Advances in maternal fetal medicine practice

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Abstract: Maternal fetal medicine (MFM) is a subspecialty of obstetrics that focuses on identified risk pregnancies. The role includes obstetric ultrasound for fetal assessment and diagnosis of anomalies, invasive prenatal diagnosis and management of pregnancies complicated by maternal medical disorders, multiple fetuses and the antenatal management of extreme prematurity. Skill specialisation within MFM includes fetal interventions such as fetal shunting procedures, intrauterine transfusion, fetoscopic laser photocoagulation of anastomotic vessels for twin to twin transfusion syndrome and ex utero intrapartum treatment. MFM specialists are actively involved in clinical and basic science research to improve maternal and neonatal outcomes. Most Australian MFM specialists are associated with metropolitan teaching hospitals. MFM subspecialisation has reduced the impact of disability associated with aneuploidy, structural anomalies, multiple pregnancy and extreme prematurity. Management aims are to give families timely counselling, appropriate intervention, and optimisation of the time and location of delivery. The aim of this paper is to update the reader regarding current advances in MFM practices.

Key words: fetal; therapy; obstetric; prenatal diagnosis.

Screening for Fetal Aneuploidy

Fetal aneuploidies are a major cause of perinatal mortality and childhood disability. Screening identifies pregnancies at increased risk of aneuploidy thereby enabling women to receive counselling and appropriate diagnostic testing. Invasive prenatal testing by amniocentesis and chorionic villus sampling is associated with a 1.4% (95% confidence interval (CI) 1.3–1.5) and 1.9% (95% CI 1.7–2.0) risk of miscarriage, respectively. Some studies have shown that the risk of amniotic fluid leakage with amniocentesis is approximately 1.7 to 2.8% if performed at 15 to 16 weeks gestation. Invasive tests are increasingly performed only in pregnancies screened using tests with low false negative and acceptable false positive rates, minimising the chance of miscarriage of a normal fetus.

During the 1980s the addition of second trimester maternal serum markers to maternal age improved the Down syndrome detection rate to 70–75% with a 5% false positive rate (5% of women are incorrectly placed in high-risk group). Subsequently nuchal translucency (NT) thickness measurement (Fig. 1) has been introduced over the last 15 years. Performed between 11 and 14 weeks gestation it offers an effective and early screening test for trisomy 21, 18, 13 and other major fetal aneuploidies. Furthermore, increased NT thickness is also associated with cardiac defects and a wide range of other fetal malformations, rare genetic syndromes and skeletal dysplasias.

Using a combined screening algorithm including maternal age, NT thickness and first trimester maternal serum analytes (free beta human chorionic gonadotrophin (f-beta hCG) and pregnancy-associated plasma protein A (PAPP-A)), as well as additional markers including fetal nasal bone measurement, ductus venosus (DV) Doppler and tricuspid regurgitation may improve detection rate of trisomy 21 to around 95% with a 2.5% false positive rate.
Maternal fetal medicine/neonatal outcomes

Second Trimester Fetal Anomaly Scan

Recent improvements in ultrasound resolution enable improved visualisation and hence performance as a screening tool for fetal structural malformations. A detailed fetal examination done at 18–20 weeks gestation, the ‘anomaly scan’, is now routine antenatal care in Australia.

One population-based study of infants born after 24 weeks gestation has showed a decrease of over 50% in the infant death rate due to congenital anomalies. The authors concluded this is likely due to widespread use of prenatal ultrasound screening. The Helsinki trial was a controlled trial that allocated women for ultrasound screening or no ultrasound assessment between 16 and 20 weeks gestation. It showed an improvement in detection rate of fetal malformations and confirmed an increased rate of termination of pregnancy and reduction in perinatal mortality in the ultrasound screening group.

The detection rate for fetal anomalies with second trimester ultrasound assessment is around 55% (95% CI – 52–58%). It ranges from 33% (cardiovascular system) to 81% (central nervous system).

In an Australian cohort study including 12 169 routine ultrasound scan over a 6-year period, a total of 123 major congenital anomalies were detected during antenatal period. There were 169 cases of fetal anomalies in the cohort giving the sensitivity of detection rate of 72.8% with routine ultrasound screening.

In the second trimester, the phenotypic characteristics of the aneuploidies will develop. Including this information along with the first trimester NT screen, (‘combined testing’), the detection rate for trisomy 21 has been reported as high as 93–96% with a 2.5% false positive rate.

Early identification of fetal congenital anomalies may provide families with the option to interrupt the pregnancy. Regardless of whether or not the family chooses to continue the pregnancy, NPs and other specialists can be called upon to provide information and supportive counselling for the family. Planning for timely delivery at a facility with appropriate neonatal and paediatric surgical facilities will optimise neonatal outcomes. There are numerous antenatally diagnosed conditions such as congenital diaphragmatic hernia (CDH), cyanotic cardiac disease, spina bifida and other malformations that will require management in an appropriate neonatal surgical facility. This will also reduce family disruption and remove the need for neonatal transportation after delivery.

Fetal Interventions

There are some specific fetal conditions where advanced interventions may be offered to parents by maternal fetal medicine specialists (MFMs) to improve perinatal outcomes:

1. Thoracocentesis and fetal pleuro-amniotic shunting

Primary fetal hydrothorax (Fig. 2) prior to 24 weeks may cause pulmonary hypoplasia and mediastinal shift resulting in generalised hydrops fetalis. Immune and non-immune hydrops fetalis can lead to secondary fetal hydrothorax. Neonatal mortality from pleural effusions is 25%, ranging from 15% in infants with isolated pleural effusions to 95% in those with gross generalised hydrops. Ultrasound-guided fetal thoracocentesis drains the effusion, reduces the mediastinal shift and provides fluid samples to investigate the potential aetiology. Single thoracocentesis may be effective management of mild cases which may not reaccumulate. Thoracocentesis prior to delivery may assist with initial neonatal resuscitation and is often recommended by NP.

Ultrasound-guided thoraco-amniotic shunting sites a pigtail catheter (Fig. 3) to continually drain pleural fluid into the amniotic cavity. Fetal survival rates in cases of hydrothorax with and without hydros fetalis are 82–90% and 58–62%, respectively. Shunting reduces the pleural fluid allowing for pulmonary expansion and reduces mediastinal shift. These procedures carry a risk of fetal demise, injury and preterm delivery but overall appear to improve survival.

2. Obstructive uropathies

Lower urinary tract obstruction (LUTO) affects 1:5000 to 1:8000 newborn males (Fig. 4) and is usually caused by posterior urethral valves or atresia. Oligohydramnios or anhydramnios secondary to LUTO at early gestations leads to pulmonary hypoplasia and secondary abdominal wall and limb abnormalities. Untreated LUTO causes renal failure and pulmonary hypoplasia. The associated mortality rate is 95%. Families who choose to continue the pregnancy when faced with such a high mortality rate may be offered vesico-amniotic shunting. Although not yet available in Australia,
Antegrade fetal cystoscopy with laser ablation of the posterior urethral valves is being evaluated overseas. The antenatal management of LUTO involves excluding other conditions such as fetal structural anomalies with poor prognosis, fetal aneuploidy and vesicoceles to assess fetal renal function before offering vesico-amniotic shunt or antegrade fetal cystoscopy. However, because antenatal assessment of pulmonary hypoplasia is inaccurate, counselling by a NP has more uncertainty attached. Recent data suggest that the survival rate may be as high as 90% with vesico-amniotic shunting. In a heterogeneous group of newborns 34% required renal transplant, 44% had persistent respiratory problems and 50% had frequent urinary tract infection.17

A recent systematic review suggested that prenatal bladder drainage improves the perinatal survival compared with no treatment (odds ratio (OR) 3.86, 95% CI 2.00–7.45). However, the long-term outcomes for renal function are still poor.18 A multicentre randomised control trial (PLUTO) is currently being undertaken to compare the perinatal mortality, renal outcomes and 5-year follow-up of a conservative approach group with an intrauterine vesico-amniotic shunting group. At the time of presentation of the initial data in February 2012, 145 women were recruited, 31 to the randomised arm (21.4%), 46 to the registry only but not in the randomised trial (31.7%) and 68 terminations of pregnancy (46.9%). Although the primary outcome showed improved perinatal survival with shunting (OR 4.00, 95% CI 1.11–14.35), the recruitment is still ongoing.19

Neural tube defects

Meningomyelocele (Fig. 5) is frequently diagnosed using ultrasound screening in the second trimester. Many Australian families chose termination of pregnancy when this diagnosis is made. The Management of Meningomyelocele (MOM) trial was a prospective randomised trial in the USA to compare the outcomes of prenatal surgery with hysterotomy (singleton primigravida at 19 to 25.9 weeks gestation with normal fetal karyotype) with standard postnatal repair of meningomyelocele at T1 to S1 level in 183 patients. The MOM trial is based on the outcomes in 158 women who underwent randomisation before 1 July 2009. Fetuses that were treated prenatally were born at an average gestational age of 34.1 weeks and 37.3 for the post-natal surgery group. The results are listed in Table 1.20

Despite these modest improvements in neonatal outcomes, there are risks associated with prenatal surgery such as preterm delivery, placenta abruption, intra-operative complications and uterine scar defects with higher rate of maternal transfusion at delivery. Although this option is offered to parents in the USA, it appears to be little call for this intervention to be offered in Australia, and this could perhaps be due to the preferences of the majority of couples who choose to terminate these pregnancies.
4 CDH
CDH is usually a sporadic anomaly occurring in 1 in 2000 to 5000 live births. When associated with other fetal structural or chromosomal anomalies it carries a poor prognosis. The common prenatal prognostic method currently in use for the prediction of post-natal lung function is the lung-to-head-ratio (LHR) performed at 22 to 28 weeks gestation. The survival rate for isolated CDH with intrathoracic herniation of the liver increased from 0% for those with an LHR of 0.4–0.7 to about 15% for an LHR of 0.8–0.9, 65% for an LHR of 1.0–1.5 and more than 80% for an LHR of 1.6 or more. Isolated CDH with LHR <1.0 has a poor prognosis. Fetal endoscopic tracheal occlusion (FETO) has been developed in a small number of European and US centres. The procedures were performed under fetal analgesia, and an endoscope is introduced into the trachea to position a detachable balloon between the carina and vocal cords. Serial ultrasound assessment is used for fetal growth and also to confirm the location of the endotracheal balloon. The balloon is removed by an MFM prenatally by fetoscopy or ultrasound-guided puncture, or by an NP post partum by tracheoscopy at the time of delivery with or without an ex utero intrapartum treatment procedure.

In one case control study of fetuses with left CDH treated with FETO, the survival rate increased from 24.1 to 49.1%, and in right CDH survival increased from 0 to 35.3% (P < 0.001). The perinatal outcomes with FETO for severe isolated CDH is also supported by two randomised clinical trials with the overall survival of 52.6–52.9% with the FETO group and 5.3–5.6% in the conservative group. A multicentre trial is underway (the TOTAL trial) and this procedure is offered at The Mater Mothers’ Hospital in Brisbane with a number of participating Australian centres.

5 Monochorionic twin pregnancy with TTTS
TTTS is a serious complication of monochorionic twin pregnancies with an incidence of about 10–20%. When untreated, the loss rate for both twins is greater than 90%. Routine ultrasound surveillance in monozygous twins should be performed especially in the second trimester of pregnancy so that appropriate treatment can be offered if required.

There are several staging systems available to categorise the severity of TTTS; the most commonly used of which is Quintero staging. Quintero et al. developed a staging system (Table 2) to define prognosis and provide treatment outcome comparison. TTTS was defined as polyhydramnios in the recipient (excessive amniotic fluid) and oligohydramnios in the donor twin (reduced amount of amniotic fluid). This is different to the historical paediatric definitions involving haemoglobin and birth weight discordance. Current treatment options include serial amnioreduction, fetoscopic laser photocoagulation of the anastomosis vessels and selective fetocide by cord occlusion (the aim being to reduce twins to a singleton pregnancy).

Since the 1990s, there have been numerous studies comparing these treatment options. The Eurofetus group reported the first prospective randomised trial to compare the efficacy of serial amnioreduction versus fetoscopic laser photocoagulation for TTTS from Quintero stage 1 to 4. The main results are presented in Table 3. Although there are several studies looking at survival rates and neonatal outcomes, there are currently still insufficient data to address optimal managements and options for stage 1 TTTS. Approximately 70% of stage 1 TTTS will either remain stable or regress. Due to the uncertainty of whether laser photocoagulation might benefit for stage 1 TTTS, further randomised controlled trials will be required.

In Australasia laser therapy for TTTS is available in Sydney, Brisbane, Melbourne, Perth and Auckland, and over 400 cases have been performed. We have published retrospective outcomes from the New South Wales Fetal Therapy Centre looking at 79 patients treated with laser therapy for stage 1 to 4 TTTS, reporting survival of at least one baby in 90.7% and of both babies in 60.0%. There was only one woman

| Table 1 | Main outcomes of prenatal and post-natal surgery for meningomyelocele |
|---------|-----------------------------|------------------|
|         | Prenatal-surgery group | Post-natal-surgery group | P-value |
| Perinatal death | 3% (2/78) | 2% (2/80) | 1.00 |
| Placement of shunt in 12 months | 40% (31/78) | 82% (66/80) | <0.001 |
| Walking independently on examination at age 30 months | 42% (26/62) | 21% (14/67) | 0.01 |

<table>
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<tr>
<th>Table 2</th>
<th>Staging of TTTS by Quintero</th>
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<td>Stage 1: donor twin bladder still visible</td>
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<tr>
<td>Stage 2: donor twin bladder no longer visible but no abnormal Doppler studies</td>
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<td>Stage 3: abnormal Doppler studies (umbilical artery/ductus venous Doppler studies)</td>
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<td>Stage 4: hydrops fetalis</td>
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<td>Stage 5: demise of one or both twins</td>
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| Table 3 | Main outcomes of Eurofetus trial to compare laser photocoagulation versus serial amnioreduction for stage 1 to 4 TTTS |
|---------|-----------------------------|------------------|
|         | Laser group | Amnioreduction group | P-value |
| Survival of at least one twin | 76% (55/72) | 51% (36/70) | 0.002 |
| Periventricular leucomalacia | 6% (8/144) | 14% (8/140) | 0.02 |
| Free from neurological complication | 52% (75/144) | 31% (44/140) | 0.003 |

TTTS, twin to twin transfusion syndrome.
with stage 1 TTTS treated with laser due to rapid progressing polyhydramnios and both twins survived. Australian outcomes for transcatheter ablation generally match the international experience.30

Selective fetocide in multiple pregnancies
Selective fetocide is a prenatal procedure that terminates one or more fetuses in a multiple pregnancy. It can be offered to improve the outcome of a multiple pregnancy in specific situations including: higher order multiples pregnancies (multifetal reduction); dichorionic twins with severe discordant growth or structural or chromosomal abnormalities; monochorionic twins with severe selective growth restriction or severe twin TTTS with associated fetal abnormality and twin reversed arterial perfusion syndrome. Current methods include laser coagulation, bipolar cautery and intrafetal radio frequency ablation. According to one series reporting on techniques for selective termination in monochorionic twins, fetoscopic cord ligation has a failure rate of 10% with overall fetal survival rate of 71%, with 80% of fetuses delivered after 35 weeks gestation. There is little data to compare the different techniques but it is suggested that cord laser photocoagulation and bipolar cord coagulation be used before and after 21 weeks gestation, respectively. Sono-endoscopic cord ligation is reserved as a backup procedure if neither of these methods is successful.31

Fetal Anaemia

Causes of fetal anaemia include; alloimmune antibodies; fetal infection including parvovirus B19, fetomaternal haemorrhage and other rare genetic or maternal conditions.

Non-invasive fetal assessment uses ultrasound measurement of fetal middle cerebral artery (MCA) peak systolic flow as a screening tool to detect fetal anaemia. MCA peak systolic velocity has a sensitivity of 88%, specificity of 82% and accuracy of 85% (95% CI – 79–90%) for the detection of fetal anaemia.32 This non-invasive method is used both to detect and monitor fetal anaemia and compares favourably to measuring the OD450 of amniotic fluid.

Currently there is no randomised control trial to demonstrate which techniques for intrauterine transfusion produce the best outcomes. Some studies suggest that transfusion via the intrahepatic vein is safest with a fetal loss rate of 1–1.4%.33,34 Recent trends include performing transfusions later in pregnancy aiming to continue the pregnancy to closer to term.35 NPs should be involved in decisions regarding whether to deliver or transfuse beyond 32 weeks.

Intrauterine Growth Restriction (IUGR)

IUGR is defined as birth weight ≤10th percentile or where a fetus has not reached its growth potential at a given gestation. Aetiologies include fetal aneuploidy, chromosomal disorders, genetic syndromes, infection, placental insufficiency and maternal factors. IUGR is associated with increased perinatal mortality and potential long-term morbidity. There are no proven antenatal therapies for IUGR. Diagnosis and appropriate monitoring aim to optimise timing of delivery.36

Doppler ultrasound measurement of the fetal umbilical artery. DV and MCA waveforms is used to assess placental function, fetal status and help optimise the timing of delivery. The MFM can assess the placental circulation and the fetal response to the increased afterload. The fetus initially displays centralisation (low resistance MCA flow) and then eventually cardiac decompen-sation with abnormal venous flow.

Umbilical Artery Doppler (UAD) waveforms (Figs 6–9) reflect the status of placental function and circulation.37 Pathology that obliterates function of the placental villus causes increased resistance resulting in decreased end-diastolic umbilical flow. Absent or reversed end-diastolic flow represents a more advanced stage of placental insufficiency and is associated with high perinatal mortality and morbidity. In a European multicentre study of 245 cases of absent or reversed end-diastolic flow, the perinatal mortality was 28%, and of the surviving infants 96% required intensive care.38

A recent Cochrane review of the use of UAD compared with no Doppler ultrasound used in 18 completed trials with over 10 000 subjects in high-risk pregnancies and demonstrated a 29% decrease in perinatal mortality, with a risk ratio of 0.71 and a 95% CI of 0.53 to 0.98.39

The GRIT study was a randomised controlled trial that examined pregnant women with fetal compromise between 24 and 36 weeks. The study does not indicate that early or later delivery necessarily improves perinatal survival in pregnancies complicated by IUGR with abnormal Doppler only. Total deaths prior to discharge were 29 (10%) in the immediate delivery group versus 27 (9%) in the delayed delivery group.40

A DV waveform (Figs 10,11) with absent or reverse a-wave suggests severe fetal compromise. It is the best predictor of acidemia and perinatal death irrespective of the umbilical artery waveform.41 A recent meta-analysis of 18 studies which included 2267 pregnancies reported that abnormal DV waveform on Doppler ultrasound predicted adverse perinatal outcome with a pooled positive likelihood ratio of 3.15 (95% CI 2.19 to 4.54) and negative likelihood ratio of 0.49 (95%
CI 0.40 to 0.59; 14 studies). The pooled estimate of sensitivity was 0.61 (95% CI 0.50–0.70). The specificity was 0.81 (95% CI 0.70 to 0.88). The presence of absent or reverse a-wave in DV for more than 7 days predicts stillbirth, regardless of gestational age with 100% sensitivity and 80% specificity (likelihood ratio = 5.0, \( P < 0.0001 \)).

The timing and location of delivery will involve discussion between MFM and NP.

**Areas of Research in MFM**

Areas of focus currently include:
- Early diagnosis of fetal abnormalities including genetic and non-genetic syndromic disorders
- Noninvasive prenatal diagnosis such as the use of cell-free fetal DNA or RNA in maternal blood to detect fetal trisomy 21
- Intrauterine fetal surgery to improve perinatal outcomes
- Causes and prevention of miscarriage and stillbirth
- Prediction and prevention of preterm delivery to improve perinatal morbidity and mortality
- The pathogenesis and early diagnosis of pre-eclampsia and fetal growth restriction and novel treatments for this condition
- Complex multiple pregnancies issues

**Conclusion**

MFM is an obstetric subspecialty that focuses on the management of high-risk pregnancy and related research. The role of the MFM includes screening, diagnosis, counselling and management of complex maternal and fetal conditions. MFM are skilled in collaborating with paediatric sub-specialists in multidisciplinary teams.
Although recent advances in ultrasound technology provide better image resolution, many malformations remain undetected due to maternal habitus, fetal position and technical failures. There remain challenges including incomplete diagnosis and our inability to predict the severity and progression of disease and ultimate neonatal outcomes with the limited information available antenatally.

In some fetal condition such as TTTS in monochorionic twin pregnancy, fetal anaemia, LUTO, fetal hydrothorax, in utero fetal therapies can be offered to parents as they have a demonstrated role. Ongoing research into IUGR and pre-eclampsia, non-invasive prenatal diagnosis, prevention and prediction of stillbirth and preterm delivery hopes to further improve fetal and neonatal outcomes in the future.

References


MCQs

1 What is the detection rate of nuchal translucency screening (maternal age, nuchal translucency thickness, maternal serum) with additional markers (ductus venosus, tricuspid regurgitation, nasal bone)?
   a) 67–74% (2.5% false positive rate)
   b) 77–83% (2.5% false positive rate)
   c) 80–84% (2.5% false positive rate)
   d) 85–90% (2.5% false positive rate)
   e) 93–96% (2.5% false positive rate)
Answer: c

2 The survival rate for at least one baby in twin to twin transfusion treated by laser photocoagulation in Australia is approximately
   a) 20%
   b) 50%
   c) 70%
   d) 90%
   e) 99%
Answer: d

3 Which of the following Doppler measurements is most closely correlated with fetal acidaemia
   a) Umbilical artery waveform
   b) Middle cerebral artery waveform
   c) Ductus venosus waveform
   d) Renal artery waveform
   e) Uterine artery waveform
Answer: c