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Experience is your child’s best teacher.

Friso® Gold, formulated with P2 Dual System, protects your child from the inside, so he is free to discover the world his way. You, your child and Friso®, growing up together.

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225 Dietary Intervention in Eczema

Eczema is a chronic inflammatory dermatosis that usually manifests in early childhood. The precise aetiology and pathogenesis of eczema are not yet fully understood, but a complex interaction between genetic and environmental factors has been implicated in the predisposition and development of the disease.

Jackelina Pando Kelly, Jonathan Hourihane

234 Infectious Disease in Pregnancy

Most infections during pregnancy will not cause long-term harm, but those that do should be recognized and treated. This review outlines prevention and screening for infections, maternal infection syndromes, important organisms with their clinical effects and management in pregnancy, and those infections that may lead to congenital abnormalities.

Sarah Logan, Laura Price
**Breast Milk Is the Best For Babies**

Mother's milk is the best for baby because it uniquely fulfills all of the baby's needs. Mothers should start breast-feeding as soon as possible within the first hour after delivery. Breast milk has several benefits – it provides the best nutrition for babies; strengthens immunity; prevents various allergic disorders; contain nutrients critical to brain development and has a reduced in chance of contamination which can occur with other forms of feeding. Breast milk contains several strains of beneficial bacteria. It contains oligosaccharides so breast fed babies are rarely constipated. To prevent a diminishing supply of breast milk, supplementary feeding or bottle feeding should not be given too early. Once a decision is made to stop breast-feeding, it is difficult to reverse. Working mothers can also continue breast-feeding. We at Dutch Lady Milk Industries Berhad support breast-feeding. Not only is it good for the baby’s health, but it is also strengthens the bond between mother and baby - a bond that lasts a lifetime.

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### Friso Family of Products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Product Description</th>
<th>Age</th>
<th>Key Supporting Nutrients</th>
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<tr>
<td>Frisolumum Gold</td>
<td>Maternal Formula</td>
<td>For Pregnant &amp; Breast-feeding mothers</td>
<td>Prebiotic (FOS)</td>
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<td>Frisolac Comfort</td>
<td>Special Infant Formula</td>
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<td>5 Nucleotides</td>
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Review Article
Obstetrics

247 Newborn Stem Cells: Types, Functions and Basics for Obstetricians
This article provides a basic knowledge of newborn stem cells and their potential clinical and
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Jennifer Sze Man Mak, Juan Bolaños, Wing Cheong Leung, Richard Boyd, Robert Kien Howe Chin

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257 Magnetic Resonance-guided Focused Ultrasound for the Management of
Uterine Fibroids
Magnetic resonance-guided focused ultrasound (MRgFUS) is a new, non-invasive method for treating
uterine fibroids. Early reports have demonstrated its safety and effectiveness in fibroid volume reduction
and symptom improvement. This article reviews the principle, patient selection criteria, treatment
procedure, potential risks, and outcome of MRgFUS.
Victor HG Ai, John KF Chan, Gladys G Lo

264 2012 Annual Index
Colonisation by gut microflora is essential

Bacterial colonisation of the gut can be significantly delayed in Caesarean-born infants, potentially delaying maturation of the immune response. NAN® Pro™ contains BL BIFIDUS®, a probiotic shown to help all infants – even those delivered by caesarean section – build a healthy intestinal microbiota. It has been shown that infants fed NAN® Pro™ may have a lower incidence of rotavirus infection and diarrhoea than infants fed a non-probiotic formula.

Important Notice:
The Ministry of Health Malaysia and the World Health Organisation (WHO) have recommended that pregnant women and new mothers be informed of the benefits and superiority of breast-feeding – in particular the fact that it provides the best nutrition and protection from illness for babies. Breastfed infants have a healthy intestinal microbiota and reduced risk of infections and diarrhoea. Mothers should be given guidance on the preparation for, and maintenance of, breast-feeding, with special emphasis on the importance of a well-balanced diet throughout pregnancy and after delivery. To stimulate better lactation, baby should be put to the breast within the first hour after birth. Working mothers can breast-feed before leaving home in the morning and again when they return home in the evening. While at work, babies may be fed with breast milk, which has been expressed and stored hygienically. Unnecessary introduction of bottle-feeding or other foods and drinks should be discouraged since it will have a negative effect on breast-feeding. Similarly, mothers should be warned of the difficulty of reversing a decision not to breast-feed. Before advising a mother to use an infant formula, she should be advised of the social and financial implications of her decision: for example, if a baby is exclusively bottle-fed, more than one can (400g) per week will be needed, so the family circumstances and costs should be kept in mind. Mothers should be reminded that breast milk is not only the best, but also the most economical food for babies. If a decision to use an infant formula is taken, it is important to give instructions on correct preparation methods, emphasizing that unboiled water, unboiled bottles or incorrect dilution can all lead to illness. The source of the infant formula product is cow’s milk origin.

Refer to:
2. International Code of Marketing of Breast Milk Substitutes, adopted by the World Health Assembly in Resolution WHA 34.22, May 1981,

References:
GYNAECOLOGY

Hormonal contraception and cardiovascular risk

A Danish registry study has provided more data about cardiovascular risks associated with hormonal contraception.

Data were obtained from four national registries over a 15-year period about non-pregnant women aged 15–49 with no history of cardiovascular disease or cancer. The data included 1,626,158 women with 14,251,063 person-years of observation, during which there were 3,311 thrombotic strokes and 1,725 myocardial infarctions. The rate of thrombotic stroke was 21.4 per 100,000 person-years and of myocardial infarction, 10.1 per 100,000 person-years. Among women using oral contraceptives including ethinyl oestradiol at a dose of 30–40 µg, the risk of thrombotic stroke was increased 1.5- to 2.2-fold according to progestin type, compared with non-users. The risk of myocardial infarction was increased 1.3- to 2.3-fold. At an ethinyl oestradiol dose of 20 µg, the increase in risk was less in general, and there was no increased risk with drospirenone as the progestin. Transdermal patches were not associated with significantly increased risk for either thrombotic stroke or myocardial infarction. Vaginal ring was associated with a significant 2.5-fold increase in risk of thrombotic stroke but a non-significant increase in risk of myocardial infarction.

Although hormonal contraception may increase the risks of thrombotic stroke and myocardial infarction, the absolute risks are low. An editorialist concludes that they are ‘safe enough’.


Midurethral sling during vaginal prolapse surgery to reduce post-operative incontinence

About a quarter of women undergoing surgery for pelvic organ prolapse who had no urinary incontinence before surgery will develop incontinence after surgery. The prophylactic insertion of a midurethral sling during prolapse surgery has become popular without good evidence of its effectiveness. A multicentre US trial has been reported.

A total of 337 women undergoing prolapse surgery but without a history of stress incontinence were randomized to insertion of a midurethral sling or a control group (sham incisions) and 327 women were followed up for 1 year. At 3 months, there was a significant reduction in urinary incontinence in the urethral sling group (23.6% vs 49.4%). At 12 months, the rates of incontinence were 27.3% vs 43.0%. The number needed to treat to prevent one case of urinary incontinence at 12 months was 6.3. Bladder perforation occurred in 6.7% of the urethral sling group but in none of the control group. There were significant increases in the sling group in urinary tract infection (31.0% vs 18.3%), major bleeding (3.1% vs 0%), and incomplete bladder emptying 6 weeks after surgery (3.7% vs 0%).

The insertion of a midurethral sling was effective in reducing the risk of postoperative urinary incontinence but at the expense of increased risk of complications.


Effect of contraception on maternal mortality rates

The Safe Motherhood Initiative begun in 1987 has four strategies to reduce maternal mortality: family planning, antenatal care, safe delivery, and postnatal care. Now, the effects of contraceptive use on maternal mortality worldwide have been estimated from three international databases.

Data were analysed from 172 countries for 2008. The number of deaths from maternal causes in 2008 was estimated at 342,203 (data from 172 countries). The estimated number of maternal deaths averted by contraception was 272,040, a 44% reduction of the potential total. It was also estimated that expansion of contraceptive use could avert another 104,000 maternal deaths each year. The number of deaths averted increased increased with increased contraceptive use. In countries with high (> 65%) contraceptive use, almost 60% of potential maternal deaths were averted, whereas in sub-Saharan Africa (22% contraceptive use), only 32% of potential maternal deaths were averted.

Increased use of contraception could prevent many maternal deaths in developing countries.

Cumulative birth rates with assisted reproduction

Rates of live birth with assisted reproductive technology have usually been reported per cycle, but for women undergoing continuous treatment, cumulative live-birth rates are more relevant. A national US database has been used to estimate cumulative rates. Data were available for 246,740 women (471,208 cycles, 140,859 live births). Live-birth rates decreased with increasing maternal age and increasing cycle number with autologous, but not with donor, oocytes. Conservative and optimal estimates of live-birth rates by the third cycle with autologous oocytes were 63.3% and 74.6% for women < 31 years old, 18.6% and 27.8% at ages 41 and 42, and 6.6% and 11.3% at age 43 or older. Using donor oocytes, the corresponding figures were 60% and 80% at all ages. Rates were higher with blastocyst embryos (transfer at day 5 or 6) than with cleavage embryos (day 2 or 3).

Live-birth rates similar to natural fecundity can be achieved with favourable maternal and embryo characteristics. The use of donor oocytes eliminates the decline in live-birth rates with age seen when autologous oocytes are used.


Urinary protein-to-creatinine or albumin-to-creatinine ratio to detect significant proteinuria in pregnancy

A systematic review and meta-analysis has addressed the use of spot urine protein-to-creatinine or albumin-to-creatinine ratio to detect significant proteinuria in pregnancy in the diagnosis of pre-eclampsia. The analysis included 20 studies (2,978 women). Threshold values for protein-to-creatinine ratio ranged from 0.13 to 0.5 with sensitivity values between 0.65 and 0.89 and specificity of 0.63 to 0.87 for the detection of 24-hour urinary protein > 0.3 g/day. The optimum threshold values for protein-to-creatinine ratio appeared to be 0.30–0.35. There was insufficient evidence about the use of albumin-to-creatinine ratio. One study suggested that a value of > 2 mg/mmol was associated with a sensitivity and a specificity both of 0.94. There is insufficient evidence about the use of either test to predict adverse pregnancy outcome.

Urinary protein-to-creatinine ratio may be useful in the diagnosis of pre-eclampsia, but there is insufficient evidence about the use of albumin-to-creatinine ratio for this purpose or about the use of either test to predict adverse pregnancy outcome.


Reducing measles mortality

One global goal was to halve measles deaths between 1999 and 2005, and that was achieved. A new goal was then set to reduce measles mortality by 90% between 2000 and 2010. There has been no endemic measles virus transmission in the Americas since 2002, and only the southeast Asia region of the World Health Organization has not set an aim of measles elimination by 2020. Measles mortality fell by an estimated 74% between 2000 and 2010, from 535,300 to 139,300 deaths. All regions except southeast Asia achieved a reduction of > 75%. In India, measles deaths fell by 25% from 88,000 to 65,500. In 2010, almost half (47%) of all deaths from measles were in India and 56% were in Africa. Achievement of the 2000–2010 goal was impeded by delayed implementation of disease control in India and outbreaks of measles in Africa. Greater political and financial commitment are needed.

The Millennium Villages project in Africa

The Millennium Villages project began in nine African countries (Nigeria, Mali, Senegal, Ghana, Uganda, Kenya, Rwanda, Tanzania, and Malawi) in 2006. In each country, a rural population (average, 35,000 people) with high levels of poverty and undernutrition was selected. Finance amounting to around US$120 per person was provided annually to support agriculture, the environment, business development, education, infrastructure, and health, in partnership with communities and local governments. Average spending per person was $27 at baseline and $116 by year 3. There were improvements in water supplies and sanitation, poverty levels, food security, stunting, and malaria prevalence at Millennium Village sites after 3 years. Under-5s mortality fell by 22% in these sites and by 33% relative to matched comparison sites. Provision of many maternal–child health interventions was improved.

The multifaceted intervention was beneficial in several ways including reduced child mortality.


Management of type 2 diabetes in children and adolescents

The increased prevalence of obesity in children and adolescents has led to an increased incidence of type 2 diabetes. The physical and emotional challenges of adolescence, together with the increased frequency of obesity and diabetes in underprivileged communities, add to the difficulties of diabetes control. Three treatment approaches have been compared in a US multicentre trial.

A total of 699 patients aged 10–17 years with type 2 diabetes (mean duration, 7.8 months) and obesity (body mass index, 85th percentile or higher for age and sex) were randomized to metformin alone (M), metformin plus rosiglitazone (MR), or metformin plus a weight-loss lifestyle intervention (MW). Over an average follow-up of 3.9 years, loss of glycaemic control (glycated haemoglobin at least 8% for 6 months or sustained metabolic decompensation needing insulin) occurred in 45.6% of participants overall. The group rates for this outcome were 51.7% (M), 38.6% (MR), and 46.6% (MW). MR was significantly better than M, but MW was not significantly different from M or MR.

MR was the best of the three options. Most young people with type 2 diabetes will probably need combination drug therapy or insulin within a few years of diagnosis.


Zidovudine, lamivudine, and ritonavir-boosted lopinavir for HIV-infected children

For mothers and infants, who have previously been exposed to nevirapine, treatment of human immunodeficiency virus (HIV)-1 infection with a regimen including ritonavir-boosted lopinavir is better than...
treatment with a nevirapine-based combination. The best treatment for children not previously exposed to nevirapine is uncertain. Now, a trial in six countries in sub-Saharan Africa and India has shown that a ritonavir-boosted lopinavir-based regimen is better than a nevirapine-based regimen for young children who are nevirapine-naive.

A total of 287 nevirapine-naive HIV-infected children aged 2–36 months were randomized to zidovudine and lamivudine with either nevirapine or ritonavir-boosted lopinavir. The median proportion of CD4+ T-cells was 15% and median plasma HIV-1 RNA level 5.7 log_{10} copies/mL. Virological failure or treatment discontinuation by week 24 occurred in significantly more children in the nevirapine group (40.8% vs 19.3%). Drug resistance was present in 19 of 32 children in the nevirapine group tested at the time of virological failure. Mortality was greater in the nevirapine group (10/147 vs 3/140), and drug toxicity was also greater.

The results were better with the ritonavir-boosted lopinavir-based regimen, but these researchers point to difficulties in introducing this treatment: the liquid formulation is unpleasant to taste and deteriorates in hot temperatures, and the cost is twice that of the nevirapine-based regimen. New drug formulations are needed urgently.


Neonatal screening with pulse oximetry for critical congenital heart defects: Systematic review and meta-analysis

Babies with congenital heart defects may be discharged from hospital before a diagnosis is made and may subsequently become suddenly and critically ill. A new systematic review and meta-analysis has confirmed that pulse oximetry screening of asymptomatic newborn babies is highly specific and moderately sensitive for the detection of critical congenital heart defects.

The review included 13 studies (229,421 babies). The sensitivity of pulse oximetry was 76.5% and the specificity 99.9%. The false-positive rate was 0.50% in the first 24 hours after birth and 0.05% when done later.

It is concluded that pulse oximetry screening should be introduced widely.


Oral immunotherapy for egg allergy in children

By the age of 2.5 years, around 2.5% of children have developed egg allergy. Complete dietary avoidance may be difficult. Now, a multicentre US trial of oral immunotherapy has given positive results.

The trial included 55 children aged 5–11 years with egg allergy without a history of severe anaphylaxis. All had raised levels of egg-specific IgE. Randomization was to oral immunotherapy (40 children) or placebo (15 children). Immunotherapy consisted of giving egg white powder in three phases, in increasing doses up to 2 g per day. Challenges with egg white were performed at 10 and 22 months. After a 5-g challenge at 10 months, no allergic symptoms (or mild symptoms) occurred in 55% (immunotherapy) vs none (placebo). At 22 months, 75% of children in the immunotherapy group passed a 10-g challenge. At 24 months, 29 of the 30 children who passed the 22 months’ challenge were re-challenged and 11 passed. All of the children who passed the 24 months’ challenge were able to eat egg at 30 and 36 months.

Oral immunotherapy may be successful in some children with egg allergy.

Important Notice: Breast Milk is still the Best Food for Infants

Breast milk is the best food for optimal growth and development in infants. This is because breast milk contains just the right amount of all nutrients needed to fulfill the infants’ total nutritional requirements during the first 6 months of life. The best time to initiate breastfeeding is within 1 hour post-delivery. Furthermore, the act of breastfeeding provides a unique biological and emotional foundation for bonding between mother and child. A complete and balanced maternal diet is important for maintaining the quality and supply of breast milk. There can be negative effects on breastfeeding if partial bottle-feeding is introduced too early. Once bottle-feeding is initiated, the decision to discontinue breastfeeding may be difficult to reverse. Prior to using infant formulas, mothers should be aware of the social and financial implications of bottle-feeding. Incorrect preparation or feeding methods may lead to health hazards in infants. Working mothers should be encouraged to continue breastfeeding for as long as possible, even after they resume their full-time jobs. Those who need support and advice can seek help from healthcare professionals.
INTRODUCTION

Eczema, also known as atopic dermatitis has been proposed as a cutaneous manifestation of a systemic disorder that also gives rise to asthma, food allergy, and allergic rhinitis. It is a common, chronic, pruritic, and relapsing inflammatory dermatosis that typically manifests during early childhood.

The current prevalence of eczema in developed countries is about 20%, representing a twofold to threefold increase during the past decades. The reason for this increase remains unclear.

PATHOGENESIS

The pathophysiology of eczema is not yet fully understood. An interaction between genetic and environmental factors has been implicated in the predisposition and development of the disease. Eczema is associated with abnormalities in genes encoding skin barrier molecules (filaggrin), markers, and cells of the inflammatory response; immunoregulatory abnormalities; increased serum immunoglobulin E (IgE); impaired delayed hypersensitivity reaction; and infectious agents.

Research has demonstrated that a combination of food allergy, defects in the gut mucosal barrier, and increased intestinal permeability may be complicit in the pathogenesis of eczema. Therefore, dietary manipulation could be of use in controlling or preventing the disease, but this still remains controversial.

It is important to remember that food allergy and eczema coexist due to their common origins as manifestations of an allergic diathesis, but that one may not automatically be implicated as a cause of the others.
We will briefly review the association between food allergy and eczema and some of the dietary strategies that have been proposed in eczema.

**FOOD ALLERGY AND ECZEMA**

Patients or parents of children with eczema commonly perceive that specific foods, more commonly cow’s milk, cause flare-ups of their child’s eczema. Other foods that have been implicated in hypersensitivity reactions in eczema include citrus, nuts, and fish. Families may wish to change their diet in the erroneous belief that an external trigger is causing their child’s eczema, rather than using prescription medications that they have been told, also erroneously, have major toxic side effects.

**Food-allergic sensitization.** Allergic sensitization to food allergens is frequent in infants and children with eczema. The highest rates of food-allergic sensitization occur during the first 2 years of life, and they closely parallel the onset of eczema.

There is a direct correlation between eczema severity and food allergen sensitization. The demonstration of food allergen-specific IgE in infancy is predictive not only of eczema severity, as shown by the fact that sensitization to food and inhalant allergens is present in 70–80% of patients with moderate-to-severe eczema, but also of eczema persistence and of the onset of allergic airways disease later in childhood.

**Food-allergic disease in patients with eczema.** Ingested food allergens are able to activate cutaneous mast cells and skin-associated lymphoid tissue, and in the sensitized host, they can produce intense pruritus, causing scratching and rubbing that lead to typical eczematous lesions.

At a cellular level, positive oral food challenges in patients with eczema result in a sharp increase in plasma histamine concentrations, activation of eosinophils, and clonal expansion of allergen-specific skin homing T-cells.

It has been reported that approximately one-third of children with moderate-to-severe eczema have food allergy and up to two-thirds of infants < 2 years with severe or refractory eczema. Only 10% of infants with mild eczema are affected by food allergy.

**The defective epithelial skin barrier as a route for allergic sensitization.** It has been proposed that allergen sensitization occurs as a secondary consequence of a defective skin barrier in which the penetration of microbes and allergens is enhanced. The recent identification of loss-of-func-
tion mutations in the epidermal structural protein filaggrin appears to be a major risk factor for severe eczema, peanut allergy, multiple atopic sensitization, and coexisting asthma.

**Phenotypes of food allergy in patients with eczema.** Food-allergic reactions have been broadly classified into allergic (IgE or non-IgE-mediated) and non-allergic hypersensitivity reactions. The allergic reactions may be immediate IgE-mediated or delayed non-IgE-mediated. Intolerance is defined as a non-allergic reaction to a food and includes food aversion, and toxic, enzymatic or pharmacological reactions to foods.

There is considerable overlap between IgE-mediated and non-IgE-mediated reactions, and most of these phenotypes can coexist in patients with eczema (Table 1). Therefore, it is important to understand the natural history and clinical presentation of food allergy in order to make or refute a diagnosis of such in patients with eczema.

IgE-mediated reactions to specific foods cause stereotyped symptoms typically within 0–2 hours (but nearly always within 30 minutes) of ingestion, affecting the skin, gastrointestinal tract, and respiratory and cardiovascular systems. These acute allergic reactions are often followed by a delayed flare of eczema.

Non-IgE-mediated reactions are typified by symptoms that involve also the skin, gastrointestinal tract, and respiratory tract (eczematous reactions, vomiting, diarrhoea or constipation, cough, wheeze). Delayed reactions to food allergens in the gastrointestinal tract predominate in infancy and early childhood and tend to improve with age.

The most common food triggers of eczema are shown in Table 2.

In infants with moderate-severe eczema, the relationship between milk ingestion and the development of eczema is likely to be more obvious. A high index of suspicion is required when evaluating an infant with the combination of infantile eczema and features of altered gut motility (colic, reflux, persistent crying, etc).

**The diagnosis of food allergy in patients with eczema.** An accurate diagnosis of food allergy is important as it allows for a targeted approach to allergen avoidance, but also for a relaxation of dietary restrictions when it has erroneously been imposed on children.

The gold standard test for food allergy diagnosis is the double-blind, placebo-controlled food challenge, but as this is not accessible to many patients, the diagnosis of food allergy needs to rely on a stepwise approach which includes a detailed allergy-focused history and food-specific allergy

<table>
<thead>
<tr>
<th>Table 1. Food allergy phenotypes</th>
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<tr>
<td><strong>IgE-mediated</strong></td>
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<td>Immediate food allergy/Anaphylaxis</td>
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<td>Oral allergy syndrome</td>
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<td>Eczema</td>
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<td></td>
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<td>Any time, peak in early life</td>
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</table>

| Cox H, Hourihane J. 2011. |

<table>
<thead>
<tr>
<th>Table 2. Common food triggers of eczema</th>
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<td><strong>Food-allergic triggers of eczema</strong></td>
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<tr>
<td>Milk</td>
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<td>Soya</td>
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<td>Wheat</td>
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The diagnosis of food allergy in children with eczema includes taking a detailed allergy-focused history.

**The history.** A detailed allergy-focused history should focus on the following areas:

- **Family history of atopy:** The risk of atopy increases if a parent or sibling has atopic disease (20–40% and 25–35%, respectively), and is higher still if both parents are atopic (40–60%).
- **Infant feeding:**
  - A history of breast vs formula feeding, detailing period of exclusive breastfeeding, and taking into account that the onset of severe eczema during a period of exclusive breastfeeding may be secondary to food proteins excreted in breast milk.
  - The relationship of eczema onset to the introduction of formula feeds.
  - The type of formula feed.
- **Gastrointestinal symptoms:** The presence of gastrointestinal symptoms, such as colic, abdominal pain, vomiting, reflux, feeding aversion, diarrhoea, constipation, blood or mucus in stools, and failure to thrive, in a patient with eczema should raise the possibility of food allergy.
- **History of immediate reactions to specific foods:** A history of immediate reactions to food is important to ascertain. This should explore the time of onset in relation to ingestion, the quantity of food required to cause a reaction,
any previous reaction or prior tolerance of that food, and whether the reaction was of sufficient severity to cause anaphylaxis. It is necessary to determine reactions to foods in infancy as well as current reaction to establish a meaningful picture of the child’s allergic status, taking into account that the natural history is for children to acquire tolerance to most food allergens over time.

- **History of eczematous or gastrointestinal reactions to specific foods**: A history of food causing an eczematous flare in patients with persistent eczema is frequently absent. In a placebo-controlled study which demonstrated a 60% improvement in eczema patients adhering to milk- and egg-free diet, there was no correlation between the parents’ suggestions that milk and/or eggs triggered their child’s eczema.

- **Current diet and prior history of tolerance to foods**:  
  - Which of the main allergenic foods are included within the current diet?  
  - Has there been any previous attempt to eliminate foods from the patient’s diet?

- **Age of onset of eczema**: Eczema onset in early infancy is far more likely to be associated with food allergy than eczema onset in a child >5 years.

- **Eczema severity**: The probability of food allergy is greater in young children, infants, and those with severe disease. When associated with symptoms of gut dysmotility, the association between food allergy and eczema is strengthened.

- **Co-morbid associations**: Food allergy and eczema can coexist with other diseases such as asthma. Asthma is a risk factor for anaphylaxis, and children, who will have food challenges, should first have their asthma well controlled.

**Allergy-specific test.** When the index of suspicion is high, the tests are useful for confirming allergy, and conversely when the index of suspicion is low, the tests are useful for ruling out a diagnosis of allergy. When there is a lack of correlation between the history and tests of specific IgE or when the history and tests are equivocal, confirmation by way of an open or blinded provocative challenge test is usually required to make the diagnosis.

**It is difficult to prove that specific foods induce the eczema because clinical cases do not always correlate well with skin prick testing and IgE levels**

Tests for the diagnosis of food allergy include skin prick tests, specific IgE tests, and the atopy patch test. None of these tests, however, confirms or refutes the diagnosis of food allergy in the absence of an individual patient history which seeks to establish the prior probability of the allergen being causal. The selection of allergens for testing should be based on the clinical history and patients’ age.

It is difficult to prove that specific foods induce the eczema because clinical cases do not always correlate well with skin prick testing and IgE levels. Clinical history is the most important tool to help with the diagnosis.

**Oral food challenges (OFCs).** OFC testing remains the gold standard for diagnosing food allergy, and the aim is to accurately identify causative allergens.
Only children with severe eczema with a history of possible reactivity to food should have allergy testing done, and this should be done by specialists in the field. Avoidance of multiple foods is potentially hazardous; therefore, OFC should be done only when needed and interpreted with care.

Severe eczema is an indication for hospital-based OFC.

It is imperative to achieve control of the eczema prior to challenge testing.

Patients with eczema need their skin treatment optimized before any reliable conclusions can be drawn about a specific food being a specific trigger of their eczema. This may require a referral to a dermatologist and an intensive treatment, including moisturizers, topical steroids, and in some cases antibiotics. The aim is to gain control of their eczematous inflammation so that the skin is relatively clear at the time of challenge.

A clarification of the presence or absence of food allergy is important, as a positive diagnosis can empower the child and family to safely proceed with an appropriate management plan and advice on specific allergen avoidance. Conversely, a negative diagnosis allows for removal of unnecessary dietary restrictions.

DIETARY MANAGEMENT IN CHILDREN WITH ECZEMA

Although there is a lack of robust studies on dietary avoidance in well-defined populations of children with eczema and food allergy, confirmed on double-blind, placebo-controlled food challenge testing, available studies support the concern that food allergy may play an important role in severe eczema, particularly when the onset is within the first few months of life. Furthermore, dietary elimination of specific food allergens proven by allergy tests and oral provocation tests result in improvement in eczema in most of such cases. There is no case for unselected elimination diets in patients with no prior diagnosis of food allergy and no case for fewer foods or elemental diets. Elimination diets therefore need to be food allergen–specific, based on a proper diagnosis of food allergy which is reached by reviewing the allergy tests within the context of a comprehensive clinical allergy history.

It is important to remember that the overall nutritional health of patients on diets, especially children, should be carefully looked at. There is concern for nutritional deficiencies that may lead to adverse growth and development outcomes in young children consuming very strict diets.
Current data do not support prolonged dietary elimination for most children with eczema. In situations where special diets are attempted, the recommendation is to do so for 4–8 weeks and then return to a normal diet to assess the efficacy of the dietary intervention. A dietician should be involved during the process, as prolonged unsupervised dietary restrictions in children can have severe nutritional consequences.

**PRACTICAL APPROACH TO SPECIFIC DIETARY ALLERGEN EXCLUSION IN ECZEMA**

An approach to the dietary elimination of foods causing reactions was proposed by a European task force in 2007 and a German guideline task force in 2009. These parameters rely on initial treatment of eczema prior to dietary elimination and OFC. If treatment of eczema leads to sustained periods of eczema clearance with minimal need for topical corticosteroids, no further dietary intervention is required unless there is a specific history of immediate reactions to food. The guidelines recommend allergy testing in all patients with suspected food allergy (Box 1).

**OTHER DIETARY STRATEGIES PROPOSED IN ECZEMA**

**Maternal dietary restriction during pregnancy.** Dietary allergens, including peanuts, cow’s milk protein and egg, are known to cross the placenta, can be detected in breast milk, and therefore, may interact with the mucosal immune system. But given the weak support for maternal dietary restriction and the possibility of harmful effects of maternal dietary exclusions to the developing foetus, it is not recommended that pregnant women pursue elimination diets with the aim to prevent or alleviate eczema in their children.

**Breastfeeding.** Breast milk has well-documented immunologic activity, including antibodies that act to neutralize foreign proteins, protect against infection, enable the establishment of a favourable intestinal microflora, and help induce tolerance.

For infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow’s milk protein formula decreases the cumulative incidence of atopic dermatitis and cow’s milk allergy in the first 2 years of life. Some studies have con-

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**Box 1. Consensus statements from the NICE guideline on atopic eczema for children aged 0–12 years**

- A diagnosis of food allergy should be considered in children with atopic eczema who have reacted previously to a food with immediate symptoms, or in infants and young children with moderate or severe atopic eczema that has not been controlled by optimum management, particularly if associated with gut dysmotility (colic, vomiting, altered bowel habit) or failure to thrive.
- A 6–8 week trial of an extensively hydrolyzed protein formula or amino acid formula in place of cow’s milk formula for bottle-fed infants aged less than 6 months with moderate or severe atopic eczema that has not been controlled by optimal treatment with emollients and mild topical corticosteroids.
- Children with atopic eczema who follow a cow’s milk–free diet for longer than 8 weeks should be referred for specialist dietary advice.
- Diets based on unmodified proteins of other species’ milk (i.e., goat’s milk) or partially hydrolyzed formulas should not be used in children with atopic eczema for the management of suspected cow’s milk allergy. Diets including soya protein can be offered to children aged 6 months or over with specialist dietary advice.

NICE = National Institute for Health and Clinical Excellence.
Transmission of these findings and have found an increase in eczema in breastfed infants compared with formula-fed infants, but there is speculation that these findings may be real, a result of reverse causation; mothers who know that their children are at increased risk of developing atopy may be more likely to breastfeed and do it for longer, in an attempt to reduce the risk of the disease in their children.

On the other hand, some studies have shown a decreased incidence of eczema in breastfed infants of mothers who followed a diet that restricted milk, egg or fish.

Overall, the results of several studies suggest that exclusive breastfeeding for a minimum of 4 months could be recommended as a potential method of eczema prophylaxis, at least for mothers of infants with a first-degree family history of atopy.

**Hydrolyzed formula.** The implication that cow’s milk allergy may have a role in the pathogenesis of eczema has led to the investigations of the use of partially and extensively hydrolyzed formulas.

Although there is some evidence that hydrolyzed infant formulas have a positive effect on the prevention of eczema, there is no evidence that these formulas offer advantages over breast milk.

**Delayed introduction of solid foods.** The World Health Organization and the Department of Public Health (UK) recommend that introduction of solid foods should be delayed until 6 months of age.

There is no current convincing evidence that delaying the introduction of solid foods beyond 6 months of age has a significant protective effect on the development of atopic disease, including eczema. This includes delaying the introduction of foods that are considered to be highly allergic, such as fish, eggs and food containing peanut protein.

Studies of the timing of introduction of solid foods into the infant’s diet have yielded results that are difficult to interpret.

**Essential fatty acids.** In recent years, the incidence of eczema in Western cultures has increased, and at the same time, the intake of essential fatty acids, such as omega-3, has decreased.

Although there is no clear evidence to support dietary supplementation with omega-3 and omega-6 fatty acids as a means of preventing eczema, they may have some benefits in decreasing the severity of the disease. Infants and pregnant and lactating women may be important populations to target for supplementation with essential fatty acids.

**Probiotics.** Probiotics are living microorganisms that enhance the microflora of the gastrointestinal tract. Some strains of *Lactobacillus* and bifidobacteria can influence the immune system. Gut microflora helps reduce local inflammation in
the gastrointestinal tract, and certain strains are involved in maintaining the integrity of the intestinal barrier in children with eczema. Breastfeeding has been shown to promote the colonization of *Lactobacillus* and bifidobacteria in the intestinal tract of infants, and this might partially explain the benefits of breastfeeding on atopic disease.

In animal models, probiotics have shown to reduce dietary antigen load by degradation of macromolecules, reducing subsequent development of dietary antigen hypersensitivity, as it is known that antigen degradation is necessary to develop tolerance to dietary antigens.

The results of several studies suggest that exclusive breastfeeding for a minimum of 4 months could be recommended as a potential method of eczema prophylaxis.

The hygiene hypothesis may explain the benefits of probiotic therapy at the same time that explains the increased burden of atopic disease in industrialized countries, where the prevalence is about 20% compared with only 5% in non-industrialized nations. This hypothesis sustains that decreased microbial exposure, as a result of extensive use of antiseptics and vaccinations in the developed world, has led to an altered immune response (T_{H2}-skewed) that ultimately increases the risk of atopy.

Probiotics have not been proven to be a viable treatment for established eczema yet, and there is conflicting evidence of their clinical effectiveness in the prevention of eczema.

Nutritional intervention to impact eczema is a complete new field, and further studies are needed to better guide patients and physicians in this area.

**FURTHER READING**


About the Authors

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<td>For infants from birth to 12 months of age</td>
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<td>- Fruit pectin and cream of rice</td>
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<td>- Low Lactose of 3g/100ml</td>
<td>- For feeding of 2 weeks during and after acute mild-to-moderate diarrhea.</td>
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**KEY NUTRIENT MIX**

**Breast milk is the best food** for infants as it provides the best nutrition, immune defence and protection from diarrhea, colic, regurgitation and constipation for infants. Breastfeeding should be initiated at once after or within one hour of delivery. Good maternal nutrition is essential to prepare and maintain breast-feeding. Mothers should be reminded of the benefits of breast milk, and also it is the most economical food for infants. Working mothers should also be encouraged to continue breastfeeding even after they resume their full time jobs. The introduction of partial bottle feeding will have a negative effect on breastfeeding. Before using infant formula, a mother should be aware of the financial and social implications and the possible health hazards of formula feeding. Inappropriate food or feeding method may lead to health hazards. However, if mothers decide to supplement with an infant formula or not to breastfeed at all, they should seek advice from their health professionals before starting the use of infant formula. Mothers should be professionally instructed on the importance of infant feeding methods, including the cost of infant formula and the health hazards of inappropriate foods or feeding methods. Mothers who are unable to breastfeed should seek professional advice. It is important to warn mothers of the difficulty of reversing a decision not to breastfeed.

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INTRODUCTION

All infectious diseases can occur in pregnant women. There are some that occur more frequently in this group owing to the immunosuppressive nature of pregnancy. There are others that cause increased concern in pregnancy owing to their potential fetal complications. In this article, we will focus on some of the general principles for management of any infection in pregnant women and then discuss some of the diseases in more detail.

PHYSIOLOGICAL CHANGES

Physiological and immune changes occur in pregnancy, making women more susceptible to infections, and these are still not fully understood. A shift from cell-mediated to humoral immunity occurs, which may affect susceptibility to and severity of some infectious diseases, including an increased incidence of certain intracellular pathogens, such as toxoplasmosis, listeriosis, influenza, and varicella.

Urinary tract infections are more common, related to progesterone effects and mechanical compression by the gravid uterus, as well as higher urinary glucose and pH facilitating bacterial growth.

Respiratory infections may be more severe for several reasons. Diaphragmatic elevation reduces secretion clearance and functional residual capacity, and with the increased oxygen demand, reduces tolerance to hypoxia, particularly in the third trimester. Gastric acid aspiration is more common, and increased interstitial lung water is seen, increasing the risk of acute lung injury.
ANTENATAL SCREENING AND PREVENTION

Screening
Since 2003, the UK Department of Health has recommended screening for hepatitis B, human immunodeficiency virus (HIV), rubella and syphilis early in pregnancy with a single blood sample, as well as asymptomatic bacteriuria (ASB) with a urine sample. There is currently no clear evidence of benefit from screening for other infections, although women may request additional screening, particularly if they have experience of health care systems overseas. Whilst the current guidance in the UK is not to screen women for group B Streptococcus (GBS), cytomegalovirus (CMV) and toxoplasmosis, each case should be considered on an individual basis, and consultation with local infectious diseases/virology services may be required. For women at high-risk for HIV, it is important to repeat the HIV test in the third trimester. A negative test at booking can be falsely reassuring, and seroconversion during pregnancy carries a higher risk of mother-to-child transmission.

Primary Prevention
Mothers are advised about primary prevention measures to avoid toxoplasmosis infection such as thorough hand washing, cooking raw meats, and avoiding contact with cat litter and soil. Listeria avoidance includes not eating unpasteurized dairy products or pate and washing salads thoroughly.

Immunization
Ideally, women should be immunized prior to conception, but there are a few situations where immunization of a pregnant woman is indicated. Live vaccines are usually avoided though, owing to the risk of fetal infection.

UK immunization programmes for rubella in childhood should protect during childbearing years. The single vaccine has been in place since 1970, and the measles-mumps-rubella (MMR) since 1988. Until recently, the UK childhood immunization rates were 92%. Following the 2003 negative press coverage, rates dropped to 80%, although they have started to increase again. Women planning a family should ensure immunity.

Live varicella vaccines are available pre-pregnancy, and zoster immune globulin (IG) should be given to pregnant women non-immune to varicella and up to 10 days following exposure. Varicella serology is also available, although immunity is usually assumed from the history of typical rash.

Pregnant women should take precaution to prevent toxoplasmosis infection.
Influenza vaccination (inactivated) may be considered and is deemed safe throughout pregnancy. In light of the recent outbreak of H5N1 influenza and its increased severity in pregnant women, all women should be offered the seasonal vaccine which will give protection to the most common circulating strains.

INVESTIGATION AND MANAGEMENT

Principles
A good history is essential, considering the pregnancy, gestational age, prior ASB, sexually transmitted infections (STIs), travel, occupation, HIV risk factors, contacts with infectious diseases, and prior tuberculosis (TB) infection. There may only be non-specific symptoms and signs, but these are important to consider, as obstetric sepsis can present this way before rapid deterioration.

Involvement of the feto-maternal multidisciplinary team is essential, including clinical microbiologists/virologists/infectious diseases, local TB services, and the critical care team when appropriate. With evidence of STIs, genitourinary physicians should be involved, and screening for other STIs should be undertaken.

Antibiotic Use in Pregnancy
In general, penicillins, cephalosporins, and macrolides such as erythromycin (although less data on clarithromycin) are safe. Clindamycin is also probably safe although clinical experience is limited. Penicillins are only 50% protein-bound and can cross the placenta to achieve fetal concentrations that are therefore 50% of maternal levels. Amoxicillin has increased renal clearance in pregnancy, therefore theoretically higher doses are needed, although in clinical practice, doses are used as outside pregnancy. Augmentin was shown to increase the risk of neonatal necrotizing enterocolitis in one study of preterm premature rupture of membranes (PROM) prevention, and although no animal studies have shown harm, further human studies are needed. Cephalosporins cross the placenta less commonly and appear to have no adverse fetal effects.

Other antibiotics are relatively contraindicated in pregnancy, but their use may be appropriate depending on the clinical situation. Nitrofurantoin is generally considered safe but should be avoided at term because of the risk of haemolytic anaemia in the neonate. There are reports of ciprofloxacin causing an arthropathy in animal studies, but no adverse human effects have been reported. Trimethoprim has also caused adverse effects in animals, so should be used with caution in pregnancy, especially as it may interfere with folic acid metabolism. It should be avoided near term when used as cotrimoxazole in combination with a sulfonamide, as the later can cause fetal kernicterus. Tetracyclines increase the risk of fulminant maternal hepatitis in the third trimester and may stain fetal teeth after 20 weeks’ gestation. Chloramphenicol should be used with caution because of the association with the ‘grey baby syndrome’ (characterized by cyanosis, flaccidity and cardiovascular collapse) when used in newborn infants. Aminoglycoside use (eg, gentamicin) risks fetal ototoxicity and should only be used if there is evidence of serious gram-negative infection. Similarly, vancomycin has been associated with fetal nephrotoxicity and ototoxicity.

MATERNAL INFECTION SYNDROMES

Sepsis
Obstetric sepsis is the most important cause of UK maternal mortality; in the most recent confidential enquiry, the mortality related to sepsis increased from 0.85 deaths per 100,000 mortalities in 2003–2005 to 1.13 deaths in 2006–2008, making sepsis
the most common cause of direct maternal death. The commonest source is the genital tract, notably from *Streptococcus pyogenes* (group A *Streptococcus*, GAS), although it is important to remember that any systemic infections can present as sepsis or septic shock.

Sepsis can present at any time before, during or following delivery, and is important to recognize and treat early, for example using early warning score systems for ward patients, and with community midwives being astute for signs of infection. Mothers often present with vague symptoms and signs, but it is important to recognize these early, as the course can be fulminant. Management of septic shock is similar to that outside pregnancy. Preventative measures include good perineal hygiene.

Most obstetric sepsis occurs post partum, and may relate to genital tract infections, mastitis, thrombophlebitis, episiotomy, and perineal tear infections, caesarean section (CS) wound infections, gastric acid aspiration, or post-general anaesthesia pneumonia.

Antepartum infections include chorioamnionitis which may follow prolonged PROM (pPROM) and prolonged labour. pPROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries, and is suspected with a suggestive maternal history and on a sterile speculum examination. Mothers should be observed 12-hourly for signs of clinical chorioamnionitis. First-line prophylaxis for pPROM is erythromycin. Diagnosis of chorioamnionitis is suggested by fever late in pregnancy, uterine tenderness, offensive vaginal discharge, and fetal tachycardia. Consequences include PROM and premature labour, increased risk of neonatal pneumonia, bacteraemia, meningitis, and death. Treatment is with broad-spectrum antibiotics (ampicillin and gentamicin) and delivery.

Endometritis is a spectrum of endometrial, myometrial and parametrial infections, all of which can be serious, especially when associated with GAS and *Streptococcus agalactiae* (GBS). GAS necrotizing fasciitis and toxic shock syndrome can occur unexpectedly following an uncomplicated pregnancy and delivery, and management includes antibiotic therapy with broad-spectrum antimicrobials according to local policy and early surgical intervention. Thirty percent of the fevers seen in women who have just delivered are due to endometrial infection. The risk is higher post CS and after a PROM, prolonged delivery or in the presence of retained products of conception. Infections are often polymicrobial, with aerobes and anaerobes, and *Chlamydia* can cause late endometritis. Endometritis can also result from CS wound incisions (more commonly seen following emergency CS), which is important to recognize, as utero-cutaneous fistulae may result requiring surgery. Late endometritis more typically follows vaginal delivery. A 2002 Cochrane review concluded that a single dose of ampicillin or first-generation cephalosporins was sufficient to reduce puerperal infections related to uncomplicated CS, given as a single dose after cord clamping.

For an excellent summary of sepsis see chapter 16 of the recent 2006–2008 confidential enquiry into maternal deaths.

**Urinary Tract Infections**

Urinary tract infections (UTIs) are divided according to the site of bacterial proliferation into ASB, cystitis, and pyelonephritis.

ASB is defined as urine colonization greater than 10⁵ colony-forming units per mL on two consecutive clean-catch urine samples (without nitrites or leucocytes on dipstick). It occurs in 4–7% of pregnant women and is important to recognize, as symptomatic UTIs develop in 20–40% of cases, and there is an increased incidence of preterm delivery and low-birth-weight infants. This has lead to
Obstetrics

UK screening being recommended (see NICE guidelines). ASB is due to Escherichia coli in 75–90% of cases, and cephalosporins are more appropriate than amoxicillin, given the 60% E coli beta-lactam resistance seen. Up to 15% will require a further course later in pregnancy.

Cystitis or bladder infection occurs in 1–4% of pregnancies and pyelonephritis, where the kidney is the focus in 2% of all pregnancies.

Pyelonephritis is a serious medical condition in pregnancy, associated with fetal and maternal morbidity, and leads to an increased risk of premature labour. Two-thirds of cases present in the second or third trimester, and 27% post partum. The right kidney is most often affected owing to dextro-rotation of the uterus. The common presenting features are fever, loin pain, rigors, and less often with symptoms of cystitis. Pyelonephritis is the most common cause of septic shock in pregnancy, and adult respiratory distress syndrome (ARDS) occurs in 1–8% of cases, so patients should be closely monitored. Diagnosis is based on the presence of significant bacteriuria following mid-stream urine culture, and the history and clinical signs. A renal tract ultrasound scan should be performed to exclude hydronephrosis and structural abnormalities. Organisms are similar to those in lower tract UTIs, with E coli in 70–80%, and Klebsiella pneumonia and Proteus species less commonly, but important in recurrent cases. Antibiotic choice reflects local guidelines, usually with a first-generation cephalosporin or combination ampicillin with gentamicin. Most will be afebrile and asymptomatic following 48 hours of appropriate antibiotic treatment, and intravenous therapy is then continued until the patient has been afebrile for 48 hours. Failure to respond after the initial 72 hours usually indicates a resistant organism, renal tract stone, or anatomical obstruction. When discharged home, the mother should be more closely watched for recurrence with monthly urine cultures. Fetal effects of untreated pyelonephritis include preterm delivery and low birth weight. If GBS is detected in maternal urine, it should be treated and appropriate intra-partum prophylaxis administered (see later).

Cranberry juice has been used traditionally to prevent and treat UTIs. It contains proanthocyanidins which prevent the adherence of bacterial pathogens to the uroepithelium. A recent Cochrane review showed a significant reduction in UTIs compared with placebo, although this was not specific to pregnancy.

Respiratory Tract Infections

Bacterial pneumonia has a similar incidence and outcome in pregnancy, although viral pneumonias are more common and run a more severe course.
in pregnancy. Investigation and management are similar, although delay in obtaining a chest X-ray is common; remember that the radiation exposure is only 0.05% that of the maximum recommended 0.2 rad. Influenza and varicella pneumonia in pregnant women have historically been associated with a higher rate of morbidity and mortality. Some important pathogens are considered below, and others, including TB, in later sections.

**Respiratory Pathogens in Pregnancy**

**Upper respiratory tract infection** – pregnant women often find that they have a persistent cold in the last trimester. Whilst this may be due to any of the common viral pathogens such as rhinovirus, there is no treatment and in the absence of lower respiratory tract symptoms does not need investigation.

**Bacterial pneumonia** – the most common cause of pneumonia in pregnant women remains the same as in the general population – *Streptococcus pneumoniae*. This is usually fully sensitive to amoxicillin (with some decreased susceptibility in strains from abroad).

**Influenza pneumonia** – influenza infection presents with similar self-limiting symptoms, but if they last more than 5 days, complications are not unusual. Pneumonia has a greater mortality rate (up to 50%) in pregnancy and may result from a secondary bacterial pneumonia (*Staphylococcus aureus, Pneumococcus*, or *Haemophilus influenzae*) or viral parenchymal infection.

Complications from pandemic influenza A (H1N1) are more common in pregnancy, notably severe ARDS. Treatment is with the neuraminidase inhibitor oseltamivir, which should be started as soon as possible until clinical improvement occurs, although data are limited in pregnancy. See World Health Organization guidelines for further details.

In cases that remain hypoxic despite maximal invasive mechanical ventilation, veno-venous extracorporeal membrane oxygenation may be required. This is a form of ‘lung bypass’ to rest the lungs while they recover, and successful cases have been reported during pregnancy and immediately post partum.

**Varicella pneumonia** – primary varicella infections are more severe in pregnancy, and progression to varicella pneumonia is more common (10–20% of those infected). Maternal mortality from varicella pneumonia is higher in pregnancy (35% versus 11%), thus prevention of primary infections is of great importance. Oral mucosal ulceration is common, and respiratory illness ranges from coryzal symptoms to severe respiratory failure requiring mechanical ventilation. Classically, the chest X-ray shows bilateral miliary nodular shadowing, and later pulmonary calcification.

**Other causes of pneumonia** – *Pneumocystis jiroveci* pneumonia (PCP, previously called *P carinii* pneumonia) in HIV-positive patients is associated with adverse obstetric outcome, and should be treated with co-trimoxazole. PCP is also increasingly being seen in immunocompetent hosts, previ-
ously only associated with immunodeficiency. One study showed that asymptomatic nasal carriage of *P jiroveci* is more common in pregnancy, and another that PCP is more severe in pregnancy. In HIV-positive women, *P jiroveci* may be transmitted perinatally.

*Chlamydia psittaci* is an unusual cause of atypical pneumonia, (ie, those organisms not causing a ‘typical’ lobar pneumonia). It is usually transmitted via infected birds and may cause a severe illness during pregnancy, but recovery is usually full. Fungal pneumonia, although unusual, may also run a more severe course in pregnancy, especially in the final trimester.

**Hepatitis**

Viruses causing hepatitis include the hepatitis viruses A–E, as well as Epstein-Barr virus, CMV, toxoplasmosis, and herpes simplex virus.

Overall, the clinical course of hepatitis A, B, C and D viruses is unchanged in pregnancy, but prevention of vertical transmission is important. Vertical transmission with maternal hepatitis A virus infection is rare, and the neonate should be given IG at birth. Hepatitis B virus is screened for antenatally as the risk of vertical transmission from asymptomatic mothers is high; rates are up to 95% if mothers are hepatitis B surface antigen- and e-antigen-positive. Vertical transmission usually occurs at delivery and is more likely if the hepatitis B virus infection is associated with a high viral load. Several strategies including vaccination and use of hepatitis B virus specific IG are in place to decrease the chance of transmission. There is sometimes a need to treat newly diagnosed pregnant women with oral anti-viral agents for her own health. All new diagnoses should be referred urgently to the local hepatitis service. There is clear guidance on management available through the Department of Health Green Book (see Further Reading).

At least 6% of hepatitis C–positive pregnant women will transmit this to their baby perinatally. This risk is increased in the presence of co-infection with HIV to 15%. Elective CS may reduce the transmission risk. There is no role for treatment of HCV in pregnancy, and there is no vaccine available. Screening is not routinely carried out but should be considered in high-risk groups – mainly those with a history of injecting drug use.

Hepatitis E virus is water-borne and transmitted faeco-orally, usually causing a mild self-limiting infection. However, in pregnancy, there is a sixfold increase in maternal mortality, especially in the third trimester, with 15% of cases leading to fulminant hepatic failure where the mortality is 5%. The mechanism may relate to immunologic imbalance associated with a predominant T helper subtype 2 cell response and suppression of cell-mediated immunity seen in pregnancy. There is no specific treatment.

*Herpes simplex virus* (usually herpes simplex virus type 2) can also lead to fulminant hepatic failure in pregnancy, often with associated pneumonitis or encephalitis. Diagnosis is made on liver biopsy and serology, and specific treatment for the mother and infant with acyclovir is available.

**Rash**

There are comprehensive guidelines on the management of rashes in pregnancy from the Health Protection Agency (www.hpa.org.uk).

The important infections to consider in the differential diagnosis include rubella, parvovirus B19, varicella, measles, enteroviruses, and infectious mononucleosis. The first three are discussed in a later section.

Measles infection in pregnancy can lead to intrauterine death and preterm delivery, although not congenital infection or damage. Indigenous measles is rare in the UK following introduction of the MMR
vaccine, although it is endemic in some countries. Human normal IG may attenuate measles, but there is no evidence that it prevents intrauterine death or preterm delivery.

Enteroviruses (including coxsackievirus A, B and echovirus) can cause a wide range of manifestations such as meningitis and myocarditis. Neonatal infection, especially with echoviruses, can have multisystem life-threatening complications. No vaccines are available except for poliovirus, and IG is advised for prophylaxis in exposed neonates.

Infectious mononucleosis is caused by primary Epstein-Barr virus infection with no specific risk to the fetus.

**SPECIFIC PATHOGENS**

**Tuberculosis**
The UK and worldwide TB infection rates are rising. Incidence peaks in the childbearing years (25–34 years). In the UK, infection is most common in Asian and West-African populations. Pregnancy is thought not to change the course of TB, although it does increase preterm births, especially in the developing world. As in the non-pregnant population, transmission of *Mycobacterium tuberculosis* is via respiratory droplets. Overall 10% of those infected (initial infection is usually asymptomatic) will develop active TB, usually 1–2 years after infection. More extra-pulmonary TB is being seen with HIV co-infection, and 5–10% of pregnant women have extra-pulmonary disease (similar to the non-pregnant population). Pregnancy and the peri-partum period is a common time for latent TB to reactivate. Diagnosis is by usual methods, and tuberculin skin testing is safe in pregnancy.

Management is similar to in non-pregnant patients. All four first-line drugs are thought safe and have been used for many years, including ethambutol and isoniazid. Pyridoxine should be added to isoniazid therapy to prevent peripheral neuropathy. Streptomycin, however, should be avoided, as fetal eighth nerve damage has been associated in a significant number of cases. Infants born to mothers with smear-positive TB should be treated with isoniazid syrup for 6 weeks as chemoprophylaxis, and then a tuberculin skin test performed. Breastfeeding can continue as normal, as minimal anti-tuberculous agents are secreted in breast milk.

**Malaria**
Malaria contributes significantly to maternal mortality and morbidity in the developing world. In the UK, 2,000 cases are reported annually, mostly in travellers from endemic areas. Untreated *falciparum* malaria is life-threatening in any population, and pregnant women are more susceptible; anaemia can be severe, and there is an increase in maternal mortality, preterm birth, miscarriage, and stillbirth.

Immunity to malaria is altered by pregnancy, especially in primiparous women with high parasite loads, although the risk is reduced with successive pregnancies. Drugs are used for prevention in endemic areas, with effective reduction in maternal anaemia, birth weight and possibly perinatal death. In the UK, women with malaria in pregnancy should be admitted as there is an increased risk of severe disease and hypoglycaemia. Suitable regimes depend on the type of malaria and local resistance patterns, and chloroquine is the choice for *Plasmodium vivax*, *P malariae*, *P ovale*, and quinine for *P falciparum*. All regimes should be supplemented with folic acid.

**Malaria prophylaxis:** travel to a malarial area in pregnancy should be avoided; getting malaria whilst pregnant increases the risk of miscarriage as well as being life-threatening to the mother. No antimalarial is 100% effective, and women should seek advice from a local travel clinic. There are guidelines available on the choice of agent to use.
The common vaginal commensal, group B Streptococcus, can lead to life-threatening neonatal effects.

Human Immunodeficiency Virus

HIV worldwide infection is increasing. UK seroprevalence in pregnant women is 0.21%, with over 300 HIV-infected women giving birth annually. There is an increased risk of preterm delivery, low-birth-weight infants and miscarriage with maternal HIV infection, worse in mothers with advanced disease and poor nutrition. Antenatal screening is done routinely in the UK.

The mother-to-child transmission rate in the UK is now less than 1%. This has been achieved through a variety of interventions, notably the use of antiretroviral combination therapy, a multidisciplinary approach to both the timing and method of delivery, post-exposure prophylaxis for the infant, and an avoidance of breastfeeding. Management of each case is highly individualized and should be done in conjunction with a team of health care professionals including a midwife, obstetrician, HIV specialist, and a neonatologist and paediatric nurse. Some antiretroviral drugs are safe in pregnancy although currently very few are licensed. Guidelines are available (see Further Reading).

Group B Streptococcus

This common vaginal commensal can lead to life-threatening neonatal effects. Of the 20% of mothers that carry it, 40–70% of infants become colonized in the first week of life. Neonatal infection can be early or late, presenting with pneumonia, sepsis, meningitis, and death in up to 10% (higher in preterm infants). As the overall UK infection rate in infants is 1%, routine screening is not currently offered. Neonatal disease is reduced by administration of intra-partum intravenous penicillin to high-risk mothers. These are identified fortuitously by high vaginal swabs performed for a variety of reasons during pregnancy, including those women complaining of vaginal discharge, those with possible preterm membrane rupture, women in preterm labour, temperature greater than 38°C in labour, preterm PROM, ROM for more than 18 hours prior to delivery, or a previously affected child.

Chlamydia trachomatis

Genital tract infection with Chlamydia trachomatis is common in the UK and may lead to ectopic pregnancy, preterm labour, puerperal infection, and ophthalmia neonatorum. Erythromycin is the advised treatment.

Bacterial Vaginosis

This STI, caused by Gardnerella vaginalis, may cause chorioamnionitis, preterm delivery, and postpartum fevers. Treatment is with erythromycin or metronidazole.

Herpes Simplex Virus

Maternal genital herpes is more virulent in pregnancy. Early miscarriage (but not fetal abnormalities) may occur, and late maternal primary infection can lead to severe neonatal infection. Genital lesions, especially in primary infection, contain
Varicella is also important to recognize and treat in pregnancy as maternal complications are more severe.
Table 1. Fetal risks associated with certain maternal infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Rubella</th>
<th>Varicella</th>
<th>Cytomegalovirus</th>
<th>Parvovirus B19</th>
<th>Toxoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital defects</td>
<td>Ocular defects, heart (PDA), SNHL, mental retardation</td>
<td>Fetal varicella syndrome: skin scars, eye defects, limb hypoplasia, developmental delay, microcephaly</td>
<td>IUGR, HSM, microcephaly, jaundice, chorioretinitis, intracranial calcification, 20% mortality. Late microcephaly, SNHL, and developmental delay (15%)</td>
<td>Fetal hydrops, IUD (1st trimester). Rarely persistent neonatal infection and anaemia</td>
<td>Hydrocephalus, mental retardation, chorioretinitis</td>
</tr>
<tr>
<td>Trimester most at risk (% risk of defects)</td>
<td>First – abnormalities in 80–90% survivors; risk 13–16 weeks of SNHL</td>
<td>All trimesters, especially 13–20 weeks (2%)</td>
<td>All trimesters</td>
<td>First trimester</td>
<td>Malformations highest in first trimester. More infections near term (2% at 8 weeks vs 75% at term)</td>
</tr>
<tr>
<td>Maternal effects</td>
<td>Arthritis</td>
<td>Pneumonia; increased mortality</td>
<td>Asymptomatic or IM syndrome</td>
<td>Febrile illness, erythema infectiosum, aplastic anaemia</td>
<td>Mostly asymptomatic or flu-like; lymphadenopathy</td>
</tr>
<tr>
<td>Available treatment</td>
<td>TOP offered</td>
<td>ZIG to mother and neonate. Acyclovir within 24 h of rash onset for mother and for infected neonates</td>
<td>None</td>
<td>Intrauterine transfusion. No vaccine</td>
<td>Spiramycin (cycled pyrimethamine, sulfadiazine, and folic acid)</td>
</tr>
</tbody>
</table>

HSM = hepatosplenomegaly; IM = infectious mononucleosis; IUGR = intrauterine growth retardation; PDA = patent ductus arteriosus; SNHL = sensorineural hearing loss; TOP = termination of pregnancy; ZIG = zoster immune globulin.

tal varicella syndrome occurs in 1% of fetuses infected before 20 weeks, especially 13–20 weeks. Note that this is less than the 85% risk of rubella fetal damage, hence there is currently no UK routine screening policy. Varicella is also important to recognize and treat in pregnancy as maternal complications are more severe.

Treatment in pregnancy is safe with acyclovir. If delivery is imminent and infection occurs within 10 days of delivery, it is advisable to wait 5–7 days for passive transfer of maternal IG if possible. If not, the neonate should be given zoster IG, as there is a 20% neonatal infection risk if the mother develops clinical chickenpox in the period 5 days prior to birth until 2 days after. Neonatal infection carries a high mortality rate.

Shingles (dermatomal reactivation of latent virus) when localized carries no apparent risk to the fetus. However, it is uncertain whether dissemination, for example in an immunocompromised patient, carries a fetal/neonatal risk.

Cytomegalovirus
Fetal CMV infection is the second most prevalent cause of mental retardation after Down syndrome. Childhood infection is common in developing coun-
tries, hence leads to herd immunity, however only 50–60% of women in developed counties have positive serology. Primary maternal infection in adults may be asymptomatic or lead to infectious mononucleosis-like syndrome. Primary infection, reactivation, or reinfection with a different strain of CMV may lead to intrauterine infection, although the fetus is rarely affected in cases of reactivation.

Primary infection leads to transplacental fetal infection in 40% of cases, and fetal sequelae may occur over a wide timescale. Up to 7% will present at birth with defects (see Table 1). The mortality is 20% in this group, and a further 15% will have abnormalities found later at follow-up.

In cases of suspected maternal infection, blood serology is helpful, ideally with a paired sample from booking to compare rising antibody titre, noting that circulating IgM may persist for months. When confirmed, fetal infection should be proven by culture and polymerase chain reaction of amniotic fluid at amniocentesis. Serial fetal ultrasound is available to identify suggestive features such as ventriculomegaly and intracranial calcification, although no findings are specific. It must be remembered that most infected neonates will in fact be unaffected. There is no specific treatment, although a vaccine is in development, and screening for maternal immunity is therefore not routine in the UK.

Parvovirus B19
Parvovirus B19 infection is common, with 50–60% of adults having been infected. Infection in the first 20 weeks of pregnancy can lead to intrauterine death and fetal hydrops. These consequences usually occur 3–5 weeks after the onset of maternal infection, but can be later. There is no evidence to suggest that reinfection is a risk to the fetus. No vaccine or preventive measures are available, and an increased incidence occurs every 3–4 years, often in schoolchildren.

Toxoplasmosis
Maternal infection is rare (2 per 1,000 in the UK; more common in France), and flu-like symptoms and lymphadenopathy occur in up to 15% of infected women. Fetal infection probably depends on the gestational age at maternal seroconversion. A French study showed that there were more congenital abnormalities (see Table 1) with early maternal infections, and more fetal infections with seroconversion at term.

Diagnosis is confirmed by amniocentesis, chorionic villus sampling or fetal blood sampling, and ultrasound findings of intracranial calcification, hepatomegaly and placental thickening are late and non-specific. Treatment with spiramycin from time of maternal infection may reduce fetal infection and, therefore, congenital abnormalities. In late (after 32 weeks) high-risk fetal infections, 3-week cycled courses of pyrimethamine, sulfadiazine and folinic acid may be added.

Syphilis
Maternal infection with the spirochaete Treponema pallidum has increased in recent years. Fetal infection can occur at any stage, but most often in primary (90%), secondary and early latent infections.

### Practice points

- Most maternal infections do not harm the fetus
- All rash illnesses should be referred for specialist assessment
- Maternal obstetric sepsis may present with non-specific symptoms and signs, and run a fulminant course
- Obstetric sepsis remains a significant cause of maternal mortality and should be identified early and managed aggressively
- The investigation of infections that can affect the fetus should be appropriate for both mother and fetus, usually in or in consultation with a feto-maternal medicine unit
- Screening is important for HIV as interventions exist to reduce vertical transmission
Most infected women are asymptomatic, and positive serology is detected at antenatal screening. Maternal infections treated with high-dose penicillin will reduce the risk of fetal infection. Twenty-five percent of fetal infections result in preterm labour and 25% in fetal loss. In survivors, congenital syphilis may result with polyhydramnios, hepatomegaly, osteochondritis, purpura, and late interstitial keratitis. Fetal infection is suggested by antigen testing of amniotic fluid or fetal blood, although these have a poor negative predictive value.

Listeria monocytogenes
Listeriosis is caused by Listeria monocytogenes, a gram-positive bacillus, and although an unusual infection, may have serious adverse outcome in pregnancy. There are about 20 cases of Listeria associated with pregnancy in the UK per year. It is food-borne, from unpasteurized dairy products, and pregnant women should avoid such high-risk foods. It can survive at low temperatures (such as the fridge) on raw vegetables, hence the importance of washing food in pregnancy. Maternal symptoms can be asymptomatic or with flu-like symptoms, and can range from mild to severe with ARDS. The diagnosis is based on a high index of clinical suspicion, and on positive Gram stain from maternal blood, liquor or neonatal samples.

Maternal infection can lead to miscarriage, premature labour, and if the infant survives, to perinatal listeriosis. Congenital listeriosis has also been reported following transplacental passage and can lead to fetal hydrops. Treatment is with high-dose ampicillin and gentamicin.

CONCLUSION
Infections during pregnancy are usually self-limiting; however, awareness is needed to identify those leading to significant maternal and fetal morbidity and mortality. Screening and vaccination programmes are important. Investigation and management of infection may be complex and the multidisciplinary approach is essential, involving the obstetric team, as well as fetal medicine, genitourinary and critical care physicians.

FURTHER READING

About the Authors
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INTRODUCTION

There is a major unmet clinical need of millions of patients globally suffering many major diseases, which, in all cases, severely compromise the quality of life and frequently lead to death. While advances are being made with more traditional drug-based therapies, it is now clear that a major new impetus is required. The potential revolution in science and medicine that stem cells represent is rapidly emerging as the new frontier in clinical therapies. Given that stem cells are ‘regenerative medicine factories’, they may be delivered as ‘stand-alone treatments’; but more likely, they will be potent adjuvants and be combined with current strategies. Clearly, a great deal of preclinical and clinical research on stem cells is required not only to capitalize on their treatment potential but also to ensure that safety and ethical requirements are met. It is also imperative to select the most appropriate source of stem cells for the variety of treatments. Ideally, these stem cells should be derived from the patients themselves to overcome any issues of immune rejection. It is now evident that the time of birth is a remarkable once-in-a-lifetime opportunity to collect and cryopreserve a panel of stem cells, which effectively represent nature’s ‘body repair kit’ for the duration of the newborn’s life. There are also stem cells available for maternal utility.

Once regarded as medical waste, the umbilical cord, based on extensive groundbreaking research, has now been revealed as an invaluable source of haematopoietic stem cells (HSCs) and pluripotent mesenchymal cells (MSCs) both of which now have increasing application in regenerative medicine. In addition, the amnion membrane is a very rich source of pluripotential MSCs which, being equivalent to embryonic stem cells (ESCs), are able to differentiate into many different types of tissues.

Accordingly, these advances in stem cell research, coupled with the ever-increasing clinical efficacy, have led to the fast-growing establishment of cord blood banks...
worldwide, which store umbilical cord blood (UCB) for future use and are of either a public or private nature. This affluence of stem cell banks started in the mid to late 1990’s in response to the potential use of cord blood transplants for the treatment of various disorders. However, the knowledge of stem cells and cord blood banking are scarce among pregnant women as shown by many studies, while most of them would like to be informed by health care professionals specifically and especially in early pregnancy so that they would have time to contemplate the virtues or otherwise of cryopreservation of their babies' stem cells.1,2 This article will therefore review the background on stem cells and UCB banking (UCBB) as well as patients’ knowledge on this issue, and the role of obstetricians in conveying adequate information to patients. Present development on stem cells will also be discussed.

BACKGROUND (HISTORY) OF STEM CELLS

Stem cells are one of nature’s most powerful ‘building blocks’. They have the unique ability to both self-renew to replenish their availability and differentiate into a variety of different cell types. Hence, they not only create the organs and tissues in the body but also maintain them and assist in the repair following damage or disease.

There are two broad types of stem cells: ESCs and adult stem cells.

Human ESCs

Human ESCs are isolated from 4- to 5-day-old post-fertilized blastocysts (Figure 1). Human ESCs are capable of indefinite ex vivo proliferation and can differentiate into any specialized cell in the human body. Adult stem cells are located in tissues throughout the body and function as a reservoir to replace damaged or ageing cells;3,4 they differentiate only into the cell lineage of the organ system in which they are located (Figure 2). UCB is a source of adult stem cells, in particular MSCs (or stromal cells), which not only have the normal capacity to differentiate into structural tissue (bone, muscle, cartilage, fat) but also have the important property of being anti-inflammatory.5

ESCs have great potential in generating tissues and organs, yet there are several major problems with them. The generation of ESCs requires destruction of discarded embryos from in vitro fertilization, which is ethically challenging if it involves destruction of life. Furthermore, by virtue of the way ESCs are produced by long-term replicative culture in vitro, there is a major safety issue: because of their rapid proliferation, ESCs form teratomas upon transplantation.6 Most importantly, we do not have our own ESCs, and therefore any ESC transplant will be allogeneic. An accessible and ethically
sound alternative is adult stem cells, which exist in virtually every tissue, albeit being difficult to identify and isolate. Adult stem cells also possess limited differentiation potential, but one of their major advantages is that they pose no risk of rejection as they are used in autologous transplants.

Newborn Stem Cells
Given the difficulty in settling the dilemmas associated with the use of human ESCs legally, with regard to the public perception of the ethical issues and the safety concerns, alternate sources of stem cells were sought after. In 1983, Edward Boyse proposed the idea of using UCB as a potential source of stem cells for haematopoietic transplantation, thereby highlighting research on placental/newborn stem cells. This was followed by experiments in irradiated mice revealing that murine blood from near-term and neonatal mice contained adequate numbers of HSCs to effect bone marrow recovery.7

Figure 2. The cell lineage of each organ system in the human body.
Obstetricians can educate pregnant women about umbilical cord blood banking.

The first pioneering haematopoietic cord blood transplant was performed to treat a 6-year-old boy with Fanconi anaemia in 1988 in Paris, France, with the first successful unrelated UCB transplant performed in the United States in 1994. The first pioneering haematopoietic cord blood transplant was performed to treat a 6-year-old boy with Fanconi anaemia in 1988 in Paris, France, with the first successful unrelated UCB transplant performed in the United States in 1994. In vitro cultures of CD34+ cells (as a marker of HSC) from umbilical cord yielded a higher rate of proliferation than similar cells from marrow. Besides, UCB HSCs may also have a greater capacity for self-renewal and long-term growth in culture. However, although UCB is proportionally rich in HSCs, its use is limited because of the relatively low volume of blood and hence total HSC dose. The transplanted cell dose is approximately 10% of a marrow transplant. HSCs can be used in allogeneic and autologous settings. In the allogeneic setting, they can be used to treat neoplastic conditions (eg, leukaemia), non-neoplastic conditions such as inherited disorders (eg, thalassaemia major), immunodeficiency, osteoporosis, and acquired conditions (eg, aplastic anaemia). In the autologous setting, they can be used to treat autoimmune disorders like aplastic anaemia; but in advance-stage solid tumours, their use is currently limited. HSCs are also being investigated for efficacy in treating cerebral palsy, stroke, and as a means of gene therapy. Autologous cord blood stem cells are not suitable for treating inborn errors of metabolism or some genetic diseases such as childhood leukaemia in which chromosomal translocations in fetal blood were detected in children who finally developed leukaemia. The use of autologous stem cells would also negate the beneficial graft-versus-leukaemic effect that occurs with allogeneic stem cells.
cell transplants by its residual T lymphocytes in the haematopoietic progenitor cell product.15

UCB as a source of HSC for transplant is more superior than, for example, bone marrow, as it appears to have a higher tolerability of HLA mismatch, which may be explained by its high content of immune suppressing cells called regulatory T cells, which are able to suppress immune responses; accordingly, they have been used for treating type 1 diabetes and multiple sclerosis. This is an important and often unrecognized value of UCB.16

THE PATIENT’S KNOWLEDGE OF STEM CELLS AND UCBB

In 2003, Fernandez et al1 examined pregnant women’s knowledge and attitudes relating to UCB and UCBB; 70% reported poor or very poor knowledge about UCB; 66% expected the physician to talk to them about cord blood collection and said they would specifically like to receive such information from health care professionals or in prenatal class (70%). Twenty-five percent overestimated the risk of a child needing a bone marrow transplant before his or her 10th birthday—the risk is reported as between 1 in 200,000 and 1 in 10,000.17 Eighty-three percent expected to be asked about UCBB before 30 weeks of pregnancy. In a post hoc analysis, this level of knowledge was not associated with the choice between public and private banking.1

In 2006, Perlow et al demonstrated that among the 425 patients recruited in the survey in USA, 37% had no knowledge of UCBB. Older patients and those more educated were more aware of UCBB. Among patients familiar with UCBB, only 2.6% felt extremely knowledgeable while 74% felt ‘minimally informed’. Seventy-one percent of patients were not planning UCBB with the main reasons of expense and insufficient knowledge. Only 14% were educated about UCBB by the nurse or obstetrician, and 90% expected their obstetrician to answer their questions on UCBB.18 Similar results were also reported by Fernandez et al and Dinç and Sahin.2

In one study, almost one-third of the participants did not realize that they had the option to retain their cord blood at delivery; only 50% were aware that they could store their cord blood in a private bank and half of the respondents thought cord blood donation to the public bank was to protect their child’s future health.19

A recent research article about our Hong Kong locality showed that among 2,000 women recruited, 93.3% completed the questionnaire. The majority (78.2%) had no idea about the chance of using self-stored stem cells. Most were unclear about which diseases other than leukaemia are amenable to treatment with UCB stem cells. This is not taking into account that if the child developed leukaemia, their UCB would not be used for haematological rescue because autologous stem cells lack the graft-versus-leukaemia effect as well as because of the fear of cancer contaminants within the UCB. Only 20.3% of women knew that stem cells are available from the Red Cross (a local public cord blood bank) in case their children needed haematopoietic cell transplantation. Hence, most patients have inadequate knowledge about stem cells and UCBB, creating an obstacle to UCBB. They would like to receive more information from health care providers, especially their obstetricians, and be provided with the relevant knowledge accordingly in early pregnancy so that they can have adequate time to contemplate their choices.20

THE OBSTETRICIAN’S ROLE IN CONVEYING DETAILED AND ACCURATE INFORMATION TO THE PUBLIC

Given this background, it is imperative that the ob-
Obstetrician be well educated of the pros and cons of stem cells so that appropriate advice to expecting parents can be given.

Advantages and Disadvantages of Cord Haematopoietic Progenitor Cells

Being an alternative to bone marrow as a source of HSCs for allergenic transplantation, cord blood has both advantages and disadvantages.\(^{21,22}\)

The advantages are as follows:

- Faster availability: patients on average receive cord blood transplantation earlier than those receiving conventional bone marrow grafts.\(^{23}\)
- Ethnic diversity allows extension of donor pool: with a greater tolerability of HLA mismatch, this allows a higher availability of specimen for transplantation.
- As a result of greater tolerability of HLA mismatch, there is lower incidence and severity of acute graft-versus-host disease with a relative risk of 0.66.\(^{24}\)
- Lower incidence of viral transmission, ie, cytomegalovirus and Epstein-Barr virus.
- No donor attrition compared with bone marrow registry.
- High proliferative capacity.
- Painless collection of stem cells.

The disadvantages are as follows:

- Low numbers of haematopoietic progenitor cells and stem cells (approximately 10% of a marrow transplant)\(^{22}\) in each cord blood unit, which may delay engraftment; this is hereby addressed by experimental procedures like ex vivo expansion of the cells and use of multiple UCB units in the same recipient to expand the progenitor pool.
- Inability to obtain addition stem cells and/or lymphocytes from the graft donor for second transplantation in case of graft failure or disease relapse.

**Indication**

HSC use is recommended especially in at-risk families for which there is a known genetic or haematological disease amenable to HSC transplantation for the affected child if HLA-compatible.\(^{25}\)

**Collection**

There are two techniques of cord blood collection: *in vivo* with placenta *in utero*, and *in vitro* with placenta *ex utero*.

A comparison of the two techniques has shown larger unit volumes and higher total nucleated cells counts with *in vivo* collection.\(^{26}\) It is recommended that collection should be done by a trained third party (ie, not by the attending obstetrician or midwife) using methods and facilities appropriate to meet the European Tissues and Cells Directive.

The collection procedure must be undertaken either during the third stage or shortly after, a time when there is a risk of postpartum haemorrhage.\(^{21}\)

It is not guaranteed that sufficient volume can be collected; successful transplantation of cord blood HSCs is related to the volume and cell dose collected. Stringent antiseptic technique is needed to avoid bacterial contamination.\(^{27}\)

**Ethical Issues**

The use of stem cells has generated lots of debate on bioethics, focusing on the principle of autonomy. It is suggested that the cord blood belongs to the property of the child, as the placenta or cord blood stem cells is biologically and genetically developed by the child.\(^{28,29}\) On the other hand, one would suggest that it is the mother’s property once the cord is cut. However, legal rights of property are not generally founded on genetic identity. Although based on the ontological status of the fetus, once it is outside the mother’s body, it is recognized as a legal individual by law but is unable to have full understanding and thus unable to give consent.
Therefore, the mother, who shares the prenatal authority, would be the one to give consent on behalf of the baby. If the cord blood is stored for the child’s use, then the mother will hold in trust till the child attains the age of 18 years, by which time the use of stem cells will be decided by the child.21 If the cord blood is donated, this may then be considered as a manipulation of human body parts without the individual’s knowledge.30 In order to translate the ethical debate from the speculative level into practice, it is important to get good informed consent for stem cells use.

A report by the Institute of Medicine has recommended that cord blood centres establish clear policies as to who must provide consent for donation with consideration of paternal objection to donation and for public cord blood banking.

Cost and Choice of Banking
Broxmeyer et al, in a study, suggested that UCB can be frozen and stored for at least 15 years with highly efficient recovery of viable and highly functional human stem cells.33 Data suggested that long-term storage is feasible and does not compromise the quality of the engraftment ability of UCB unit.34 The great therapeutic potential of UCB and the demonstration of the feasibility of cryopreserving collected units and their utility for up to 15 or more years led to the development of cord blood banks. A cord blood bank is an establishment for collection, processing, and storage of cord blood. There has been an emergence of public and private banking in the past two decades.

Public banks, being community-based, promote allogeneic donation of both related and unrelated cord blood, which is subsequently accessible by the general population. Patients should be informed that they relinquish property rights to the cord blood units after donation.

Private banks, which are commercially based, store cord blood for autologous use with cost associated with specimen processing and storage for the harvested cord blood as a family biological in-

Consent
Obstetricians should not be obligated to obtain consent for private UCBB.31
A report by the Institute of Medicine has recommended that cord blood centres establish clear policies as to who must provide consent for donation.
surance, which can also be used for other family members.

It is recommended that balanced information for both autologous and allogeneic donation should be provided to pregnant patients in the antenatal period.32

In public banks, the donated cord blood is not assured of being banked or being made available to donors if required in the future. Safety is a concern as the donated cord blood may carry genetic defects for disorders, such as congenital anaemia or immunodeficiency, that are not apparent in the donor for months or years, by which time all identifying information has been removed while the recipient could have developed these disorders.

Private banks provide a life insurance by having the cord blood available for the lifetime, depending on its commercial viability of the enterprises,35 and the estimated utility of autologous UCB is approximately 1 in 20,00028 to 37 in 100,000 (1 in 2,700).20

Regulatory Issues
To establish a uniform standard for collection and quality assurance, it is important that establishments provide standardization of procurement, testing, processing, storage, distribution, documentation, labelling, equipment control, and cord blood bank operations.
In the United Kingdom, cord blood collection is regulated by the Human Tissue Authority (HTA); for an HTA-licensed establishment, a third party agreement is required. The HTA stresses on four aspects of cord blood collection: safety, quality, consent, and lawfulness. The HTA does not regulate or provide advice about the effectiveness of treatments using cord blood.36

In the United States, many cord blood banks have undergone voluntary accreditation through the American Association of Blood Banks or the NetCord Foundation for the Accreditation of Cellular Therapy. In our locality, we do not have an establishment as such, and there is currently no guideline available on cord blood collection or use of collected stem cells. Therefore, health care providers, especially obstetricians, should help in conveying detailed and balanced information on stem cells to couples to ensure thorough understanding and aid their decisions.

**FUTURE DEVELOPMENT**

Stem cell research has heralded a new horizon in clinical medicine. While appreciating the value of cord blood, it is recognized that there is a variety of progenitor cells, besides HSCs, in cord blood and placenta; they are the MSCs in umbilical cord, chorion, and placenta, namely, MSCs in umbilical cord tissue (Wharton’s jelly), amniotic MSCs, and amniotic epithelial stem cells (Figure 3), which may be a new platform for tissue transplant, ie, bone, cartilage, fat, myocardial muscle, and neural tissue, owing to its anti-inflammatory, immunosuppressive, and pro-reparative properties (Table 1).

As addressed above, allogeneic transplantation with UCB in adult recipients is limited by a low CD34+ cells from UCB in *vitro*. However, human placenta can now serve as a novel source of human mesenchymal progenitor cell for *in vitro* expansion. Human placenta-derived mesenchymal progenitor cells support culture expansion of long-term culture-initiating cells from cord blood CD34+ cells.44

Besides placenta and cord blood, more focus has been put on the amnion, which is made by the baby and therefore is a safe and effective alternative to ESCs. Amniotic epithelial stem cells have remarkable potential to form virtually all cells in the body and have strong anti-inflammatory properties, and can be considered for repair of tissues. They have been used for over 15 years to treat burns and cornea. Currently, there is research on stems cells in adult lung disease like pulmonary fibrosis and the immune system. The immune system degenerate drastically with age and causes problems like being at high risk for opportunistic infections, poor vaccine responses, higher incidence and complications of cancer, risk of death from infection and relapse after chemotherapy and radiotherapy, and failure to recover from human immunodeficiency virus infections. Therefore, this generates immense research on using amniotic epithelial stem cells to reverse the ageing process to restore the thymus function.

Therefore, newborn cells can be regarded as a natural body repair kit. Yet this novel information is scarce to the public, thus limiting the

<table>
<thead>
<tr>
<th>Table 1. Conditions for the use of mesenchymal cells for repair</th>
</tr>
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<tbody>
<tr>
<td>Lung fibrosis, chronic obstructive pulmonary disease37,38</td>
</tr>
<tr>
<td>Heart and vascular damage39</td>
</tr>
<tr>
<td>Spinal disc injury40</td>
</tr>
<tr>
<td>Suppress graft-versus-host disease in allogeneic bone marrow transplant</td>
</tr>
<tr>
<td>Inhibit autoimmunity, eg, multiple sclerosis, diabetes, arthritis41</td>
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potential clinical use of invaluable pluripotent stem cells. Health care providers should serve as an important channel to convey such invaluable information to the public.

CONCLUSION

This article reviews the current trends in UCB storage, as well as recent consensus in the ethical and commercial activities related to private and public UCBB. Adult stem cells offer a new and realistic approach for the treatment of diseases, without the ethical and medical risks associated with the use of ESCs.

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REFERENCES


Magnetic Resonance-guided Focused Ultrasound for the Management of Uterine Fibroids

Victor HG Ai, MBChB, FRCR; John KF Chan, MBBS, FRCR; Gladys G Lo, MD, DABR

OVERVIEW

Leiomyomas (fibroids) are benign tumours of the uterus occurring in as many as 70–80% of women. While most are asymptomatic, some may cause substantial symptoms affecting the patient’s quality of life, including pelvic pain, pressure, menorrhagia, dysmenorrhea and urinary symptoms. For symptomatic women who have completed their families, hysterectomy and myomectomy have been the most common treatments. However, these surgical procedures carry a 17–23% morbidity rate, and usually involve days of hospitalization and weeks of convalescence. Uterine artery embolization, a less invasive alternative, has been shown to decrease both fibroid volume and clinical symptoms. However, it often requires hospitalization and can occasionally cause serious complications.

Ablative techniques, such as laser ablation, cryoablation and magnetic resonance-guided focused ultrasound (MRgFUS) ablation, have also been used for fibroid treatment. They are increasingly popular because of the perceived advantage of minimized recovery time and minimum morbidity. MRgFUS is the least invasive treatment method for uterine fibroids, as the procedure does not involve any incision, puncture, anaesthesia, or ionizing radiation. It can be performed in an outpatient setting and appears to be safe and effective. This article reviews the principle, patient selection criteria, treatment procedure, potential risks and outcome of MRgFUS.

PRINCIPLE

The capability of ultrasound to thermally ablate biological tissues has been known and studied for decades. Medical diagnostic ultrasound operates at frequencies of 2–20 MHz. In focused ultrasound (FUS) ablation (also referred to as high-intensity focused ultrasound), the ultrasound energy is brought to a tight focus within a target volume. This focusing minimizes the thermal damage to surrounding and overlying tissues, since ultrasound intensities are much lower outside the focal spot. Heat is generated in the focal spot owing to absorption of acoustic energy, as well as mechanical phenomena like cavitation, microstreaming and radiation forces.
If the tissue temperature is raised above 56°C during a 1-second or longer exposure, instantaneous coagulative necrosis can be achieved. \(^{11}\) It has been shown histologically that the necrotic lesion margin is very sharp, the boundary between dead and unaffected tissues being only a few cell layers. \(^{12}\) A single 2-second exposure results in an ellipsoidal necrotic lesion, typically 1.5–2 cm in length and 1.5–2 mm in diameter. \(^{11}\) A large tissue volume can then be ablated spot by spot with multiple overlapping single exposures.

MRgFUS combines FUS with magnetic resonance imaging (MRI) which, aside from providing excellent anatomical detail for guidance and post-procedural assessment of the extent of tissue necrosis, allows for real-time thermometry monitoring during treatment. This is performed during the delivery of each ultrasound wave, or ‘sonication’, by measuring the change in proton resonance frequency of water in response to temperature change. \(^{13}\) This allows the operator to determine whether an appropriate thermal dose has been accurately delivered to a specific spot, thus evaluating the effectiveness of each sonication. \(^{14}\) If required, the parameters of the sonication may be adjusted to improve performance (eg, the power may be increased).

In 2004, the MRgFUS device, ExAblate 2000 (InSightec, Haifa, Israel), was approved by the United States Food and Drug Administration (FDA) specifically for treatment of uterine fibroids. It consists of three major components: a modified MRI table containing an embedded phased array FUS transducer (MRgFUS table; Figure 1), a FUS workstation, and a control computer. All three units are integrated with the MRI scanner (Signa; GE Medical Systems, Wisconsin, USA) in a closed-loop system. The FUS transducer (120 mm in diameter, 211 elements, 1.15 MHz principal frequency) and the motion system are enclosed in a tank filled with degassed water. The window above the FUS transducer is covered with a thin Mylar membrane. An integrated two-part pelvic coil is used for MRI. Acoustic coupling between the transducer and the patient is achieved with a layer of degassed water mixed with ultrasound coupling gel spread on top of the Mylar membrane, and a gelatin patient pad is immersed in a small bath of degassed water formed inside a plastic patient drape tucked inside the opening in anterior part of the coil. The patient is positioned prone on the MRgFUS table, which is subsequently advanced into the bore of the MRI scanner for imaging and treatment.

PATIENT SELECTION

Fibroid Size, Type, Morphology and Number

The fibroids that are most suitable for MRgFUS treatment are those between 3 cm and 10 cm in size. Since the total treatment volume is limited by treatment time, fibroids larger than 10 cm are difficult to treat in one session. For example, treating an 8-cm fibroid can take approximately 3 hours of sonications. \(^{17}\) If such a fibroid needs to be treated, one can perform two or more sessions of treatment, or consider treatment with gonadotrophin-releasing hormone agonist to shrink the fibroid prior to MRgFUS. \(^{18,19}\)

Submucosal, intramural and subserosal fibroids may be treated by MRgFUS. These treated fibroids remain inside the uterus and are slowly absorbed by the body, translating to volume reduction and decrease in symptoms. Pedunculated fibroids with narrow stalks should not be treated, to avoid releasing the fibroid into the abdominal cavity. \(^{17}\)
The efficacy of MRgFUS correlates with the signal intensity of fibroids on T2-weighted magnetic resonance images. Fibroids that have low or intermediate T2 signal intensity compared with myometrium are suitable for MRgFUS, whereas those with high signal intensity are not. The high signal intensity in these fibroids may be related to increased vascularization, which may decrease heat deposition during MRgFUS by dissipating energy away from the lesion.

Contrast-enhanced MRI can differentiate between fibroids with intact vasculature and those that are devascularized or necrotic. An absence of contrast enhancement indicates that the fibroid is already non-perfused and therefore will not benefit from MRgFUS treatment.

Patients with more than six symptomatic uterine fibroids may not be good candidates for MRgFUS, although they should be considered based on the accessibility of the fibroids and their presumed role in the patient’s symptoms.

Accessibility of Fibroid
The ExAblate system allows a focal treatment area to be generated up to 12 cm from the skin of the anterior abdominal wall. Thus, a fibroid located too posteriorly with more than 50% of its volume outside the treatment boundaries should be excluded from treatment. Mitigation techniques are possible to reduce the distance between the fibroid and the transducer, such as filling the rectum with water in order to push the uterus and the fibroid more anteriorly. Evaluation of tissues along the ultrasound beam path before treatment.

Figure 2. a) Sagittal contrast-enhanced T1-weighted magnetic resonance image of a large anterior wall uterine fibroid before magnetic resonance-guided focused ultrasound (MRgFUS) treatment. The fibroid is homogeneously enhanced. Pre-treatment volume of fibroid: 296 mL. b) Contrast-enhanced magnetic resonance imaging immediately after MRgFUS treatment (81 sonications). Non-perfused volume (NPV): 232 mL. NPV ratio = 78%. The patient had good symptom improvement.
is important. Anterior to the uterus, attention should also be paid to extensive abdominal scarring. Abdominal scars have enhanced energy absorption, which may lead to skin burn or pain at the site of the scar.\textsuperscript{22} The ultrasound beam should also be clear of air-containing tissues, including bowel, or bone.\textsuperscript{17} The air in the bowel may cause increased heat deposition and injury. Mitigation techniques, eg, manipulating bladder volume and beam angulation, are sometimes useful to avoid these structures.

In the far field of the ultrasound beam, the structures of concern are the pelvic bone and nerves. Bone absorbs ultrasound and heats up more readily than soft tissue. Nerves that are adjacent to a heated bone surface may produce pain and, in extreme cases, be damaged.\textsuperscript{22} Fibroids that are close to the lumbosacral plexus or a bone surface should be considered carefully before being deemed suitable for MRgFUS.

**TREATMENT PROCEDURE**

MRgFUS can be done as an outpatient procedure. Patient preparation includes placement of a peripheral intravenous line, urinary bladder catheterization and leg compression stockings. The patient is asked to shave her lower abdomen from umbilicus down to the pubic bone before arriving for treatment.

The patient lies prone on the MRgFUS table. T2-weighted planning images are obtained to ensure optimal positioning of the fibroids for treatment. The images are transferred to the ExAblate planning program. The target area is defined and manually drawn by the radiologist, and the target volume is analyzed with superimposed ultrasound beam paths in all three planes. This three-dimensional assessment is made to prevent any ultrasound beam from passing through structures such as major scars, bowel loops, bones or pelvic nerves. Mild sedative is given to the patient, allowing her to remain fully conscious and comfortable with little or no pain during the procedure.

MRgFUS is the least invasive treatment method for uterine fibroids, as the procedure does not involve any incision, puncture, anaesthesia, or ionizing radiation.

The procedure begins with the delivery of low-power sonifications and simultaneous real-time thermometry. The operator adjusts the focal spot according to the resulting thermal map. The power is gradually increased until the therapeutic dose is reached. The planned sonifications are then delivered. With each sonication, the magnetic resonance images illustrate the local heating, and the ExAblate screen shows the resultant temperature change. One aims for a temperature of 65\textdegree C to 85\textdegree C, which ensures tissue necrosis. The number of sonifications depends on fibroid size, and a treatment session usually lasts 3 to 6 hours. The patient's blood pressure, heart rate, oxygenation, and comfort level are monitored throughout the procedure.

Once the procedure is finished, contrast-enhanced MRI is performed to assess treatment result. The treated tissues are no longer perfused and show as non-enhancing area on contrast-enhanced T1-weighted images (Figure 2). The non-perfused volume is measured, and a non-perfused volume ratio indicating the percentage of treated fibroid volume is obtained. The anterior abdominal wall is examined for burns, and the patient is observed for a short time before being discharged home. The patient can resume normal activities the next day.

**POTENTIAL RISKS**

MRgFUS for the treatment of fibroids has a good safety profile. No mortality has been reported, and complications are uncommon.\textsuperscript{23} Skin burns were reported in 5\% of patients in an early study.\textsuperscript{20} However, these sites were noted to correlate with areas of residual hair on the lower abdomen. Skin burns have been virtually eliminated with shaving of the skin, cleaning of the skin with alcohol, and an awareness of scars in the treatment path.\textsuperscript{23} Inflammation of fat and abdominal wall musculature is now a more commonly seen adverse effect, reported in 11\% of patients in one study.\textsuperscript{24} Fortunately, these inflammatory changes cause minimal discomfort to the patients.

Damage to adjacent organs, such as
bowel perforation, is a potential complication, although no urgent surgical intervention or bowel injuries have been reported. Use of real-time magnetic resonance images generated with each sonication to monitor for changes in the position of structures, such as the bowel, uterus or bladder, is important in minimizing the risk. In addition, targeting of the fibroid with a distance of 15 mm or more from the serosal surface is recommended to prevent injury to adjacent structures.23

Sometimes heating of pelvic bones and nerves in the far field of the beam path can occur. Rarely the patient may develop pain or leg paraesthesia after treatment.22 The symptoms are usually temporary, but it is recommended that sonications be performed at least 4 cm from bony structures to minimize heating of the bone, which can in turn heat the fat surrounding the nerves leading to nerve stimulation or damage.23

Lastly, because of the length of the procedure, development of deep venous thrombosis can potentially occur. The use of compression stockings can decrease the likelihood of thrombosis.

POST-TREATMENT ASSESSMENT AND RESULTS

Treatment efficacy is assessed by both MRI and symptomatic improvement. Improvement in symptoms is measured by the Symptom Severity Score (SSS), using a validated health and symptom-related quality of life questionnaire specific for fibroids known as the Uterine Fibroid Symptom and Quality of Life.25 The SSS assesses menorrhagia and bulk-related symptoms on a single 100-point scale, with higher scores indicating worse symptoms. A 10-point improvement from baseline signifies significant symptom improvement. This testing method has been one of the primary measures used to determine the efficacy of MRgFUS in research and clinical settings.

Early studies reported feasibility and safety of phase I and II trials.26,27 A phase III trial reported that, among 109 patients treated with MRgFUS, 79.3% had significant symptom improvement 6 months after treatment, despite the fact that only about 25% of the fibroid volume was treated due to FDA regulatory restrictions.22 A follow-up study found 51% of the 82 patients had sustained relief from their fibroid symptoms at 12 months after treatment.20

Patients with larger treatment volumes have better symptom improvement. In a study comparing two protocols using different treatment volumes, 73% of patients had significant symptom improvement under a protocol with smaller treatment volume, compared with 91% when larger treatment volume was allowed. At 12 months, 37% of the patients in the first protocol required alternative treatment because of continued symptoms, compared with 28% in the modified protocol.16

Another study which reviewed the treatment of 359 women with 24 months follow-up also found that patients with larger treatment volumes had better symptom improvement initially at 6, 12 and 24 months, and required fewer alternative treatments. Haematocrit level was also increased more in anaemic patients with increasing volumes of fibroid treatment.28

The fibroids appear to decrease in size over time after treatment. An early study showed a 13.5% decrease in the mean volume of the treated fibroids 6 months after treatment.19 Another study reported about a 25% decrease in size of ablated fibroids 12 months after treatment.28 Both studies were conducted under FDA guidelines with multiple restrictions limiting the amount of treatment volume. As more patients are now treated with off-research protocol, allowing larger volumes to be treated, fibroid volume reduction is expected to exceed earlier studies.

MRgFUS AT HONG KONG SANATORIUM AND HOSPITAL – EARLY RESULTS

The ExAblate 2000 system was installed at our hospital in 2007. Our patient selection criteria and treatment protocol were as outlined above. Since FDA-imposed research restrictions were not applicable, we were able to target larger fibroid volumes.
A total of 17 patients successfully completed MRgFUS treatment without complication. The mean treatment time was 3.4 hours (2–5 hours). The mean non-perfused volume ratio at the end of the procedure measured 67%. Follow-up MRI was done for six patients at 3 months. The fibroids reduced in volume by 25% ± 12%. The mean SSS reduced significantly from 37.5 to 25.6 at 3 months. No delayed complication was encountered.

**CONCLUSION**

MRgFUS is a promising alternative method in the treatment of uterine fibroids. It is a safe, non-invasive procedure with minimal morbidity. It has been shown to be effective in both fibroid size reduction and symptom improvement. Proper patient selection is important to ensure best treatment results.

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**REFERENCES**

This continuing medical education service is brought to you by the Medical Progress Institute, an institute dedicated to CME learning, in partnership with the Malaysian Medical Association. Read the article ‘Magnetic Resonance-guided Focused Ultrasound for the Management of Uterine Fibroids’ and answer the following questions for 1 CME Point.

Instructions
1. Please use the ANSWER FORM for submission.
3. Your answers should reach the Malaysian Medical Association by 30 June 2013.

One CME point will be awarded only to registered candidates for each module according to Category 5 of the MMC-CME Grading System.

CME Points: 1 Point
Magnetic Resonance-guided Focused Ultrasound for the Management of Uterine Fibroids

Please indicate on your answer sheet whether the following statements are True or False.

1. Magnetic resonance-guided focused ultrasound (MRgFUS) ablation can be used for treatment of fibroids in an outpatient setting.
2. During MRgFUS treatment, the effectiveness of each sonication can be monitored by real-time thermometry.
3. Submucosal fibroids should not be treated by MRgFUS.
4. Pedunculated fibroids with narrow stalks should not be treated by MRgFUS.
5. Fibroids that have high T2 signal intensity compared with myometrium on magnetic resonance imaging (MRI) are most suitable for MRgFUS treatment.
6. Fibroids that show no contrast enhancement on MRI are most suitable for MRgFUS treatment.
7. Large abdominal scarring in the treatment area may lead to skin burn or pain at the site of the scar.
8. Damage to adjacent bowel structures is a potential complication.
9. Pain or paraesthesia in the legs after treatment is usually permanent and irreversible.
10. Larger treatment volumes are usually correlated with better symptom improvement.
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