significantly.[3] Current recommendations from the National Institute for Clinical Excellence are that all pregnant women should be offered a test that provides the current standard of a detection rate of above 60% with a false positive rate of less than 5%. By April 2007 the NHS is required to provide a test that has a detection rate above 75% and a false positive rate of less than 3%. Only the combined, integrated, quadruple, and serum integrated tests will meet the more stringent criteria (box 1).

Diagnostic tests

Recent developments in fluorescence in situ hybridisation and quantitative fluorescence polymerase chain reaction techniques have led to rapid reporting times (1-3 days) for Down's syndrome as well as other trisomies. The introduction of rapid testing of all prenatal samples has raised the question of whether full karyotype analysis and reporting should be done

Box 1: Screening tests for Down's syndrome

11-14 weeks
- Nuchal translucency (NT)
- Combined test (NT, hCG, and PAPP-A)

14-20 weeks
- Triple test (hCG, AFP, and uE_3)
- Quadruple test (hCG, AFP, uE_3, and inhibin A)

11-14 weeks and 14-20 weeks
- Integrated test (NT, PAPP-A, inhibin A, hCG, AFP, and uE_3)
- Serum integrated tests (PAPP-A, inhibin A, hCG, AFP, and uE_3)

for these samples. Most women who undergo invasive testing do so because they have been identified as being at high risk by a particular screening method. Full karyotype analysis may detect abnormalities of unknown significance (small "marker" chromosomes, balanced chromosome rearrangements, or regions of variability), which may be inherited and thus of minimal if any importance. These findings often cause difficulties in counselling and raise ethical issues for patients in how to interpret and choose between termination of pregnancy or ongoing anxiety for the rest of the pregnancy. Overall, around 0.07-0.14% of pregnancies karyotyped will have a clinically significant chromosome abnormality that would not be detected by rapid testing.[4 5]

Preimplantation genetic diagnosis is now established as a reliable early prenatal diagnostic technique for chromosome abnormalities arising from parental balanced translocations or rearrangements.[6 7] This technique can also be used to screen embryos of in vitro fertilisation pregnancies. It is expensive and invasive, however, and is only suitable for women at particularly high risk due to a chromosome rearrangement or those who are having in vitro fertilisation.

Non-invasive prenatal diagnosis

As all current screening methods involve a invasive diagnostic test (for example, amniocentesis or chorionic villous sampling), which carries a small but definite risk of miscarriage, attempts have been made to develop less invasive diagnostic techniques that probe the fetal genome through either isolation and characterisation of DNA from fetal cells identified in the maternal circulation or analysis of free fetal DNA in maternal plasma.

Circulating fetal nucleated red blood cells, mesenchymal stem cells, and trophoblast have all been used for various prenatal diagnostic tests.[8–10] The main limiting factor seems to be the rarity of such cells in the maternal circulation (so enrichment techniques are needed to increase the yield), as well as the availability of a unique and reliable fetal marker. Estimates of the number of fetal cells in the maternal circulation vary depending on the stage of gestation and the method used for analysis. In any case, circulating fetal cells are rare, with estimates ranging from one fetal cell in 10^4 to one in 10^9 maternal cells in normal pregnancy.[11] Free fetal DNA, which progressively increases during pregnancy, has been estimated to account for approximately 3% to 6% of total DNA in maternal plasma, with smaller amounts in serum. It is rapidly cleared from the maternal circulation and is undetectable within two hours of delivery. Fetal DNA concentrations are increased in aneuploidy pregnancies.[12] Extending beyond plasma DNA, a new field of investigation has also been developed in the analysis of plasma RNA, which holds promise for non-invasive profiling of gene expression.[13]

Non-invasive methods are not yet in general clinical use. However, providing technical difficulties are overcome, such methods will probably render invasive testing for karyotype obsolete.

Newer imaging modalities

Fetal magnetic resonance imaging

Although high resolution ultrasonography permits the detection of many anomalies, it does have limitations. Poor views due to maternal obesity or oligohydramnions can be surmounted by ultrafast fetal magnetic resonance imaging. Faster imaging sequences now permit a single slice to be obtained in less than 400 ms, thereby eliminating most fetal motion artefacts. No harmful effects to the developing fetus have yet been found. The main contraindications to magnetic resonance imaging during pregnancy are the presence of a pacemaker in the mother and the presence of other mechanical devices such as clips on cerebral aneurysms.

Fetal magnetic resonance imaging is particularly useful for the evaluation of abnormalities of the central nervous system (fig 1). One study found that it provided additional information about abnormalities in the brain in 55% of fetuses.[14] One further advantage is its usefulness in evaluating changes in the developing brain due to neuronal migration, gyral formation, and myelination.

Magnetic resonance imaging is also increasingly useful in the evaluation of fetuses with other anomalies such as sacrococcygeal teratoma, diaphragmatic hernia, and spinal abnormalities. Image acquisition times will probably fall further as magnets become more powerful, thereby enabling almost any organ in the fetus to be visualised with great clarity.

Three dimensional ultrasonography

Three dimensional ultrasonography is a relatively new method of investigation. For a long time it seemed to provide only aesthetic images without any more value than a good two dimensional ultrasound image. In

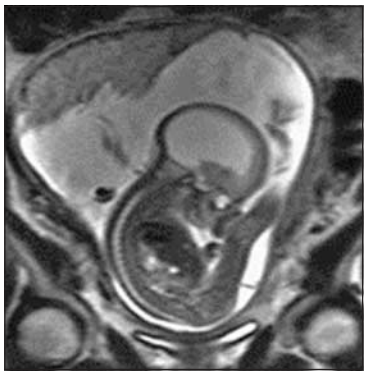

Fig 1 Magnetic resonance image of fetus with severe hydrocephalus

some clinical and research settings, however, three dimensional ultrasonography has been shown to be beneficial in evaluating the fetus.[15 16]

The indications for three dimensional ultrasound are not yet clear. Most reports have dealt with the detection of abnormalities of the fetal surface, especially cleft lip and palate and spina bifida. However, very few studies have looked at the ability of three dimensional ultrasonography to assess deeper structures. In addition, three dimensional ultrasonography allows accurate measurement of the volume of any fetal organ. Only a few studies have explored the clinical utility of fetal volume measurements. Again, as this technology evolves and real time three dimensional images improve, it is likely to become the imaging modality of choice.

Multiple pregnancy

Twin-twin transfusion syndrome (box 2)

Twin-twin transfusion syndrome complicates approximately 15% of monochorionic twin pregnancies and despite contemporary obstetric and neonatal management strategies is associated with 30-50% perinatal mortality.[17] The haemodynamic changes in twin-twin transfusion syndrome are due to unbalanced chronic interfetal transfusion. In addition, substantial morbidity occurs and neurodevelopmental outcome is poor in surviving infants owing to complications of the disease itself and the high rate of preterm birth that invariably accompanies this condition.[18] The old neonatal criteria of haemoglobin discrepancy and birth weight discordancy have been superseded by an ultrasound stage based classification.[19]

Overall rates of perinatal survival have improved as a result of a range of treatment modalities, including amnioreduction, septostomy, selective reduction, and laser ablation. However, even in the best series most affected pregnancies lose at least one baby. Amnioreduction offers good results in early stage disease, with at least one fetus surviving in more than 85% of cases and two surviving in 66.7% of cases with stage I or stage II disease.[20]

The overall survival rate for cases presenting before 28 weeks and treated by laser was 58% in a recent meta-analysis, similar to that for aggressive serial amnioreduction, with single survival in 32% and double survival in 42%.[21] Laser treatment increases the proportion of single survivors, by reducing the number of both double survivors and double deaths.

The key factor in managing pregnancies complicated by twin-twin transfusion syndrome is early referral to a tertiary fetal medicine unit experienced in the care of monochorionic pregnancies. These patients need careful evaluation and counselling before any interventions, which can often be complex and individualised. Selective termination of pregnancy in severe twin-twin transfusion syndrome is one option that is done in only a handful of centres in the United Kingdom.

Multifetal pregnancy reduction

Fetal reduction can be either selective or non-selective. In selective fetal reduction, one of the fetuses may be discordant for an anomaly that may be lethal or its continued presence may jeopardise the survival of its cotwin(s). Non-selective fetal reduction is usually done earlier in gestation in high order multiple pregnancies to reduce the likelihood of high order births with all their attendant complications; which fetus to terminate does therefore not depend on any specific criteria but is often random. Fetal reduction therefore has the dual objective of preventing the birth of a baby that may have a significant abnormality as well as reducing the substantial risk of preterm delivery that is often associated with multiple pregnancy. Depending on chorionicity, multifetal pregnancy reduction can be done by using ultrasound guided intracardiac potassium injection, bipolar cord coagulation, or interstitial laser.

In high order multiple pregnancies (triplets or greater) multifetal pregnancy reduction confers a clear benefit in terms of perinatal outcome. This mainly translates into reduced risks for prematurity, cerebral palsy, and pregnancy related complications.

Unless discordance exists between the fetuses for an anomaly that might result in a significant risk of handicap, most fetal terminations in the United Kingdom are done before 24 weeks' gestation; most are done between 11 weeks and 14 weeks of gestation. Several reasons exist for choosing this gestation interval. Technically, it is more difficult to do transabdominal procedures before 10 weeks because of the small fetal size and the inaccessibility of the fetuses when the uterus is still essentially a pelvic organ. In addition, before this time, the spontaneous loss of a fetus may occur. Multifetal pregnancy reduction is usually done between 11 weeks and 14 weeks, primarily because of a lower miscarriage rate (5.4%) compared with the risk of spontaneous miscarriage (12%). The transabdominal technique has almost entirely replaced the transvaginal technique.[22]

As the perinatal outcome of reduced twins approaches, but does not quite reach, that of spontaneous twins, the reduction of higher order multiple pregnancies to a finishing number of two is now standard practice, as many groups feel that the perinatal mortality and morbidity of twin pregnancies are acceptable. The Human Fertilisation and Embryological Authority has now decreed that a maximum of two embryos should be replaced at any one time, principally to decrease the risks associated with higher order multiples.

In the most recent analysis from the International Registry, in 3513 patients before 24 weeks' gestation undergoing multifetal pregnancy reduction in 11 centres, the overall rate of loss of pregnancy was 9.6%, with 3.7% very preterm deliveries between 25 weeks and 28 weeks of gestation,[22] both of which seem substantially better than the published outcomes for unreduced multiple pregnancies.[23] A strong correlation occurred between the starting number of fetuses and the finish-

Box 2: Twin-twin transfusion syndrome

- Stage based classification
- High perinatal morbidity and mortality
- Treatment options are serial amnioreduction with or without septostomy, laser ablation of communicating placental vessels, or selective termination
- Early referral to tertiary unit is essential

ing number after multifetal pregnancy reduction, with the likelihood of poor pregnancy outcome (losses and prematurity) increasing with higher order multiples.

Fetal therapy

Accurate diagnosis of a fetal anomaly allows appropriate counselling and transfer to a tertiary unit, planned delivery, and specialised neonatal therapy. In many situations the abnormality is not amenable to either in utero or neonatal treatment, and sadly the option of termination of pregnancy has to be discussed with the parents. The allure of fetal surgery is the possibility of interrupting the in utero progression of an otherwise treatable disease (box 3). To date, the major hurdles for the development of fetal surgery have been defining criteria for patient selection, developing appropriate surgical techniques, devising fetal and uterine monitoring, tocolysis after surgery, and minimising maternal and fetal risks.

The first open fetal surgical procedure was done by Harrison and colleagues in 1982 for obstructive uropathy.[24] Although the procedure was a technical success, unrecognised renal dysplasia and pulmonary hypoplasia led to neonatal death. Over the past two decades successful fetal treatment has been done for spina bifida, congenital diaphragmatic hernia, cystic adenomatoid malformations, and obstructive uropathy.[25–29]

Exposure to amniotic fluid may damage the neural tissue in cases of spina bifida and cause subsequent paralysis and hydrocephalus. Closure of the defect in utero may prevent this. Severe arteriovenous shunting in sacrococcygeal teratomas may cause fetal hydrops and the maternal mirror syndrome. Excision of the teratoma or in utero ablation of its vascularity by using sclerosants or laser may preclude these complications. The development of pulmonary hypoplasia secondary to cystic adenomatoid malformation can sometimes be prevented by aspirating, shunting, or excising in utero the macrocystic component of a cystic adenomatoid malformation; in congenital diaphragmatic hernia, tracheal occlusion can be done by using a clip or balloon catheter. Lower urinary tract obstruction secondary to posterior urethral valves can be diagnosed and treated with a cystoscopic approach (fig 2).[30 31] Stenotic cardiac valves can now be treated by in utero valvuloplasty, thereby improving the prospects for a biventricular repair after birth.[32 33]

Because many of these procedures are complex and need input from clinicians across specialties, they are only done in major tertiary centres. The treatment of some of these rare conditions has been assessed in randomised controlled trials, which on occasion have found that in utero treatment is no better than optimal postnatal care. For example, one study found that fetal tracheal occlusion for congenital diaphragmatic hernia did not improve survival or morbidity.[34] A similar trial is under way in the United States for spina bifida.

Box 3: Fetal therapy

- Fetoscopy and laser
- Cystoscopy
- Cardiac valvuloplasty
- Open repair of spina bifida
- Excision of fetal tumours

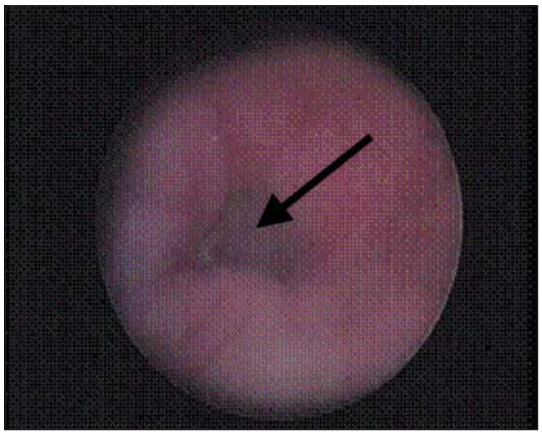

Fig 2 Fetal cystoscopy showing bladder neck and dilated posterior urethra (arrow)

Fetal red cell and platelet alloimmunisation

Fetal Rh or Kell status can now be ascertained non-invasively by using circulating fetal DNA in maternal plasma. This technological advance has rendered early invasive testing redundant in alloimmunised pregnancies. Although in utero transfusions remain the treatment of choice for anaemic fetuses affected by red cell alloimmunisation, methods for monitoring the at risk fetus have evolved. In the past, serial amniocentesis was needed to measure optical density 450 levels before deciding on the timing of the next transfusion. Each amniocentesis carried a risk of miscarriage or preterm labour, and as some pregnancies needed several of these procedures the risk was not inconsequential. The advent of Doppler velocity assessment in the fetal middle cerebral artery has revolutionised the management of fetal anaemia regardless of the cause. This method has a 100% sensitivity with a 12% false positive rate and allows accurate timing of intrauterine transfusions without any need for additional invasive procedures.[35]

Feto-maternal alloimmune thrombocytopenia is caused by feto-maternal incompatibility for human platelet antigens. Fetal intracranial haemorrhages can occur in 10-20% of cases. The available treatment options include maternal treatment with high dose intravenous immunoglobulin, corticosteroids, a combination of both, or serial intrauterine platelet transfusions. A recent European collaborative study on the antenatal management of feto-maternal alloimmune thrombocytopenia concluded that the start of treatment can now be stratified on the basis of sibling history and supports the use of first line maternal immunoglobulin treatment, thereby avoiding multiple invasive procedures.[36]

Conclusions

Although the diagnosis of many fetal abnormalities is now possible antenatally, the conundrum of what is the most appropriate treatment remains. Open fetal surgery is technically possible for some of these

Additional educational resources

Websites

- National Institute for Clinical Excellence (www.nice.org.uk)
- Institute for Reproductive Development and Biology, Imperial College London (www.med.ic.ac.uk/divisions/58/irdb.asp)
- Center for Fetal Diagnosis and Therapy, Children's Hospital of Philadelphia (fetalsurgery.chop.edu)

Ongoing research study

Management of myelomeningocele study (MOMS) (www.spinabifidamoms.com)—The National Institute of Child Health and Human Development, a part of the National Institutes of Health, has funded this study to determine how babies who have prenatal surgery for spina bifida do compared with those who have postnatal surgery. There are three participating MOMS Centers: the University of California at San Francisco in San Francisco, CA; the Children's Hospital of Philadelphia in Philadelphia, PA; and Vanderbilt University Medical Center in Nashville, TN. The study will be coordinated by the Biostatistics Center of the George Washington University in Rockville, MD. The goal is to find out if either treatment is better for the baby

conditions, but the question of whether it makes a difference to the ultimate outcome is still unanswered. Minimally invasive techniques and improved imaging coupled with novel strategies to prevent preterm labour will probably make a wider range of therapeutic interventions possible.

Rapid advances in genomics and proteomics and stem cell research will also make the in utero treatment of some genetic conditions possible. The challenge for the future is to apply the explosion of knowledge in basic science and the advances in technology rationally with a clear understanding of achievable goals.

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1 James D. Fetal medicine. *BMJ* 1998;316:1580-3.
2 Egan JF, Benn P, Borgida AF, Rodis JF, Campbell WA, Vintzileos AM. Efficacy of screening for fetal Down syndrome in the United States from 1974 to 1997. *Obstet Gynecol* 2000;96:979-85.
3 Smith-Bindman R, Chu P, Bacchetti P, Waters JJ, Mutton D, Alberman E. Prenatal screening for Down syndrome in England and Wales and population-based birth outcomes. *Am J Obstet Gynecol* 2003;189:980-5.
4 Thein AT, Abdel-Fattah SA, Kyle PM, Soothill PW. An assessment of the use of interphase FISH with chromosome specific probes as an alternative to cytogenetics in prenatal diagnosis. *Prenat Diagn* 2000;20:275-80.
5 Ryall RG, Callen D, Cocciolone R, Duvnjak A, Esca R, Frantzis N, et al. Karyotypes found in the population declared at increased risk of Down syndrome following maternal serum screening. *Prenat Diagn* 2001;21:553-7.
6 Scriven PN, Flinter FA, Braude PR, Ogilvie CM. Robertsonian translocations—reproductive risks and indications for preimplantation genetic diagnosis. *Hum Reprod* 2001;16:2267-73.
7 Pettenati MJ, Von Kap-Herr C, Jackle B, Bobby P, Mowrey P, Schwartz S, et al. Rapid interphase analysis for prenatal diagnosis of translocation carriers using subtelomeric probes. *Prenat Diagn* 2002;22:193-7.
8 Choolani M, O'Donnell H, Campagnoli C, Kumar S, Roberts I, Bennett PR, et al. Simultaneous fetal cell identification and diagnosis by epsilon-globin chain immunophenotyping and chromosomal fluorescence in situ hybridization. *Blood* 2001;98:554-7.
9 Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood* 2001;98:2396-402.
10 Oudejans CB, Tjoa ML, Westerman BA, Mulders MA, Van Wijk IJ, Van Vugt JM. Circulating trophoblast in maternal blood. *Prenat Diagn* 2003;23:111-6.
11 Krabchi K, Gros-Louis F, Yan J, Bronsard M, Masse J, Forest JC, et al. Quantification of all fetal nucleated cells in maternal blood between the 18th and 22nd weeks of pregnancy using molecular cytogenetic techniques. *Clin Genet* 2001;60:145-50.
12 Zhong XY, Burk MR, Troeger C, Jackson LR, Holzgreve W, Hahn S. Fetal DNA in maternal plasma is elevated in pregnancies with aneuploid fetuses. *Prenat Diagn* 2000;20:795-8.
13 Costa JM, Benachi A, Olivi M, Dumez Y, Vidaud M, Gautier E. Fetal expressed gene analysis in maternal blood: a new tool for noninvasive study of the fetus. *Clin Chem* 2003;49(6 pt 1):981-3.
14 Levine D, Barnes PD, Madsen JR, Li W, Edelman RR. Fetal central nervous system anomalies: MR imaging augments sonographic diagnosis. *Radiology* 1997;204:635-42.
15 Timor-Tritsch IE, Platt LD. Three-dimensional ultrasound experience in obstetrics. *Curr Opin Obstet Gynecol* 2002;14:569-75.
16 Dyson RL, Pretorius DH, Budorick NE, Johnson DD, Sklansky MS, Cantrell CJ, et al. Three-dimensional ultrasound in the evaluation of fetal anomalies. *Ultrasound Obstet Gynecol* 2000;16:321-8.
17 Hecher K, Plath H, Bregenzer T, Hansmann M, Hackeloer BJ. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. *Am J Obstet Gynecol* 1999;180(3 pt 1):717-24.
18 Haverkamp F, Lex C, Hanisch C, Fahnenstich H, Zerres K. Neurodevelopmental risks in twin-to-twin transfusion syndrome: preliminary findings. *Eur J Paediatr Neurol* 2001;5:21-7.
19 Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;19(8 pt 1):550-5.
20 Quintero RA, Dickinson JE, Morales WJ, Bornick PW, Bermudez C, Cincotta R, et al. Stage-based treatment of twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2003;188:1333-40.
21 Fisk NM, Taylor MJO. The fetus with twin-twin transfusion syndrome. In: Harrison M, Evans M, Adzick S, Holzgreve W, eds. *The unborn patient: the art and science of fetal therapy*. Philadelphia: W B Saunders Company, 2000.
22 Evans MI, Berkowitz RL, Wapner RJ, Carpenter RJ, Goldberg JD, Ayoub MA, et al. Improvement in outcomes of multifetal pregnancy reduction with increased experience. *Am J Obstet Gynecol* 2001;184:97-103.
23 Yaron Y, Bryant-Greenwood PK, Dave N, Moldenhauer JS, Kramer RL, Johnson MP, et al. Multifetal pregnancy reductions of triplets to twins: comparison with nonreduced triplets and twins. *Am J Obstet Gynecol* 1999;180:1268-71.
24 Harrison MR, Golbus MS, Filly RA, Nakayama DK, Callen PW, de Lorimier AA, et al. Management of the fetus with congenital hydronephrosis. *J Pediatr Surg* 1982;17:728-42.
25 Tulipan N, Hernanz-Schulman M, Lowe LH, Bruner JP. Intrauterine myelomeningocele repair reverses preexisting hindbrain herniation. *Pediatr Neurosurg* 1999;31:137-42.
26 Bruner JP, Tulipan N, Paschall RL, Boehm FH, Walsh WF, Silva SR, et al. Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. *JAMA* 1999;282:1819-25.
27 Harrison MR, Adzick NS, Longaker MT, Goldberg JD, Rosen MA, Filly RA, et al. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. *N Engl J Med* 1990;322:1582-4.
28 Adzick NS, Harrison MR. Management of the fetus with a cystic adenomatoid malformation. *World J Surg* 1993;17:342-9.
29 Quintero RA, Homsy Y, Bornick PW, Allen M, Johnson PK. In-utero treatment of fetal bladder-outlet obstruction by a ureterocele. *Lancet* 2001;357:1947-8.
30 Welsh A, Agarwal S, Kumar S, Smith RP, Fisk NM. Fetal cystoscopy in the management of fetal obstructive uropathy: experience in a single European centre. *Prenat Diagn* 2003;23:1033-41.
31 Kumar S, Fisk NM. Distal urinary obstruction. *Clin Perinatol* 2003;30:507-19.
32 Tworetzky W, Jennings RW, Wilkins-Haug LE, Benson CB, Marshall AC, Colan SD, et al. Balloon dilation of severe aortic stenosis in the fetus: technical advances. *J Am Coll Cardiol* 2003;41(6 suppl B):496.
33 Kohl T, Sharland G, Allan LD, Gembruch U, Chaoui R, Lopes LM, et al. World experience of percutaneous ultrasound-guided balloon valvuloplasty in human fetuses with severe aortic valve obstruction. *Am J Cardiol* 2000;85:1230-3.
34 Harrison MR, Keller RL, Hawgood SB, Kitterman JA, Sandberg PL, Farmer DL, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med* 2003;349:1916-24.
35 Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med* 2000;342:9-14.
36 Birchall JE, Murphy MF, Kaplan C, Kroll H, European Fetomaternal Alloimmune Thrombocytopenia Study Group. European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. *Br J Haematol* 2003;122:275-88.

Endpiece

Illness

Illness is a convent which has its rule, its austerity, its silences, and its inspiration.

Albert Camus (1913-60), author, Nobel prize winner for literature 1957

Fred Charatan, retired geriatric physician, Florida