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144 The Neuroprotective Role of Magnesium Sulphate in Preterm Infants: Clinical Review

Neuroprotection in preterm infants should be considered a healthcare priority, since the survival rates of this population is improving progressively. The results of systematic reviews of RCTs on humans have been found to be consistent with those obtained from studies conducted on animal models, thereby supporting the role of magnesium sulphate for neuroprotection. Further trials are required to address the existing uncertainties before it can be accepted universally as a neuroprotective agent.

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CORRIGENDUM

We regret an error in the article “Hyperhomocysteinaemia in Pregnancy: Complications and Management”. The name of Institution of Dr. Laxmi Rachakonda is MGM Medical College, instead of Government Medical College (Vol. 4, No.4 April 2013 issue)

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Children are more sensitive to radiation than adults, and it is important to keep radiation exposure in children to a minimum. There has been controversy about the risk involved in computed tomographic (CT) scanning. Previous risk estimates of the risk of cancer following CT scans have been based on projections from Japanese data after the atomic bombs. Now, a study of data from National Health Service (NHS) hospitals in England, Wales, and Scotland has provided direct correlation between radiation dosage from CT scans in childhood and later risk of leukaemia or brain tumour.

With the use of hospital records and NHS Central Registry, data were available for 178,604 patients for the leukaemia study and 176,587 for the brain tumour study about people who had a first CT scan between 1985 and 2002 when they were < 22 years old. Follow-up for leukaemia began 2 years after the first scan and for brain tumours after 5 years, with an average follow-up of 10 years. Compared with a cumulative CT radiation dose of < 5 mGy, a cumulative bone marrow radiation dose of 30 mGy or greater increased the leukaemia risk by a factor of 3.18 and a cumulative brain dose of 50–74 mGy increased the brain tumour risk by a factor of 2.82.

CT scanning in childhood is associated with small but significant increases in risk of leukaemia or brain tumour. The absolute risks are small. For every 10,000 first head scans in children under the age of 10 years, there might be one extra case of leukaemia and one of brain tumour. The benefits of CT scanning will usually outweigh the risks, but dosage should be kept to a minimum and the use of other imaging techniques should be considered if appropriate.


Paediatric ventricular assist device prolongs survival

Heart failure is much less common in children than in adults but carries a poor prognosis. Heart transplantation in children is effective (83% survival at 3 years), but a paucity of donor hearts means a high waiting list mortality. Extracorporeal membrane branefate a high waiting list mortality. Extracorporeal membrane oxygenation (ECMO) may be used to keep some children alive until transplantation, but it can be used for only 10–20 days, which is not long enough for many children. Researchers in North America have reported the use of a ventricular assist device as a bridge to heart transplantation in children. The EXCOR Pediatric Ventricular Assist Device (Berlin Heart GmbH, Berlin, Germany) has been assessed in a multicentre, single-group study.

The study included 48 children up to the age of 16 years in two groups according to body surface area (< 0.7 m² or 0.7 to < 1.5 m²) with 24 in each group. Survival was compared with that of propensity score–matched historical control groups who underwent ECMO as a bridge to heart transplantation. Among children with a body surface area < 0.7 m², median survival time had not been reached at 174 days whereas in the matched ECMO control group it was 13 days. Among children with a body surface area of 0.7 to < 1.5 m², the corresponding median survival times were 144 days and 10 days, respectively. Major bleeding, infection, and stroke were common in both EXCOR device and ACMO groups.

Use of the ventricular assist device increased survival times.

Intermittent preventive treatment during infancy (IPTi) with sulfadoxine–pyrimethamine has been shown to reduce the incidence of clinical malaria in infancy in countries with moderate or high malaria transmission. IPTi is given at 8–10 weeks, 12–14 weeks, and 9 months at times of routine vaccination (second and third diphtheria-tetanus-pertussis doses and measles dose). It is not known whether IPTi could affect responses to immunization. Now, a study in Ghana, Tanzania, Mozambique, and Kenya (two sites) has shown that IPTi did not affect serological responses to vaccinations.

A subset of 1,904 infants, out of 8,416 infants in five studies of IPTi, were included in the present study. Of these, 1,904,970 had received IPTi and 934 placebo. A non-protective response to measles vaccine was detected in 6.3% (IPTi) vs 6.4% (placebo). Use of drugs other than sulfadoxine–pyrimethamine for IPTi did not affect the results. Serological response data for other vaccinations were available for 2,396 children, and IPTi did not reduce responses.

IPTi does not impair responses to routine immunizations in infancy. Lancet commentators point out that there is uncertainty whether IPTi is associated with an increase in overall mortality. More data are needed.


Strict blood glucose control in ICU after paediatric cardiac surgery: No benefit

Hyperglycaemia is common in infants and young children recovering from cardiac surgery, but there is controversy about its treatment. Strict blood glucose control might provide some advantages, but there is concern about insulin-induced hypoglycaemia. A trial in two US cardiac intensive care units (ICUs) has shown a low rate of severe hypoglycaemia with carefully monitored intensive glucose control but no clinical benefits.

The trial included 980 children aged 0–36 months recovering from cardiac surgery with cardiopulmonary bypass in ICUs in Boston, Massachusetts, and Ann Arbor, Michigan. Randomization was to tight glucose control (target blood glucose, 4.4–6.1 mmol/L) with an insulin-dosing algorithm and a continuous subcutaneous blood glucose monitor, or standard care. Insulin was given to 91% in the tight control group and 2% of the standard care group. Blood glucose control was achieved earlier in the tight control group (6 vs 16 hours) and maintained for longer (50% vs 33% of the critical illness period). The rate of severe hypoglycaemia in the tight control group was 3%. The rates of health-care-associated infection on the ICU was 8.6% (tight control) vs 9.9% (standard care), a non-significant difference. There were no significant differences between the groups in mortality, length of stay on ICU, or rates of organ failure.

Tight blood glucose control did not confer any clinical advantages.


Effectiveness of rotavirus vaccination in a high-income country

Reports of the effectiveness of rotavirus vaccination have come largely from low- or middle-income countries. Now, a report from Belgium has shown that it is effective in a high-income country.

The study included 215 children admitted to hospital with community-acquired, polymerase chain reaction–confirmed rotavirus gastroenteritis and 276 age- and hospital-matched controls, all from a random sample of 39 Belgian hospitals between February 2008 and June 2012. The effectiveness of two doses of monovalent rotavirus vaccine was 90% overall, 91% among children aged 3–11 months, and 90% among children aged 12 months or older.

Rotavirus vaccination is effective in Belgium for the prevention of rotavirus gastroenteritis in young children leading to hospital admission.

was 90% overall, 91% among children aged 3–11 months, and 90% among children aged 12 months or older.

Rotavirus vaccination is effective in Belgium for the prevention of rotavirus gastroenteritis in young children leading to hospital admission.


Inhaled steroid in childhood and adult height

Children treated with inhaled steroid for asthma lose on average about 1.0 cm of growth in the first few years of treatment, but growth then resumes at a normal pace and the effect on adult height is uncertain. Now, a multicentre US trial has shown a reduction in final height of about 1 cm with inhaled steroid.

In the Childhood Asthma Management Program (CAMP) trial, a total of 1,041 children aged 5–13 years with mild-to-moderate asthma were randomized to inhaled budesonide 200 µg twice daily, inhaled nedocromil 8 mg twice daily, or placebo, for 4–6 years. The adult height of 943 participants (mean age, 24.9 years) was 171.1 cm in the budesonide group, 172.1 cm in the nedocromil group, and 172.3 cm in the placebo group. The difference of 1.2 cm between the budesonide and placebo groups was significant, but the 0.2 cm difference between nedocromil and placebo groups was not. For each microgram per kilogram of body weight increase in daily dose of budesonide in the first 2 years of treatment, there was a 0.1 cm reduction in final height. The reduction in final height with budesonide was similar to the reduction seen after 2 years of treatment.

Inhaled steroid in childhood reduced attained height 2 years later and final height by an average of 1.2 cm.


Violence against handicapped children

Child abuse is common. It is estimated that in 2001, some 53,000 children were murdered and 223 million were sexually abused. About 5% of children (3% in high-income countries and up to 6% in low- or middle-income countries) have moderate or severe disability. It is known that adults with disability are particularly vulnerable to violence and is suspected that the same applies to children with disability. A systematic review and meta-analysis of observational studies of violence in disabled children has confirmed this susceptibility whilst criticizing the quality of current evidence.

The analysis included 17 studies. The prevalence of violence of any kind against children with any disability was 26.7%, for physical violence it was 20.4%, and for sexual violence 13.7%.

Compared with other children, children with a disability were almost four times more likely to suffer violence of any kind, more than three times more likely to suffer physical violence, and almost three times more likely to suffer sexual violence.

The analysis confirms the increased prevalence of violence in disabled children compared with other children, but much more needs to be known about risk factors and means of prevention.


DTaP vaccine in USA: Re-emergence of pertussis after fifth dose

In the USA, children receive five doses of the diphtheria, tetanus, acellular pertussis vaccine (DTaP) at 2, 4, 6 and 15–18 months and at 4–6 years. Despite this, there has been a resurgence of whooping cough and the duration of protection after the fifth dose has been questioned. Now, a report from California has suggested that protection deteriorates quite rapidly.

The study, in the Kaiser Permanente organization, included children who had been fully vaccinated against pertussis using DTaP between 2006 and 2011. Cases were 277 children with pertussis confirmed by polymerase chain reaction testing, and there were 3,318 polymerase chain reaction–negative controls and 6,086 matched population controls. The children with pertussis had received the fifth dose of DTaP at a younger age than the children in either set of controls. It was calculated that after the fifth dose, the risk of pertussis increased by 42% each year. New vaccines that give longer-lasting protection are needed.

CEREBRAL PALSY: A MAJOR SOCIAL BURDEN

Recurrent cerebral palsy (CP) is defined as abnormal control of movement and posture, resulting in limitation of activity. It is often the result of non progressive damage to the developing foetal or infant brain. With a reported prevalence of 2–3 per 1000 births, it is the most common cause of chronic motor disability in childhood.

The principal risk factors for CP include: preterm birth (less than 34 weeks’ gestation) and very low birth weight infants (≤1500 gm). Infants born at less than 34 weeks constitute nearly 25% new cases of CP every year. Risk of CP is, in fact, inversely proportional to the gestational age.

Multiple gestation is yet another risk factor for CP. It has been found that, twins have seven times and triplets are 47 times more prone of developing CP as compared to their singleton counterparts. This increased risk is, partly attributable to the increased risk of preterm deliveries in multiple gestations. Other factors like twin to twin transfusion syndrome may also play a role.

The resulting chronic disability leads to burdens not only in the healthcare system and economy, but also leads to emotional and social distress. A lifetime cost of an individual with CP include direct costs (like costs for physician visits, hospital stays, medications etc.) and indirect costs incurred due to loss of productivity. A recent study
has analysed the lifetime cost for an individual with CP and found it to be approximately $860,000 for a man and $800,000 for a woman.\(^9\)

Owing to improvements in obstetric and neonatal care, the survival rates of very preterm and very low birth weight infants have improved dramatically in the recent years. Hence, there is an increase in the population at risk of having CP. This has led to the search for a neuroprotective agent, which would protect the foetal brain from injury that ultimately leads to CP.

### NEUROPROTECTIVE EFFECTS OF MAGNESIUM SULFATE: EVIDENCE FROM LITERATURE

Magnesium sulphate has been in obstetric use for several years now: owing to its role in the preven-

<table>
<thead>
<tr>
<th>Trial details</th>
<th>Number of participants (foetuses)</th>
<th>Gestational age (weeks)</th>
<th>Control</th>
<th>Primary outcome</th>
<th>Dose of magnesium sulfate used</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAM trial, Rousse et al 2008(^5)</td>
<td>2444</td>
<td>24–31</td>
<td>Placebo</td>
<td>Neuroprotection</td>
<td>Loading dose 6 gm, maintenance dose 2 gm/hours for 12 hours</td>
<td>Significant decrease in the risk moderate or severe CP</td>
</tr>
<tr>
<td>MagNET trial, Mitten-dorf et al 2002(^14)</td>
<td>59 (NP arm); 101 (tocolytic arm)</td>
<td>25–33</td>
<td>Placebo or any other tocolytic</td>
<td>Neuroprotection</td>
<td>NP arm: loading dose 4 gm tocolytic arm: loading dose 4 gm and maintenance 2–3 gm/hours</td>
<td>Worse perinatal outcome in the magnesium group, in a dose dependant manner</td>
</tr>
<tr>
<td>ACTO MgSO(_4), Crowther et al 2003(^16)</td>
<td>1255</td>
<td>&lt;30</td>
<td>Placebo</td>
<td>Neuroprotection</td>
<td>Loading dose 4 gm; maintenance 1 gm/hours</td>
<td>Total mortality, CP and the combined outcome of both lower in MgSO(_4) group (though not statistically significant)</td>
</tr>
<tr>
<td>MAGPIE follow up trial, magpie trial follow up study collaborative group, 2007(^19)</td>
<td>1593 foetuses</td>
<td>&lt;37</td>
<td>Placebo</td>
<td>Long–term effects of in utero exposure to MgSO(_4) given for maternal neuroprotection</td>
<td>Loading dose 4gm, maintenance 1gm/hour IV or Loading dose 4 gm IV+ 10 gm maintenance dose 5 gm every 4 hours</td>
<td>17 surviving children had CP, 10 were exposed to placebo and 2 arose during embryogenesis Trend showing lower risk in MgSO(_4) group</td>
</tr>
<tr>
<td>PreMAG Trial, Marret et al 2007(^17)</td>
<td>688 foetuses</td>
<td>&lt;33</td>
<td>Placebo</td>
<td>Neuroprotection</td>
<td>Loading dose 4 gm</td>
<td>Non significant ↓ in risk of white matter injury</td>
</tr>
<tr>
<td>PreMAG follow up trial, Marret et al 2008(^18)</td>
<td>472 children (follow up at 18 months of age)</td>
<td>&lt;33 weeks</td>
<td>Placebo</td>
<td>Neuroprotection</td>
<td>Loading dose 4 gm</td>
<td>Significant beneficial effect of MgSO(_4); significant ↓ in combined outcome of death and gross motor or cognitive dysfunction</td>
</tr>
</tbody>
</table>

* Adapted from Goojha C\(^4\); CP: cerebral palsy; NP: neuroprotective
tion and treatment of eclamptic convulsions and as a tocolytic agent for prevention of preterm birth. In the recent years, there has been an emerging consensus, based on convincing evidence from the literature, regarding its use as a neuroprotective agent in preventing CP, when given antenatally to women at risk for imminent preterm birth. Evidence is available from observational studies, randomised controlled trials (RCTs) as well as systematic reviews.

Initial observational studies: Kuban et al demonstrated that prenatal exposure to magnesium sulphate in babies with birth weight <1500 gm, reduced the risk of intraventricular haemorrhage from 18.9% to 4.4%. In another case control study, Nelson and Grether followed up 15,000 infants till at least 3 years of age. Only 7% of very low birth weight infants, who were exposed to antenatal magnesium sulphate, developed CP vis-a-vis 36% of the matched but unexposed group (OR 0.14, 95% CI 0.05-0.51).

Similar findings were noted by other studies also. All these studies had used antenatal magnesium sulphate for seizure prophylaxis in the mothers and its neuroprotective effect on the foetuses, was an unexpected finding.

Randomised controlled trials: There are, at least, five major RCTs reported in the literature, which have evaluated the use of magnesium sulphate for preterm neuroprophylaxis. Two were from the United States, MagNET (Magnesium and Neurological Endpoints Trial, Mittendorf et al); BEAM Trial (Beneficial Effects of Antenatal magnesium sulphate, Rouse et al); other from Australia and New Zealand, ACTOMgSO4 Trial (Australasian Collaborative Trial of magnesium sulfate, Crowther et al); PREMAG and the follow up trials (Marret et al) from France and the MAGPIE follow up trial (magnesium sulphate for Prevention of Eclampsia), conducted in 19 countries across five continents. The first four trials recruited women in preterm labour and Magnesium was used primarily for neuroprophylaxis, although MagNET trial had a tocolytic arm also. The 5th one, the MAGPIE trial, however, included women at all gestational ages, with pre-eclampsia or eclampsia, who received antenatal magnesium sulphate for seizure prophylaxis.

Details of the five RCTs are shown in Table 1. Although the results from each trial showed a positive correlation between magnesium sulphate and neuroprotection, the results of only one trial showed statistically significant results in favour of magnesium sulphate.

Meta-analyses: So far, 3 meta-analyses, have evaluated the use of magnesium sulphate for preterm neuroprophylaxis. All of them have included the five trials mentioned above and have drawn similar conclusions. (Table 2) The main conclusions of the Cochrane Systematic Review, include:

- Overall, antenatal magnesium sulphate had no significant effect on combined outcome of “death or CP” (RR 0.94; 95% CI 0.78–1.12). However, on doing subgroup analysis of the ‘neuroprotective’ trials, after excluding the MAGPIE trial and the tocolytic arm of the MagNET trial, there was a significant reduction in the combined outcome in the Magnesium group (RR 0.85; 95% CI 0.74–0.98).

- There was a significant reduction in the risk of CP, especially that of moderate and severe CP among preterm neonates, who had in utero exposure to magnesium sulphate. A significant reduction in the risk of gross motor dysfunction was also noted in the same group.

- There was no significant effect on the stillbirth or paediatric mortality rates.
MECHANISM OF ACTION

It is hypothesised that magnesium sulphate provides neuroprotection by preventing hypoxia and inflammation mediated injury to the neurons. The preterm foetal brain has immature pre-oligodendrocytes which are precursors of oligodendrocytes, constituents of major glial population in the white matter. They are highly susceptible to damage, resulting in periventricular white matter injury, a lesion most commonly implicated in the aetiology of CP.24 The oxidative stress and excitotoxicity, resulting from excessive stimulation of ionotropic N-methyl-D-aspartate (NMDA) receptors on the pre-oligodendrocytes, are the most important causes of white matter injury in foetal brain.25 Magnesium sulphate, being an NMDA receptor antagonist, prevents this excitotoxicity.

Besides, magnesium sulphate is also known to possess anti-inflammatory properties. It is well known that maternal infection is a major risk factor for preterm labour. Animal models have shown that preterm birth due to inflammation and cytokine production, leads to neuronal insult.26 Magnesium sulphate has been shown to attenuate cytokine production in cultured endothelial cells.27 Burd et al have demonstrated that magnesium sulphate prevents lipopolysaccharide (the gram negative bacterial endotoxin) mediated brain injury in foetal mice.28

Another mechanism by which magnesium is supposed to act, is by inhibiting the action of matrix metalloproteinase (MMP).9 This enzyme is responsible for breakdown of the blood brain barrier, secondary to sepsis and allowing the release of proinflammatory cytokines into the brain and causing damage.29

GUIDELINES FOR CLINICAL USE OF MAGNESIUM SULPHATE AS A NEUROPROTECTIVE AGENT

**Indications:** Women with preterm premature rupture of membranes, preterm labour with intact membranes and indicated preterm delivery are ideal candidates for its use. One trial,15 while assessing the neuroprotective function of magnesium, had recruited predominantly women with preterm...
premature rupture of membranes (PPROM), whereas others had enrolled women in preterm labour with intact membranes.16,17

Contraindications: The use of magnesium sulphate is contraindicated in women with myasthenia gravis, myocardial compromise, cardiac conduction defects, severe pulmonary disorders and renal failure. Magnesium should not be given for neuroprotection in case of foetuses with lethal anomalies.30,31

Gestational age: The use of magnesium sulphate for neuroprotection should be restricted to women who are at least 24 weeks pregnant, but less than 32 weeks.30 According to the Australian and Canadian guidelines, gestational age should be <30 and ≤31+6 weeks respectively.32,33 It has been suggested that the lower limit of gestational age for its use could be modified, based on the institutional policies of neonatal resuscitation.31

Timing of administration: Magnesium Sulphate is administered when preterm delivery is likely to occur in the next 24 hours.30,32 In case of an induced preterm labour, it should be administered at least 4 hours prior to anticipated birth.32 The Society of Obstetricians and Gynaecologists of Canada recommends, commencing magnesium sulphate once the patient enters active labour (cervical dilatation ≥4 cm).33 In case, an urgent preterm delivery is warranted due to impending foetal or maternal compromise, it should not be withheld in order to administer magnesium sulphate.32

Dosage: The dosing regimens used in various trials is shown in Table 1. The preferred dosing regimen is: loading dose of 4 gm given intravenous, over 20–30 minutes followed by maintenance intravenous infusion at the rate of 1 gm/hour for 24 hours or till delivery whichever commences first.30–33 One might be led to question the efficacy of this low dose protocol, which is in accordance with the doses used in trials which failed to demonstrate the beneficial effect of magnesium sulphate, in a statistically significant manner.16,17 This could be explained on the basis of their small sample size, since statistical significance was attained when the results were put together in a meta-analysis.34 It has further been suggested that the optimum dose (least dose which is effective) for preterm neuroprophylaxis maybe in the range of 4 gm–10.5 gm.34

A recent meta-analysis of four RCTs (includ-

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>Magnesium n/N (%)</th>
<th>Control n/N (%)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apgar &lt; 7 at 5 mins</td>
<td>3</td>
<td>351/2,169 (16.2)</td>
<td>351/2,218 (15.8)</td>
<td>1.03 (0.90–1.18)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ongoing respiratory arrest</td>
<td>3</td>
<td>980/2,169 (45.2)</td>
<td>1,069/2,218 (48.2)</td>
<td>0.94 (0.89–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Intraventricular haemorrhage</td>
<td>4</td>
<td>467/2,254 (20.7)</td>
<td>493/2,298 (21.5)</td>
<td>0.96 (0.86–1.08)</td>
<td>0.51</td>
</tr>
<tr>
<td>Periventricular leukomalacia</td>
<td>4</td>
<td>71/2,254 (3.1)</td>
<td>76/2,298 (3.3)</td>
<td>0.93 (0.68–1.28)</td>
<td>0.67</td>
</tr>
<tr>
<td>Neonatal convulsions</td>
<td>3</td>
<td>55/2,169 (2.5)</td>
<td>70/2,218 (3.2)</td>
<td>0.80 (0.56–1.13)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* Adapted from Doyle et al35; RR: relative risk; CI: Confidence intervals
ing the high dose protocol BEAM trial), however, showed that there were no substantial adverse effects on the newborns with the dosages used (Table 3). This could be explained by the fact that total dose exposure to magnesium sulphate in all these trials was low. The median total dose exposure was: 4 gm (PREMAG trial); 10.5 gm (ACTOMgSO₄ trial) and 31.5 gm (BEAM trial). Cumulative doses of magnesium sulphate ≥50 gm has been shown to be associated with increased paediatric mortality.

Magnesium sulphate, when used for seizure prophylaxis in women with severe pre-eclampsia, has a narrow therapeutic window. The same might be true for its neuroprotective properties as well. Therefore, one needs to exercise caution when prescribing magnesium sulphate for neuroprotection, in higher doses.

**Retreatment**: Retreatment was allowed in only one of the five major RCTs. If >6 hours had elapsed since the cessation of therapy, and the woman was at risk of having imminent preterm birth again (onset of regular uterine contractions), a loading dose followed by maintenance infusion was repeated. If <6 hours had elapsed, only the maintenance infusion was readministered.

According to the Australian guidelines on use of magnesium sulphate as a neuroprotective agent, a repeat dose may be considered at the discretion of the attending health professional. The Canadian guidelines, on the other hand, do not recommend repeat doses, stating there is insufficient evidence regarding retreatment.

The fear with retreatment is, logically, magnesium toxicity to the foetus. These fears have, however, been dispelled by Rouse et al, who in a subsequent analysis, have compared pregnant women exposed to the highest doses with those exposed to the lowest doses of magnesium sulphate. They found no difference in the rates of perinatal deaths in both the groups (OR 1.01; 95% CI 0.48–2.10). Moreover, the OR of death for neonates with the highest levels (3.4–5.4 meq/L) versus ones with lowest levels (<0.4–1.7 meq/L) of cord blood magnesium was 0.82 (95% CI 0.36–1.84).

A recent retrospective study, analysing 475 neonates between 24–32 weeks of gestation, who had in utero exposure to magnesium sulphate for neuroprotection, has demonstrated conflicting results. The study showed significant increase in the infant mortality rates with increasing levels of serum magnesium, measured within the first 24 hours of life. The infant mortality rate in group with serum magnesium levels <2.5 meq/L was only 5%, in comparison to 16.9% (p<0.05), in the subset of neonates with serum levels >4.5 meq/L.

**Side-effects**: Maternal side-effects can be minor, like flushing, diaphoresis, nausea, vomiting, lethargy, blurred vision, pain and abscess at the injection site. More serious side-effects include tachycardia and hypotension. Severe side-effects are rarely associated with its use and include: death, pulmonary oedema, cardiac and respiratory arrest, and post partum haemorrhage.

**Monitoring of women on magnesium therapy**: Urine output and presence of deep tendon reflexes should be closely monitored in patients on magnesium sulphate therapy. The maintenance infusion should be discontinued if the maternal respiratory rate is <12/minute, patellar reflexes are absent or urine output in last four hours is <100 ml. The dose of maintenance infusion needs to be adjusted in women with serum creatinine >1.0 mg/
There is, however, no role of routine monitoring of serum magnesium levels when it is being used for neuroprophylaxis.32

Use of concomitant tocolysis: Another area of concern, is the biased use of magnesium sulphate as primary tocolytic agent, owing to its neuroprotective properties.

Magnesium sulphate, as a tocolytic agent, has been shown to be no better than placebo for preventing preterm birth within 48 hours.36 Whenever concomitant tocolysis is warranted, use of indomethacin or a calcium channel blocker like nifedipine is advocated.30,31

Indomethacin therapy is initiated with oral loading dose of 50 gm followed by 25 gm, given orally every 6 hours till 48 hours. This drug is contraindicated in gestational age >32 weeks (since it causes premature closure of the ductus arteriosus), platelet dysfunction or bleeding disorders, hepatic or renal insufficiency, gastrointestinal ulcers and in patients with history of anaphylaxis to aspirin.31

Nifedipine, (calcium channel blocker), can be given with an oral loading dose of 30 mg, followed by 10 mg, given orally, every 6 hours for 48–72 hours. Its use is contraindicated in patients with hypotension (BP <90/50 mm Hg), cardiac disease and severe renal impairment.40

There is a theoretical risk of neuromuscular blockade when nifedipine and magnesium sulphate are used concurrently.41 These fears have, however, been unfounded in clinical trials.35 Moreover, the largest trial on efficacy of magnesium sulphate till date, had 30% of enrolled subjects exposed to both these drugs together, yet no adverse events were reported.20

Data regarding the optimum time for initiating concomitant tocolysis is lacking. It has been proposed that it can be started with the loading dose of magnesium sulphate, during the administration of the maintenance infusion or after the cessation of the same.31

Cost effectiveness of magnesium therapy for neuroprotection: It has been hypothesised that, approximately, 620 new cases of CP would be prevented annually by treating all women at risk of delivering before 34 weeks with antenatal magnesium sulphate.27 The number of such women who need to be treated (NNT) to prevent one case of CP is 52 (95% CI 31–154).27 Based on a cost decision analysis, the total cost of administering magnesium sulphate as a tocolytic is $197.90/patient.43 Thus the increase in cost for preventing one case of CP would be $10,291, (cost/person NNT) 95% CI 6135–30,477.22 Honeycutt et al estimated the average lifetime costs with a person with CP at $921,000.8

Scope of further research: Further RCTs are required to determine the optimum dosage of magnesium sulphate for neuroprophylaxis, optimal gestational age, timing of administration and the need for retreatment.44 Adequately powered trials, performed using the low dose protocol, will shed light on the optimum dosage required for neuroprophylaxis. The efficacy of intervention in multiple gestations needs to be addressed separately.

Long term follow up of foetuses exposed to magnesium in utero is required. Most of the studies have followed up infants till 2–3 years of age, whereas the diagnosis of CP and other neurodisabilities cannot be reliably made till much later. Reassessment of survivors of RCTs at least at school going age will help determine the motor and higher cognitive functions.75

CONCLUSION

Neuroprotection in preterm infants should be
considered a healthcare priority, since the survival rates of this population is improving progressively. The results of systematic reviews of RCTs on cerebral palsy have been consistent with those obtained from studies conducted on animal models, thereby supporting the role of magnesium sulphate for neuroprotection. Further trials are required to address the existing uncertainties before it can be accepted universally as a neuroprotective agent.

Acknowledgement: We thank Miss Catherine Trumun, our dedicated pharmacist for her valuable input and in helping us with the extensive literature search.

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REFERENCES
Case Report

A 22 years old lady was presented with complaints of heavy bleeding per vagina since 5 days, with passage of clots, used 5–6 pads per day with mild pain in lower abdomen.

Two months back patient underwent termination of pregnancy for foetal anomalies (neural tube defect). After expulsion of foetus, check curettage was done. Bleeding stopped after 5 days. She had her periods the following month with moderate flow for 5 days. She had no complaints of giddiness, syncopal attacks.

Patient was married for 4 years, her obstetric history was P1L1A1 (MTP). She had a full-term vaginal delivery 3 years back and delivered a healthy baby with no antenatal or postnatal complications. She used an IUCD after pregnancy which had expelled spontaneously after 1 year. Patient conceived the second time after treatment for secondary infertility with ovulation induction. Early scan was told to be normal and patient was given folic acid supplements. However, scan at 13 weeks showed: occipital meningoencephalocele, lower-lumbar spina bifida and bilateral enlarged polycystic kidneys hence was advised MTP. Pregnancy was terminated outside-local prostaglandin followed by curettage. Patient had regular menstrual cycles in the past with moderate flow and no dysmenorrhea.

She was admitted and treated for fever 1 month back with no significant past illness. On examination she was moderately built and nourished with a BMI of 20.3 kg/m². She appeared pale and her vitals were stable. Cardiovascular and respiratory systems were normal. Abdomen was non-tender and soft on palpation. There was no organomegaly and bowel sounds were heard. Speculum examination showed bleeding through cervix with clots. Vaginal examination revealed an anteverted uterus of normal size with adnexa being free and no cervical motion tenderness.

Her haemoglobin was 9.4 gm%, platelet count was within normal limits. β-HCG was negative. Ultrasonography with Doppler showed uterus of 8.5 cm length, anteverted, ET−8 mm with cystic area in right wall of 12X6 mm with pulsatile blood flow. Right uterine artery was dilated (Figure 1).

On the basis of clinical features and imaging reports, what is your diagnosis?

(Continued on page 170)
INTRODUCTION

Recurrent pregnancy loss (RPL), also referred to as recurrent miscarriage or habitual abortion affects 0.5%–3% of women in the reproductive age group. Where about 15% of all clinically recognised pregnancies result in spontaneous loss, 30–50% of the conceptions abort spontaneously before the end of first trimester. Hyperhomocysteinaemia, which is biologically defined by a fasting value >15 µmol/l, is a significant risk factor for unexplained recurrent pregnancy loss. High levels of homocysteine may be due to an inadequate dietary intake of folate and vitamin B12 and also inherited defects within the methionine-homocysteine pathway such as methylene tetrahydrofolate reductase (MTHFR) C677T gene polymorphism.

RISK FACTORS FOR RECURRENT PREGNANCY LOSS

Parental Hyperhomocysteinaemia, C677T MTHFR Polymorphism and DNA Damage

Govindaiah and colleagues in their case controlled study found that the following
factors increase the risk for RPL:

- Maternal hyperhomocysteinaemia [mean: 11.6+/-5.0 vs. 8.6+/-4.2 µmol/L, odds ratio (OR): 4.48]
- Paternal hyperhomocysteinaemia [mean: 19.6+/-9.5 vs. 14.2+/-7.4 µmol/L, OR: 6.92]
- Paternal age [OR: 1.16]
- Paternal MTHFR 677T allele [OR: 2.30]
- DNA damage

A positive correlation of DNA damage with plasma homocysteine and MTHFR 677T allele was also observed in their study.

High Levels of Homocysteine and Folate Deficiency

A case-control study, by Nelen et al\(^5\) measured and compared homocysteine (fasting and after-load), folate (serum and red cells) and vitamin B12 concentrations in women from 2 groups:

- Women who had at least two consecutive spontaneous early pregnancy losses each
- Healthy controls

It was reported that women with recurrent spontaneous early pregnancy losses as compared to healthy controls had significantly lower serum folate concentrations, but elevated homocysteine, with fasting value greater than 18.3 micromol/L and afterload greater than 61.5 micromol/L.

Vitamin B6 and Folate Deficiency

*Preconception folate and vitamin B6 deficiency leads to spontaneous abortion: A study by Ronnenberg in Chinese women*\(^6\)

Primigravid women, 21–34 years old, were included in the study and categorised into two groups:

- **Study group:** (n=49) women with a clinically recognised pregnancy who experienced a foetal death before 100 days’ gestation.
- **Control group:** (n=409) women who maintained a pregnancy that ended in a live birth.

The researchers when measured plasma homocysteine, folate, and vitamins B6 and B12 concentrations obtained before conception, observed that:

- Mean vitamin B6 concentration was lower in patients than in controls (as shown in figure 1).
- The risk of spontaneous abortion was four-fold higher among women with suboptimal plasma concentrations of both folate and vitamin B6 (folate less than or equal to 8.4 nmol/L and vitamin B6 less than or equal to 49 nmol/L) than in those with higher plasma concentrations of both vitamins.

This study concluded that the risk of clinical spontaneous abortion may increase, especially when both preconception folate and vitamin B6 levels are suboptimal.

Low Levels of Vitamin B12 and Hyperhomocysteinaemia

*Vitamin B12 deficiency may lead to high homocysteine levels causing foetal loss: Study design by Bennett M.*\(^7\)

The researcher analysed the obstetric histories of
14 women patients presenting with 15 episodes of vitamin B12 deficiency, where
- Four episodes showed the presence of infertility (two to eight years)
- Eleven episodes featured recurrent foetal loss.

It was found that in six episodes, periods of recurrent foetal loss were followed by periods of infertility greater than one year. The study suggested that when vitamin B12 deficiency developed, the increase in homocysteine levels caused hypercoagulability which may lead to foetal loss.

**Link between low vitamin B12 levels with high homocysteine levels and recurrent miscarriage: A study in Syrian women**

Serum folate, vitamin B12, methylmalonic acid and plasma homocysteine were determined in two groups of Syrian women:
- Women with unexplained recurrent abortion (n=43)
- Pregnant controls (n=32)

The study reported:
- Significantly decreased vitamin B12 in patients with recurrent abortion as compared to controls (mean concentrations 197 vs. 300 pg/mL, p=0.004) (Figure 2).
- The lowest mean serum vitamin B12 (172 pg/mL) in primary aborters.
- Elevated homocysteine in aborters vs. controls (8.3 vs. 7.1 micromol/L, p=0.093).

**CLINICAL EVIDENCES SHOWING PRESENCE OF HIGH SERUM HOMOCYSTEINE LEVELS IN WOMEN WITH RECURRENT PREGNANCY LOSS**

- Jerzak et al. determined fasting total homocysteine concentration in follicular fluid or serum of women who experienced RPL and found that these women had significantly higher serum homocysteine concentration as compared to normal healthy women.
- A comparative study by Micle et al. compared homocysteine levels in pregnant women patients with risk of abortion (study group) and healthy pregnant women (control group). It was seen that homocysteine concentration was higher in the study group as compared to the control group (Figure 3).
REFERENCES

INTRODUCTION

Menstrual problems are said to be one of the major causes for gynaecological problems, especially among adolescent females. These disorders are often the source of anxiety for female adolescents and their families at large. The common menstrual disorders for female adolescents are dysmenorrhoea, amenorrhoea, abnormal/excessive uterine bleeding, and premenstrual syndrome. In developing countries, a recent review of menstrual disorders revealed high rates of menstrual morbidity in population-based studies. It is the least understood and tackled complaint, questionably under diagnosed and under-treated.

In woman of reproductive age of all menstrual complaints, dysmenorrhoea is by far the most common gynaecological condition regardless of age and nationality and directly influences a woman’s quality-of-life. Further, dysmenorrhoea is the most common gynaecological complaints in young women who present to clinicians and the most frequent cause of gynaecological referrals. Fifty percent of women experience some degree of pain with menstruation, and in 10% this is sufficiently severe to interfere with daily activity.

The term dysmenorrhoea is derived from the Greek word “dys”, meaning difficult/painful/abnormal, meno, meaning month, and “rrhea”, meaning flow. It is defined as painful menstruation or difficult menstrual flow which refers to lower abdominal pain or back muscles, with or without other symptoms such as nausea, vomiting and diarrhoea before, during or after menstruation.

Dysmenorrhoea has been classified into primary and secondary. Primary dysmenorrhoea is described as the chronic, cyclic, pelvic, spasmodic pain associated
with menstruation in the absence of identifiable macroscopic pathology. It is typically known as menstrual cramps or period pain. A true dysmenorrhoea, is of uterine origin and directly due to menstruation, also be described as spasmodic, intrinsic, essential or functional dysmenorrhoea. Primary dysmenorrhoea thought to affect approximately one half of all menstruating women, with 10% of women having symptoms severe enough to interfere with daily responsibilities. Secondary dysmenorrhoea is also called as organic dysmenorrhoea as it is a cyclic menstrual pain associated with underlying macroscopic or anatomic pelvic pathology. The pain of secondary dysmenorrhoea often begins 1–2 weeks prior to menses and persist until a few days after cessation of bleeding. This condition is most often observed in women aged 30–45 years.

The dysmenorrhoea is well known symptom from dawn of the history. Hippocrates (5th century BC) father of medicine hypothesised that stagnation of menstrual blood secondary to cervical obstruction causes painful menstrual periods. Soranus of Ephesus advised local application of a bladder filled with hot oil held over the aching lower abdomen. He was also aware that dysmenorrhoea could affect the older parous patients and described uterine subinvolution as one of its causes. Maimonides believed that retention of menstrual fluid resulted in heaviness in the body, loss of appetite, shivering and pain in the neck. He also believed that dysmenorrhoea does not occur when menstrual flow is regular and adequate in amount. Dysmenorrhoea was first documented in Synopsis of Prescriptions of the Golden Chamber by Zhongjing Zhang of Donghan Dynasty (AD196). According to Traditional Chinese medicine, primary dysmenorrhoea is usually caused by emotional factors, invasion of 6 exogenous pathogenic factors and stagnation of Qi and blood; or by retention of blood in the Paogong due to liver depression and Qi stagnation resulting from emotional upsets; or by cold, dampness attacking the lower Jiao and lodging in the Paogong due to walking in water during menstruation or sitting on damp ground; or by constitutional deficiency of Qi and blood, or consumption of Qi and blood due to serious diseases and prolonged illness. Avicenna (980–1037 AD) described various causes of dysmenorrhoea such as cervical stenosis, dis temperament, genital cancer, inflammation of the uterus, uterine ulcer etc. Further, he also mentioned just before menses backache may occur because of involvement of uterus. Edward (1863) of Germany outlined his own ideas of menstruation. He believed that during the cycle increasing pressure was set up in the growing Graffian follicle. This caused a reflex irritation which sent nerve impulses via the ovarian nerves to the spinal cord, and this in turn caused pelvic congestion, which led to painful menstruation. Iscovesco (1912) practiced as a gynaecologist in Paris and used ovarian extract, called ‘gynocrinol’, for the treatment of dysmenorrhoea and amenorrhoea. Kurzok and Lieb (1930) were first to discover that the extracts of seminal vesicles or human semen (prostaglandins) caused contractions of uterine smooth muscles and vasodilatation with lowering the blood pressure. They also reported the effects of

<table>
<thead>
<tr>
<th>Primary dysmenorrhoea</th>
<th>Secondary dysmenorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset shortly after menarche</td>
<td>Onset can occur at any time after menarche (typically after 25 years of age)</td>
</tr>
<tr>
<td>Lower pelvic or abdominal pain is usually associated with onset of menstrual flow and lasts 8–72 hours</td>
<td>Women may complain of change in time of pain onset during menstrual cycle or in intensity of pain</td>
</tr>
<tr>
<td>Headache, diarrhoea, back and thigh pain, nausea, and vomiting may be present</td>
<td>Other gynaecological symptoms (such as abnormal bleeding, dyspareunia infertility, dysuria), may be present</td>
</tr>
<tr>
<td>No abnormal findings on examination</td>
<td>Pelvic abnormality on physical examination</td>
</tr>
</tbody>
</table>
fresh human seminal fluid on human uterus. John E. Markee (1932) observed the vascular changes leading up to menstruation and found that the coiling of the endometrial arterioles increased markedly. This was followed by a period of slow circulation, then vasoconstriction, 4–24 hours before bleeding. Pickles (1957) was first to demonstrate prostaglandin activity in human menstrual fluid. Inhibitors of PG synthesis have proved most useful in dysmenorrhea and menorrhagia.

Epidemiology

Prevalence and Incidence: The incidence of dysmenorrhoea is affected by social status, occupation and age. School girls and college students, factory workers and women members of armed forces each provide different statistics. The prevalence of dysmenorrhoea worldwide is, with rates ranging from 15.8–89.5%, with higher prevalence rates reported in adolescent populations. In spite of advances in the treatment of primary dysmenorrhoea, a recent study of 1,546 menstruating Canadian women found that 60% were having the disorder. Severe or moderate pain was present 60% of the dysmenorrheic women. Limitation of activities was reported in 51% and 17% reported absenteeism. Thus, there appears to be underuse of currently available OTC and prescription medications, or there is insufficient dissemination of information about PD to targeted young populations.

The true incidence and prevalence of dysmenorrhoea are not clearly established in India. Nag et al (1982) reported the incidence of dysmenorrhoea in 33.5% among adolescent girls in India. In recent times, George and Bhaduri, concluded that dysmenorrhoea is a common problem in India with prevalence of 87.87%. One more study conducted in Gwalior showed the prevalence of dysmenorrhoea in adolescent girls was 79.67% and 39.96%, suffered severe dysmenorrhea regularly. Another study carried in Kadapa district of Andhra Pradesh showed a high prevalence of dysmenorrhoea, 65.02% among adolescent girls. However, they found that 68.4% and 61.2% were from the urban

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**Classification and aetiology of dysmenorrhoea**

**Primary**
- (Increased level of prostaglandin is cause of pain)
  - Risk factors
    - Age of menarche
    - Duration of menstrual flow more than 5 days
    - Cigarette smoking
    - Obesity
    - Stress
    - Family history
  - Uterine causes
    - Adenomyosis
    - Pelvic inflammatory disease
    - Cervical stenosis and polyp
    - Leiomyoma (intracavitary or intramural)
    - IUCD
    - Malformation of uterus (imperforate hymen, transverse vaginal septum, bicornuate uterus)
    - Asherman’s syndrome
  - Extrauterine causes
    - Endometriosis
    - Inflammation and scarring (adhesions)
    - Functional ovarian cysts
    - Benign or malignant tumours of ovary, bowel or bladder, or other site
    - Inflammatory bowel disease
    - Pelvic congestion
    - Broad ligament varicocele

**Secondary**
- (Increased level of prostaglandins and anatomic mechanism is cause of pain)
and rural areas respectively. Sickness absenteeism was seen among 47.9% dysmenorrheic girls and quality of life was significantly reduced among them. Almost 73.1% of rural girls rely on self-help technique to manage the dysmenorrhoea as compared to urban girls (55.2%).

In a study, dysmenorrhoea (pain during menstruation) was reported by 72% of the study subjects of which about 28.5% were having moderate to severe dysmenorrhoea and 48.8% of those suffering from dysmenorrhoea had reported to be absent from school merely due to the pain. A study done among Malaysian school girls reported 67.7% patients had dysmenorrhoea. In the study done in the US by Banikarim et al., dysmenorrhoea was
the leading cause of short-term school absenteeism. This is the single greatest cause of absence from school and work among women of menstruating age. In adolescents, absenteeism from school work, due to dysmenorrhea ranged from 14% to 51% of girls and decreased participation in school-related functions ranged from 29% to 50%. In those with severe dysmenorrhea, 50% missed school. Such absences diminish opportunities for successful educational, psychosocial, and cognitive development during the critical period of adolescent growth.

Girls on an average miss out 25% more classes in school compared to boys due to pain during menses. About 1 in 10 women are unable to perform their normal routine work for 1–3 days each menstrual cycle due to severe uterine cramping. Menstrual problems are often the source of anxiety for female adolescents and their families at large.

**Age:** Adolescent girls tend to have a higher prevalence of primary dysmenorrhea than older women. More than half of the adolescent girls throughout the world suffer from dysmenorrhea and needs attention. The prevalence of primary dysmenorrhea decreases with increasing age: prevalence is highest in the 20–24 year old age group and decreases progressively thereafter with most of the severe episodes occurring before 25 years of age. The prevalence rate is reduced with increasing age, the pain has been found to decrease with advancing age.

**Marital status:** Primary dysmenorrhea also occurs more frequently in unmarried women than in married women (61% vs. 51%), decreases with age, and does not appear to be related to the type of occupation or physical condition of the woman. It is not necessarily gets relieved by pregnancy and vaginal delivery.

**Burden of dysmenorrhea:** Because young women constitute a significant percentage of the adult work force in the United States, about 600 million working hours, or 2 billion dollars are lost annually because of incapacitating dysmenorrhea, if adequate relief is not provided from 1–2 days absenteeism from a month, as a result of primary dysmenorrhea. It has been estimated to cause the loss of 140,000,000 work hour’s annually. Women who continue to work or to attend classes have been shown to have lower work output or scores during their dysmenorrhea. In consequence, dysmenorrhea is associated with emotional, social and economic burdens.

**Familial:** A familial tendency towards severe symptoms has been noted in several studies. It is found that the pain history of mothers and daughters found a strong correlation between pain ratings. This is sometimes attributed to a ‘modeling effect’ where the daughter learns from her mother what to expect from menses.

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**Figure 3. Flow chart of management of a case of dysmenorrhea after failed first line therapy**

**First-line medical treatment:**
- Oestrogen/progestin or progestin alone contraceptive

**Not successful**
- GnRH agonists + add back therapy where appropriate, danazol; multidisciplinary, including psychological and/or acupuncture or TENS

**Successful**
- Operative diagnosis and treatment laparoscopy
- Failure - consider alternative diagnosis and further work up
- Adjunctive medical therapy and maintenance
- Recurrence - consider definitive surgical treatment therapy

**TENS:** Transcutaneous electrical nerve stimulation

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Risk factors: Factors that have been consistently shown to be associated with an increased risk for severe dysmenorrhea are early menarche, heavy menstrual flow, obesity, long menstrual periods, smoking, stress, family history of severe dysmenorrhea in mother or sister. Exercise does not appear to have any significant effect on the incidence of dysmenorrhea.

Aetiology: The aetiology of primary dysmenorrhea has been the source of considerable debate. Until recently, many medical and gynaecological texts described the source of dysmenorrhea to be emotional or psychological problems like emotional instability, anxiety, a faulty outlook on sex and menstruation and imitation of the mother’s feelings about menstruation.

Faulty outlook: Some girls experience dysmenorrhea mainly because of their education and outlook on sex is faulty. The expectation of pain is fostered by over anxious parents and by curtailment of normal activities during menstruation. Women are less efficient physically and more unstable emotionally, during and just before menstruation; these factors alone lower the pain threshold and lead to exaggeration of minor discomfort. Dysmenorrhea may even be an excuse to avoid doing something, which is disliked.

Psychological factors: Psychological factors were thought to play a primary role before the pathophysiology of dysmenorrhea was known. The pain was often explained by the young women “rejection of the female role.” Emotional and behaviour problems may exacerbate menstrual cycle problems and dysmenorrhea. These factors can certainly influence the reactive component of pain and therefore the perception of apparent increased intensity of pain. Anticipation of severe dysmenorrhea each month can itself be expected to engender quite a bit of stress. It is more common in working women and in women who scored higher on the Hassle scale, which is a measure of the stresses or difficulties experienced. Such a stressful event as dysmenorrhea has been demonstrated to reduce the immune response of the woman on day 26 and days 1 and 2 of the cycle. Although psychological factors have not been demonstrated convincingly to be the cause of primary dysmenorrhea, their contribution should be considered in patients who have not responded to medical therapy and in the absence of any visible pelvic pathology to account for the pain.

General health: The inherent pain threshold varies from one individual to another. It is lowered by ill health of any kind, so general debilitating diseases may be associated with dysmenorrhea, and even an acute illness can cause periods to be painful temporarily.

Environmental factors: Circumstances which lead to nervous tension may make dysmenorrhea worse even if they do not cause it; these include unhappiness at home or at work, unsatisfied sex urge, fear or loss of employment and anxiety over examinations. Toxic influences can manipulate internal homeostatic balance and alter the gynecological health of women. Environmental exposure to herbicides, insecticides, and by-products of industrial wastes such as polychlorinated biphenyls, dioxins, bisphenol A, lindane, and atrazine promote menstrual disorders. These toxins act as oestrogen receptor agonists therefore, blocking the proper influence of oestrogen on the menstrual cycle. Dysmenorrhea has been linked to toxic mercury conventional sources such as contaminated food sources, the work environment or dental amalgam fillings. The hazard of mercury exposure is exempli-
fied in a study of Chinese women who subsequently developed dysmenorrhea and menstrual disorders from their work environment. The risk of dysmenorrhea was nearly twice as high in women smoking 10–30 cigarettes per day and this risk increased as the duration of smoking was increased. Research on tobacco smoking suggests its contribution to uterine arterial vasoconstriction that may lead to dysmenorrhea. Inhalation of second hand smoke was found to increase the occurrence of pelvic pain in nonsmoking, newly wed females with no history of dysmenorrhea. The incidence of dysmenorrhea increased by 13.3% when a household member smoked up to 10 cigarettes a day in the home.

Theories of Causation of Abnormal Uterine Actions

Cervical obstruction: The classic belief that dysmenorrhea was secondary to mechanical cervical obstruction led to clinical trials of cervical dilatation. Severe uterine flexion was also thought to contribute to trapped menstrual blood and obstructed menses. It is no longer acceptable scientifically.

Hormonal imbalance: Hormones are postulated key influencers for triggering menstrual pain. Dysmenorrheic have higher levels of prostaglandins, leukotrienes, vasopressin hormone and platelet-activating factor in menstrual fluid. Collectively, these key elements facilitate pelvic pain associated with arterial vasoconstriction, menorrhagia, blood clot formation, and increased uterine contractility. Spasmodic dysmenorrhea has some connection with the hormone stimulus to the uterus. If the uterus has not been exposed to progesterone, as in the case of all anovular bleeding, pain is never experienced. Indeed, it occurs only in ovular cycles and it is suggested, but not proved, that the occurrence of anovular menstruation explains the absence of dysmenorrhea during few years following the menarche and the occasional painless period even at a later age.

- **Vasopressin**: Involvement of vasopressin in the pathogenesis of primary dysmenorrhea is still controversial. Vasopressin is a powerful muscle-contracting hormone and is shown to contract the uterus 5 times greater in dysmenorrheics. Increased levels of circulating vasopressin during menstruation reported in women with primary dysmenorrhea can produce dysrhythmic uterine contractions that reduce uterine blood flow and cause uterine hypoxia. In limited studies, vasopressin antagonists were able to neutralise the effect of endogenous vasopressin and relieve dysmenorrhea. Other investigators could not confirm elevated plasma vasopressin in women with primary dysmenorrhea and found that the vasopressin antagonist atosiban had no effect on menstrual pain, intrauterine pressure, or uterine artery pulsatility index in dysmenorrheic women.

- **Prostaglandin**: Current evidence suggests that primary dysmenorrhea, which occurs only during ovulatory cycles, is largely due to excess endometrial prostaglandins production, which is released during menses, giving rise to increased abnormal activity. Hence, the most favoured view is that it is associated with an excess of prostaglandins. The significance of prostaglandins in dysmenorrhea was first suspected by Pickles and associates and since then several lines of evidence have supported their role.

- **Progesterone**: Is the principle trigger of the cascade of events leading to menstrual cramp. When progesterone levels fall at the end of the secretory phase, pain ensues as uterine spiral arteries of the endometrium constrict to create ischaemia and necrosis. The release of prostaglandin $F_2\alpha$ from disintegrating endome-
trial cells stimulates free nerve endings, which consequently produce pain. Prostaglandin $F_2\alpha$ also increases platelet aggregation which causes blood clots to accompany dysmenorrhoea. The prostaglandin hypothesis also explains the extra genital manifestations of primary dysmenorrhoea. The intravenous injection of prostaglandin can produce diarrhoea, vomiting, headache and syncope, often seen in conjunction with severe primary dysmenorrhoea. Further compelling evidence to support the prostaglandin theory is the efficacy of drugs that inhibit prostaglandin synthesis and effectively decreases pain in patients with primary dysmenorrhoea. The local action of prostaglandin is threefold. Firstly, they act directly on the uterine musculature to increase basal intrauterine pressure, as well as the intensity and frequency of myometrial contractions. Secondly, they cause constriction of uterine arteries with subsequent tissue ischaemia and pain. Finally, increases the sensitivity of peripheral pain.

Leukotrienes: The cardinal signs of inflammation are exacerbated during menses because of excessive amounts of leukotrienes. Leukotriene suppression is a targeted method to control pain in the estimated 10–30% of females who do not respond to anti-prostaglandin drugs such as non-steroidal anti-inflammatories.

Genetic factors: Genetics is related to the development of primary dysmenorrhoea. New exploration of the human genome, at the 22nd chromosome, purports a genetic link between polymorphisms of enzyme producing proteins cytochrome (P450 2D6) and glutathione S-transferase mu with dysmenorrhoea. Cytochrome (P450 2D6) is involved in the degradation of toxins and synthesis of cholesterol, steroids and other lipids. Glutathione S-transferase mu is a component of a biological pathway that forms antioxidants. Variant genotypes of either are jointly associated with an increased risk of recurrent or severe dysmenorrhoea and carcinogenesis unrelated to the reproductive system.

Cold environmental temperature may create conditions for experiencing primary dysmenorrhoea. It is hypothesised that cold temperature promotes vasoconstriction of uterine arteries significantly enough to produce dysmenorrhoea. A study reported dysmenorrhoea (71%) were related to cold exposure and physical workload at another poultry and canning factory.

Muscular incoordination: Spasmodic dysmenorrhoea could be due to the incoordinate muscle action of the uterus as a whole. This could be explained by an imbalance in autonomic nervous control of muscle, one in which an overactive sympathetic system leads to hypertonus of the circular fibers of isthmus and internal os.

Neuronal hypothesis: The perception of pain requires transmission of impulses from the uterus to the brain. Dysmenorrhoea has long been treated by surgical disruption of these pathways that may alleviate the pain with procedures such as presacral neurectomy and uterosacral ligament transaction.

Pathophysiology: Prostaglandin synthesis is initiated by lysosomal enzymes that are released in the late luteal phase in the menstrual cycle. These enzymes are stimulated and released by the action of gonadal steroids directly on the endometrium. Phospholipids are then released from the cell
membranes and provide the precursor fatty acids that are necessary for the synthesis of prostaglandin. The first step in the conversion of arachidonic acid into PG is the formation of PGG₂, a cyclic endoperoxide. The formation of PGE₂ and PGF₂ alpha occurs rapidly from PGG₂. Advances in the last 3 decades and current understanding suggest that in primary dysmenorrhoea there is abnormal and increased prostanoid and possibly eicosanoid secretion, which in turn induces abnormal uterine contractions. The contractions reduce uterine blood flow, leading to uterine hypoxia. Thus increased vasoactive prostanoid secretion is responsible for the aetiology of primary dysmenorrhoea is supported by:

♦ The striking similarity between the clinical symptoms of primary dysmenorrhoea and the uterine contractions and adverse effects observed in prostaglandin-induced abortion and labour,

♦ Substantial evidence demonstrating and correlating the amount of menstrual prostanoids in women with primary dysmenorrhoea compared with eumenorrheic women, and

♦ Many clinical trials demonstrating the efficacy of cyclooxygenase (COX) inhibitors in relieving the pain of primary dysmenorrhoea through prostaglandin suppression and quantitative decrease of menstrual fluid prostaglandins.

Prostanoids: In primary dysmenorrhoea, there is increased abnormal uterine contractility, similar to uterine contractility induced with prostaglandins or their analogues for labour or abortion. Pickles and his colleagues postulated that “menstrual stimulant” or prostaglandins were elevated in menstrual extracts of women with primary dysmenorrhoea compared with eumenorrheic women. With availability of radioimmunoassay and specific antiserum, several laboratories, were able to measure small quantities of prostanoids in endometrium and menstrual fluid with greater precision. In most but not all women with primary dysmenorrhoea, there is increased endometrial secretion of menstrual prostaglandin F₂ during the menstrual phase. The release of prostaglandins into the menstrual fluid is a continuous discontinuous process that is the amount of menstrual fluid and prostaglandins varies throughout any window of time. The intensity of the menstrual cramps and associated symptoms of dysmenorrhoea are directly proportional to the amount of PGF₂ released. When a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen is taken during menstruation, the menstrual fluid prostaglandins are significantly inhibited to levels similar to or lower than those found in eumenorrheic women and clinical relief is obtained. Similarly, when the patient is on a combined oral contraceptive her menstrual fluid prostaglandins are significantly suppressed, with an accompanying reduction in menstrual fluid volume/bleeding and concomitant relief of pain. Despite advances with prostaglandins in the aetiology of primary dysmenorrhoea, there are patients with normal laparoscopic finding and severe dysmenorrhoea who do not have elevated menstrual PGF₂ to account for the severe cramping. The prevalence of such patients is currently not known.

The role of prostanoids such as thromboxane A₂, prostacyclin, and leukotrienes in the pathogenesis of primary dysmenorrhoea is neither fully understood nor adequately explored. Prostacyclin, a potent vasodilator and uterine relaxant, appears to be reduced in primary dysmenorrhoea. This heightens the uterine activity and vasoconstriction because the uteronic and vasoconstrictive effects of the other prostaglandins are less impeded. Increased leukotrienes produced by the 5-lipoxygenase enzyme pathway rather than the COX pathway may account for some forms of primary dysmenorrhoea that are not responsive to NSAIDs. Human endometrium and myometrium can synthe-
size leukotrienes, thus confirming the functional activity of the 5-lipoxygenase pathway and that leukotrienes are involved in myometrial contractions.

In women with primary dysmenorrhoea, there are significantly higher concentrations of menstrual leukotrienes, especially leukotriene C4 and leukotriene D4, than in women without dysmenorrhoea. Because specific binding sites for leukotriene C4 are demonstrable in myometrial cells, it is likely that leukotrienes contribute to the uterine hypercontractility seen in primary dysmenorrhoea. Prostaglandins and prostanoids are biosynthesised from arachidonic acid through the COX pathway after production of arachidonic acid from hydrolysis of phospholipids by phospholipase. When pregnancy does not occur, progesterone levels decline during the late luteal phase. This causes labilisation of lysosomes and release of their phospholipase enzyme, which then hydrolyses the cell membrane phospholipids to generate arachidonic acid as well as eicosatetraenoic acid. These compounds then serve as the precursors for the COX and lipoxygenase pathways.

**Uterine contractions:** In normal eumenorrheic women, the uterus has well defined contraction patterns that are influenced by sex steroids, prostaglandins, and other uterotonic substances throughout the menstrual cycle. Of particular interest and relevance to the pathogenesis of primary dysmenorrhoea is the uterine contraction pattern during menstruation when the symptoms of dysmenorrhoea occur. During menstruation in normal women, the uterine basal tone is minimal (less than 10 mmHg), there are 3–4 contractions during each 10 minute interval with active pressures at the peak of a contraction reaching up to 120 mmHg (comparable to the intrauterine pressure during the second stage of labour with pushing), and the contractions are synchronous and rhythmical. In patients with primary dysmenorrhoea, four contraction abnormalities alone or in combination have been reported. They include elevated basal tone (more than 10 mmHg), which is frequently seen, elevated active pressures (more than 120 mmHg, often more than 150–180 mmHg), increased number of contractions per 10 minutes (more than 4 or 5), and non-rhythmical or incoordinate uterine contractions. These abnormalities lead to poor uterine reperfusion and oxygenation, thus giving rise to pain. If more than one contraction abnormality is present, they synergise with each other. So that the pain threshold is exceeded with much smaller changes in each parameter than if only one anomaly were present.

**Uterine blood flow:** Studies to determine uterine blood flow in women have been difficult because of the highly invasive methods and technically challenging requirements involving hydrogen clearance, nitrous oxide, electromagnetic flow meters, and the microsphere methods. In eumenorrheic women the uterine contractions do not affect uterine blood flow. By contrast, the strong and abnormal uterine contractions in dysmenorrheic women reduce uterine blood flow and cause myometrial ischaemia, resulting in pain. Such changes can be produced with pharmacologically induced uterine contractions which, if excessive, will reduce blood flow and produce cramp like pains. Administration of an uterotonic agent, such as a calcium channel blocker or NSAID, abrogates the hypercontractility and restores blood flow to normal. These earlier studies are now supported by Doppler flow studies. The pulsatility index and resistance index of both uterine arteries and the arcuate artery were significantly higher on the first day of menstruation in women with primary dysmenorrhoea, suggesting increased blood flow impedance and indicating uterine vasoconstriction as a cause of the pain.
Impact of dysmenorrhoea on sleep: A study showed that the sleep may be affected not only by physical pain in women with dysmenorrhoea but also directly by the increase in PG during menstruation, PGD$_2$ induces sleep, and PGE$_2$ induces wakefulness in rats. Women with dysmenorrhoea had more disturbed and poorer sleep quality than asymptomatic women when compared with other times during the menstrual cycle. Interestingly, it is found that signs of homeostatic and hormonal imbalance in women with primary dysmenorrhoea even when they were not experiencing menstrual pain, their nocturnal body temperature were higher and REM sleep was shorter than those of asymptomatic women in the mid-follicular and mid luteal phases.39

Aetiopathogenesis of secondary dysmenorrhoea: Secondary dysmenorrhoea is caused by pathological conditions in the pelvis and causes cyclic or chronic pelvic pain.29 The secondary dysmenorrhoea is also associated with other gynecologic symptoms such as dysuria, dyspareunia, abnormal bleeding or infertility. Prostaglandins are also implicated in secondary dysmenorrhoea, nevertheless, anatomic mechanisms can also be identified, depending on the type of accompanying pelvic diseases.40

In the uterus, cervical stenosis, congenital malformation, adenomyosis, leiomyomas, polyps, and IUCD can lead to secondary dysmenorrhoea.12

Cervical stenosis: It is narrowing of the cervical which can be congenital or acquired, caused by infection or trauma from surgical procedures such as cervical conisation or cryotherapy. Cervical stenosis causes increased pressure in the uterus resulting in increased pain and cramping as well as retrograde flow that may result in endometriosis. Women usually complain of light to no menstrual flow associated with severe cramping. Studies have shown that retrograde flow is increased when the cervical diameter is less than 4.75 mm the average cervical diameter in a nulliparous patient is 5 mm. The cotton swab diameter is approximately 4.75 mm therefore, the inability to pass a cotton swab into the cervix is consistent with the diagnosis of cervical stenosis and increases the risk of retrograde flow and endometriosis.29

Endometriosis: Secondary dysmenorrhoea arising after the age of 30 years always suggests the possibility of endometriosis.12 Endometriosis is the most common cause of secondary dysmenorrhoea and responsible for 70–80% of causes of chronic pelvic pain.29 The uterus frequently contracts with greater amplitude and displays greater basal pressure tone in comparison to women without endometriosis. Bulletti et al. have shown that mechanical displacement by irregular uterine contractions occurs in 73% of women with endometriosis.27 The retrograde menstrual flow, coelomic epithelial metaplasia, lymphatic and vascular metastasis, immunologic defects, and genetic causes are theories suggested for the aetiology of endometriosis.29

Adenomyosis is the endometrial tissue implants in the myometrium leading to severe cramping and heavy menstrual flow.29

Pelvic congestion: The Allen-Master syndrome and pelvic congestion involves the peritoneum and causes secondary dysmenorrhoea.12 Pelvic congestion syndrome is also caused by dilatation of the veins in the broad ligament (varicocele) and ovarian veins leading to pain29 or the ovary may be the seat of an endometrioma or other tumours.12 This condition is diagnosed by visualising engorged vessels in the broad ligament and pelvic side wall with laparoscopy.29
Congenital malformation of the uterus: In congenital malformation of the uterus, the abnormal muscle arrangement in the septate or bicornuate uterus can give rise to intractable if not severe colic, but the unicornuate uterus or uterus didelphys are causes less trouble. Imperforate hymen or transverse vaginal septum cause cyclical pain once a haematometra develops. The possibility of a uterus malformation should be suspected in a young patient, if she complains one sided spasmodic dysmenorrhoea.12

Other causes of one sided dysmenorrhoea are endometriosis, a small leiomyoma at the uterotubal junction, the site of origin of uterine contractions. Rudimentary horn also causes pain, because it does not communicate with the uterine canal.12

Intrauterine devices: Copper releasing intrauterine device may lead to an increase in prostaglandins after insertion resulting in increased cramping and pain.29

Pelvic infections: From either Chlamydia or gonorrhoea may lead to abscess or adhesion formation. The pathology that results from these infections may cause pelvic pain and dysmenorrhoea.29

CLINICAL FEATURES

The initial onset of primary dysmenorrhoea is usually 6–12 months after menarche, with the onset of ovulatory cycle.22 The pain is usually most severe on first or second day of menstrual flow in more than half of the woman,31 due to highest level of PGF$_2\alpha$ in menstrual blood. The pain usually begins a few hours prior to or just after the onset of a menstrual period and may last as long as 48–72 hours. The pain is labour like characterised by sharp, fluctuating, suprapubic cramping and may be accompanied by lumbosacral backache, pain radiating to anterior thigh, headache, diarrhoea, nausea, vomiting22,26 anxiety, diarrhoea, syncope, abdominal bloating,13 and fatigue.41 During severe attack the patient looks drawn and pale, sweat, nausea and vomiting are common. Diarrhoea, rectal and bladder tenesmus may also be present in this condition.12

On examination vital signs are normal. The suprapubic region may be tender on palpation. Bowel sounds are normal; there is no upper abdominal tenderness or abdominal rebound tenderness. Bimanual examination at the time of dysmenorrhoeic episode often reveals abdominal tenderness; however, severe pain with movement of the cervix or palpation of the adnexal structures is absent. The pelvic organs are normal in primary dysmenorrhoea.41

DIAGNOSIS

Primary dysmenorrhoea should be diagnosed as a specific entity, as there is no laboratory test for it.13,22,31 Its diagnosis of is one of exclusion.35 The practitioner is challenged in the diagnosis by its common and remote conditions.27 Menstrual pain is the major symptom of primary dysmenorrhoea.18 Pain is difficult to quantify, and its assessment usually is reliant on subjective assessments. Furthermore, dysmenorrhoeic pain is very variable,39 its causes are not well understood. Currently, there are no methods available to measure or quantify menstrual discomfort biologically and must rely on women’s reports to describe it.

PD can be diagnosed only in the absence of an identifiable cause of pelvic pain. Careful attention to the patient’s history and a well thought out approach to the physical, laboratory and other evaluation, will result in a correct diagnosis and facilitate successful treatment.

A typical history should include the age of
onset, the character, location, radiation and associated factors that make the symptoms better, worse and no pain at other times, the menstrual cramps are noted after the age of 20 in the presence of a history of regular and presumably ovulatory cycles, an organic cause must be sought.

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Case of the Month
A 22 Yyear Old Lady Presented with Complaints of Heavy Bleeding Following Post-abortal Curettage
Madhushree Vijaykumar, AS Shylaja, Priyanka Rani

Introduction
Pseudoaneurysm or arterio-venous malformation is a rare clinical entity. It is also described as cirrroid aneurysm, arterio-venous fistula, arterio-venous aneurysm, pulsating angioma. Recognition of these abnormalities as the cause of haemorrhage is important, since these abnormalities can be treated safely and effectively with transcatheter arterial embolisation.

Diagnosis and Management
Draining veins showed pulsatile blood flow suggestive of pseudoaneurysm of right posterolateral uterine wall with arteriovenous fistula (Figure 2,3).

Interventional Radiologist opinion was sought as patient was young and desired future fertility. This particular patient underwent selective catheterisation of both uterine arteries done via left brachial artery. Bilateral uterine artery embolisation done under local anaesthesia using Micro nester coil 4x12 cm for right and Mcreys coil 4x4 cm for left uterine artery. Patient was discharged 2 days later without complications. Follow-up scan showed no abnormal vascularity in uterine wall. She conceived 4 months later with uneventful pregnancy till now.

Discussion
Pseudoaneurysm is a rare cause of haemorrhage. Uterine curettage or surgical trauma can cause uterine vascular abnormalities, including pseudoaneurysms, acquired arteriovenous malformations (AVM), arteriovenous fistulas, and rupture of vessels. Uterine AVMs should be considered as a possibility in cases of refractory intrauterine bleeding. Recognition of these abnormalities as the cause of haemorrhage is important, since these abnormalities can be treated safely and effectively with transcatheter arterial embolisation but may be worsened by uterine curettage, precipitating massive uterine bleeding.

Ultrasoundography is the most commonly performed initial imaging examination for evaluation of abnormal uterine bleeding. Colour and duplex Doppler ultrasoundography image shows that the cystic structure is filled with blood and has varying colours.
sound allows convincing detection and diagnosis of these vascular abnormalities and helps differentiate vascular abnormalities that require embolisation from nonvascular abnormalities.4,5

In cases of pseudoaneurysms, colour and duplex Doppler ultrasound shows a blood-filled cystic structure with swirling arterial flow. In cases of AVMs, colour Doppler ultrasound shows an intense vascular tangle, whereas duplex Doppler US shows low-resistance, high-velocity arterial flow. Cases of an AVM combined with a pseudoaneurysm demonstrate the findings of both AVMs and pseudoaneurysms.

Transcatheter arterial embolisation after angiography is the therapy of choice for these vascular abnormalities, with the advantage of retained reproductive capacity. Routine use of colour and Duplex Doppler ultrasound during examination of abnormal uterine bleeding is recommended to identify and characterise the vascular abnormality.

Pregnancy following conservative medical management of AVM and even after successful embolisation, although rare has been reported in literature.5,7,8

Conclusions

Although not a common complication of curettage, the diagnosis should be considered in those patients with post-abortive bleeding and cystic lesion in the pelvis on ultrasonography. Uterine artery embolisation is an effective method of treating hemorrhage secondary to a pseudoaneurysm of uterine artery with high success rate.

References


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Rupture of Unscarred Uterus in a Primigravida at 18 weeks of Gestation

Smriti Agrawal, Yashodhara Pradeep

INTRODUCTION

Rupture of uterus (scarred or unscarred) is an extremely catastrophic event. Literature has plentiful of cases of dehiscence of previous cesarean scar. However, rupture of unscarred uterus in a primigravida has not been reported so far. Garnet et al.¹ have proposed aetiological classification of rupture of uterus: rupture of previous scar (myomectomy, hysterectomy), traumatic rupture (accident, version) of unscarred uterus, spontaneous rupture of unscarred uterus with pathology (anomalies, multiparity) and spontaneous rupture of unscarred uterus in a primigravida with no apparent pathology. Herewith a case of primigravida with no prior uterine surgery/pathology presented with rupture uterus at 18 weeks of gestation is reported.

CASE HISTORY

A 35 years old primigravida patient is presented at 18 weeks pregnancy with history of sudden pain lower abdomen for 12 hours associated with two episodes of vomiting and fainting. Patient was admitted to a local hospital where she was booked for antenatal checkup and was managed conservatively with fluids and antibiotics. However, her condition deteriorated. Sonography was done which revealed empty uterus and presence of foetus and free fluid in peritoneal cavity. Thereafter patient was referred to tertiary hospital. She did not give any history of trauma (accident or abuse) or any prior uterine surgery or any drug intake e.g., oxytocics. Patient was being investigated for infertility and conceived in the same cycle following endometrial biopsy. On examination, patient was admitted in a state of shock. Clinically, she was very pale her pulse rate was 136/minute and BP 90/60 mmHg, temperature 99°F and RR was 36/mm. Abdomen was distended with diffuse tenderness throughout, bowel sounds were absent. Uterine contour

Figure 1. Transverse rupture along the fundus of uterus
could not be made out. On per speculum examination, there was no bleeding. On per vaginum examination uterus was extremely tender and exact size could not be made out. Paracentesis revealed frank blood. Her haemoglobin was 6.5 g/dl, blood urea was 33 mg/dl, serum creatinine 0.8 mg/dl and electrolytes Na+/K+ were 135/3.5 meq/L. Patient was taken up for laparotomy. Interoperatively, haemoperitoneum was present. Uterine rupture was present all along the fundus of uterus (Figure. 1). Placenta and foetus was lying in abdominal cavity. After discussing the condition of the patient and prognosis regarding future conceptions, fundal repair was done in 2 layers with bilateral tubal ligation. Patient received 4 units of blood post-operatively. There were no further complications. Patient was discharged on 12th post-operative day in satisfactory condition.

DISCUSSION

Spontaneous rupture of uterus are usually seen intrapartum in women with great parity, particularly associated with foetal disproportion and/or oxytocin use. Uterine rupture in primigravida in early pregnancy with no previous uterine surgery has not been reported and this can be the first case so far.

The incidence of spontaneous rupture in unscarred uterus ranges from 1 in 8000 to 1 in 15,000. Sweeten KM reported 2 cases of rupture of spontaneous unscarred uterus. However, in both the cases it was seen in multigravid women at term and associated with delivery of macrosomic foetus. Oxytocic stimulation of labour was another added feature. Another case has been reported where primigravida with no prior antecedent factors had posterior uterine rupture during labour at 30 weeks of gestation.

However, uterine rupture before onset of labour is a rare phenomenon. Blumenthal et al reported a case where rupture took place at 16 weeks of pregnancy in multigravid women without labour. Similarly, another case had rupture at 18 weeks of pregnancy. Both the patients were multigravid women and hence gradual thinning of uterine musculature could be a postulated cause.

The cause for uterine rupture at 18 weeks pregnancy in this patient is intriguing. Endometrial biopsy per se is a relatively innocuous procedure and in all likelihood, a less convincing explanation for the uterine rupture. Congenital uterine muscle weakness could result in uterine rupture in the first pregnancy itself. Though rare, it is considered as a possibility in this patient.

Treatment options depend on the extent of rupture, parity and patient’s condition. If future conception is desired repair of uterus can be done with close supervision of subsequent pregnancy. However, if rupture is extensive or patient multiparous, repair with bilateral tubal ligation/hysterectomy can be done. In this case, rupture without any pathology occurred in primigravida at 18 weeks of pregnancy itself and as future conceptions could prove hazardous, patient and relatives opted for repair with bilateral tubal ligation.

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REFERENCES
Male Infertility

VCY Lee, MRCOG, FHKAM(OG); EHY Ng, MD, FRCOG; PC Ho, MD, FRCOG

EPIDEMIOLOGY

Infertility generally affects one in seven couples and is a growing problem worldwide.1,2 This is illustrated by the increase in the number of assisted reproductive technology (ART) treatment cycles worldwide in 2009–2010, ranging from an increase of 5.9% to over 100%.3–5 Male subfertility is one of the major causes, as a sole factor accounting for 29.7% and as a contributor for another 10.3–29.7% in the United Kingdom and Hong Kong.3,5 There is some evidence suggesting that there might be a decline in semen concentration of men born in the 1930’s to 1980’s.6–8

DEFINITION

In the investigation of an infertile couple, semen analysis has all along been performed for the assessment of the fertility status of the male partner. The World Health Organization manual for examination and processing of human semen has been recognized as the global standard for semen analysis. The most recent World Health Organization manual for semen analysis was published in 2010 and set the lower ‘reference’ limits of semen parameters according to the fifth centile of men, whose partners had a time-to-pregnancy of 12 months or less, worldwide (Tables 1 and 2).9 Therefore, men with semen parameters below the lower reference limits (other than those with azoospermia) are not necessarily infertile. It is recommended that semen samples should be collected by masturbation after 2–7 days of sexual abstinence without the use of lubricants. The process of analysis should be carried out within 1 hour of collection, and two or more samples are required especially for abnormal results.

AETIOLOGY

The aetiology of male infertility can be classified as pre-testicular, testicular, and post-testicular (Table 3).10,11 The management of male infertility should be based on the aetiology if it is known. However, the exact aetiology is often not known.

Pre-testicular causes include hypogonadotrophic hypogonadism due to Kallmann syndrome (with anosmia), brain tumours, radiotherapy for brain tumours, gene mutations (such as luteinizing hormone receptor mutation), and idiopathic hypogonadotrophic hypogonadism. Post-testicular causes are mostly obstructive, which include iatrogenic obstruction (vasectomy), congenital bilateral absence of the vas deferens (CBAVD), and post-inflammation or infection. Testicular causes include genetic causes, infection, systemic diseases, and trauma. Coital dysfunction in the form of erectile and ejaculatory dysfunction is another possible cause of infertility. Retrograde ejaculation can be due to anatomical causes including bladder neck surgery and posterior urethral valves, neurogenic causes including diabetes mellitus and spinal cord injury, and drug-induced like alpha-receptor blockers and antipsychotics.12

CLINICAL WORKUPS

History and Physical Examinations

When infertile couples first attend the
infertility clinic, semen analysis reports should preferably be available for review. A detailed clinical history and clinical examination of the men should be conducted, and further investigations would be dependent on the severity of abnormal parameters. Clinical history includes history of torsion, trauma and infection/inflammation of the testicles (which may damage the testis), drug history like chemotherapy/radiotherapy, surgical history such as orchidopexy for cryptorchidism, and social history especially smoking history, sauna habit and occupation. Physical examination should include the size and consistency of the testes (which are indicators for testicular function), any distension of the epididymis (which may indicate obstructive causes), and the absence of vas deferens (which is indicative of CBAVD).

Genetic Tests
Genetic tests, including karyotype and Y chromosome microdeletion test, should be arranged if there is severe oligozoospermia or azoospermia. Karyotype abnormality and Y microdeletion account for about 15–21% and 8.5–10% of non-obstructive azoospermia (NOA), respectively. Klinefelter syndrome (KS), including 80% non-mosaic type and 20% mosaic type, is the major cause of karyotype abnormality. Most Y chromosome microdeletions occur on the long arm (q) and are subdivided into three azoospermia factor (AZF) regions: AZFa, AZFb, and AZFc. There is evidence that the prevalence of karyotype anomalies and AZF deletions increases with decrease in semen concentrations. The prevalence of karyotype anomalies in oligozoospermic men with semen concentration below 5 million/mL is 8%, which increases to 15% in azoospermic men, while the prevalence of AZF deletion also increases from 5% to 10%. Based on the prevalence of abnormalities of karyotype and Y microdeletion in 295 oligozoospermic or azoospermic men from Hong Kong with different sperm concentrations, we recommend performing a karyotype and Y microdeletion test only if the semen concentration is below 2 million/mL.

Screening for cystic fibrosis genetic mutation should be done in men with CBAVD. The prevalence of cystic fibrosis transmembrane conductance regulator (CFTR) gene in Caucasian men with CBAVD is high, ranging from 71% to 87% in different Western countries, and it warrants proper testing followed by screening of the female partner if a mutation is present. However, the prevalence of cystic fibrosis and the carrier rate of CFTR gene mutation in the Chinese population are very low. As

<table>
<thead>
<tr>
<th>Table 1. Semen parameters according to the World Health Organization (2010)</th>
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<td><strong>Parameter</strong></td>
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<tr>
<td>Semen volume, mL</td>
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<tr>
<td>Total sperm number, × 10⁶ per ejaculate</td>
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<tr>
<td>Sperm concentration, × 10⁶/mL</td>
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<tr>
<td>PR, %</td>
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<tr>
<td>Total motility (PR + NP), %</td>
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<tr>
<td>Sperm morphology (normal forms), %</td>
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<tr>
<td>Vitality (live spermatozoa), %</td>
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NP = non-progressive motility; PR = progressive motility.

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<th>Table 2. Nomenclatures of abnormal semen parameters according to the World Health Organization (2010)</th>
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<tr>
<td><strong>Oligozoospermia</strong></td>
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<td><strong>Asthenozoospermia</strong></td>
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<td><strong>Teratozoospermia</strong></td>
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<tr>
<td><strong>Azoospermia</strong></td>
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<tr>
<td><strong>Crypzoospermia</strong></td>
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<td><strong>Aspermia</strong></td>
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Any combinations of oligozoospermia, asthenozoospermia and teratozoospermia mean the combination of abnormal parameters shown in semen analysis.
the main aim of genetic testing is to avoid full-blown cystic fibrosis in the offspring by prenatal diagnosis or preimplantation genetic diagnosis if the partner is also a carrier of the mutation, the tests for the mutation would not be necessary in the Chinese.

**Hormonal Tests**

Hormonal tests, including those for follicle-stimulating hormone (FSH) and testosterone, should be considered in azoospermic men. High gonadotrophin and normal/low testosterone levels (hypergonadotrophic hypogonadism) indicate gonadal failure, and low gonadotrophin and low testosterone levels indicate hypogonadotropic hypogonadism. Hormonal tests are likely to be normal in azoospermia of obstructive aetiology. The treatment would be completely different. However, there is controversy over the use of hormonal levels and other factors like inhibin B and anti-mullerian hormone to predict the success in surgical retrieval of sperm in men with gonadal failure, and there is no consensus on the cut-off value of these tests in the prediction.18–21 The association of hyperprolactinaemia with or without pituitary adenoma and male infertility is not clearly defined, yet hypogonadism caused by hyperprolactinaemia (resulting in erectile dysfunction) may be a contributing factor.22 Dopamine agonists, such as bromocriptine, can normalize the prolactin level. However, they would not improve the infertility problem in terms of hormonal profiles, semen parameters and pregnancy outcome in hyperprolactinaemic patients or idiopathic infertile men.22,23

**Miscellaneous**

Transrectal ultrasound scanning is used to confirm the diagnosis of obstructive causes and also to delineate the extent of obstruction to see if reconstructive surgery is feasible.24

Tests on sperm DNA integrity and fragmentation are some of the most controversial investigations in male infertility. It has been shown that fertilization and subsequent embryo development depend in part on the inherent integrity of the sperm DNA, and there seems to be a threshold of sperm DNA damage in terms of DNA fragmentation, abnormal chromatin packaging and protamine deficiency.

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**Table 3. Aetiology of male infertility**

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<thead>
<tr>
<th>Pre-testicular causes</th>
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<tr>
<td>• Idiopathic (~50%) (idiopathic hypogonadotrophic hypogonadism)</td>
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<tr>
<td>• Hypothalamic-pituitary-gonadal axis problems (Kallmann syndrome; gene mutations, eg, luteinizing hormone receptor mutation; brain abnormality, eg, pituitary tumour)</td>
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<table>
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<tr>
<th>Testicular causes</th>
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<tr>
<td>• Congenital including anorchia and cryptorchidism</td>
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<tr>
<td>• Genetic diseases (chromosomal including Klinefelter syndrome and balanced translocation; Y microdeletion)</td>
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<tr>
<td>• Infection/inflammation (eg, tuberculosis, prostatitis)</td>
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<tr>
<td>• Systemic diseases or medical therapy including chemotherapy and radiotherapy</td>
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<tr>
<td>• Trauma to testicles or torsion</td>
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<tr>
<td>• Varicocele</td>
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<tr>
<th>Post-testicular causes</th>
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<tr>
<td>• Congenital bilateral absence of the vas deferens (with or without cystic fibrosis mutation)</td>
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<tr>
<td>• Iatrogenic (post-vasectomy)</td>
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<tr>
<td>• Post-inflammation (epididymitis)</td>
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<tr>
<th>Coital dysfunction</th>
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<tr>
<td>• Erectile or ejaculatory problem</td>
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<tr>
<td>• Retrograde ejaculation (anatomical causes, eg, surgery to prostate and bladder neck, and posterior urethral valves; neurogenic causes, eg, diabetes mellitus and spinal cord injury; drug-induced, eg, alpha receptor blockers for benign prostate hyperplasia and antipsychotics)</td>
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resulting in impaired embryo development. The American Society for Reproductive Medicine recommends that there is no proven role for routine DNA integrity testing as the results do not predict pregnancy outcomes in spontaneous conception and ART treatment cycles and there is no effective treatment available for abnormal DNA integrity. Therefore, tests for DNA fragmentation should not be used routinely for infertility investigations.

TREATMENT

Treatment would depend on the aetiology of the male factor, the severity of abnormalities in semen parameters, and the presence of female factors such tubal status and woman’s age. In men with mildly abnormal semen parameters to severe oligoasthenoteratozoospermia, intrauterine insemination (IUI) and in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) can improve the pregnancy rate. In men with azoospermia, treatment would be dependent on the underlying reasons. The algorithm is shown in Figure 1.

Azoospermia

Azoospermia can be classified as NOA and obstructive azoospermia (OA). NOA can further be classified as due to gonadal failure or hypogonadotrophic hypogonadism. Surgical retrieval of sperm is the treatment for OA and gonadal failure. There are different techniques including percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA)/testicular sperm extraction (TESE), and microscopic or microdissection testicular sperm extraction (mTESE).

Obstructive azoospermia. PESA and MESA are used in OA to retrieve epididymal sperm from distended tubules in the epididymis. PESA can be done under local anaesthesia. It involves percutaneous puncture of the scrotal skin into the epididymis using a fine needle (eg, 26-gauge), and aspiration can be repeated in multiple sites. MESA involves an open operation under an operating microscopy and is able to retrieve greater number of sperm and minimize contamination of the sample with blood. Some urologists advocate MESA over PESA in patients with OA who would consider more than one IVF cycle, as MESA typically results in sperm with adequate motility for effective cryopreservation for multiple treatment cycles. There is so far no direct comparison between MESA and PESA. A Cochrane review commented that there is only scarce evidence on the choice of surgical technique in sperm retrieval. So, the choice of surgical technique would mainly depend on personal preference and surgical expertise. If no sperm is obtained from the epididymis, direct retrieval of sperm from the testicles can be performed in the same setting. MESA can be combined with reconstructive surgery in selected cases.

NOA – gonadal failure. Surgical retrieval of testicular sperm is the mainstay of treatment for hypogonadotrophic hypogonadism. TESE/TESA involves retrieval of sperm directly from the testicles using different techniques. mTESE requires an operation under microscopy and helps in visualization of the larger, more opaque, whitish tubules, presumably containing more intratubular germ cells with active spermatogenesis. A higher retrieval rate was reported with mTESE than with conventional TESE. The successful retrieval rate in NOA patients is typically quoted as less than 50%, although a higher retrieval rate may be possible with mTESE.

The use of TESE or mTESE, together with ICSI in IVF treatment cycles, is the only option for KS men to bear their own genetically linked children, and the success rate of surgical retrieval of sperm was reported to be similar with other NOA men with no karyotype abnormality. One group reported a higher retrieval rate of 68% and 72% in KS men using mTESE or conventional TESE, respectively. Not only is karyotype abnormality a predictor of the success of retrieval, the presence of AZF microdeletions on the Y chromosome is also a good predictor. Men with AZFc microdeletions alone have a similar success rate of surgical sperm retrieval on TESE, while those with AZFa or AZFb microdeletions will almost definitely have no sperm retrieved for ICSI. Therefore, genetic tests would be extremely useful in counselling before the surgical retrieval of sperm and for examining the inheritance of the mutation in the next generation.

NOA – hypogonadotrophic hypogonadism. Induction of spermatogenesis with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins, ie, human chorionic gonadotrophin (hCG) or FSH, is the treatment of choice for men with hypogonadotrophic hypogonadism. Both treatments have been shown to in-
duce spermatogenesis successfully. Although some investigators showed that the use of pulsatile GnRH was related to a greater testicular growth and faster induction of spermatogenesis, the ‘take-off’ for this kind of treatment is limited by the high cost of the drug and the difficulty in handling the pump system. The high success rate of gonadotrophins, ranging from 53% to 78%, implies that it is the treatment of choice in some localities. The usual recommended treatment consists of twice weekly injection of hCG 1,500 IU to 2,000 IU, with further dosage increment after review of the hormonal levels in 4 to 6 weeks’ time. In men suffering from hypogonadotrophic hypogonadism after puberty, hCG alone is usually sufficient.
for induction of spermatogenesis, with the median sperm count of 8 million/mL, when their partners get pregnant.43 Whereas in men suffering prepubertal hypogonadism, the treatment usually requires FSH together with hCG injection in order to induce spermatogenesis.42,43 Prior androgen administration was shown to be related to a slower induction of spermatogenesis. The average treatment duration may be up to 25 to 30 months before the men can impregnate their partners.43

Abnormal Semen Parameters
The treatment would be dependent on the severity of abnormal semen parameters, after taking into consideration the woman’s age and tubal status. IUI and IVF can be offered.

Artificial insemination using husband’s semen may be performed with intravaginal insemination, intracervical insemination, or IUI. IUI is currently the most commonly performed method in the management of male infertility. It is used in men with 2–5 million total motile spermatozoa after processing. The criteria differ in various clinics, with the lowest threshold of 1 million total motile spermatozoa in the inseminate.44 Sperm morphology (strict criteria) seems to be predictive of the success rate of IUI, with a significantly higher pregnancy rate when the morphology is ≥ 4%.45 However, different centres should have their own criteria for recruitment for IUI. There is contradicting evidence on the protocol of IUI. It was suggested that IUI has no significant benefit over timed intercourse and ovarian stimulation does not improve the outcome.46 However, it was shown that gonadotrophin for ovarian stimulation offers a significantly better pregnancy outcome than does anti-oestrogen, while there was no difference between anti-oestrogen and aromatase inhibitor. There was also no benefit in using either GnRH agonist or antagonist in IUI in terms of pregnancy rate. Low-dose gonadotrophin was suggested, as doubling the dose would only increase the complication rate, namely multiple pregnancy rate and ovarian hyperstimulation syndrome, but not the pregnancy rate.47 As there is no robust evidence, further properly designed trials are needed to confirm the present suggestions.

In vitro fertilization consists of follicular development with various ovarian stimulation protocols, oocyte retrieval, fertilization inside laboratory environment, and transfer of embryos to the uterine cavity. Since the first report of the use of ICSI in human that resulted in a pregnancy, ICSI has become the routine practice for severe male infertility48 ICSI is the procedure of injecting a single sperm directly into an oocyte. Although sperm morphology was reported to be more relevant to fertilization failure,49 the prediction of fertilization failure by morphology or other parameters is still poor40 and so different centres have their own set of criteria for using ICSI. The development after fertilization including the blastulation rate was shown to be not affected by sperm morphology.50 A study showed that the use of ICSI in non-male infertility was associated with a lower implantation rate when compared with conventional insemination52; thus, ICSI should be reserved for severe male factor infertility. As shown by a recent review, there is a slight increase in de novo chromosomal abnormalities and the major congenital malformation rate is similar for IVF and ICSI (~3–4%).53

Miscellaneous therapies. (a) Antioxidant. There is evidence suggesting that reactive oxygen species (ROS)-mediated damage to sperm is a significant contributing pathology in 30–80% of male factor infertility. There are two principal mechanisms of ROS-related infertility. Firstly, ROS damage the sperm membrane, impairing the sperm’s motility and ability to fuse with the oocyte. Secondly, ROS causes sperm DNA damage, compromising the paternal genomic contribution to the embryo.54 Raised ROS levels are usually associated with smoking, genital tract or systemic infections, and varicocele.55,56 It has been shown that embryos formed from fertilization with sperm having high DNA damage are of poorer quality and have a decreased cleavage rate.57

As antioxidants (namely vitamins C and E, folate, zinc, selenium, carnitine, and carotenoids) are scavengers of ROS, they have been studied in male factor infertility. A Cochrane review indicated that the use of antioxidants, such as vitamin C and zinc, may improve the pregnancy outcome in ART cycles based on evidence from small randomized trials, and larger trials are needed to confirm the results.58 There is also evidence of improvement of sperm parameters and spontaneous conceptions. However, the trials were all small and had significant methodological and clinical heterogeneity. Drawing a conclusion from these trials may not be appropriate.59 and so antioxidants should not be recommended routinely.
(b) Treatment of varicocele. There is a hot controversy on the effectiveness of varicocele treatment (including surgical and radiological methods) on semen parameters and pregnancy outcomes. Some investigators reported no improvement\(^6\) while others showed significant improvement in spontaneous conceptions.\(^6\) According to the recommendation of the American Society for Reproductive Medicine, treatment of varicocele should be considered if all of the following conditions are met: (1) the varicocele is palpable on physical examination of the scrotum; (2) the couple has known infertility; (3) the female partner has normal fertility or a potentially treatable cause of infertility; and (4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Moreover, it explicitly expressed that varicocele treatment for infertility is not indicated in patients with normal semen qualities and a subclinical varicocele.\(^6\) As some trials included men with subclinical varicocele, the outcome in men with clinical varicocele would be difficult to interpret. Nevertheless, the evidences come from the comparison between expectant management and varicocele treatment in spontaneous conception while there is no evidence of the effectiveness in ART cycles including IUI and IVF cycles. Different surgical approaches were compared in one randomized trial, which revealed that subinguinal microsurgical varicocelectomy had better outcomes than open inguinal and laparoscopic varicocelectomy.\(^6\)

(c) Lifestyle modification. Tobacco smoking is associated with male factor infertility, probably related to the increase in ROS and DNA damage. There are many studies showing poorer semen quality in smokers compared with non-smoking counterparts.\(^6\) However, there is no evidence showing that quitting smoking may improve semen parameters.\(^7\) Nonetheless, smoking has been shown to reduce significantly the pregnancy rate in IVF treatment cycles.\(^8\) It would be sensible to advise both partners to quit smoking before commencement of treatment cycles, not only for the ART cycles but also for their general health.

Coital Dysfunction
Psychosexual counselling is the mainstay of treatment for coital dysfunction. The use of phosphodiesterase inhibitors, such as sildenafil and vardenafil, should be considered in men with erectile dysfunction after excluding contraindications.\(^9\) If these first-line treatment methods fail, intra-penile injections, vacuum constriction devices and implantation of a penile prosthesis for the treatment of their erectile dysfunction can be considered.\(^10\) If the couple fails to conceive naturally after these measures or if the semen quality is not good, ART like IUI or IVF may also help.

For retrograde ejaculation, treatment of the underlying causes is needed. Drug treatment is the first-line treatment, including alpha agonistic drugs and parasympathomimetics. If the drug therapy fails, penile electrovibration stimulation and sperm retrieval from the urine with oral sodium bicarbonate a few hours before collection of urine can be offered.\(^11\)

Other Options
In men who have NOA and no sperm retrieved from surgery, or men with AZFa or AZFb deletion, use of donor sperm should be counselled. Couples should be fully counselled on the implications of the use of donor gametes. The couple also needs to understand the regulation of the law and the code of practice in different countries and regions, like the Human Fertilisation and Embryology Authority in the United Kingdom and the Council on Human Reproductive Technology in Hong Kong. Adoption and childlessness are the other two options.

CONCLUSION
Semen analysis is the most common method for assessment of fertility status of the male partner, although its prognostic value is limited except in the case of azoospermia. The management of male infertility should be based on the aetiology if it is known. For male infertility with unknown cause, empirical treatment methods such as IUI, IVF and ICSI can be offered. The development of these methods offers hope for couples suffering from male infertility, even for those with severe sperm problems or azoospermia.

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A complete list of references can be obtained upon request to the editor.