CME ARTICLE

Dehydroepiandrosterone (DHEA) – The Answer to Diminished Ovarian Reserve?

JOURNAL WATCH

Hypertension in Pregnancy

PAEDIATRICS

Evaluation of the Acute Abdomen

GYNAECOLOGY

The Management of Perimenopausal Menstrual Symptoms

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HOW DUTCH LADY GROWING UP MILK WITH 5x DHA* CAN HELP CHILDREN ACHIEVE MORE EVERYDAY.

Brain growth is at its most rapid during the early childhood years. It is important to ensure that mothers give their child the right nutrition for brain development from the start. DHA is found abundantly in the brain. It is as important to the brain as calcium is to the bones. Which is why Dutch Lady Growing up milk now comes with 5 times more DHA*.

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Meets the European Food Safety Authority’s recommended DHA level per day.

The smarter choice for your child

*In comparison with previous milk powder formulation.
49 Hypertension in Pregnancy

Hypertension is a common complication of pregnancy and remains a major cause of maternal and perinatal morbidity and mortality worldwide. Patients with hypertensive disorders of pregnancy warrant cautious care with consultant obstetric, neonatal and anaesthetic involvement to optimize both maternal and fetal outcomes.

Fergus P McCarthy, Louise C Kenny

Review Article

Paediatrics

61 Evaluation of the Acute Abdomen

Evaluation of the acute abdomen in infants and children can be challenging. The authors review a structured approach to assessment and define the management of some of the more serious acute abdominal conditions seen in children such as intussusception, appendicitis, and malrotation/volvulus.

Erica Makin, Mark Davenport
Range of Annum™ products for Pregnancy, Lactation and Childhood

<table>
<thead>
<tr>
<th>For Pregnant Moms</th>
<th>For Breastfeeding Moms</th>
<th>For 1 year old &amp; above</th>
<th>For 3 years old &amp; above</th>
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Important Notice: Breast Milk is still the Best

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 fulfil 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.
Review Article
Gynaecology

74  The Management of Perimenopausal Menstrual Symptoms

Abnormal bleeding around the time of the menopause is common and may be a sign of premalignancy such as endometrial hyperplasia or even endometrial carcinoma. As such, all will need uterine assessment which may include transvaginal scan combined with endometrial biopsy, hysteroscopy or a sonohysterogram. Having excluded (pre) cancer, treatment can then be offered.

John Eden, Sheila O’Neill

Continuing Medical Education

81  Dehydroepiandrosterone (DHEA)—The Answer to Diminished Ovarian Reserve?

Optimal ovarian response is one of the major prerequisites for successful IVF treatment. Thus, women with diminished ovarian reserve remain one of the greatest challenges in modern infertility care. Supplementation with DHEA is one of the potentially effective clinical approaches and is attracting worldwide attention.

Tracy Wing Yee Yeung, Pak Chung Ho

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Lisa Low, Illustrator
DUTCH LADY
Growing up milk is now improved with 5xDHA

Meets the European Food Safety Authority’s recommended DHA level per day.

The smarter choice for your child

*In comparison with previous milk powder formulation.
GYNAECOLOGY

HRT and cardiovascular risk in early menopause

There is controversy about the risks and benefits of hormone replacement therapy (HRT) during the menopause. Now, a study in Denmark has shown that HRT begun early in the menopause protects against heart disease.

The trial was primarily aimed at investigating the effect of HRT on osteoporosis. A total of 1,006 recently postmenopausal or perimenopausal women aged 45–58 were randomized to HRT with 17-β-estradiol plus norethisterone acetate (or 17-β-estradiol alone if post-hysterectomy) or no treatment, for about 11 years. The primary end point (death, myocardial infarction, or heart failure) was reached by 3.2% (HRT) vs 6.5% (controls), a significant 52% reduction in the HRT group. There was a non-significant 43% reduction in mortality with HRT. After 16 years of follow-up, there was still a significant difference in the proportions reaching the primary end point (6.6% vs 10.5%), and mortality was non-significantly 34% less in the HRT group (5.4% vs 7.9%). There was no significant difference in the rate of stroke between the two groups (2.2% vs 2.8%) or in the rate of venous thromboembolism, which was low in both groups. The groups did not differ significantly in the incidence of breast or other cancers. The rate of death or breast cancer was significantly 46% lower in the HRT group (4.4% vs 7.9%).

HRT begun early in the menopause reduced cardiovascular risk without increasing the risks of cancer or thromboembolism.


OBSTETRICS

Maternal obesity and neonatal death in Africa

Overweight and obesity have become more common in developing countries. The children of obese mothers are more likely to die perinatally, to be admitted to the neonatal intensive care unit, to be macrosomic, and to have low Apgar scores. Data from 27 countries in sub-Saharan Africa have illustrated the dangers of maternal obesity.

Pooled data from cross-sectional Demographic and Health Surveys from the 27 countries were analysed. Of 81,126 women, 15,518 (19%) were overweight, among whom 4,266 (5% of the total) were obese, 52,006 (64%) were of normal weight, and 13,602 (17%) were underweight. Maternal obesity (body mass index, 30 kg/m² or higher) was associated with a 46% increase in risk of neonatal death in a singleton live birth in the previous 5 years. This increased risk was entirely for neonatal deaths within 48 hours of birth; there was no significant association between maternal obesity and later neonatal deaths.

In sub-Saharan Africa, maternal obesity is associated with increased neonatal mortality within 2 days of birth. Suggested mechanisms include prematurity, intrapartum events, and infections. Obese mothers should be advised to deliver in well-equipped units.


Comparing drugs for tocolytic therapy

A systematic review and network meta-analysis had addressed the question of which are the best agents for delaying delivery when preterm birth is threatened.

The study included 95 randomized controlled trial. Compared with placebo, the odds ratio for delay of delivery by 48 hours was 5.39 for prostaglandin inhibitors, 2.76 for magnesium sulfate, 2.71 for calcium-channel blockers, 2.41 for beta mimetics, and 2.02 for atosiban (an oxytocin receptor blocker). Tocolytics did not reduce the risk of neonatal respiratory distress syndrome. Side effects leading to a change of medication were more likely with beta mimetics, magnesium sulfate, or calcium-channel blockers. Overall, prostaglandin inhibitors and calcium-channel blockers were perhaps the most effective drugs.

Prostaglandin inhibitors and calcium-channel blockers appear to be the most effective tocolytics, but whether delaying delivery is beneficial for the baby remains a valid question.

Single progesterone level to detect non-viability of early pregnancy

For women with bleeding or pain in early pregnancy, a single progesterone test may indicate non-viability, according to a recent meta-analysis. The analysis included 26 cohort studies (9,436 women), 19 studies of women with symptoms alone, and seven of women with both symptoms and inconclusive ultrasound assessment. Among women with symptoms and inconclusive ultrasound findings, a progesterone test (cut-off values, 3.2–6.0 ng/mL) had a sensitivity of 74.6% and a specificity of 98.4% for a non-viable pregnancy (positive likelihood ratio, 45; negative likelihood ratio, 0.26). The overall median prevalence of non-viable pregnancy was 73.2%, and the probability increased to 99.2% with a low progesterone level. For women with symptoms alone and using a 10 ng/mL threshold, the sensitivity was 66.5% and specificity 96.3% (positive likelihood ratio, 45; negative likelihood ratio, 0.26). The overall probability of non-viable pregnancy was 73.2%, and the probability increased to 99.2% with a low progesterone level. A single progesterone test for symptomatic women in early pregnancy can rule out viability.

Equity in maternal and child health interventions

As countries strive to reach Millennium Development Goals (MDGs) for maternal and child health, effective interventions have been increased. Take-up of these interventions is often greater in more prosperous communities, leading to inequalities in coverage. Progress towards MDGs is monitored in 75 countries by the Countdown to 2015 collaboration, these countries accounting for > 95% of all maternal and child deaths. Now, repeated surveys in 35 countries have been used to assess the relationship between increased intervention coverage and equity.

Data were obtained from 35 Countdown countries with two surveys done at an average interval of 9.1 years. Although the rich often had greater coverage, increased coverage for skilled birth attendants, measles vaccination, and an increase in a composite coverage index were associated with improved equity. For use of insecticide-treated bed nets by children, countries achieving rapid progress reached rich and poor almost equally. National increases in coverage were mainly due to increased coverage among the poor.

Equity needs to be taken into account as well as total coverage in assessing progress to MDGs.

Changes in money given for maternal, newborn, and child health in Countdown countries

The global financial crisis may be affecting funding for Millennium Development Goals 4 and 5. As part of Countdown to 2015, recent changes in official development assistance (ODA) to maternal, newborn, and child health have been assessed in 74 Countdown priority countries.

Since 2003, giving to maternal, newborn, and child health increased in all countries up to US$6,511 million in 2009 but fell slightly for the first time to US$6,480 million dollars in 2010. The rate of increase in ODA for maternal and child health has decreased since 2008. Targeting of ODA to countries with high maternal mortality increased between 2005 and 2010, as did targeting to child health but to a lesser extent.

ODA may have slowed as a result of the global financial crisis.

PAEDIATRICS


**PEER REVIEWED**

**Journal Watch**

**MDG 4 success of Niger**

Only 23 of 74 Countdown countries look like achieving Millennium Development Goal (MDG) 4 (a two-thirds reduction in under-5s mortality between 1990 and 2015). Niger is ranked 186 of 187 countries on the Human Development Index and the average woman has seven children. Although total official development assistance (ODA) fell between 2003 and 2008, ODA to maternal and child health increased considerably with a threefold increase in funding per live birth and almost sixfold increase per child. Data now show that Niger has achieved remarkable reductions in child mortality.

Mortality in children < 5 years old fell by 43% from 226 deaths per 1,000 live births in 1998 to 128 in 2009, a rate of decrease of 5.1% per year, although neonatal mortality remained high. Achieving MDG 5 needs an annual fall of 4.3% in under-5s mortality. The improvement in Niger has far exceeded those in neighbouring countries (Benin, 2.2% per year; Burkina Faso, 0.8%; Chad, 0.9%; Mali, 1.8%; Nigeria, 2.0%). The prevalence of wasting decreased by about 50% over the same period although there was only a slight decrease in stunting. Child survival interventions — such as insecticide-treated bed nets, improved nutrition, vitamin A supplementation, appropriate treatment of diarrhoea, improved care seeking for fever, malaria, or pneumonia, and vaccinations — all improved.

Several programme strategies have been important in Niger’s success: high government priority for universal access to free primary health care for women and children, mass campaigns for insecticide-treated bed nets, measles vaccination and vitamin A supplementation, and an attack on child undernutrition.


**Clinicians’ ‘gut feeling’ about serious infection in children**

Serious infections in children may easily be missed on clinical examination with potentially disastrous results. Routine clinical assessment may be normal, but the doctor may be left with a ‘gut feeling’ that all is not well. A study in general practice has shown the value of gut feeling.

The study included 3,369 children presenting with an acute illness that had lasted for up to 5 days. Among children in whom other features did not cause concern, a gut feeling that the child was unwell increased the risk of serious infection by a factor of 25. It had a sensitivity of 33% and a specificity of 99%. The gut feeling was most often based on decreased conscious level, tachypnoea, or parental concern.

Clinicians should take their gut feelings seriously.


**BMI and cardiovascular risk factors in children**

A systematic review and meta-analysis has suggested that a high body mass index in childhood is more strongly associated with cardiovascular risk factors than previously thought.

The analysis included 63 studies of children aged 5–15 years in developed countries (49,220 children). Among overweight children, systolic blood pressure was raised by an average of 4.54 mm Hg compared with children with a normal body mass index. Among obese children, the rise of systolic blood pressure was 7.49 mm Hg. The average increases in diastolic blood pressure were 2.57 and 4.06 mm Hg, respectively. Obesity was also associated with significant increases in total serum cholesterol and low-density lipoprotein cholesterol. Both overweight and obesity were significantly associated with increases in fasting insulin levels, insulin resistance, increased triglycerides, and decreased high-density lipoprotein cholesterol levels.

Overweight and obese children may be at increased cardiovascular risk in later life.
Physical activity interventions in children

Encouraging more physical activity in children seems instinctively to be a worthwhile endeavour. Current UK guidelines suggest at least 60 minutes of moderate to vigorous exercise a day for all children and adolescents, but few achieve it and activity levels tend to drop off in adolescence. A systematic review and meta-analysis has illustrated the difficulties in encouraging exercise.

The analysis included 30 studies (6,153 children) with physical activity measured by accelerometer throughout the day at baseline and follow-up. The pooled intervention effect was small to negligible for total physical activity and small for moderate or vigorous physical activity. It equated to an extra 4 minutes of walking and running per day.

The effects of the physical activity interventions were small or negligible. Editorialists insist that research should continue with the aim of finding more effective interventions.

High-sugar drinks and body weight in children and adolescents

High intake of sugar-sweetened drinks has been associated with increased body mass index (BMI) in children. Two studies reported in the *New England Journal of Medicine* have shown that reducing the intake of sugar-sweetened drinks may reduce levels of obesity and overweight in children and adolescents.

In Amsterdam, the Netherlands, an 18-month double-blind trial included 641 normal-weight children aged 4 years 10 months to 11 years 11 months at eight schools. Randomization was to receive 250 mL on each school day and at weekends of either a sugar-containing drink with 104 kcal or an artificially sweetened, sugar-free, calorie-free drink. The BMI z score increased by a mean of 0.15 SD units (sugar) and 0.02 SD (sugar-free), a significant difference. The increase in weight was 7.37 kg vs 6.35 kg, also a significant difference. There were also significant reductions in increase of skinfold thickness, waist-to-height ratio, and fat mass in the sugar-free group.

A US study included 224 overweight or obese adolescents (mean age, 15 years). Randomization was to an intervention group (multicomponent intervention to reduce consumption of sugar-sweetened drinks with provisions of non-calorie drinks, motivational telephone calls, and check visits) or a control group, for 1 year of intervention and a further year of follow-up. At 2 years, there was no significant difference in change in BMI between the two groups. At 1 year, however, the change in BMI was 0.57 kg/m² less in the intervention group.

Reduced intake of sugar-sweetened drinks was associated with reduced weight gain in normal-weight Dutch children aged 5–12 years. In American overweight and obese adolescents, a 1-year programme of reduced intake of sweetened drinks was associated with reduced increase in BMI at the end of the intervention but not 1 year later. Several US organizations have called for measures to reduce the consumption of sugar-sweetened drinks in children and adults.

Classroom-based CBT for adolescents at risk of depression: Not effective

There is evidence that classroom-based cognitive behavioural therapy (CBT) might prevent depression in some adolescents, but there has been no rigorous study. Now, a study in eight schools in the UK has shown no effect from classroom-based CBT.

The study included 5,030 school students aged 12–16 years, among whom 1,064 (21%) were identified as at high risk of depression. Outcome data were available for 846 (80%) of the at-risk group. Randomization was to classroom-based CBT, attention control, or usual provision. At 12 months, adjusted mean scores on the short mood and feelings questionnaire were similar in the three groups. Reported self worth and anxiety were not significantly different between groups. There was a small increase in negative thoughts in the CBT group.

Classroom-based CBT did not reduce symptoms of depression in at-risk adolescents.

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INTRODUCTION

Hypertension is a frequently encountered complication of pregnancy and has a number of possible aetiologies. In the United Kingdom, the number of maternal deaths from hypertension in pregnancy has fallen steadily over the past few decades, as have the complication rates. However, hypertensive disorders remain a major cause of maternal and perinatal morbidity and mortality worldwide. Interventions to prevent hypertensive disorders in pregnancy including pre-eclampsia in the general population have been disappointing, and the mainstay of treatment involves close antenatal supervision of mother and fetus and timely delivery to prevent deterioration of the condition and subsequent morbidity and mortality.

HYPERTENSION IN PREGNANCY

Classification and Diagnosis of Hypertension
The classification of hypertension in pregnancy by Davey et al remains the most widely accepted and appropriate classification (Box 1).

- Women who are hypertensive and pregnant must be subdivided into those with:
  - chronic hypertension
  - pregnancy-induced or gestational hypertension.

Women with pregnancy-induced hypertension are subdivided further:
- the majority have non-proteinuric pregnancy-induced hypertension, a condition associated with minimal maternal or perinatal mortality/morbidity
- a minority have the major pregnancy complication of pre-eclampsia.
  Pre-eclampsia is associated with significant maternal and perinatal morbidity
and mortality. As such, it is imperative that every effort is made to accurately classify women with hypertension in pregnancy as having chronic hypertension, non-proteinuric pregnancy-induced hypertension or pre-eclampsia, as the aetiology and management of the three conditions is very different.

**Measurement of Blood Pressure**

Blood pressure should be measured with the woman rested and seated at a 45-degree angle with the arm at the level of the heart. It is imperative that an appropriately sized cuff should be used. To avoid incorrect measurement of blood pressure, if the mid-arm circumference is greater than 33 cm, a large cuff should be used. Korotkoff phase 1 should be used to measure systolic blood pressure, and Korotkoff 5 is the appropriate measurement of diastolic blood pressure. The method used to record blood pressure should be consistent and documented.

Pregnancy-induced Hypertension

Gestational or pregnancy-induced hypertension is a rise in the blood pressure in the absence of proteinuria after 20 weeks’ gestation. True non-proteinuric pregnancy-induced hypertension does not appear to be associated with an increase in maternal or fetal morbidity. However, the risk of progression from pregnancy-induced hypertension to pre-eclampsia is approximately 20–30% and therefore vigilance is required. This rate increases to approximately 50% when pregnancy-induced hypertension develops before 32 weeks’ gestation. As a result of this risk of progression to pre-eclampsia, weekly urinalysis and blood pressure checks are generally recommended in women with pregnancy-induced hypertension.

Chronic Hypertension

Chronic hypertension is defined as hypertension preceding pregnancy. Blood pressure falls in the first and second trimesters. Therefore, women with high blood pressure before the 20th week of pregnancy are assumed to have pre-existing or essential hypertension. As many women of reproductive age only present for the first time when pregnant, chronic hypertension is often revealed in the first half of pregnancy. Approximately 90–95% of cases of chronic hypertension are considered to be essential. Secondary causes which account for approximately 5–10% are listed in Table 1. In women presenting with hypertension in the first half of pregnancy, it is important to look for an underlying cause. These investigations should at least include:

- urine analysis (looking for blood, protein or glucose)
- urea and electrolytes
- renal tract ultrasound.

Women with underlying renal disease are at significantly increased risk of poor pregnancy outcome and require multidisciplinary care.
Treatment of Chronic Hypertension in Pregnancy

The use of antihypertensive drugs in the hypertensive women without renal impairment is considered by some to be beneficial in preventing sudden increases in blood pressure, cerebral haemorrhage or hypertensive encephalopathy. However, a clear benefit of antihypertensive agents in mild-to-moderate chronic hypertension remains unproven, as treatment does not prevent placental abruption or superimposed pre-eclampsia, or influence perinatal outcome. There are differing opinions regarding the timing of initiation of treatment in hypertensive disorders in pregnancy. This is compounded by the fact that a single blood pressure of 140/90 mm Hg or above is not uncommon in pregnancy and was reported in nearly 40% of pregnant women in one study, while persistent high blood pressure occurs in approximately 12–22% of pregnancies. Until recently, the focus remained on treating elevated blood pressure based on the diastolic reading with groups recommending treatment for sustained diastolic blood pressures of greater than 105–110 mm Hg. There is now however increasing awareness on the importance of increases in, as well as the absolute values of, systolic blood pressure. Generally, the aim of antihypertensive therapy in women without underlying medical problems is to keep the systolic blood pressure at 130–155 mm Hg and diastolic blood pressure at 80–105 mm Hg.

Both Centre for Maternal and Child Enquiries (CMACE) 2006–2008 and National Institute for Health and Clinical Excellence (NICE) clinical guideline on hypertension in pregnancy recommend that all pregnant women with a systolic blood pressure of 150 mm Hg or more require antihypertensive treatment. Consideration should also be given to initializing treatment at lower pressures if the overall clinical picture suggests rapid deterioration and/or where the development of severe hypertension can be anticipated.

In the 2006–2008 CMACE report, particular emphasis was placed on the implementation of effective antihypertensive treatment in women with systolic blood pressures greater than 150 mm Hg. A systolic blood pressure greater than 180 mm Hg should be considered a medical emergency, and quick effective treatment is advocated to prevent haemorrhagic stroke.

Women with chronic hypertension taking ACE inhibitors or angiotensin II receptor blockers should be counselled that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy. There are multiple alternative antihypertensive agents available which may be used in pregnancy. These can be used independently or

<table>
<thead>
<tr>
<th>Table 1. Causes of secondary chronic hypertension</th>
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<tr>
<td><strong>Idiopathic</strong></td>
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<td>Connective tissue disorders</td>
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in conjunction with a second or third agent.

- Labetalol is a popular first-line antihypertensive of choice in the treatment of hypertension. Labetalol is a combined $\beta$-adrenoceptor blocker that also blocks $\alpha$-adrenoceptors. Ordinary $\beta$-adrenoceptor blockers are unsuitable for producing a quick antihypertensive effect because a quick fall in blood pressure triggers a compensatory sympathetic discharge that increases the peripheral vascular resistance via $\alpha$-adrenoceptors. Blocking the $\beta$-adrenoceptors alone cannot prevent this compensatory response, but the addition of an $\alpha$-adrenoceptor blocker can. It is this action that renders labetalol suitable for gaining quick control of the blood pressure. Labetalol, like all $\beta$-adrenoceptors, is contraindicated in women with a history of asthma.

- Nifedipine is a calcium channel blocker used in the treatment of chronic hypertension in pregnancy. Data suggest that it is safe, but cumulative evidence is not as extensive as with older drugs such as labetalol and methyldopa. The principal side effect is headache, which can be severe, lasts for several days after commencing treatment and may return after increasing the dose. Use of the long-acting once-daily preparation improves compliance. Nifedipine is a potent antihypertensive agent and should not be given sublingually as it may cause a precipitate fall in blood pressure, which can lead to fetal distress.

- $\alpha$-Methyldopa (a centrally acting $\alpha$-adrenergic agonist that inhibits vasoconstricting impulses from the medulla oblongata) has traditionally been the most commonly used agent for the control of blood pressure during pregnancy. Its safety has been well established both in pregnancy and in the long-term follow-up of the infants. One of the most frequent side effects is sedation, which can be profound. This is often poorly tolerated and leads to unpredictable compliance. However, $\alpha$-methyldopa remains the preferred agent of the National High Blood Pressure Education Programme. ACE inhibitors and angiotensin receptor blockers and diuretics should be avoided in pregnancy. Diuretics may reduce uteroplacental perfusion.

- Second- and third-trimester exposure to ACE inhibitors appears to be fetotoxic, producing fetal hypocalvaria and renal defects. The cause of these defects seems to be related to fetal hypotension and reduced renal blood flow. Anuria associated with oligohydramnios can produce fetal limb contractures, craniofacial deformations and pulmonary hypoplasia. Intrauterine growth restriction, preaturity, persistence of a patent ductus arteriosus, severe neonatal hypotension, neonatal anuria, and neonatal or fetal death have all been observed with use of these drugs, and they should therefore be discontinued preconceptually or as early in the first trimester as possible. Angiotensin receptor blockers are newer agents that have not been formally studied in pregnancy; they are probably best

### Table 2. Numbers of direct deaths attributed to eclampsia and pre-eclampsia and mortality rates per 100,000 maternities; United Kingdom: 1985–2008

<table>
<thead>
<tr>
<th>Triennium</th>
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CI = confidence interval.
avoided given their common pathway with ACE inhibitors.

PRE-ECLAMPSIA

Introduction

Pre-eclampsia is a potentially life-threatening hypertensive disorder of pregnancy characterized by vascular dysfunction and systemic inflammation involving the brain, liver, and kidneys of the mother. The incidence of pre-eclampsia has risen in countries such as the United States of America, but maternal mortality from pre-eclampsia has decreased significantly in the UK since 1992 (Table 2).

Pre-eclampsia is twice as common in primigravid women as in women having second or later pregnancies

Pre-eclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as gestational hypertension of at least 140/90 mm Hg on two separate occasions measured at least 4 hours apart, accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine, arising de novo after the 20th week of gestation in a previously normotensive woman and resolving completely by the 6th postpartum week. It usually occurs during the second half of pregnancy and complicates 2–8% of pregnancies, depending on population studied. Pre-eclampsia is twice as common in primigravid women as in women having second or later pregnancies. Women who become pregnant with donor eggs are at increased risk of developing pre-eclampsia while particular men are at increased risk of fathering a pre-eclamptic pregnancy. Table 3 highlights other risk factors for pre-eclampsia.

Pre-eclampsia also carries implications in adult life, with offspring of affected pre-eclamptic pregnancies demonstrating poor growth in childhood and an increased risk of hypertension, heart disease and diabetes.

Pathophysiology of Pre-eclampsia

Pre-eclampsia is thought to result from a combination of impaired trophoblast differentiation and invasion during the first trimester resulting in the failure of trophoblast cells to destroy the muscularis layer of the spiral arterioles resulting in the development of a poorly perfused placenta. However, this reduced placental perfusion alone is not sufficient to cause the maternal syndrome of pre-eclampsia, and it is thought that this process...
requires the influence of additional maternal factors including genetic make-up and environmental factors (such as obesity and diet), which together result in widespread endothelial dysfunction and hypertension.

Management of Pre-eclampsia

Ideally, women at high risk of pre-eclampsia should be reviewed pre-conceptually and advised to take 75 mg of aspirin daily from 12 weeks’ gestation until the birth of their child. Women considered at high risk of pre-eclampsia include those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Investigations and monitoring of the suspected pre-eclamptic patient should include:

- Full blood count: this may demonstrate a raised haematocrit (indicating haemoconcentration) and thrombocytopenia (which is an indicator of severe pre-eclampsia). Thrombocytopenia may also occur as a result of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets).
- Urea and electrolytes: uric acid is a particularly sensitive measure of pre-eclampsia and perinatal outcome, but it is only of clinical significance if the levels are increasing or are very high.
- If the platelet count is normal, it is not necessary to perform a coagulation screen (prothrombin time, activated partial thromboplastin time and international normalized ratio) in cases of non-severe pre-eclampsia and gestational hypertension.
Urine analysis with a 24-hour urine collection or protein creatinine ratio. Significant proteinuria is the most important clinical variable predicting both maternal and perinatal outcome. All pregnant women should be assessed for proteinuria. Urinary dipstick testing may be used for screening for proteinuria when the suspicion of pre-eclampsia is low. The degree of positivity on urine dipstick correlates with the quantity of proteinuria as follows: 1+ = 0.3 g/L, 2+ = 1 g/L and 3+ = 3 g/L.

Considerable observer error may occur with visual dipstick assessment, and this may be overcome by the use of automated dipstick readers, which significantly improve both false-positive and -negative rates. A reading of 1+ or more should prompt further evaluation. Clinically significant proteinuria is defined as a 24-hour urine protein excretion of ≥ 0.3 g and is based on a 95% confidence interval for urinary protein in pregnancy. An elevated protein to creatinine ratio of greater than 30 mg/mmol correlates with a 24-hour urine excretion greater than 300 mg and may be used to check for significant proteinuria.

Ultrasound: increased fetal surveillance with ultrasound assessment to evaluate fetal weight, progression of fetal growth, amniotic fluid index, and umbilical artery Doppler velocimetry should be performed at the time of diagnosis of pre-eclampsia once every 4 weeks thereafter with more frequent monitoring if any parameters are abnormal.

The pharmacological treatment of pre-eclampsia focuses on controlling maternal hypertension. No drugs in current clinical use beneficially affect the human placenta. As a result, management involves treatment of maternal hypertension and close antenatal supervision of the mother and fetus with timely delivery to prevent deterioration of the mother and fetus. Pre-eclampsia can occa-
sionally be managed conservatively. Maternal and fetal monitoring should continue until fetal maturity has been achieved, at which stage the cervix is assessed with Bishop’s scoring and, if favourable, induction of labour is carried out.

Patients with pregnancy-induced hypertension may be monitored through a combination of general practitioners and hospital day care units. Severe pre-eclampsia necessitates inpatient care with a close monitoring of the symptoms, signs and biochemical parameters. No one definition defines ‘severe’ pre-eclampsia. However, the following features generally indicate the development of severe pre-eclampsia:

- Eclampsia
- Severe hypertension, eg, a systolic blood pressure over 160 mm Hg with at least 2+ proteinuria
- Moderate hypertension associated with any of:
  - severe headache with visual disturbance
  - epigastric pain
  - signs of clonus
  - liver tenderness
  - platelet count falling to below 100 × 10^9/L
  - creatinine 100 mmol/L
  - alanine aminotransferase rising to above 50 IU/L.

In extreme prematurity, transfer to hospital with adequate neonatal facilities (with steroid administration to enhance lung maturity) is indicated. Severe pre-eclampsia presenting prior to fetal viability is an indication for termination of pregnancy.

The optimum time of delivery is of crucial importance and remains a balance between the risks of major complications to the mother and intrauterine growth retardation in the fetus against the risks of delivery and prematurity to the fetus. The mode of delivery is a balance between caesarean section and vaginal delivery. Caesarean section is a better option for rapid deteriorating maternal and fetal condition, or alternatively for those remote from term with an unfavourable cervix. Epidural analgesia may be beneficial by preventing the increase of catecholamine release, in order to prevent further elevations of blood pressure during uterine contractions. It may also allow a more controlled second stage. Evidence from the HYPITAT trial suggests that women with gestational hypertension and non-severe pre-eclampsia should be induced after 37 weeks’ gestation. This was associated with a significant reduction in adverse maternal outcome including progression to pre-eclampsia. Furthermore, no differences were observed in neonatal outcomes or caesarean section rates.

Oral antihypertensive are discussed above. In severe pre-eclampsia, there are two antihypertensive regimens to choose from:

- Labetalol (200 mg) can be given orally prior to or in the absence of intravenous access; if there is no response within 30 minutes, a second oral dose can be given. If there is no initial response to oral therapy or if it is not tolerated, a bolus of 50 mg given intravenously over at least 5 minutes can be administered, repeated to a maximum of 200 mg, at 10-minute intervals. Following this, or as treatment for moderate hypertension, a labetalol infusion can be commenced (5 mg/mL at 4 mL/h via a syringe pump, the infusion rate being doubled every 30 minutes to a maximum of 32 mL [160 mg/h until the blood pressure has dropped and stabilized at an acceptable level]). Labetalol is contraindicated in women with asthma and should be used with caution in cardiac disease.
- Hydralazine is given by bolus infusion (10–20 mg over 10–20 minutes measuring the blood pressure every 5 minutes). This may be fol-
Box 2. Management of hypertension in pregnancy

Screening
- Women should be screened for signs of hypertension using blood pressure checks and urinalysis monthly until 30 weeks’ gestation, fortnightly from 30 weeks’ gestation and weekly from 36 weeks’ gestation
- If elevated blood pressure +/- proteinuria, refer for admission or monitoring in antenatal day unit

Maternal assessment
- Repeat (at least 4-hourly) blood pressure measurement
- Quantitative measurement of protein in urine (pre-eclampsia = 0.3 g protein 24-hour urine collection)
- Platelet count, serum uric acid concentration, and tests of liver function (alanine and aspartate aminotransferase levels)
- Coagulation screen if altered liver function

Antihypertensive therapy
- Consider admission, monitor closely and treat if blood pressure is persistently above 160/100 mm Hg

Anticonvulsant therapy
- If convulsions occur, use magnesium sulphate, intravenously or intramuscularly
- In cases of severe pre-eclampsia, consider prophylactic magnesium sulphate

Fetal management
- Give prophylactic steroids if the duration of gestation is less than 34 weeks
- Perform an ultrasound assessment of fetal weight on initial presentation and repeat fortnightly
- Doppler ultrasonographic assessment of umbilical blood-flow velocity if evidence of growth restriction
- Regular cardiotocography (non-stress tests)
- Ultrasonography at least twice a week for liquor volume
- Multidisciplinary approach regarding timing and mode of delivery

Postpartum care
- Continued close monitoring of the mother by experienced carers
- If on magnesium therapy, continue for at least 24 hours post partum until stable
- Careful fluid balance (total 80 mL/h intake) and early use of diuretics if pulmonary oedema secondary to fluid overload is suspected
- Decrease dose of antihypertensive agents as indicated. Avoid sudden cessation immediately post partum as rebound hypertension likely

Follow-up
- Long-term follow-up to make sure that the blood pressure falls (within 6 weeks post partum), and suitable referral if it does not
- Discussion about the illness and the significance for the future
- Recommend pre-conceptual counselling for future pregnancies
Followed by an infusion (40 mg hydralazine in 40 mL normal saline, which should run at 1–5 mL/h [1–5 mg/h]). Management of hypertension is summarized in Box 2.

In pre-eclampsia, magnesium sulphate is indicated as the first-line anticonvulsant. Formal clinical review should occur every 4 hours, observing for side effects (motor paralysis, absent reflexes, respiratory depression and cardiac arrhythmia). The antidote is 10 mL 10% calcium gluconate given slowly intravenously. Of the magnesium sulphate, 97% is excreted in the urine. Oliguria (< 80 mL per 24 hours) can thus lead to toxicity. Therefore, in the presence of oliguria, magnesium sulphate should be reduced or withheld. If magnesium is not excreted, levels should not fall. Box 3 highlights key management steps in the treatment of patients with severe pre-eclampsia.

### Eclampsia

Eclampsia refers to the occurrence of one or more generalized convulsions and/or coma in the setting of pre-eclampsia and in the absence of other neurological conditions. The UK Obstetric Surveillance System (UKOSS) report gives an estimated incidence of 27.5 cases per 100,000 maternities with a case fatality rate estimated to be 3.1%. This was

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**Box 3. Key points in the management of the severe pre-eclamptic patient**

- Insert an indwelling catheter and measure hourly urine output until stable
- Record blood pressure and pulse every 15 minutes until stable and then half hourly
- Oxygen saturation should be measured continuously and charted with the blood pressure. If saturation falls below 95%, then medical review is essential to outrule pulmonary oedema and other complications
- Strict fluid balance should be recorded with detailed input and output measurements
- Respiratory rate should be measured hourly. A reducing respiratory rate may indicate magnesium toxicity
- Temperature should be measured 4-hourly
- When present, central venous pressure and arterial lines should be measured continuously and charted with the blood pressure
- Neurological assessment should be performed hourly using either the AVPU (alert/verbal/painful/unresponsive) or Glasgow Coma scales
- Fetal well-being should be monitored using a cardiotocography
- Blood tests should be repeated at least every 12 hours whilst on the magnesium sulphate protocol. In the event of complications such as haemorrhage or abnormal or deteriorating haematological and/or biochemical parameters, more frequent blood tests should be taken, eg, every 4–8 hours

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**Box 4. Diagnostic criteria used for eclampsia**

Any woman with convulsion(s) during pregnancy or in the first 10 days post partum, together with at least two of the following features within 24 hours of the convulsion(s):

- Hypertension (a booking diastolic pressure of < 90 mm Hg, a maximum diastolic of ≥ 90 mm Hg and a diastolic increment of ≥ 25 mm Hg)
- Proteinuria (at least + protein in a random urine sample or ≥ 0.3 g in a 24-hour collection)
- Thrombocytopenia (platelet count of less than 100 × 10⁹/L)
- Raised plasma alanine aminotransferase concentration (≥ 42 IU/L) or an increased plasma aspartate aminotransferase concentration (≥ 42 IU/L)
almost a halving of the incidence of eclampsia since 1992. Eclampsia remains to be associated with significant maternal morbidity, in particular cerebrovascular events (2.3%). The benefit of magnesium sulphate in the prevention of eclampsia has been well demonstrated, and magnesium sulphate has been shown to halve the risk of eclampsia among women with pre-eclampsia. Box 4 indicates the diagnostic criteria for eclampsia. Cerebral haemorrhage has been reported to be the most common cause of death in patients with eclampsia, and stroke is known to be the most common cause of death (45%) in women with HELLP syndrome.

POSTPARTUM MANAGEMENT OF HYPERTENSION IN PREGNANCY

Blood pressure rises progressively over the first five postnatal days, peaking on days 3–6 after delivery. Research has focused on the antenatal complications, for both mother and baby, and the risks and benefits of administering antihypertensive therapy prior to delivery. There is very little information on how best to manage postpartum hypertension, regardless of type or severity, to optimize maternal safety and minimize hospital stay. Women with postpartum hypertension may also experience longer hospital stays and, possibly, heightened anxiety about their recovery. General NICE recommendations for postnatal care of women with hypertension in pregnancy include stopping methyldopa within 2 days of birth and asking the woman about severe headache and epigastric pain every time blood pressure is measured. In cases of mild or moderate pre-eclampsia platelet count, transaminases and serum creatinine should be measured 48–72 hours after birth or step-down. These do not need to be repeated if results are normal. In most cases of gestational hypertension and pre-eclampsia, there is a rapid and complete resolution within 6 weeks of delivery of the fetus. Patients requiring antihypertensives can be weaned off slowly, and medications should not be stopped suddenly as there may often be a rebound hypertension.

Postnatal Follow-up

All women who have had pre-eclampsia should be offered a medical review at the postnatal review (6–8 weeks) after the birth. Women who have had pre-eclampsia should be educated regarding their increased risk of development of cardiovascular disease, renal disease and cardiovascular risk fac-
tors for several years following pregnancy, and regular blood pressure checks with their general practitioner should be recommended. Women with severe pre-eclampsia have an increased risk of recurrence in their next pregnancy (about 1 in 6 [16%] pregnancies) but the disorder is generally less severe and manifests 2–3 weeks later than in the first pregnancy. This risk increases to about 1 in 4 (25%) pregnancies if the pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks. The risk of recurrence is about 1 in 2 (55%) pregnancies if the pre-eclampsia led to birth before 28 weeks' gestation. Women with essential hypertension should be encouraged to present for pre-conceptual counselling as antihypertensive medications such as ACE inhibitors are contraindicated in pregnancy and should be changed pre-conceptually. The use of low-dose aspirin in women with chronic hypertension moderately reduces the risk of developing superimposed pre-eclampsia, intrauterine growth retardation and perinatal death, and should be offered to all women at an early booking visit. The findings from the CLASP trial do not support routine treatment with aspirin of all women at risk of pre-eclampsia.

**CONCLUSION**

Hypertensive disorders are one of the commonest complications of pregnancy and may be associated with significant maternal and fetal morbidity and mortality. Although the aetiology of these disorders is becoming increasingly better understood, interventions to prevent hypertensive disorders of pregnancy have had poor results. The mainstay of treatment remains the use of antihypertensive medications, the use of magnesium sulphate in the prevention of eclampsia, and multidisciplinary input to ensure a timely delivery.

**FURTHER READING**


About the Authors

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INTRODUCTION

There is a multiplicity of causes of acute abdominal pain during childhood although for the purposes of this article those presenting predominantly during the neonatal period will be excluded. Although common sense tells us that most children with acute abdominal pain will have self-limiting conditions, it is important to identify those where there is a more serious surgical or medical emergency. The history of the complaint is the beginning of the diagnostic process and certain conditions are much more common in a particular age group, eg, intussusception. Still, accurate diagnosis can be challenging in the young non-verbal child or those with learning difficulties.

HISTORY AND SYMPTOMS

The timeline of symptoms should be ascertained with particular attention to onset, progression, location and the characteristics of other associated features, eg, fever, vomiting, stooling (constipation, diarrhoea), urinary symptoms, and gynaecological history in pubertal girls. History of accidental/non-accidental trauma, previous surgery or existing medical conditions should be ascertained. If a child is old enough to localize pain, this can be particularly helpful. In the younger child, parents may infer abdominal pain from the drawing up of legs, irritability, and inconsolability.

Figure 1 shows possible surgical causes of abdominal pain based upon situation and lateralization, while Figure 2 illustrates a spectrum of causes by typical age group affected. Table 1 illustrates diagnosis by the characteristics of the vomit.
PHYSICAL EXAMINATION

A thorough examination should be undertaken preferably when the child is comfortable. Appropriate analgesia should be given, although in the past this practice has been controversial. It was felt that provision of opiate analgesia may mask clinical findings and potentially cause a delay in making an accurate diagnosis. Randomized controlled trials in children have shown that administration of effective analgesia (intravenous opiates) does not delay in making an accurate diagnosis of appendicitis for instance. Repeated examination by the same physician is beneficial when the diagnosis is uncertain at presentation, although shift patterns in hospital conspire against this. Rectal examination in children has to be reserved for specific situations where the procedure is potentially life-saving (eg, rectal decompression in the enterocolitis of Hirschsprung’s disease) or when the information gained is likely to be specific (eg, faecal impaction in those with idiopathic constipation). There is generally no role for rectal examination in the trauma setting, and if there are genuine concerns over a potential perineal/perianal injury then an examination under anaesthetic is more appropriate.

PERITONITIS

Peritonitis, the definitive sign of an acute abdomen, can be localized or generalized and usually occurs secondary to spreading microbial sepsis or soiling following perforation of a hollow viscus.

The physical sign of peritoneal involvement is muscle guarding – that is a reflex contraction of the abdominal wall muscles – initially voluntary because probing hurts and then involuntary with onset of muscular rigidity. Peritoneal afferent nerve fibres become hypersensitive with inflammation, and palpatory tests such as percussion or rebound are designed to detect this. As rigidity supervenes, breathing becomes painful and rapid to avoid peritoneal irritation. The phenomenon is largely clinical, and ancillary aids such as X-ray are merely confirmatory. Pneumoperitoneum may be detectable – but be conscious of where the air might be risen to on a plain abdominal film. Maximize the chance of finding it using erect positioning or a shoot-through lateral film in the supine abdomen.

Occasionally, children with ascites due to end-stage liver disease, nephrotic syndrome or on peritoneal dialysis may get ‘spontaneous’ bacterial peritonitis and lack a septic focus. The commonest pathogens are Streptococcus pneumoniae and E coli.
Diagnosis is confirmed by aspiration and microscopy, looking for presence of bacteria or a neutrophil count more than 250/mm⁢³.

**COMMON CAUSES OF ACUTE ABDOMINAL PAIN**

**Appendicitis**

Appendicitis was only really recognized as a distinct entity in the 1880s, followed by a huge increase in prevalence over the period of the 20th century. Over the past 20 years or so, there is some evidence that this surge has now come to an end and is now receding. This dramatic epidemiological variation has been attributed to the wider population's better access to clean water, better sewage disposal and the decline of all-pervading spectre of infantile gastroenteritis – another manifestation of the so-called hygiene hypothesis. This has had the result of deferring exposure to pathogens later in life with possibly rapid lymphoid hyperplasia lead-

<table>
<thead>
<tr>
<th>1–12 months</th>
<th>1–5 years</th>
<th>6–12 years</th>
<th>13–18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile colic</td>
<td>Non-specific abdominal pain</td>
<td>Appendicitis</td>
<td>Mesenteric adenitis (viral-associated abdominal pain)</td>
</tr>
<tr>
<td>Intussusception</td>
<td></td>
<td>Appendicitis</td>
<td>Gastritis/gastroenteritis</td>
</tr>
<tr>
<td>Incarcerated hernias (inguinal, rarely umbilical)</td>
<td></td>
<td>Constipation</td>
<td>Cholecystitis/pancreatitis</td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td></td>
<td>Pharyngitis/tonsilitis</td>
<td>Cohn's disease/ulcerative colitis</td>
</tr>
<tr>
<td>Hirschsprung's</td>
<td></td>
<td>Internal hernias</td>
<td></td>
</tr>
<tr>
<td>Midgut volvulus</td>
<td></td>
<td>Omental torsion, Meckel’s diverticulum</td>
<td>Ovarian torsion Pelvic inflammatory disease</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td></td>
<td></td>
<td>Urinary calculi</td>
</tr>
</tbody>
</table>

**Notes:** Surgical, Non-surgical, Common, uncommon.

**Table 1. Differential diagnosis related to characteristics of vomit with abdominal pain**

<table>
<thead>
<tr>
<th>Vomitus</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilious (green)⁴</td>
<td>Intestinal obstruction Malrotation/volvulus Sepsis</td>
</tr>
<tr>
<td>‘Coffee grounds’</td>
<td>Gastritis Oesophagitis Gastric ulcer</td>
</tr>
<tr>
<td>Fresh blood</td>
<td>Oesophagitis Gastritis Gastric/duodenal ulcer Mallory-Weiss tear</td>
</tr>
<tr>
<td>Food/stomach contents</td>
<td>Gastroenteritis Early intestinal obstruction</td>
</tr>
<tr>
<td>‘Faeculent’</td>
<td>Late intestinal obstruction</td>
</tr>
</tbody>
</table>

⁴Bile is golden yellow as it is secreted into the duodenum, becoming green when exposed to stomach acid.
ing to luminal occlusion in the base of the appendix triggering appendicitis.

Appendicitis is the commonest acute surgical emergency and overall accounts for over 40,000 admissions in the UK every year. It is commonest in those aged 10–20 years and slightly more prevalent in boys. It is commonly quoted that the lifetime risk for the development of appendicitis is about 7%. It is also increasingly recognized that there may be two distinct strands of appendicitis; one with rapid and early progression to perforation and perhaps gangrene and the other more indolent and slow-burning.

Clinical Features
The classical features are of ‘visceral’ poorly localized periumbilical pain shifting to the right lower quadrant (RLQ) and becoming ‘parietal’ in character with localization of tenderness, cough, and movement exacerbation. Mild fever, limited vomiting and anorexia complete the picture. The length of history is important, specifically in those with pain greater than 48-hour duration, then it is either likely to be complicated appendicitis or alternatively non-specific abdominal pain. Palpation of a tender mass in the RLQ is indicative of a so-called appendix mass which is simply an appendicitis enveloped by omentum and surrounding bowel loops. In the younger child of less than 5 years, possibly due to the absence of omentum, the perforation and complication rate is high and has been reported up to 70%.

While no symptom or sign is invariable in every case, when enough are present then little more is required to make the diagnosis. There are however two problematic positions of the appendix and one problem age group where diagnosis is not straightforward.

Pelvic appendicitis (20%) is almost always misdiagnosed initially, as there is no RLQ pain or tenderness and there are often contrary features. The symptoms are usually supra-pubic and with increasing peritonitis in the pelvic pouch, involvement of the bladder causing dysuria, and the rectum causing feelings of incomplete but painful defaecation (tenesmus) of loose stool. Urine tests may well be falsely positive, and most have been partly treated with antibiotic as a urinary tract infection or gastroenteritis.
Retrocaecal or retrocolic appendicitis (20%) is misdiagnosed because the local signs are masked by the overlying bowel and the separation of the site of retroperitoneal inflammation from the peritoneal cavity. The appendix tip may well be much higher, leading to tenderness being in the right upper quadrant rather than the RLQ and because of the delay will have often formed a collection or abscess by the time of admission. Extending the hip may exacerbate pain due to involvement of the iliopsoas muscle, and these children often lie on the bed with their hip flexed.

The teenage girl has many possible causes for right iliac fossa (RIF) pain that are not only gynaecological (e.g., pelvic inflammatory disease, ovarian torsion, ‘mittelschmerz’ pain, and even pregnancy, ectopic or otherwise) or urological but also related to more functional intestinal problems such as irritable bowel. This group has the highest ‘white’ appendicectomy rate among large surgical series of appendicectomies testifying to the diagnostic difficulties. All such girls should have urine tested for infection (dipstick for nitrites and leucocytes, and microscopy for cells) and exclusion of pregnancy (β-human chorionic gonadotropin test) and there should be a low threshold for pelvic ultrasound before committing to theatre even in the ‘obvious’ case of appendicitis.

### Investigations

The simplest are used to reflect inflammation and infection and include a white blood cell count and specifically neutrophil count and the acute-phase C-reactive protein. The latter may rise within 2–4 hours of insult and has a short half-life of 18 hours in the circulation. Levels of more than 10 mg/L are considered abnormal and suggestive of pathology. However, neither test is specific to appendicitis, and perhaps they have more value in longer-duration pain where one might expect a change to have occurred and conversely if resolutely normal confirming an impression of non-specific abdominal pain.

In case of diagnostic doubt – and teenage girls – an ultrasound scan should be the next step. It is non-invasive and widely available; but it is user-dependent and reported accuracy varies with sensitivities of 74–100% and specificities of 88–99%. Visualizing a tender thick-walled tubular structure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain migrating to RLQ</td>
<td>1</td>
<td>Pain migrating to RLQ</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>Anorexia</td>
<td>1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>Nausea/vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Fever &gt;38°C</td>
<td>1</td>
<td>Fever &gt;37.3°C</td>
<td>1</td>
</tr>
<tr>
<td>RIF tenderness</td>
<td>2</td>
<td>RIF tenderness</td>
<td>2</td>
</tr>
<tr>
<td>Pain with cough/percussion/hopping</td>
<td>2</td>
<td>Rebound tenderness</td>
<td>1</td>
</tr>
<tr>
<td>WBC &gt;10,000 cells/mL</td>
<td>1</td>
<td>WBC &gt;10,000 cells/mL</td>
<td>2</td>
</tr>
<tr>
<td>Neutrophils &gt;7,500 cells/mL</td>
<td>1</td>
<td>Raised neutrophils</td>
<td>1</td>
</tr>
<tr>
<td>Total score</td>
<td>10</td>
<td>Total score</td>
<td>10</td>
</tr>
</tbody>
</table>

Notes: RIF = right iliac fossa; RLQ = right lower quadrant; WBC = white blood cell count.
The differential diagnosis for right iliac fossa pain in the teenaged girl includes gynaecological, urological and intestinal causes.

Computed tomographic (CT) scans with contrast (oral/rectal) have possibly the highest overall sensitivity (94%) and specificity (95%) in diagnosing appendicitis but are much more often used in adults with suspected appendicitis than in children. The hazards of ionizing radiation are clear. A single abdominal CT scan in a 5-year-old gives estimated lifetime excess risk of radiation-induced cancer of 26 per 100,000. CT is much better at arriving at alternative diagnoses masquerading as appendicitis, eg, Crohn’s disease, ulcerative colitis and, even in children, abdominal neoplasms such as lymphoma and carcinoid tumours. Measures such as ‘focused CT’ (limited to lower abdomen) may improve acceptability and reduce the radiation exposure.

One approach, which does seem to focus the mind of the clinician, is the use of clinical scoring tools, of which there are two currently in use (Table 2). These are the Paediatric Appendicitis Score (PAS) and the Alvarado score. Both virtually overlap in terms of the items assessed, and each requires a blood test although there are slight differences in thresholds and weighting. Using PAS, the extreme scores $\leq 2$ suggests not-appendicitis and discharge home while $\leq 7$ is consistent with appendicitis and advises operation. In a large study from Vancouver, Canada, the use of a PAS score was tested in 849 children with suspected appendicitis. Using the thresholds mentioned, three children would have been sent home with appendicitis whereas 29 would have had normal appendices removed from the 123 (24%) children who had appendicectomy.

The concept of ‘active observation’ was encouraged by Peter Jones, a surgeon from Aberdeen, and this implied admission of children with suspected appendicitis and repeated clinical examination (by the same examiner). Those with appendicitis would then declare themselves after 12–24 hours and the rest would get better. While admirable, in this shift-driven era and conscious of the European Working Time Directive, such continuity may be difficult to achieve.

Laparoscopy as a diagnostic tool is becoming the definitive investigation for persisting undiagnosed RLQ pain, following a non-diagnostic ultrasound in children. This should resolve doubt and provide an alternative explanation for most pain. In those where the appendix looks normal, then the consensus is to remove it.
Surgery of Appendicitis

Appendicectomy remains the surgical therapy of choice although there have been some studies in adults looking at the value of antibiotic-only regimens for uncomplicated appendicitis. These have tended to show absence of real benefit and a tendency to recurrence even if the first episode was successfully treated. Surgery should be performed expeditiously but seldom as an emergency and be preceded by a period of appropriate fluid resuscitation and adjuvant antibiotics effective against gram-negative and anaerobic organisms as the likeliest source of intra-peritoneal sepsis. Classically, a RIF muscle-splitting incision has been used, but appendicectomy can also be accomplished safely with either multiple or single laparoscopic ports. However performed, the hospital stay should be short and day-case surgery has even been reported in children. Those with complicated appendicitis (eg, perforation, peritonitis, gangrene) require a longer period of therapeutic antibiotics and should be monitored assiduously for problems and complication such as surgical site infection.

INTUSSUSCEPTION

Intussusception is a life-threatening surgical emergency, most commonly occurring between 3 months and 2 years of age. It occurs when a segment of bowel (the intussusceptum) invaginates into the distal bowel (the intussuscipiens). This results in initially venous and lymphatic congestion, bowel obstruction, and eventually necrosis and perforation. Any part of the intestine can become intussuscepted, but it most commonly affects the terminal ileum into the ascending colon. The initiating aetiological factor in most cases is a pathological ‘lead point’ such as a polyp, although in some instances of post-operative intussusception this appears difficult to define.

Almost 90% of cases are described as idiopathic and occur in the typical age group. It is suggested that in this population, there is a normal if profound hyperplastic change occurring in distal ileal lymphoid tissue due to weaning, exposure to gastrointestinal viruses, and pathogens, etc, which acts as a lead point. There is therefore some evidence to implicate viruses such as adenovirus, rotavirus, human herpesvirus 6, etc, together with other causes of bacterial enteritis such as Salmonella spp, Escherichia coli, Shigella and Campylobacter. Therefore, even if a child presents with recurrent severe abdominal pain and diarrhoea with a positive stool culture, it can be important to exclude an intussusception if the symptoms do not resolve.

In the remaining cases, a pathological lead
Gastroenteritis is a common non-surgical cause of acute abdominal pain in children.

Clinical Features
Typically, this is of a young child with a recent viral illness who presents with vomiting and intermittent colicky abdominal pain manifest as inconsolable crying. Diarrhoea may be reported in about a third, and passage of altered blood and mucus is a characteristic red currant jelly stool. On abdominal examination between the episodes of pain the child is often lethargic, and an abdominal mass should be sought either in the right upper quadrant or the epigastrium – the RIF having a characteristic emptiness (Dance’s sign). Unfortunately, many of these symptoms are non-specific, and the condition can go unrecognized until quite late with the child becoming progressively shocked.

Investigations
Abdominal X-ray is a reasonable option and may show a paucity of gas in the RIF, distended loops of small bowel due to the obstruction, and a soft-tissue mass. There are two specific signs: the ‘target sign’ which appears as two concentric circles superimposed over the right kidney shadow caused by peritoneal fat surrounding and within the intussusception, and the ‘crescent sign’ where there is a soft-tissue mass projecting into bowel gas. Less commonly, there may be free air in the peritoneal cavity indicative of perforation.

However, the preferred diagnostic modality is abdominal ultrasound, which has a sensitivity and specificity of more than 95% and may also show the ‘target sign’ or the ‘pseudo-kidney sign’ as it appears in longitudinal section.

Management
These children require intravenous fluid resuscitation as they are prone to dehydration secondary to prolonged vomiting and small bowel obstruction. Antibiotics should also be given because of the ischaemic bowel and tendency to bacterial translo-
cation. If the child is haemodynamically stable and there are no signs of bowel perforation (on examination or abdominal X-ray), then a non-operative reduction can be attempted.

Air enema reduction has superseded the original barium enema technique, but reported success rates can vary between 50% and 80%. Certainly pneumatic reduction appears safe, and pressures can be monitored more accurately than before. A maximum pressure of about 120 mm Hg can be used, and the reduction is done under fluoroscopic screening. A successful reduction is confirmed when there is free flow of air into the terminal ileum. If there is doubt, then a repeat ultrasound can be performed to confirm complete reduction. If it is initially unsuccessful, the procedure can be repeated assuming the child remains stable.

Surgery is indicated when air enema reduction has failed or in cases where there is obvious pneumoperitoneum or the signs strongly suggest necrotic bowel. Formerly, the time from onset of symptoms was regarded as an important indicator as to contrast enema reduction or surgery although this is less clear now, and each case should be judged on its own features. A conventional open approach involved a right-sided transverse incision where the mass can be delivered into the wound and the intussusceptum pushed out. The bowel should be examined carefully and, if there is an obvious cause (eg, Meckel’s diverticulum), dealt with appropriately. Resection may also be needed if there has been necrosis. Laparoscopic reduction can be done, but actual manipulation and reduction can be much more difficult using instruments.

Recurrence may occur in up to 15% of air contrast reductions and 5% of operative reductions and be an early or late phenomenon. Certainly if it keeps on happening, there must be strong suspicion of a pathological lead point. Some authors also suggest the use of glucocorticoids to treat recurrence in the idiopathic group because of the putative relationship to lymphoid hyperplasia.

**MIDGUT MALROTATION AND VOLVULUS**

Malrotation is the intestinal feature which in itself may be completely without symptoms, but volvulus is the complication and can be catastrophic. The primary symptom is bilious vomiting and is indicative of duodenal obstruction and should never be disregarded.

Although rotational anomalies of the intestine are probably common and estimated to occur between 1 in 200 live births, the frequency with which it becomes symptomatic is much less common, possibly 1 in 6,000 live births. Typically, it presents within the first year of life but can present at any age even into adulthood.

**Embryology of the Midgut**

There are three distinct stages. From the 5th to 10th week, there is rotation of the duodeno-jejun-
nal (DJ) flexure anticlockwise behind the superior mesenteric axis (artery [SMA] and vein [SMV] axis) to lie in the left upper quadrant. Then from about the 10th week, there is a 270° rotation of caecocolic loop from left lower quadrant coming to lie in front of the DJ flexure. Finally, from the 11th week onwards, the anticlockwise rotation of the caecocolic pole continues bringing it to the RLQ. Retropertoneal fixation occurs to the duodenum and the ascending and descending colon. The two ends of the small bowel should therefore be fixed and lie in opposite quadrants.

Non-rotation refers to failure of the whole process, with malrotation referring to various degrees of failure to complete the process. The commonest variant is where the final 90° does not happen with the caecum in the right upper quadrant or epigastrium overlying the duodenum and bringing together the DJ flexure and caecum. There is now a pronounced ‘bottle neck’ to the small bowel, making volvulus that much easier. Should it occur, the lumen of the duodenum and mesenteric vessels become compromised, and if complete duodenal obstruction occurs then potentially catastrophic venous infarction may follow. The situation of the caecum overlying the duodenum itself may cause external duodenal compression, attributed to the so-called Ladd’s peritoneal bands, but obviously without any vascular compromise.

Clinical Features
Over 80% will present within the first week of life, and all symptomatic cases will present with signs of duodenal obstruction and therefore bilious vom-
iting. When there is bowel ischaemia and potentially infarction due to volvulus, the abdomen should be tender with signs of peritonism. There may be evidence of gastrointestinal haemorrhage from either end, resulting in circulatory collapse and shock due to blood loss and fluid sequestration with endotoxaemia and sepsis.

Malrotation may have a more chronic course with intermittent bilious vomiting. Cases have been described where volvulus has happened without actual infarction but leading to small bowel oedema and protracted symptoms of failure to thrive, malabsorption and food intolerance, protein losing enteropathy, and chylous ascites.

Malrotation may be associated with other conditions such as gastroschisis, exomphalos, diaphragmatic hernias, duodenal atresia, jejunal atresia, biliary atresia, various heterotaxy syndromes, and trisomy 21.

Investigations

In an infant presenting with an acute abdomen, bilious vomiting and shock then every minute counts and sometimes there is no time for diagnostic imaging, beyond perhaps an abdominal X-ray. Although this is rarely specific, its very featureless and gasless appearance supports the diagnosis. Urgent fluid resuscitation and laparotomy are indicated and should be performed without delay in an attempt to save any viable bowel. Still, mortality is high and the morbidity of short bowel is significant.

However, if the child is stable, the key diagnostic modality is an upper gastrointestinal contrast study (barium or water soluble) to assess the position of the DJ flexure. Typically, the normal position is defined as the DJ flexure should lie to the ‘left of the left pedicle and in the transpyloric plane’. Initial proximal jejunal loops should then be on the left of the abdomen. Malrotation is suggested by abnormal positioning of the DJ flexure; volvulus is suggested if there is absence of passage of contrast from the duodenum or a corkscrew or spiral orientation of the proximal jejunum. The false-negative rate is 6–14% and the false-positive rate is 7–15%. If there is doubt over the diagnosis, a delayed plain abdominal X-ray may be useful to assess the position of the caecum.

Abdominal ultrasound is of no use for determination of bowel orientation but may be used to try and determine the orientation of the SMA and SMV with the former normally located to the left of the latter. The so-called ‘whirlpool’ sign suggests volvulus.

Management

The principles of surgical management are to untwist a volvulus and save as much bowel as possible. Frankly, necrotic bowel should be resected, but borderline segments may be left to a second-look laparotomy at 36–48 hours. The classical treatment of malrotation is to widen the mesentery and separate the ends of the small bowel as far apart as possible. This is best accomplished by replicating the original non-rotated state with the duodenum and small bowel on the right and the large bowel on the left – the Ladd’s procedure.

INTRA-ABDOMINAL: ‘MEDICAL’ AND UNUSUAL CAUSES

(i) Acute bacterial and viral gastroenteritis – is clearly very common, but the pain, if any, should be colicky and associated with vomiting and diarrhoea. Family members and foreign travel may be involved. There should be no peritonism. Haemolytic uremic syndrome, seen typically in toddlers, may be an extreme example of verotoxin producing E coli sepsis.

(ii) Foregut inflammation (eg, gastritis, oesophagitis, duodenal ulceration) – may be re-
Learning objectives

After reading this article, you should be able to:
- understand the principal causes of the acute abdomen in infants and children
- develop a structured approach to the assessment of the abdomen in order to reach a differential diagnosis
- utilize investigative modalities appropriately, eg, laboratory tests, radiology
- distinguish between medical and acute surgical causes of abdominal pain
- understand the management of common causes of abdominal pain

EXTRA-ABDOMINAL AND SYSTEMIC CAUSES

Abdominal pain may be a symptom of a disease process/condition in an adjacent region or as part of a systemic illness.

(i) Lower lobe pneumonia – caused by inflammatory pleuritic involvement of the diaphragm and lower chest wall.

(ii) Pharyngitis and tonsillitis – particularly that caused by group A beta-haemolytic streptococci.

(iii) Sickle cell disease (SCD) and abdominal crisis – gene mutation causing single amino-acid substitution in the β-globin gene (usually HbSS, but also HbSC) and leading to abnormally rigid red cells prone to sickling. Common in those of Afro-Caribbean origin, West Africa being the epicentre of the disease, but is sometimes found in eastern Mediterranean countries and India. Is seldom silent when homozygous and detectable on newborn screening. Vaso-occlusion in mesenteric or solid organ capillary beds leads to severe recurrent abdominal pain. Treated conservatively with rehydration, oxygenation, and blood transfusion. Genuine intra-abdominal pathology is also more common in sickle cell disease – gallstones, splenic sequestration, and infarction. Appendicitis is said, however, to be less common in SCD.

(iv) Familial Mediterranean fever – autoinflammatory condition affecting lining membranes such as the peritoneum, tunica vaginalis, pericardium, etc, and caused by single gene mutation (AR) which leads to a defect in the protein pyrin. The gene is present in Eastern Mediterranean populations (eg, Turkey, Lebanon, Armenia). May present as abdominal pain due to ‘peritonitis’ in older children, with a rash seen
in about 20%. C-reactive protein is invariably high, and colchicine is a specific treatment.

(v) Henoch–Schönlein purpura (HSP) – a systemic vasculitis caused by IgA immune complex deposition in various capillary beds. The trigger or cause of HSP, though, is unknown but may follow an upper respiratory infection. It occurs more in boys and most are under 6 years of age. The rash is predominantly purpuric (purple and 3–10 mm in diameter), non-blanching and occurs largely over the legs and buttocks. Central, colicky abdominal pain is a feature in about 60% and may precede the rash. Joint pain is also common and should be sought. Gastrointestinal bleeding may occur and be due to actual intussusception. Palpate for a mass and obtain early ultrasound in atypical cases.

(vi) Mycobacterium tuberculosis – fortunately this is now a rare cause of chronic bacterial peritonitis but should be considered in children with a positive family history, recent travel to endemic countries, those who have not been vaccinated, and the immunocompromised.

(vii) Diabetic ketoacidosis – severe abdominal pain may be the presenting feature for usually adolescents with type 1 diabetes. There may be vomiting and diarrhoea adding to the invariably severe dehydration. Specific clues are the air hunger Kussmaul-type breathing pattern and ketotic smell. Whatever the abdomen feels like, such patients need intensive rehydration, correction of their electrolyte and glucose imbalance before making a surgical commitment.

(viii) Testicular torsion – abdominal or groin pain may be the only volunteered symptom from a shy teenage boy. Testicular examination should be part of a routine abdominal examination.

FURTHER READING


About the Authors

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INTRODUCTION

The forties are often a time of hormonal turbulence in a woman’s life. Fluctuating sex-hormone levels and anovulatory cycles can affect the brain causing flushes, sweats and mood swings, the breasts causing swelling and pain, and the uterus causing abnormal uterine bleeding (AUB). It is this latter dilemma, namely AUB, that is the focus of this article. For this paper, the search engine Sirius was used via the University of New South Wales Library website using the keywords – perimenopause, abnormal uterine bleeding, investigation, terminology, management, fibroid, adenomyosis, polyp, endometrial hyperplasia, endometrial cancer, hormone replacement, levonorgestrel intrauterine device, endometrial ablation, hysterectomy, contraceptive pill, progestin, and tranexamic acid.

Preference was given to reviews, especially meta-analyses and systematic reviews.

Perimenopause is defined as the time of menstrual irregularity leading up to the last period (menopause) and the 12 months following the last period. The Stages of Reproductive Ageing Workshop (STRAW) suggested the term ‘menopause transition’ leading up to the last menstrual period and divided this phase into two parts. ‘Stage 0’ is menopause (last period). ‘Stage 2’ (early menopause transition) is characterized by more than 7 days of cycle variation compared with normal and ‘stage 1’ (late menopause transition) as greater than two skipped cycles with at least 60 days of amenorrhoea.

Pelvic pathology is also commonly found in this age group. As such, some women will need to be investigated to exclude (pre-) malignancy and to help decision making about the best treatment option. A Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) working group has classified AUB into nine categories – Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory disorders, Endometrium, luteogenic, and Not Classified (acronym: ‘PALM-COEIN’).
Leiomyoma (L) are further subclassified into those who have at least one sub-mucus fibroid (Lsm) and those with fibroids which do not impact on the endometrial cavity (Lo). Endometrial hyperplasia and malignancy and occasionally cervical cancer can present with AUB. The Coagulopathy group includes conditions such as von Willebrand disease, although this usually declares itself in the teenage years and is often associated with abnormal bleeding after childbirth, dental work or surgery, gum bleeding, bruising, and epistaxis. Endometrial causes suggest a primary problem in the endometrium, and as research in this area progresses, it is likely that specific biochemical and/or genetic problems will be defined. The Iatrogenic group includes breakthrough bleeding on hormone preparations such as the oral contraceptive pill (OCP), hormone therapy (HT), and levonorgestrel-releasing intrauterine systems (LG-IUS).

There is a lack of consensus of definitions and terminology of AUB and outcome measures (Confino 2007). Until recently, there has been an abundance of old descriptive terms for AUB which have not been helpful.

**WHEN TO INVESTIGATE**

A concise history and examination need to be performed first. Large fibroids may present with the woman noticing a pelvic mass or bladder frequency, but most will be concerned about a change in their menstrual pattern. Menstrual history should focus on frequency, cycle regularity, duration, and heaviness of flow. Frequent, heavy and/or prolonged bleeding usually requires some investigations as does postmenopausal bleeding.

Physical examination may reveal a polyp, a fibroid uterus, or some other lesion. Pallor may indicate anaemia. Laboratory tests may include a Papanicolaou smear, cervical cultures, full blood...
count, iron studies, and occasionally tests for bleeding disorders.

All women with AUB who are in the perimenopausal age range will need their uterus assessed because many will have structural anomalies and some premalignant and malignant conditions, the commonest being endometrial hyperplasia. Around 70% of women presenting with AUB will have a benign cause, 15% carcinoma, and 15% a premalignant condition. Management algorithms have been published, but in the end, if endometrial hyperplasia is suspected, then the endometrium will need to be assessed and most will require at least transvaginal pelvic ultrasound (TVUS).

Risk factors for endometrial hyperplasia or cancer include obesity, age over 40 years, polycystic ovary syndrome, exposure to unopposed oestrogen therapy, tamoxifen usage, and postmenopausal bleeding. Many will present with AUB. It is not the intent of this review of perimenopausal menstrual symptoms to describe the management of endometrial hyperplasia; although it needs to be stated that any degree of atypia will usually necessitate hysterectomy because of the risk of small occult carcinoma being already present as well as the significant risk of progression to carcinoma.

**INVESTIGATIONS**

The guidelines of the American College of Obstetricians and Gynecologists mandate that all women over 35 years with AUB should have an endometrial assessment (ACOG Committee on Practice Bulletins 2001). The tests available will vary according to location but include TVUS, endometrial biopsy (EB), sonohysterogram (SHG; or saline infusion sonogram), dilation and curettage (D&C), and hysteroscopy.

Historically, D&C was the mainstay of endometrial assessment. However, its main drawbacks include the need for a general anaesthetic, missed pathology, or incomplete removal of an intra-cavity lesion, free floating tissue left in situ, and a high false-negative rate. Complications included uterine perforation and intrauterine adhesions.

**EB COMBINED WITH TVUS**

Office EB using the Pipelle device is a cost-effective tool for investigating AUB especially when combined with TVUS. Endometrial hyperplasia and carcinoma are unlikely if the endometrial thickness (ET) is 4 mm or less. This is very useful for assessing postmenopausal bleeding (later), but unfortunately many perimenopausal women will have thick ET because of unopposed oestrogen surges and so some form of tissue sampling is very helpful in this group (the National Institute for Clinical Excellence recommends EB in all cases of AUB, age > 40). The Pipelle device can provide a histological diagnosis of most endometrial pathologies with some limitations (Table 1). Typically, the Pipelle system is very good at detecting pathologies that involve most of the endometrial cavity but can miss small focal lesions, including cancers. In one study, Pipelle sampling was done prior to hysterectomy for known endometrial cancer. Over 95% of the sample were

<table>
<thead>
<tr>
<th>Table 1. Limitations of endometrial biopsy</th>
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</thead>
<tbody>
<tr>
<td><strong>Factors that might make it difficult to perform an endometrial biopsy:</strong></td>
</tr>
<tr>
<td>• Cervical stenosis (cervical surgery, multiple caesarean sections)</td>
</tr>
<tr>
<td>• Pain</td>
</tr>
<tr>
<td>• Sharply anteverted or retroverted uterus</td>
</tr>
<tr>
<td><strong>Has the cavity been adequately sampled? Considerations:</strong></td>
</tr>
<tr>
<td>• Uterine shape and size (eg, bicornuate uterus)</td>
</tr>
<tr>
<td>• Location of a lesion (eg, it is difficult to sample a cornual lesion)</td>
</tr>
<tr>
<td>• Size of lesion</td>
</tr>
<tr>
<td>• Is the lesion affecting most of the endometrium or localized?</td>
</tr>
</tbody>
</table>
adequate for histological examination, and the sensitivity for picking up the malignancy was 83%.

HYSTEROSCOPY

Hysteroscopy allows the entire uterine cavity to be visualized, and any lesions found can be visualized and biopsied. This is can be performed in the office or in theatre. Hysteroscopy cannot assess the myometrium and so may miss adenomyosis and will not allow evaluation of the size and depth of fibroids.

SONOHYSTEROGRAM

Saline instilled into the uterine cavity permits ultrasound to visualize its contents. It is an accurate test and cheaper than hysteroscopy. If a lesion is found, then hysteroscopy and biopsy will be indicated. Meta-analyses have shown that SHG misses around 7% of lesions (usually a small endometrial polyp).

TVUS VERSUS HYSTEROSCOPY VERSUS SHG

Farquhar performed a systematic review of all three modalities and found that all three tests were moderately accurate in detecting intrauterine pathology. SHG and hysteroscopy were better than TVUS for detecting sub-mucus fibroids. Hysteroscopy is considered the ‘gold standard’ test to assess the endometrium, especially for endometrial hyperplasia and cancer. However, in clinical practice, each test has its place and can help both with diagnosis and selection of the best treatment option for the individual patient.

For all patients with AUB, a TVUS will be the first test ordered, backed up with an EB. According to Royal College of Obstetricians and Gynaecologists guidelines, if there is persistent intermenstrual bleeding in a woman aged 40 years or above and failed or ineffective treatment, then an EB is indicated to exclude endometrial cancer or atypical hyperplasia.

The guidelines of the American College of Obstetricians and Gynecologists mandate that all women over 35 years with AUB should have an endometrial assessment

If a focal lesion is found on TVUS, then hysteroscopy can be used to visualize and biopsy the lesion. If a uterine anomaly such as a septum is found on TVUS, then a LG-IUS is likely to be expelled. Fibroids are common in this age group, and TVUS is accurate in detecting, measuring and locating them (with perhaps the exception of sub-mucus fibroids). These factors will be important in determining the likely success of treatment options such as LG-IUS, hormonal therapies, and endometrial ablation. If a fibroid uterus is found on examination or at TVUS, then a SHG can be helpful in assessing sub-mucus fibroids prior to attempting hysteroscopic resection. SHG can also detect most polyps.

POSTMENOPAUSAL BLEEDING

Bleeding after menopause always requires uterine assessment. Numerous trials and systematic reviews have shown that TVUS is a very good first test, and if the ET is 4 mm or less then significant endometrial pathology is unlikely. ET greater than 4 mm (5 mm or more) or repeated episodes of postmenopausal bleeding (even if the ET is 4 mm or less) is an indication for SHG or (usually) hysteroscopy.
Non-steroidal anti-inflammatory drugs reduce menstrual blood loss by 25% on average, tranexamic acid by around 50%. The latter drug has also been shown to induce necrotic changes in fibroids. Many perimenopausal women will be troubled by irregular menstrual cycles, sometimes short, and other times long and variable flow. Thus, treatment goals are usually menstrual regulation, reduction of menstrual loss, and the prevention of endometrial hyperplasia. The next section will focus on the LG-IUS, OCPs, sequential HT, and endometrial ablation.

**LEVONORGESTREL-CONTAINING INTRAUTERINE SYSTEM**

The LG-IUS is an excellent option for menstrual control for many perimenopausal women. Irregular bleeding is common immediately after insertion, but this can be minimized if the ET is thin at insertion.

If there are no contraindications (Table 2), then a low-dose OCP can control both the irregular cycle and the symptoms of the perimenopause. Long-cycle regimens can be used to ‘skip’ periods. There are scant data on the use of OCP in women over 50 years, although OCPs containing oestradiol, rather than ethinyl-oestradiol, are now available. Theoretically, these should be safer for perimenopausal women, although definitive data are not yet available.

**PROGESTINS AND SEQUENTIAL HT**

Progestins have anti-oestrogenic, anti-proliferative and atrophying effects on the endometrium. Their impact depends upon the type, dose and regimen used. These can be given alone or in combination with oestrogens as in the OCP or HT. Continuous progestins, in adequate dosage, can completely suppress menstruation (eg, depot injection of medroxyprogesterone acetate), but most commonly progestins are given cyclically. Ten days of luteal...
phase progestin has not been shown to be effective for AUB, whereas a 21-day cyclical progestin regimen can reduce menstrual blood loss by around 50%. Moderately high doses of norethisterone (eg, 15 mg or more daily) are commonly used to control heavy menstrual loss acutely. Around one in eight women will develop premenstrual tension-type side effects with progestins, including bloatedness, mood swings (even depression), and fluid retention.

If HT is used in the menopause transition, then standard continuous HT often induces heavy breakthrough bleeding and so sequential HT is usually given. Irregular bleeding is common, particularly in the first three cycles, but if it persists then women on HT with AUB should be investigated as described above. Long-term trials of HT have shown that commercially available regimens do prevent oestrogen-induced endometrial hyperplasia. However, as already described, uterine pathology is common in this age group and hyperplasia and carcinoma can still occur in women taking standard HT regimens. HT has not been adequately investigated as a therapy for AUB. Typically, in clinical trials of HT, patients with AUB are excluded.

ENDOMETRIAL ABLATION

This is an effective treatment for AUB and is useful for those who fail hormonal therapy or for those who do not wish to take a hormone treatment and avoids hysterectomy. Endometrial hyperplasia is at least a relative contraindication, but hyperplasia with atypia and genital tract cancer are absolute contraindications. It is essential that endometrial hyperplasia and cancer be excluded prior to the ablation. Sub-mucus fibroids can be hysteroscopically resected and then endometrial ablation performed in the one procedure. If significant adenomyosis is present, then endometrial ablation can result in severe pain, sometimes requiring hysterectomy.

Early techniques involving laser or roller-ball electrocoagulation have largely been replaced by second-generation techniques such as thermal balloon ablation and impedance-controlled electrocoagulation. Typically, over 80% of patients are satisfied with the results after one of these ablative procedures. If there is a significant amount of adenomyosis, then severe pelvic pain may occur after an ablation. Between 10% and 20% of patients who have had endometrial ablation will go on to have a hysterectomy.

HYSTERECTOMY

In the past, hysterectomy was the mainstay for persistent AUB. The LG-IUS and endometrial ablation have resulted in far fewer hysterectomies being performed now. Increasingly, hysterectomy is performed laparoscopically. The main indications for hysterectomy in perimenopausal phase include as part of a staging procedure for endometrial cancer, endometrial hyperplasia (especially if atypia is present), large symptomatic fibroids, in some cases of adenomyosis or endometriosis when medical measures have failed.

CONCLUSIONS

AUB during the menopause transition is common. Apart from taking a clinical history and performing...
an examination, all will need some type of uterine assessment. For most, this will be an EB backed up with a TVUS. SHG is a cost-effective method for assessing the endometrium. If a focal lesion is found on imaging, then hysteroscopy and biopsy will be indicated. Having excluded endometrial hyperplasia and uterine carcinoma, polyps and sub-mucus fibroids in particular, medical options will usually be the first-line treatment. Of these, the most effective is the LG-IUS, although some women will prefer to try an oral medication first such as tranexamic acid, a low-dose OCP, or cyclic progestins. HT has not been adequately evaluated as a treatment for AUB.

Surgery is usually a second-line option; however, if sub-mucus fibroids or polyps are present, then these can be resected hysteroscopically. Endometrial ablation and the LG-IUS have been shown to give similar results for most patients with heavy menstrual bleeding.

FURTHER READING


About the Authors

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### Infant Formula
For infants from birth to 12 months of age

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novalac +DHA &amp; ARA</td>
<td>Prebiotic GOS • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • DHA and ARA • 5 Nucleotides • Whey: Casein ratio of 60:40</td>
</tr>
<tr>
<td>Novalac 1</td>
<td>Adapted carbohydrate mix of lactose 5.3g/100ml and maltodextrin 2.2g/100ml • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • Whey: Casein ratio of 60:40</td>
</tr>
<tr>
<td>Novalac IT</td>
<td>Modified level of Lactose and Magnesium • Ca/P ratio of 2 • Medium chain triglycerides • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • Whey: Casein ratio of 60:40</td>
</tr>
<tr>
<td>Novalac AR</td>
<td>Treated corn starch enriched with amylopectin that thickens only in low pH (stomach) • Medium chain triglycerides (MCT) ease gastric emptying • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3)</td>
</tr>
<tr>
<td>Novalac AC</td>
<td>Low Lactose of 3g/100ml • Maltodextrins enriched with amylopectin • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • Whey: Casein ratio of 60:40</td>
</tr>
<tr>
<td>Novalac NovaRice</td>
<td>Hydrolysed rice-based formula • Lactose-free, sucrose-free, gluten-free • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • DHA and ARA • 5 Nucleotides • Also an alternative formula for allergies of cow’s milk protein and soy protein and intolerance of lactose and sucrose</td>
</tr>
</tbody>
</table>

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### Growing-up milk
For children from 1 to 5 years of age

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novalac +DHA Grow</td>
<td>Prebiotic GOS • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • DHA • 5 Nucleotides • Sucrose-free</td>
</tr>
<tr>
<td>Novalac Grow</td>
<td>Adapted carbohydrate mix of lactose and maltodextrin • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • Sucrose-free</td>
</tr>
<tr>
<td>Novalac IT Grow</td>
<td>Modified level of Lactose and Magnesium • Ca/P ratio of 2 • Medium chain triglycerides • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3) • Whey: Casein ratio of 60:40 • Sucrose-free</td>
</tr>
</tbody>
</table>

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### Special Formula
For infants from birth to 12 months of age

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novalac AD</td>
<td>Lactose-free, replaced with maltodextrin and monosaccharides • Modified electrolytes level with low osmolality • Fruit pectin and cream of rice • Fat mix with essential fatty acids – Linoleic Acid (omega-6) and α-Linolenic Acid (omega-3)</td>
</tr>
</tbody>
</table>

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The benefits and superiority of breastfeeding

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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Dehydroepiandrosterone (DHEA)—
The Answer to Diminished Ovarian Reserve?

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INTRODUCTION

Since its introduction in 1978, in vitro fertilization (IVF) has helped millions of infertile couples to conceive. In line with the natural decline in fecundity, treatment success with IVF also reduces with age, mainly because of the reduced ovarian reserve, reduced oocyte and embryo quality, and increased miscarriage rates. Apart from the physiological decline with age, some women suffer from premature ovarian ageing and diminished ovarian reserve (DOR).

Because optimal ovarian response is one of the major prerequisites for successful IVF treatment, women with DOR due either to physiological ageing or premature ovarian ageing remain one of the greatest challenges in modern infertility care.

In our centre, the ongoing pregnancy rate per IVF cycle initiated for women younger than the age of 35 is over 35%, while the ongoing pregnancy rate for women with DOR remains pretty low at ~10%. The prevalence of poor ovarian reserve in women is increasing, and a lot of attention has been drawn to identify ways in improving ovarian reserve and thus optimizing their chances of success.

Supplementation with dehydroepiandrosterone (DHEA), which is one of the potentially effective clinical approaches, is attracting worldwide attention. Following the initial paper published by Casson et al in 2000 which first described improved oocyte yields in IVF cycles supplemented with DHEA, a recent survey of IVF centres has revealed that approximately one-third of all IVF centres worldwide (196 centres in 45 countries) have started DHEA supplementation in women with DOR.

WHAT IS OVARIAN RESERVE?

It is a well-accepted concept that women are born with their complete oocyte pool for life. There are approximately 2 million primordial follicles at birth, which contain oocytes arrested in meiotic prophase I and remain quiescent until they are being recruited into follicle maturation. At menarche, the primordial pool has already...
dropped to 500,000; progressive loss occurs over the reproductive years, and there are around 25,000 remaining at a mean age of 37–38. Thereafter, the loss accelerates and falls below 1,000 at a mean age of 50–51, which marks the average age of natural menopause.4

While the non-recruited primordial follicles represent the genuine total ovarian reserve, the term ‘ovarian reserve’ that we commonly use in clinical practice often carries a different meaning.

ASSESSING OVARIAN RESERVE

Serum follicle-stimulating hormone (FSH), anti-Mullerian hormone (AMH) and antral follicle counts (AFCs) measured by transvaginal scan are the most commonly used methods to assess the ‘ovarian reserve’. Instead of the absolute total reserve, we are measuring one’s functional ovarian reserve, ie, the small portion of follicles that have been recruited from a particular cohort at the late stage of oocyte maturation. Serum FSH reflects the larger follicles that are gonadotrophin-sensitive, while the AMH and AFC reflect the pool of the smaller post-primordial preantral follicles.5–8

Serum AMH and AFC measurements are considered as reliable tests for predicting the ovarian response to ovulation induction. However, none of the currently employed tests of ovarian reserve can reliably predict pregnancy after assisted conception.

Recently, some researchers have incorporated the evaluation of FMR1 (fragile X) gene in assessing ovarian ageing.9,10 It is well known that FMR1 premutation is associated with premature ovarian failure, and it is now being shown that individuals with intermediate or even high normal CGG triple nucleotide repeats are also associated with premature ovarian ageing or DOR.11–14

The American College of Medical Genetics and the American College of Obstetrics and Gynecology have recommended the screening for FMR1 gene premutation in women presenting with DOR because of its neurological and psychiatric consequences that extend through successive generations.15,16

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DIMINISHED OVARIAN RESERVE

So far, there has not been any consensus in defining the term ‘poor/diminished ovarian reserve’. Some clinicians consider women with abnormally elevated age-specific baseline FSH or abnormally low age-specific AMH,17–19 defined by 95% confidence intervals at all ages, as having DOR. Some clinicians would include all women over the age of 40 owing to the expected physiological ovarian ageing.

POOR OVARIAN RESPONSE

Again, there is no consensus on its definition. Commonly used criteria include the previous poor response to vigorous gonadotrophin stimulation, with peak oestradiol attained being < 450 to 500 pg/mL and number of mature follicles or oocytes retrieved being ≤ 2 to < 4.2,20

OVARIAN AGEING

Female age is the most important determinant of ovarian age and reserve. Apart from the quantitative loss of primordial follicles, ovarian ageing is also characterized by reducing pace of follicular recruitment, decreasing number of follicles in folliculogenesis21 and decreasing egg quality, resulting in impaired embryo quality and spontaneous fecundity, decreased oocyte and embryo number and pregnancy rate in IVF treatment,17,22,23 and increased aneuploidy and miscarriage rates.24,25

WHAT IS DHEA?

DHEA is a mild androgen and an essential precursor of human sex steroid biosynthesis in both males and females. In females, about half of the daily production comes from conversion of cholesterol in the zona reticularis of adrenal glands, while the rest are produced by ovarian theca cells and peripheral tissues.26 It circulates in
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high amounts in reproductive-age women, but its level declines progressively with age, along with the natural decline in ovarian function. This raised the speculation that DHEA may play a role in age-related reduction in ovarian function and its supplementation may help in countering the decline.

HOW DOES DHEA WORK?

The exact mechanism of how DHEA works to improve ovarian reserve and response is still uncertain. It has been proposed that DHEA supplementation enhances serum-free insulin-like growth factor 1 (IGF-1) concentrations and amplifies hepatic and end-organ IGF-1 response to growth hormone, which may potentiate the gonadotrophin action in the milieu of the ovarian follicle.\(^2\)

Another proposed mechanism was based on a previous observation in which circulating DHEA-sulfate acts as a prohormone for much of the production of ovarian follicular sex steroids.\(^27\) DHEA supplementation may thus provide a more readily available pool of ovarian steroidogenic prohormone and facilitate follicular function and growth.

On the other hand, a recent study in a mouse model demonstrated the critical importance of androgen in regulating ovarian development and function. Androgens have been shown to promote preantral follicle growth while preventing follicular atresia. In contrast to the longstanding belief of the antagonistic effect of androgens to normal follicle development, DHEA supplementation may indeed play a central role in the early phase of follicular development.\(^28\)

EVIDENCE FOR DHEA USE IN FERTILITY PRACTICE

Despite the growing popularity of DHEA among fertility practice and patients, good-quality evidence based on randomized controlled trials (RCTs) in this area is lacking. It has been argued that women with DOR are reluctant to join studies with the possibility of receiving placebo\(^29,30\) and so far only one small-scaled RCT has been published.

Wiser et al enrolled 33 women with DOR and randomized them into the DHEA
and placebo groups. The study was designed for two consecutive cycles, with cycle outcomes and pregnancy outcomes being compared. DHEA was given at 75 mg daily orally for at least 6 weeks prior to the first IVF cycles. While no significant differences were demonstrated in the number of oocytes retrieved, embryos available for transfer, embryo quality and pregnancy rates in individual cycles, patients in the DHEA group were found to have a higher live birth rate (23.1% vs 4.0%; \( P = 0.05 \)) when the results of both cycles were compared together with the control.31

Additional data supporting the use of DHEA come from case reports, small case series and case-control studies.

**Increase in Oocytes and Embryo Yields**

The first published data on the use of DHEA in fertility practice was from a case series in which five patients with previous poor ovarian response were given DHEA supplementation at 80 mg/day for 2 months prior to the next IVF cycle. It showed an increased responsiveness with significantly higher peak oestradiol concentration and oestradiol/ampoule of gonadotrophins by a mean of 2.94 ± 0.5 fold \( (P = 0.012) \). The mean number of mature follicles increased from 1.0 to 2.2, and one patient conceived and delivered a twin pregnancy.2

A few years later, Barad and Gleicher published a series of studies on the potential effects of DHEA. They first published a case report in which a 43-year-old woman underwent nine consecutive cycles of IVF, with self-administration of oral micronized DHEA at 75 mg daily started after the first cycle without letting her clinician know. The oocytes retrieved with each cycle increased progressively, as did the number of embryos that was available for cryopreservation. In the first to third cycle, there were an average of 3.0 oocytes and 3.0 embryos; in the fourth to fifth cycle,
an average of 6.0 oocytes and 5.5 embryos were obtained; and those were further increased to 14.5 oocytes/9.5 embryos and 18.0 oocytes/13.5 embryos in the sixth to seventh, and eighth to ninth cycle, respectively. The dose of gonadotrophin had to be reduced in the ninth cycle to avoid ovarian hyperstimulation in one patient who had poor ovarian response in the initial cycles.32

**Improvement in Oocyte and Embryo Quality**

Following the unexpected and dramatic improvement in ovarian response in a single patient with DHEA supplementation during her IVF treatment,22 the researchers extended their investigation to a series of 25 women with proven decrease in ovarian reserve.29

Based on the previous findings of improved ovarian response after 4 months of DHEA supplementation, which were in keeping with the interval required for normal follicular initiation of recruitment and growth,33 all women in this study were given a minimum of 16 weeks of DHEA prior to the start of the new IVF cycle. They were given the same maximal gonadotrophin stimulation before and after DHEA supplementation. The dose of gonadotrophin had to be reduced in the ninth cycle to avoid ovarian hyperstimulation in one patient who had poor ovarian response in the initial cycles.32

**Improvements in Pregnancy Rates**

With the encouraging preliminary results, further studies have been conducted to assess the more important outcomes in IVF treatment—the pregnancy rates.

In a case-control study involving 190 women with DOR, 89 women in the study arm were given DHEA supplementation at 25 mg three times daily for up to 4 months (mean, 3.8 ± 0.3 months).30 Overall clinical pregnancy rates were significantly higher in study patients (28.1% vs 10.9%; P < 0.01). Almost half of all pregnancies were established spontaneously before IVF started. Even within the patients reaching IVF, there was a strong trend towards higher pregnancy rates (20.6% vs 11.9%). Interestingly, the miscarriage rates were also lower in the study group (20% vs 36%), suggesting a beneficial effect of DHEA on oocyte and embryo quality as well.

Sonmezer et al. published another case-control study using pre-DHEA treatment cycles as control in 19 women with DOR. Significant increases in follicles > 17 mm, metaphase II oocytes, and top-quality day 2 and day 3 embryos after DHEA supplementation were observed. The cycle cancellation rate was much reduced from 42.1% to 5.3% (P < 0.01), and the pregnancy rate per patient (47.4% vs 10.5%; P < 0.01) and clinical pregnancy rate per embryo transfer (44.4% vs 0%; P < 0.01) were also much improved after DHEA supplementation.20

**Reduction in Aneuploidy**

Along with the improvement in pregnancy rates, there is also evidence showing a reduction in miscarriage and aneuploidy rates after DHEA supplementation.

A retrospective case-control study involving 73 DHEA pregnancies reported a clinical miscarriage rate of 11/73 (15.1%). The total miscarriage rate based on the national USA registry in the same time period was 17.6%, with an odds ratio of 0.49 (95% confidence interval, 0.25–2.95; P = 0.04), suggesting a reduction in miscarriage risk of approximately 50%. The reduction in miscarriage rate is particularly marked in women older than 35 after age stratification. When taking the higher expected miscarriage rate in women with DOR, who required DHEA supplementation, into account, the adjusted reduction in miscarriage rate was even more significant at 80% (P < 0.0001).34

Since approximately 80–80% of spontaneous miscarriages are attributable to chromosomal abnormalities,35,36 it raises the question of whether the reduction in miscarriage rate after DHEA supplementation is achieved through a reduction in aneuploidy rate.

In order to verify such a postulation, another case-control study was conducted in an attempt to provide direct evidence from pre-implantation genetic screening (PGS).19 Twenty-two DOR patients who underwent IVF and PGS with DHEA supplementation were matched with 44 DOR women without DHEA supplementation. PGS was performed utilizing fluorescence in situ hybridization with seven probes (X, Y, 13, 16, 18, 21 and 22) on day 3 after fertilization when the embryos reached six- to eight-cell stages. The numbers of embryos transferred, embryos cryopreserved and embryos undergoing PGS, and the embryo...
grades were similar between the groups. While the two groups were matched in age (37.9 in DHEA group vs 37.2 in control), with age being considered as the most important risk factor for aneuploidy, aneuploid embryos in the DHEA group were significantly less prevalent compared with those of the controls (2.8 ± 2.5 vs 4.5 ± 3.1; \( P = 0.03 \)), as were the percentages of aneuploidy (38.2% ± 24.4% vs 61.0% ± 22.4%; \( P < 0.001 \)).

Hodges et al suggested that abnormal chromosome alignments in the meiotic spindle of oocytes increase the risk of non-disjunction errors and aneuploidy.24 If the initial evidence showing reduction in miscarriage and aneuploidy rates after DHEA supplementation is indeed true, something amenable to manipulation by DHEA must be present during oocyte maturation and meiotic segregation, in contrast to the long-held belief of irreversible ageing in primordial oocytes.37,38

It has been postulated that the ovarian environment in which follicle maturation takes place may be the real culprit. DHEA level is at its peak in the mid-20s and declines with age, along with the observed increase in aneuploidy and miscarriage rates. It would be interesting to explore whether DHEA supplementation in the late reproductive life may indeed improve the ovarian environment, leading to reduction of meiotic segregation error, better oocyte quality and reduced risk of aneuploidy.

### SIDE EFFECTS OF DHEA

DHEA is a mild androgen, and possible side effects include oily skin, acne, hair loss, and deepening of voice. Based on the existing data, these effects seem to be minimal at a daily dose of 75–80 mg.20,30–32 There has not been any reported case of increased fetal abnormalities associated with DHEA supplementation.

### LIMITATIONS

Except for one small RCT published by Wiser et al.,31 which has been criticized for the study design and results interpretation, most available data are from observational studies with inherent limitations. The fact that most publications actually come from the same group of authors, who were listed as the co-inventors of a US patent that claims beneficial effects from DHEA supplementation in women with DOR on ovarian function and pregnancy rates, may warrant caution in the interpretation of results. While it has been argued that an RCT is difficult if not impossible to be conducted in patients with DOR, we still believe that well-conducted RCTs would give a more comprehensive and unbiased account on the use of DHEA in this regard.

### SUMMARY

Women having DOR either due to premature ovarian ageing or physiological age-related decline are assuming an increasing clinical importance in modern fertility practice. In contrast to the existing focus and investigation on the final stage of follicular maturation during the gonadotrophin-sensitive phase, DHEA supplementation appears to improve folliculogenesis at much earlier stages and...
has attracted vast attention. Existing data from animal studies and observational studies have demonstrated an improvement in ovarian reserve and ovarian response to gonadotrophins, improved oocyte and embryo yields, improved embryo qualities, and reduced rates of aneuploidy and early miscarriage. Improved live birth rates have also been demonstrated in a small, randomized, controlled trial.

At present, it is a widely held belief that ‘ovarian ageing’ is not amenable to treatment and remains one of the unresolved issues in modern infertility care.

The new concept of improving the ovarian environment by DHEA supplementation to reduce the detrimental effects of ageing on follicular maturation and meiotic segregation definitely deserves more attention.

CONCLUSION

Existing data on the use of DHEA supplementation in women with DOR have shown encouraging results with improvement in pregnancy rates.

While DHEA is readily available to patients as a dietary supplement in countries including the United States and locally in Hong Kong, we believe that further well-designed, randomized, controlled studies with adequate power are key to verifying this potentially revolutionary approach in managing women with DOR before its wider use.

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CME Article 1 Point
Dehydroepiandrosterone (DHEA)—The Answer to Diminished Ovarian Reserve?

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

1. Women go into menopause when their pools of primordial follicles are completely depleted.
2. Functional ovarian reserve refers to the total non-recruited primordial follicles in ovaries.
3. Serum follicle-stimulating hormone, serum anti-Mullerian hormone and antral follicle counts are reliable tools to predict pregnancy rates in reproductive treatments.
4. DHEA is an endogenous androgen produced in adrenal glands, ovaries, and peripheral tissues.
5. DHEA has been used in a third of fertility centres worldwide to improve pregnancy outcomes in women with diminished ovarian reserve.
6. Androgens have been shown to promote preantral follicle growth while preventing follicular atresia.
7. DHEA has been shown to improve embryo number and quality in randomized controlled trials.
8. It has been postulated that DHEA can reduce the rate of aneuploidy by stimulating the production of new primordial oocytes which are not subjected to ageing.
9. Up to 80% of spontaneous miscarriages are attributable to chromosomal abnormalities.
10. We should widely promote the use of DHEA, since it has been proven to improve ovarian response and pregnancy rates, and reduce miscarriage rates.