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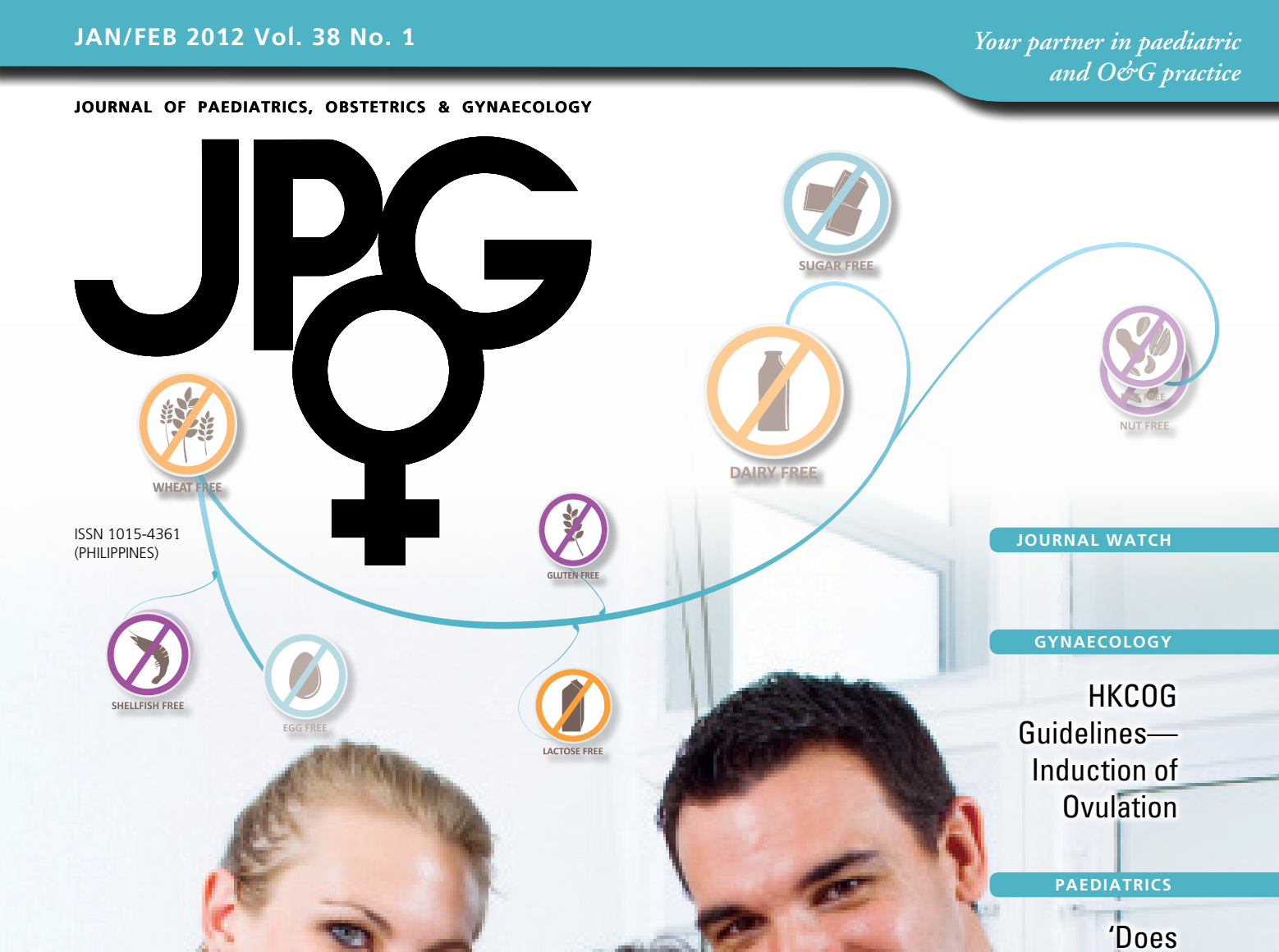

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HKCOG Guidelines—Induction of Ovulation

PAEDIATRICS

'Does My Child Have a Food Allergy?'

CME ARTICLE

Management of Pregnancies With Previous Caesarean Section

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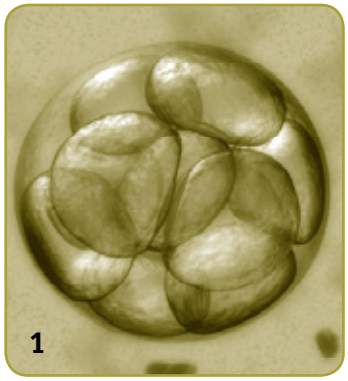



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Review Articles

Gynaecology

5 HKCOG Guidelines—Induction of Ovulation

This guideline by The Hong Kong College of Obstetricians and Gynaecologists (HKCOG) covers the classification of ovulation disorders, treatment options of various ovulation disorders, and their associated risks.

Yeung Wing Yee Tracy, Lee Chi Yan Vivian, Li Hang Wun Raymond, Ng Hung Yu Ernest; for The Hong Kong College of Obstetricians and Gynaecologists

Paediatrics

26 'Does My Child Have a Food Allergy?'

Avoidance, education about management of an acute reaction and optimal treatment of other atopic conditions, particularly asthma, are the mainstays of treatment of food allergy in children.

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Review Article

Continuing Medical Education

37 Management of Pregnancies With Previous Caesarean section

This article reviews the recommendations on vaginal birth after previous caesarean section (VBAC) by different professional societies, the favourable and unfavourable factors in considering VBAC, the associated maternal and fetal benefits and risks, as well as the non-medical concerns that play a role in the decision-making process.

Yung WK, Lau WL, Leung WC

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OBSTETRICS

Asthma in pregnancy: Treatment guided by F_ENO measurement

Fraction of exhaled nitric oxide (F_ENO) is a measure of airway inflammation. A study at two hospitals in Australia has shown that the management of asthma in pregnancy might be improved by using measurements of F_ENO to guide therapy.

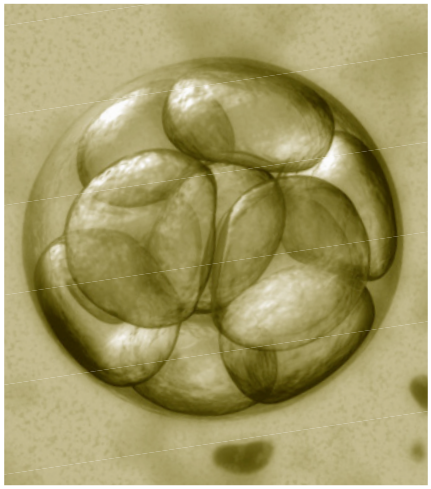
A total of 220 pregnant, non-smoking women with asthma were randomized at 12–20 weeks' gestation to management using a clinical symptoms algorithm or an F_ENO algorithm. With the latter, the dose of inhaled steroid was increased at $F_ENO > 29$ ppb and reduced at $F_ENO < 16$ ppb, at monthly visits to the antenatal clinic. The rate of asthma exacerbations was 0.288 per pregnancy in the F_ENO group and 0.615 per pregnancy in the control group, a significant 50% reduction in the F_ENO group. The number-needed-to-treat was 6. Quality of life was improved significantly in the F_ENO group; the mean daily dose of steroid was less and more women received long-acting β_2 agonist therapy. Neonatal outcomes tended to be better in this group.

Use of the F_ENO algorithm could improve the management of asthma in pregnancy.

Powell H et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. Lancet 2011; 378: 983–990; Szefler SJ. Personalised medicine for asthma management in pregnancy. Ibid: 963–964 (comment).

Women exposed to DES *in utero*: More on adverse health outcomes

It has been known for 40 years that diethylstilbestrol (DES) given to mothers during pregnancy induces clear-cell adenocarcinoma of the vagina and cervix in their daughters in adolescence and early adulthood. Later, developmental defects of the genital tract and complications of pregnancy were added to the long-term effects. Now, three US cohort studies combined have provided more long-term data.



Altogether, the three studies, with follow-up to an average age of 48 years, included 4,653 women exposed to DES *in utero* and 1,927 unexposed controls. The risks of 12 outcomes were assessed in exposed women and controls up to the age of 45 for reproductive outcomes and 55 for other outcomes. The risks for all 12 outcomes were increased in exposed women compared with controls. The rates for exposed women versus controls and hazard ratios were: infertility, 33.3% vs 15.5% (2.37); spontaneous abortion, 50.3% vs 38.6% (1.64); ectopic pregnancy, 14.6% vs 2.9% (3.72); loss of second-trimester pregnancy, 16.4% vs 1.7% (3.77); preterm delivery, 53.3% vs 17.8% (4.68); preeclampsia, 26.4% vs 13.7% (1.42); stillbirth, 8.9% vs 2.6% (2.45); neonatal death, 2.4% vs 0.56% (8.12); early menopause 5.1% vs 1.7% (2.35); cervical intraepithelial neoplasia grade 2 or greater, 6.9% vs 3.4% (2.28); breast cancer at age 40 years or older, 3.9% vs 2.2% (1.82); and clear-cell adenocarcinoma, 0.09% vs 0.0% (infinity). Vaginal epithelial changes at baseline increased the risk of most outcomes.

The daughters of women who took DES in pregnancy have increased lifetime risks for a wide range of adverse outcomes.

Hoover RN et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. NEJM 2011; 365: 1304–1314.

Hospital delivery policy in China and neonatal mortality

In many countries, a major obstacle to reducing mortality in children < 5 years old is refractoriness of neonatal mortality. In China, home births have been discouraged and birth in hospital is now the rule. Less than half of all births were in hospital in 1988, but in 2008 almost all babies were born in hospital. This policy appears to have been accompanied by a marked fall in neonatal mortality.

A population-based epidemiological study was carried out at 116 surveillance sites (37 urban, 79 rural) between 1996 and 2008; during this time, neonatal mortality fell by 62% (from 24.7 to 9.3 per 1,000 live births). Most neonatal deaths (82%) occurred in the first week of life and more than half were in the first 2 days. Neonatal mortality was lower in urban than in rural areas and highest in the most deprived rural areas. Neonatal mortality declined in almost all regions and from almost all causes.

These researchers attribute the reduction in neonatal morality to the policy of hospital births and improvements in obstetric and neonatal care. Commentators advise caution in the interpretation of these results.

Feng XL et al. China's facility-based birth strategy and neonatal mortality: a population-based epidemiological study. Lancet 2011; 378: 1493–1500; Bassini DG, Roth DE. China's progress in neonatal mortality. Ibid: 1446–1447 (comment).

Polycystic ovary syndrome: Adverse pregnancy outcomes



The incidence of polycystic ovary syndrome has been reported as 3–15% of women of reproductive age. The features include hyperandrogenism, anovulation, and polycystic ovaries. Meta-analyses have shown that the condition is associated with increased risks of gestational diabetes, pre-eclampsia, preterm birth, and perinatal mortality. It has been unclear, however, whether the risks are due to the polycystic ovary syndrome itself or to the associated features such as obesity or fertility treatments with increased risk of multiple pregnancy. Now, a study in Sweden has shown that polycystic ovary syndrome is associated with adverse pregnancy outcomes irrespective of the use of assisted reproductive technology.

Using national birth and patient registers, data were obtained for all singleton births in Sweden between 1995 and 2007. There were 1,195,123 births, and in 3,787 cases the mother had polycystic ovary syndrome. The risks of adverse pregnancy outcomes (gestational diabetes, pre-eclampsia, low Apgar score, meconium aspiration, small or large for gestational age, macrosomia) were adjusted for maternal characteristics, socioeconomic factors, and use of assisted reproductive technology. Comparing women with polycystic ovarian syndrome with women without the syndrome, affected women were more likely to be obese (61% vs 35%) and to have used assisted reproductive technology (14% vs 2%). They were 45% more likely to have pre-eclampsia, 2.2 times more likely to have very preterm delivery, and 2.3 times more likely to have gestational diabetes. Among their infants, there was a 39% increase in largeness for gestational age, a twofold increase in meconium aspiration, and a 40% increase in low Apgar score at 5 minutes.

Women with a diagnosis of polycystic ovary syndrome are at increased risk of adverse pregnancy outcomes irrespective of whether they have used assisted reproductive technology or not.

Roos N et al. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. BMJ 2011; 343: 835 (d6309); Macklon NS. Polycystic ovary syndrome. Ibid: 804–805 (d6407) (editorial).

PAEDIATRICS

Vitamin A supplements for children in developing countries: Systematic review and meta-analysis

A systematic review and meta-analysis has confirmed the value of vitamin A supplements given to children in developing countries.

The study included 16 trials (194,483 children aged 6 months to 5 years). Vitamin A supplementation was associated with a 24% reduction in mortality. There was a significant 28% reduction in diarrhoea mortality and a non-significant 20% reduction in measles mortality. There were significant reductions in prevalence of Bitot's spots of the bulbar conjunctiva (by 55%), night blindness (by 68%), and xerophthalmia (by 69%).

Vitamin A supplementation for children aged 6 months to 5 years reduces the incidence of diarrhoea and overall mortality. It also results in significant reductions in the features of vitamin A deficiency and might prevent blindness from this cause.

Mayo-Wilson E et al. Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. BMJ 2011; 343: 519 (d5094); Thorne-Lyman A, Fawzi WW. Improving child survival through vitamin A supplementation. Ibid: 487–488 (d5294) (editorial).

Adenoidectomy for recurrent URTIs in children: Negative trial

It has long been suspected that early adenoidectomy is not beneficial for children with recurrent upper respiratory tract infections (URTIs). A trial in the Netherlands has confirmed these suspicions.

A total of 111 children aged 1–16 years selected for adenoidectomy by ear, nose and throat surgeons because of recurrent URTIs were randomized to adenoidectomy (with or without myringotomy) within 6 weeks or a strategy of wait-and-see. Follow-up was for up to 24 months. The rate of URTIs was 7.91 episodes per child-year (adenoidectomy) versus 7.84 episodes per child-year (controls). The rate of new URTIs was similar over time in the two groups, with a gradual decrease. The groups did not differ significantly on follow-up in the rate of fever with ear symptoms or in quality-of-life measures. The adenoidectomy group had more days with fever during follow-up (20 vs 16 days per child-year). During the trial, 40% of the control group underwent adenoidectomy, but their presurgery URTIs were not more severe than those of the 60% who did not undergo surgery and they fared no better than those 60% after surgery.

Early adenoidectomy does not benefit young children with recurrent URTIs.

Van den Aardweg MTA et al. Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections: open randomised controlled trial. BMJ 2011; 343: 520 (d5154); Kvaerner KJ. Adenoidectomy in children with recurrent upper respiratory infections. Ibid: 488–489 (d5274) (editorial).

Benefits of routine rotavirus vaccination for US children

Routine infant vaccination with pentavalent rotavirus vaccine (RV5) was introduced in the USA in February 2006. Before that, there were an estimated 400,000 visits of children < 5 years old nationally to physicians' offices for rotavirus diarrhoea, with 200,000 visits to emergency departments, 55,000 hospital admissions, and 20–60 deaths each year. MarketScan databases (containing information from insurance claims) were used to obtain information about RV5 coverage and diarrhoea-associated health problems in children < 5 years old in the periods July 2001 to June 2006 and July 2007 to June 2009. By the end of December 2008, 73% of children < 1 year old had received at least one dose of RV5. Rates of hospital admission for diarrhoea in this age group were 52 per 10,000 person-years in 2001–2006, 35 per 10,000 person-years in 2007–2008, and 39 per 10,000 person-years in 2008–2009. Rates of hospital admission for rotavirus diarrhoea in these periods were 14, 4, and 6 cases per 10,000 person-years, respectively. Indirect benefit from the vaccine (among unvaccinated children) was shown by reductions of diarrhoea illness in January to June 2008 but not in the same period in 2009. Nationally in 2007–2009, there were an estimated 64,855 fewer hospital admissions for diarrhoea among children < 5 years old with a saving in health-care costs of US$278 million.

The introduction of routine infant vaccination with RV5 was followed by substantial reduction in diarrhoea among the under-5s and substantial saving in health-care costs.

Cortes JE et al. Rotavirus vaccine and health care utilization for diarrhoea in US children. NEJM 2011; 365: 1108–1117.

Millennium Development Goals 4 and 5: An update on progress

The targets for Millennium Development Goals (MDGs) 4 and 5 are a reduction in under-5 mortality by two-thirds and in maternal mortality ratio by three-quarters between 1990 and 2015. A further update on progress has been reported using recent surveys, censuses, vital registration, and verbal autopsy data.

It is estimated that under-5 deaths will have fallen to 7.2 million in 2011 with 2.2 million early neonatal deaths, 0.7 million late neonatal, 2.1 million postneonatal infantile, and 2.2 million of children aged 1–4 years. The rate of decline of under-5 mortality was greater in 2000–2011 than in 1990–2000 in 106 countries. There has been no progress towards MDG-4 in four countries. Maternal mortality has fallen from 409,100 in 1990 to 273,500 in 2011. In 2011, it is estimated that 56,100 maternal deaths will be human immunodeficiency virus–related. Twenty developing countries show no progress towards MDG-5. Current estimates suggest that 31 countries will achieve MDG-4, 13 will achieve MDG-5, and nine will achieve both targets. Fourteen countries are likely to achieve both targets by 2020. *Lancet* commentators question the value of frequent, differing estimates of progress. Most developing countries will not achieve the targets of MDG-4 and MDG-5 until many years after 2015.

Lozano R et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. Lancet 2011; 378: 1139–1165; Byass P, Graham WJ. Grappling with uncertainties along the MDG trail. Ibid: 1119–1120 (comment).

Immunoglobulin for neonatal sepsis: Not effective

The results of trials of immunoglobulin as prophylaxis or treatment for neonatal sepsis have been variable, and there is still no consensus about its value. A large international trial has shown no benefit of intravenous immunoglobulin for the treatment of neonatal sepsis.

At 113 centres in nine countries, a total of 3,493 newborn infants (birth weight < 1,500 g) receiving antibiotic treatment for proved or suspected sepsis were randomized to polyvalent IgG immunoglobulin 500 mg/kg, or placebo, repeated after 48 hours. The primary outcome (death or major disability at age 2 years, adjusted for gestational age) occurred in 39% of each group. Death before hospital discharge occurred in 17% of each group, and there were no differences between the groups in other secondary outcomes.

Treatment with intravenous immunoglobulin did not affect outcomes.

The INIS Collaborative Group. Treatment of neonatal sepsis with intravenous immunoglobulin. NEJM 2011; 365: 1201–1211.

Acyclovir suppressive therapy after treatment of neonatal herpes

After neonatal herpes simplex virus (HSV) infection, the risk of sequelae depends on the initial clinical picture. Superficial disease (skin, eye, and mouth) is associated with a low risk of neurological impairment, although there may be skin recurrences. With disseminated disease, there is a 30% mortality rate and a 20% risk of neurological damage in survivors. Central nervous system (CNS) infection carries a 6% mortality and a 70% risk of permanent neurological sequelae. Two paralleled multicentre

trials in the USA, reported together, have shown that 6 months of oral acyclovir after initial parenteral treatment may be beneficial.

The two trials together included 74 neonates with HSV infection, 29 with superficial disease, and 45 with CNS involvement. They were treated with parenteral acyclovir for 14 days (superficial disease) or 21 days (CNS disease). Randomization was then to oral acyclovir or placebo three times daily for 6 months. Acyclovir suppressive therapy prolonged the time to two cutaneous recurrences in the CNS disease group but not in the superficial disease group. Among the 45 infants with initial CNS disease, three had a CNS recurrence within 12 months of entering the study, one assigned to acyclovir and two to placebo. On the Mental Development Index of the Bayley Scales of Infant Development, performed at 12 months of age on 28 of the 45 infants, the mean score was significantly lower in the placebo group (68.12) than in the acyclovir group (88.24). There was a trend towards more neutropenia in the acyclovir group.

Six months of oral suppressive therapy with acyclovir after initial parenteral therapy may improve neurodevelopmental outcomes after neonatal HSV infection. An editorialist favours treating all children with either superficial or CNS disease.

Kimberlin DW et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. NEJM 2011; 365: 1284–1292; Gershon AA. Neonatal herpes simplex infection and the three musketeers. Ibid: 1338–1339 (editorial).

Malaria and bacteraemia in children

Bacteraemia is common in children in sub-Saharan Africa. Human immunodeficiency virus (HIV) infection, malnutrition, and sickle-cell disease all contribute to the susceptibility. Malaria is also thought to make children susceptible to invasive bacterial infections. Sickle-cell trait (HbAs), however, provides protection against malaria, and researchers in Kenya have taken advantage of this to perform a mendelian randomization study.



First, they studied 292 children aged 3 months to 13 years with bacteraemia and 528 control children. Bacteraemia was associated with sickle-cell disease, HIV infection, undernutrition, and leukocyte haemozoin pigment. Sickle-cell trait was associated with a 64% reduction in risk of bacteraemia. Next, they performed a longitudinal case-control study with 1,454 cases (children with bacteraemia) and 10,749 controls. Between 1999 and 2007, the rate of hospital admission for malaria fell from 28.5 to 3.45 admissions per 1,000 child-years because of more effective malaria control. At the same time, the protection provided by sickle-cell trait against bacteraemia fell and hospital admissions for bacteraemia, largely Gram-negative bacteraemia including cases due to non-typhoidal salmonella, decreased in parallel with those for malaria, from 2.59 to 1.45 per 1,000 child-years. Malaria parasitaemia increased the risk of bacteraemia 6.7-fold. In 1999, the prevalence of parasitaemia in the community was 29%, and 62% of cases of bacteraemia were attributed to malaria.

Malaria control should reduce the prevalence of bacteraemia.

Scott JAG et al. Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. Lancet 2011; 378: 1316–1323; Obaro S, Greenwood B. Malaria and bacteraemia in African children. Ibid: 1281–1282 (comment).

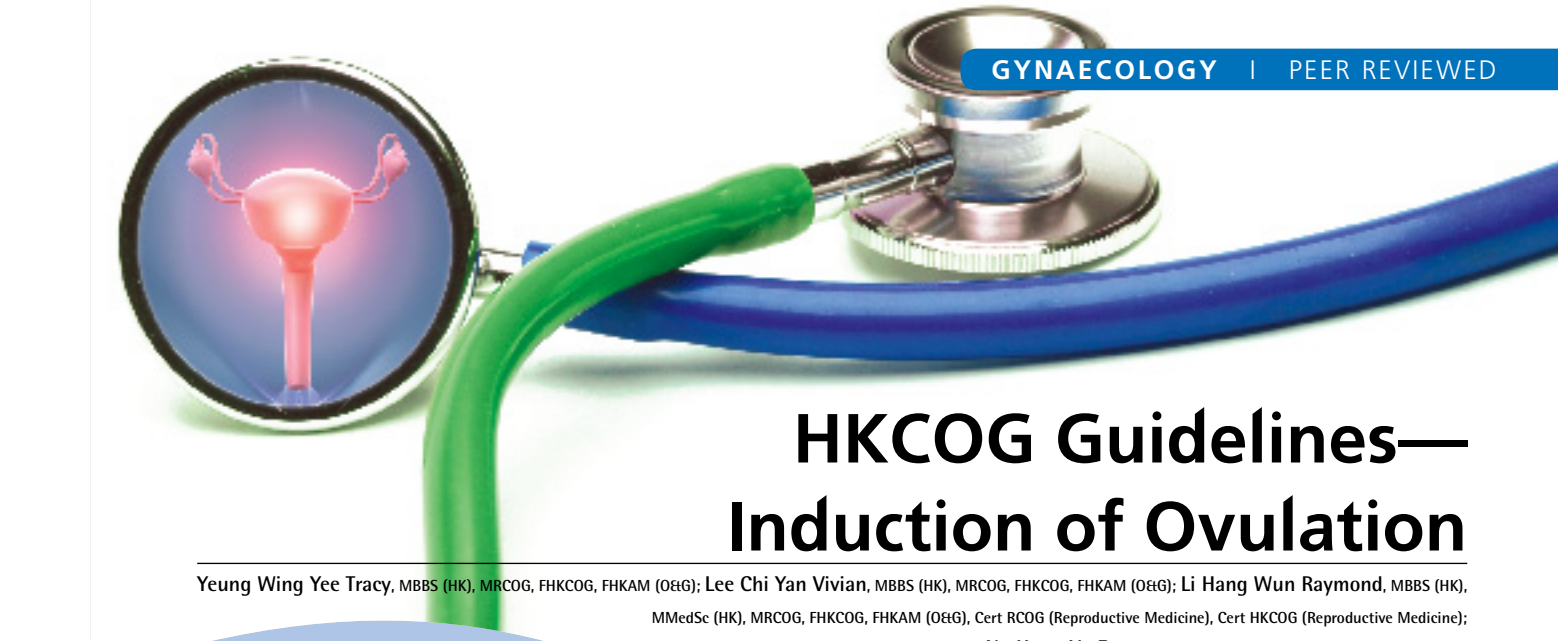
Adjuvanted influenza vaccine for children

Many countries recommend seasonal influenza vaccination for children, but the trivalent inactivated vaccine (TIV) produces poor immune responses in young children. Now, the addition of MF59, an oil-in-water emulsion, as an adjuvant to TIV, has been shown to increase the immunogenicity of TIV and to give greater efficacy.

A total of 4,707 children aged 6 to < 72 months were randomized to TIV without adjuvant, TIV with adjuvant (ATIV), or a control (non-influenza) vaccine. The vaccines were given as two doses, with an interval of 28 days, during the influenza seasons of 2007–2008 and 2008–2009 in Germany and 2008–2009 in Finland. The rates of influenza-like illness were 0.7% (ATIV), 2.8% (TIV), and 4.7% (controls), and the vaccine efficacy rates against all influenza strains were 86% (ATIV) and 43% (TIV). Among children aged 6 to < 36 months, the efficacy was 79% (ATIV) and 40% (TIV). Among children aged 36 to < 72 months, the corresponding efficacies were 92% and 45%. The antibody titres achieved were greater with ATIV. There were more systemic reactions with ATIV in the older children. The rate of adverse reactions was similar in all three groups.

ATIV was more efficacious than TIV in infants and young children.

Vesikari T et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. NEJM, 2011; 365: 1406–1416.



HKCOG Guidelines—Induction of Ovulation

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PURPOSE AND SCOPE

This guideline covers the classification of ovulation disorders, treatment options of various ovulation disorders, and their associated risks.

INTRODUCTION

Ovulation disorders account for 20% of the causes of subfertility.[1] The goal of ovulation induction is to achieve development of a single follicle and subsequent ovulation in women with anovulation. The selection of the most appropriate treatment for ovulation disorders depends upon reaching the correct diagnosis. Patients should be fully informed of the treatment options available, the success of each treatment option, and the associated risks.

CLASSIFICATION

Ovulation disorders can be classified according to the anatomical site where the hypothalamic-pituitary-ovarian axis is deficient (Table 1). The corresponding World Health Organization (WHO) classification[2] is also given for reference (Figure 1).

Adequate history and physical examination are essential. Further investigations are necessary to pinpoint where the defect in the hypothalamic-pituitary-ovarian axis is occurring. Based on the results of the investigation, the causes of anovulation can be divided into four distinct categories.[3]

Table 1: Classification of ovulation disorders

1. Intrinsic ovarian failure (WHO group III)
- Genetic, autoimmune, following chemotherapy or radiotherapy

2. Secondary ovarian dysfunction

a. Disorders of gonadotrophin regulation

Specific
- Hyperprolactinaemia
- Kallmann's syndrome (WHO group I)

Functional (WHO group I)
- Weight loss, exercise, drugs, idiopathic

b. Gonadotrophin deficiency (WHO group I)
- Pituitary tumour, pituitary necrosis or thrombosis

c. Disorders of gonadotrophin action (WHO group II)
- Polycystic ovary syndrome

WHO = World Health Organization.

Hyperprolactinaemia

Hyperprolactinaemia can be found in 15% of women with anovulation, and in 75% of women with both anovulation and galactorrhoea.[4] It interferes with the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) and impairs normal ovarian function. Causes of hyperprolactinaemia include a prolactin-producing adenoma, other tumours of the pituitary region blocking the inhibitory control of the hypothalamus, primary hypothyroidism, chronic renal failure, and a variety of drugs.

Prolactin molecules form irregular high-molecular-weight polymers to produce a biologically inactive form called macroprolactin. Macroprolactinaemia has no clinical significance and does not require any treatment. It should be considered in patients with no apparent hyperprolactinaemic symptoms.[5] The correct diagnosis can be made using prolactin chromatography and polyethylene glycol immunoprecipitation. It has been suggested that routine screening for macroprolactin in sera from subjects with suspected hyperprolactinaemia is cost-effective and should be performed to prevent inaccurate diagnosis and unnecessary intervention for hyperprolactinaemia.[6]

Asymptomatic patients with hyperprolactinaemia may not require treatment, and periodic observation should then suffice. When a woman with a macroprolactinoma wishes to become pregnant, it is necessary to plan conception to occur after serum prolactin is normalized and the tumour volume is significantly reduced in order to avoid or reduce the risk of compression of the optic chiasm during pregnancy.[7]

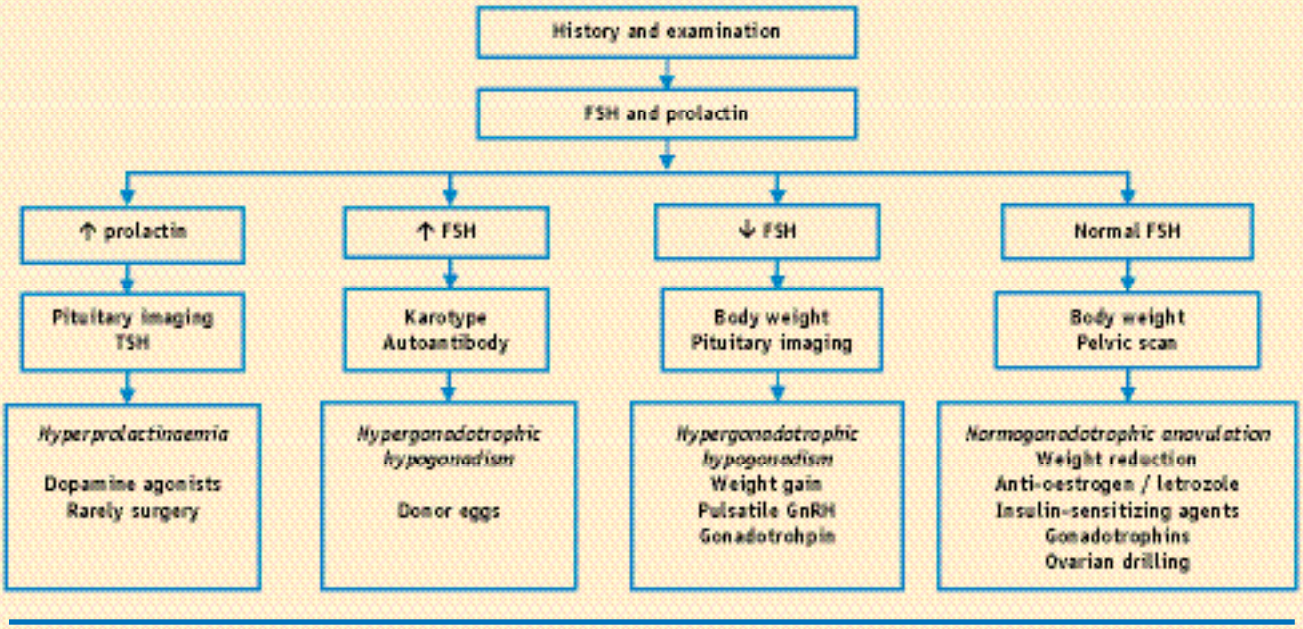
The first-line treatment is the use of dopamine agonists, which lower prolactin concentration and cause shrinkage of a prolactinoma if present. Surgery in the form of trans-sphenoidal pituitary adenomectomy is seldom indicated in the presence of a prolactinoma because of high recurrence rate and possibility of panhypopituitarism.[8,9] Radiotherapy is used very infrequently and is considered only if both medical and surgical treatments fail or are contraindicated.

Hypergonadotrophic Hypogonadism (WHO Group III)

Hypergonadotrophic hypogonadism or ovarian failure may be due to chromosomal abnormalities, autoimmune disorders, infection (mumps oophoritis), and irradiation or cytotoxic drugs. Many cases, however, are idiopathic even after extensive investigations. These women present with primary or secondary amenorrhoea with low endogenous oestrogen and highly elevated follicle-stimulating hormone (FSH) levels. There is no advantage in performing laparoscopy and ovarian biopsy to detect the presence of follicles in the resistant ovary syndrome because of the invasive nature and the doubtful value of the procedure.[10,11]

About half of young women with spontane

Figure 1: Flowchart of diagnosis and treatment



FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; TSH = thyroid-stimulating hormone.

ous hypergonadotrophic hypogonadism experience intermittent and unpredictable ovarian function, and spontaneous pregnancies have been reported in approximately 5–10% of cases subsequent to the diagnosis.[12] Although there have been case reports of successful ovulation induction treatment, any form of ovulation induction is not advisable in these women. The only realistic treatment for these patients is the use of donor eggs in an *in vitro* fertilization setting. In addition, they should be offered long-term hormone replacement therapy to protect their bones from the deleterious effects of hypooestrogenism.

Hypogonadotrophic Hypogonadism (WHO Group I)

These patients present with primary or secondary amenorrhoea. They have very low serum oestradiol concentration due to low FSH and luteinizing hormone (LH) secretion from the pituitary gland (hypogonadotrophic hypogonadism). It can be due to either congenital causes such as Kallmann's syndrome (isolated gonadotrophin deficiency and anosmia) or acquired causes such as pituitary tumour, pituitary necrosis (Sheehan's syndrome), stress, and excessive weight loss (anorexia nervosa).

Surgery is clearly indicated in patients with central nervous system tumours. Patients with anorexia nervosa may benefit from psychotherapy and weight gain after extensive counselling. Pulsatile GnRH or gonadotrophins containing both FSH and LH[13] are offered to patients with other hypogonadotrophic causes or with persisting anovulation despite weight gain.

Normogonadotrophic Anovulation (WHO Group II)

This includes a heterogeneous group of patients who can present either with regular cycles, oligomenorrhoea, or even amenorrhoea. The mid-

Patients seeking treatment for ovulation disorders should be fully informed of the treatment options available, the success of each treatment option, and the associated risks.



luteal serum progesterone is low, FSH levels are in the normal range, and prolactin is normal. Most of these patients are likely to have polycystic ovary syndrome (PCOS). Other causes include congenital adrenal hyperplasia, adrenal tumours, and androgen-producing ovarian tumours. In these conditions, the patient may have clinical symptoms or signs of hyperandrogenism such as hirsutism, which should require more detailed investigations such as measurement of dehydroepiandrosterone sulfate and 17-hydroxyprogesterone.

Obese PCOS women will benefit from weight loss, as this might lead to resumption of spontaneous periods and ovulation and will also improve their response to ovulation induction. They usually respond well to clomiphene citrate (CC) or aromatase inhibitors, failing that, to gonadotrophins for ovulation induction. Insulin-sensitizing agents or laparoscopic ovarian drilling may be considered in those not responding to CC. Specific causes, such as adrenal or ovarian tumours, should be treated by removing the cause. Congenital adrenal hyperplasia benefits from corticosteroid therapy.

TREATMENT

Effective use of ovulation induction agents requires understanding of their mechanism of action, proper indications, different regimens, monitoring methods, and potential complications.

Weight Reduction

Body mass index (BMI) is more representative of body fat and is calculated as weight in kilogrammes divided by height in metres squared. Overweight is defined as BMI ≥ 25 kg/m^2 and obesity is BMI ≥ 30 kg/m^2.[14] Overweight and obese women have a higher incidence of menstrual disturbance, ovulation disorders, and subfertility.[15] They may require higher dosage of ovulation drugs to achieve successful ovulation but have lower ovulation rates and delayed responses to various treatments of ovulation induction, if needed.

Ovulation induction with CC in overweight and obese women results in lower ovulation rates[16] and lower cumulative live birth rates for women with a BMI > 30 kg/m^2.[17] The dose of CC required to achieve ovulation is positively correlated with body weight.[18] Ovulation rates following gonadotrophin therapy in overweight women are lower owing to higher cancellation rates,[19,20] but this decreased success rate is not found in all studies.[21] Women with BMI of 25–28 need a gonadotrophin dose 50% higher than normal-weight women.[22] Obese women are also more prone to pregnancy complications such as miscarriage,[23] gestational diabetes, hypertension, macrosomia, and difficult delivery.[24]

Multiple observational studies report that weight loss is associated with improved spontaneous ovulation rates in women with PCOS,[15] even after losing < 5% of body weight.[25] Weight loss

is therefore recommended as first-line therapy in obese women with and without PCOS seeking pregnancy. This recommendation is based on extrapolation from the benefits of weight loss seen in medical conditions, such as diabetes and cardiovascular disease. There is a paucity of studies suggesting that weight loss prior to conception improves live birth rate in obese women with or without PCOS.[26]

The guidelines for dietary and lifestyle intervention in PCOS have been proposed.[26] Lifestyle modification is the first form of therapy, combining behavioural (reduction of psychosocial stressors), dietary, and exercise management. Reduced-energy diets (500–1,000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7–10% over a period of 6–12 months. Structured exercise is an important component of a weight-loss regime; aim for > 30 minutes per day. These interventions should be conducted prior to pregnancy and not during ovulation induction, as the effects of calorie restriction and increased physical activity in the periconceptional period are unknown.[27]

Medical Induction of Ovulation

Dopamine Agonists

Three dopamine agonists, bromocriptine, cabergoline and quinagolide, are licensed for treatment of hyperprolactinaemia. Experience with bromocriptine is far more extensive, and therefore for women undergoing ovulation induction this drug remains the treatment of choice, with cabergoline and quinagolide as acceptable second-line drugs in patients who are intolerant of bromocriptine.[28]

Mechanism of action. The secretion of prolactin from the lactotroph cells in the anterior pituitary gland is mainly regulated by the tonic inhibitory control of a prolactin inhibiting factor, which in humans is predominantly dopamine. Drugs with dopaminomimetic activity lower prolactin secretion, restore gonadal function, and shrink a prolactinoma, if present.

Regimen and monitoring. Bromocriptine is given at a daily dosage of 2.5–20 mg in divided doses 2–3 times a day. Serum prolactin concentrations are regularly measured, and ovulation is checked by mid-luteal progesterone concentrations. Other forms of monitoring for ovarian response are not required, as its use is not associated with multiple pregnancy or ovarian hyperstimulation syndrome (OHSS).

Cabergoline and quinagolide have longer biological half lives than bromocriptine. Cabergoline can be taken once or twice weekly and quinagolide once daily.

Experience with bromocriptine is far more extensive, and therefore for women undergoing ovulation induction this drug remains the treatment of choice

In patients who do not ovulate even when prolactin concentrations are within normal range, dopamine agonists can be combined with anti-oestrogen or gonadotrophin as appropriate.

Results. Bromocriptine can normalize serum prolactin concentrations in 80–90% of patients with microprolactinomas and about 70% of those with macroprolactinomas, together with a decrease in tumour size.[7,9] Dopamine agonist therapy restores ovulation in about 90% of women with anovulation related to hyperprolactinaemia.

A prospective study suggested that the overall

estimated rates of remission at 5 years in patients treated with bromocriptine were 76% among patients with non-tumoural hyperprolactinaemia, 67% among those with microprolactinomas, and 57% among those with macroprolactinomas.[29]

Cabergoline[30,31] and quinagolide[32,33] are shown to be significantly more effective than bromocriptine in restoring normal prolactin concentrations and ovulatory cycles. Quinagolide is probably less effective than cabergoline in hyperprolactinaemic patients.[28]

It is recommended that the minimal length of dopamine agonist therapy in patients with prolactinoma should be 1 year.[7] Normalization of magnetic resonance imaging prior to the withdrawal of dopamine agonists and longer duration of the drug therapy are significant predictors of remission.[34] If a patient has normal prolactin concentrations after dopamine agonist therapy for at least 3 years and the tumour volume is markedly reduced, a trial of tapering and discontinuation of these drugs may be initiated. Long-term follow-up is essential with close monitoring for recurrent hyperprolactinaemia and renewed tumour growth.

Side-effects. Side-effects with bromocriptine are common and include nausea, vomiting, abdominal cramps, vertigo, postural hypotension, headaches, and drowsiness. Although they are usually transient and mild, around 12% of patients discontinue the treatment for this reason.[28] The side-effects can be minimized by increasing the dose gradually from a low starting dose given with a meal in the evening, or by administering vaginal bromocriptine. A slow-release oral preparation may also reduce the incidence of side-effects. Significantly lesser side effects were reported in patients taking cabergoline and quinagolide when compared with bromocriptine.[28]

There is no increase in the incidence of multiple pregnancy, OHSS and spontaneous abortion with dopamine agonists.

Bromocriptine, cabergoline or quinagolide has not been associated with any detrimental effect on pregnancy or fetal development.[28] It is still recommended that patients with microprolactinomas or idiopathic hyperprolactinaemia stop bromocriptine treatment once pregnancy has been confirmed in order to avoid any potential harmful effects. Continuation of bromocriptine therapy during pregnancy may be considered in cases of macroprolactinoma or where there is evidence of tumour expansion.[7,9]

While there is considerable experience of bromocriptine use in women undergoing ovulation induction and during pregnancy, data on other dopamine agonists used in pregnancy are still limited.

The European Medicines Agency has recommended new warnings and contraindications for ergot-derived dopamine agonists as a result of the risk of fibrosis, particularly cardiac fibrosis, associated with chronic use. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine, and patients should be monitored during treatment.[35] Women who are planning pregnancy are further advised to stop taking cabergoline 1 month before they try to conceive.

Anti-oestrogens

Clomiphene citrate

Clomiphene citrate is commonly used as the first-line drug in women who suffer from normogonadotrophic anovulation (WHO group II).

Mechanism of action. It is an orally active non-steroidal compound with both oestrogenic and anti-oestrogenic properties with its primary mechanism of action based on the anti-oestrogenic property. It displaces endogenous oestrogen from oestrogen receptors in the hypothalamic-pituitary axis, which diminishes its negative feedback and

increases the secretion of GnRH and thus gonadotrophins. The increase in FSH and LH stimulate the production of ovarian follicles and subsequent ovulation.

Regimen and monitoring. CC should be started at 50 mg per day for 5 days following a spontaneous or progestin-induced withdrawal bleeding. The recommended maximum dose is 150 mg per day as there was no clear evidence of efficacy at higher doses and the US Food and Drug Administration (FDA) recommended a maximum of 750 mg per treatment cycle.[27] Starting from day 2, 3, 4 or 5 of the cycle was not shown to influence the results.[36]

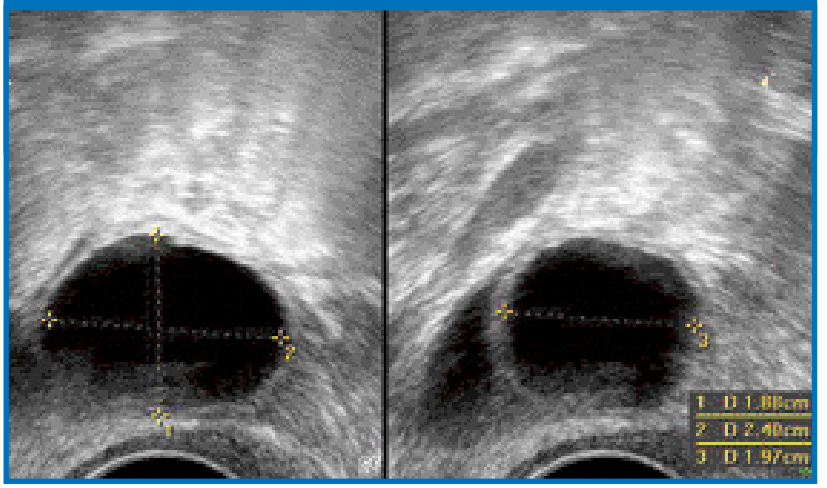
Ovulation usually occurs within 5–10 days after the last tablet. If there is no ovulation, the dose is increased at increments of 50 mg per cycle until ovulation occurs, or a maximum dose of 150 mg daily is reached.

While 50 mg per day is the recommended dose in the first cycle, a meta-analysis of 13 published reports suggests that only 46% will ovulate at this dose, a further 21% will respond to 100 mg and another 8% will ovulate with 150 mg per day.[37]

Although results of large trials suggest that monitoring by ultrasound or progesterone is not mandatory to ensure good outcome,[17] it is recommended to monitor the response at least during the first treatment cycle to ensure that an appropriate dose is received.[38] Transvaginal pelvic ultrasound should be used to monitor follicular growth and endometrial thickness. Patients who have no or excessive response to the current dose of CC and show reduced endometrial thickness can be identified. Serum progesterone concentrations could also be measured in mid-luteal phase to check for ovulation.

Duration of treatment. Treatment should generally be limited to six (ovulatory) cycles.[39] A course of six ovulatory cycles is usually sufficient to know if pregnancy will be achieved. Studies have reported that 71–87.5% of pregnancies achieved with CC occur within the first three cycles of treatment.[16,40,41]

The goal of ovulation induction is to achieve development of a single follicle and subsequent ovulation in women with anovulation.



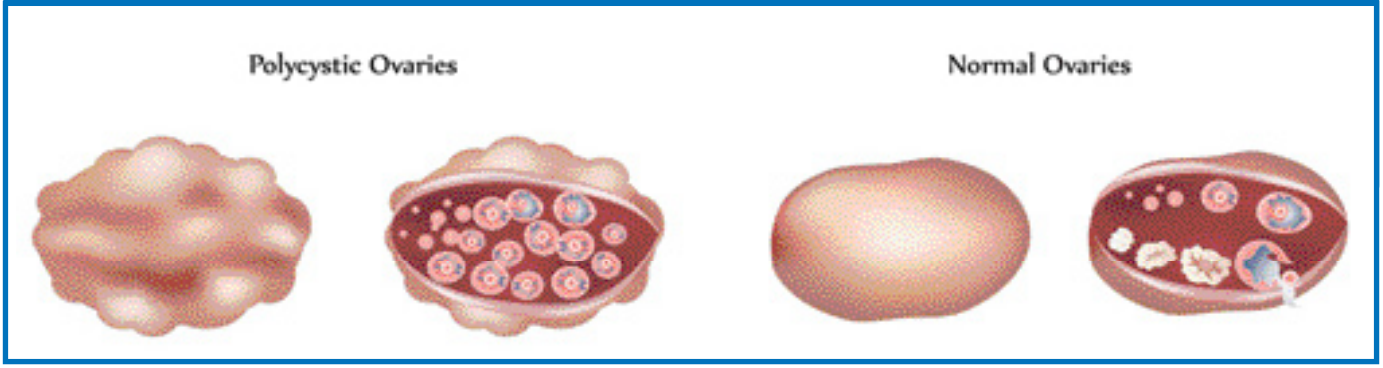
Further cycles (with a maximum of 12 in total) may be considered on an individual basis after discussion with the patient. However, second-line treatment should be considered for patients not conceiving after six ovulatory cycles of CC.

Further use of CC beyond 12 cycles has been found to be associated with an increased risk of ovarian cancer (relative risk [RR], 11.1; 95% confidence interval [CI], 1.5–82.3)[42] and is thus not recommended.

Results. A compilation of published results from 5,268 patients revealed an ovulation rate of 73% per patient, pregnancy rate of 36% per patient, and live birth rate of 29% per patient.[39]

A Cochrane meta-analysis[43] of three studies[44–46] comparing CC versus placebo in patients with anovulatory subfertility showed a large and consistent benefit of CC compared with placebo (odds ratio [OR], 5.77; 95% CI, 1.55–21.48; $P < 0.009$). Analysis for ovulation rate (per woman) also

Most patients with normogonadotrophic anovulation are likely to have polycystic ovary syndrome.



showed a benefit of CC compared with placebo (OR, 7.47; 95% CI, 3.24–17.23; $P < 0.00001$). There is no increase in spontaneous abortion or congenital abnormalities in CC-induced pregnancies.

CC in combinations. One small randomized controlled trial (RCT)[47] of 20 participants comparing CC (50 mg) plus tamoxifen (20 mg) versus CC (100 mg) alone showed no significant differences in pregnancy (OR, 3.32; 95% CI, 0.12–91.60) and ovulation rate (OR, 14.54; 95% CI, 0.67–316.69) between the two groups. There were no instance of OHSS in either group, and all pregnancies were singleton.

One RCT[48] comparing CC (up to 150 mg) plus ketoconazole 400 mg with CC alone showed no evidence of difference in pregnancy rate (OR, 2.37; 95% CI, 0.88–6.40), multiple pregnancy rate (OR, 1.18; 95% CI, 0.37–3.78), and miscarriage rate (OR, 0.28; 95% CI, 0.01–7.08).

One RCT[49] comparing CC (200 mg) plus bromocriptine (7.5 mg) versus CC (200 mg) showed no evidence of difference in pregnancy (OR, 0.98; 95% CI, 0.33–2.96) and ovulation rate (OR, 1.33; 95% CI, 0.47–3.79).

Analysis of three RCTs[50–52] comparing CC (50–200 mg) plus dexamethasone (0.5–2.0 mg) with CC (50–200 mg) showed a large and consistent benefit of pregnancy rate in the CC plus dexamethasone group (fixed OR, 9.46; 95% CI, 5.05–17.7; $P < 0.00001$). When the study[50] using 0.5 mg was excluded and only the two studies[51,52] using 2 mg were analysed, the OR was 25.3 (95% CI, 13.7–46.6; $P < 0.00001$) in favour of CC plus dexamethasone. There was no significant difference in the incidence of multiple pregnancies per women (OR, 7.71; 95% CI, 0.38–155.64). No side effects were reported in either group.

One RCT[53] comparing CC (100 mg) plus combined oral contraceptive pills which are given for 1 month prior to CC versus CC (100 mg) showed a benefit of CC plus combined pills in the pregnancy rate (OR, 27.18; 95% CI, 3.14– 235.02) and the number needed to treat (NNT) was 2.0 (95% CI, 1.4–3.4). Ovulation rate also showed a benefit in favour of CC plus combined pills (fixed OR, 26.71; 95% CI, 4.91–145.[38]) and the NNT was 1.6 (95% CI, 1.2–2.4). There was no evidence of difference in miscarriage rate (OR, 1.0; 95% CI, 0.06–16.97) or multiple pregnancy rate per woman (OR, 7.98; 95% CI, 0.39–163.33) between the two groups.

Analysis of two RCTs[54,55] showed no significant difference in pregnancy rate between the two groups with or without human chorionic gonadotrophin (hCG) (OR, 1.18; 95% CI, 0.59–2.36). There was also no difference in the incidence of spontaneous abortion or miscarriage reported (OR, 0.70;

95% CI, 0.19–2.62). Multiple pregnancy rate was reported in one study,[55] which showed no significant difference (OR, 2.21; 95% CI, 0.19–24.98)

One RCT[56] showed no significant difference for ovulation rate (OR, 1.34; 95% CI, 0.42–4.27), pregnancy rate (OR, 0.42; 95% CI, 0.07–2.46) or incidence of adverse events between the groups with or without hormone supplementation.

Failure of CC treatment. Women who do not ovulate while receiving the 150 mg dose are considered to be CC-resistant. Inability of CC to induce ovulation is more likely in patients who are obese, insulin-resistant and hyperandrogenic compared with those who do respond.[16]

Only about 50% of women who ovulate with CC will conceive. This may be partly explained by the peripheral anti-oestrogenic effect of CC at the level of endometrium and cervical mucus or by hypersecretion of LH. The two most common causes of failure to conceive in response to CC are the presence of other subfertility factors and the failure to persist with repeated attempts.

Side effects. Side effects of CC are related to its combined oestrogenic and anti-oestrogenic properties, which include hot flushes, breast discomfort, abdominal distension, nausea, vomiting, nervousness, sleeplessness, headache, mood swings, dizziness, hair loss, and disturbed vision. CC is usually very well tolerated with the side effects being dose-dependent and usually completely reversible once CC is stopped.

Approximately 7% of pregnancies resulting from CC-induced ovulation are twin pregnancies, and 0.5% are triplet pregnancies.[57] While mild ovarian enlargement is relatively common, severe OHSS is very rare.

Tamoxifen

Tamoxifen is a triphenylethylene derivative with a structure similar to CC. The suggested dose in ovulation induction is 20–40 mg daily, beginning on cycle day 3 for 5 days.

A meta-analysis[58] including four RCTs[59–62] comparing tamoxifen and CC showed similar ovulation rates (OR, 0.755; 95% CI, 0.513–1.111). There were no significant differences in pregnancy rate per cycle (OR, 1.056; 95% CI, 0.583–1.912) and per ovulatory cycle (OR, 1.162; 95% CI, 0.632–2.134) between the two groups.

There were no instances of OHSS or multiple pregnancies, and there was no difference in the incidence of miscarriage in one trial[60] reporting this outcome (OR, 0.37; 95% CI, 0.01–9.45).

While efficacy and safety of tamoxifen in ovulation induction has been shown, tamoxifen is not licensed for that purpose and patients should be counselled for its off-label use.

Insulin-sensitizing Agents

Mechanism of action. Insulin resistance is one of the recognized metabolic disturbance associated with PCOS, and may arise from either genetic defects or obesity. Insulin-sensitizing agents increase the insulin responsiveness in target tissues and hence reduce the compensatory hyperinsulinaemia, thereby ameliorating the associated metabolic effects. They include the biguanides and thiazolidinediones.

Metformin is one of the most commonly used biguanide. It does not stimulate insulin release and hence does not cause hypoglycaemia when used alone. In PCOS patients, it has been shown to improve glucose tolerance and lipid profiles, and decrease proinflammatory markers.

Regimen. Five hundred milligrams thrice daily or 850 mg twice daily with meals.

Efficacy. A recent Cochrane review[63] assessed the effectiveness of insulin-sensitizing drugs in fertility treatment for women with PCOS.

Metformin monotherapy. Metformin used

alone improves the ovulation rate (OR, 2.12; 95% CI, 1.5–3.0) and clinical pregnancy rate (OR, 3.86; 95% CI, 2.18–6.84) compared with placebo or no treatment, but not the live birth rate (OR, 1.0; 95% CI, 0.16–6.39).

Compared with CC, metformin gives lower ovulation rate (OR, 0.48; 95% CI, 0.41–0.57) and clinical pregnancy rate (OR, 0.63; 95% CI, 0.43–0.92), and a non-significant trend of lower live birth rate (OR, 0.67; 95% CI, 0.44–1.02). There are no difference in the miscarriage rate (OR, 0.94; 95% CI, 0.42–2.07) and the multiple pregnancy rate (OR, 0.33; 95% CI, 0.02–6.69) between the two treatments.

Metformin co-treatment with CC. Co-treatment with metformin and CC improves the ovulation rate (OR, 1.76; 95% CI, 1.51–2.06) and clinical pregnancy rate (OR, 1.48; 95% CI, 1.12–1.95), but not live birth rate (OR, 1.05; 95% CI, 0.75–1.47) compared with CC alone.

Previous subgroup meta-analyses indicated a higher clinical pregnancy rate after co-treatment with metformin and CC compared with CC alone in obese patients only (OR, 3.72; 95% CI, 1.23–11.22) but not in non-obese patients (OR, 2.71; 95% CI, 0.96–7.63), and in CC-resistant subjects only (OR, 9.62; 95% CI, 2.95–31.45).[64]

Another systematic review[65] also indicated that metformin plus CC led to higher live birth rates than CC alone only in CC-resistant women (RR, 6.44; 95% CI, 1.19–34.90) but not in CC-naive women (RR, 1.04; 95% CI, 0.82–1.33).

Side effects. Side effects include dose-dependent gastrointestinal upset including nausea, vomiting, and diarrhoea. Lactic acidosis is a rare though serious complication, and hence metformin should not be prescribed to patients with renal, hepatic or major cardiovascular disease or hypoxia.

Use of other insulin-sensitizing agents in PCOS patients. Examples include rosiglitazone and pioglitazone. It was shown that rosiglitazone improved ovulation rate (OR, 31.0; 95% CI, 3.76–255.30) but result in a higher incidence of weight gain.[63] On the other hand, these drugs are classified as FDA category C. There are no data on the role of pioglitazone in fertility treatment.

Insulin resistance is one of the recognized metabolic disturbance associated with PCOS

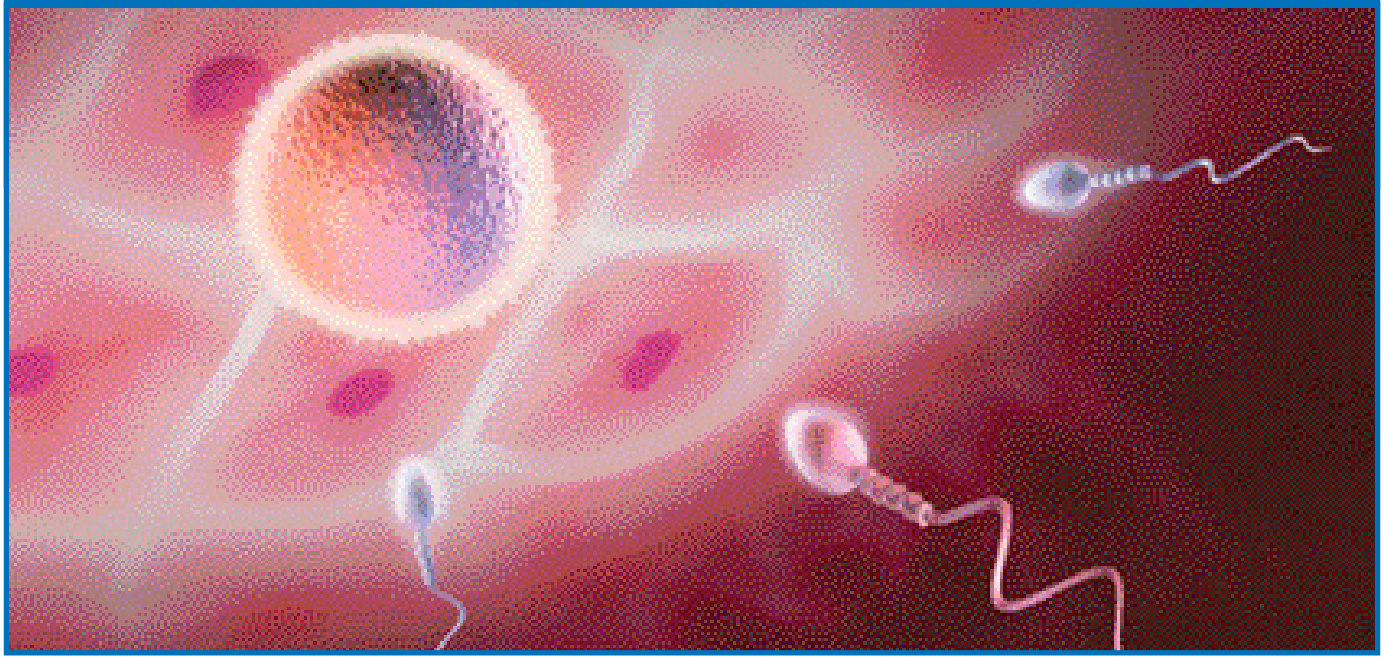
Aromatase Inhibitors

Aromatase inhibitors have been used for many years as an adjunct treatment for breast cancer and are gaining in popularity as an agent for ovulation induction in patients with PCOS. Its use in combination with gonadotrophin in ovarian stimulation protocol for patients, in whom high oestradiol level would be contraindicated, for example breast cancer patients, is also advocated.

Letrozole is a third-generation aromatase inhibitor and is the most commonly used agent in ovulation induction. When compared with CC, letrozole does not have the anti-oestrogenic effects and has a much shorter half-life. However, the use in ovulation induction is an off-label use.

Mechanism of action. Aromatase catalyses the rate-limiting final step in oestrogen production, the hydroxylation of androstenedione to oestrone and of testosterone to oestradiol. By blocking

Ovulation disorders account for 20% of the causes of subfertility.



oestrogen production, it increases FSH secretions with a decrease in the oestrogenic negative feedback of the hypothalamic-pituitary axis. Because aromatase inhibitors block high levels of oestrogen from androgen conversion, the effects in women with PCOS are more prominent.

Regimen and monitoring. The regimen is 2.5 to 5 mg per day for 5 days from days 3–7 of the period[66–68], or as a single dose of 20 mg on day 3 of the period.[69] A prolonged duration for 10 days has been evaluated.[70]

The monitoring is similar to that of CC and usually starts on day 7 of menses. Further monitoring depends on the growth of the follicles. With the split-dose regimen, multiple developing follicles appear on cycle day 7, but at mid-cycle only a single dominant follicle is found.

Results. In a review,[71] letrozole gave an ovulation rate of 70–84% and a pregnancy rate of 20–27% per cycle in PCOS women resistant to CC. Both of the single-dose and split-dose regimens achieved similar clinical pregnancy rates.[69] More follicles developed and a higher clinical pregnancy rate were reported in the longer letrozole regimen (2.5 mg daily for 10 days) when compared with the standard regimen (5 mg daily for 5 days).[70]

Other aromatase inhibitors have been compared with letrozole. In a prospective study,[72] 22 PCOS women were assigned to letrozole (2.5 mg per day for 5 days) and 18 to anastrozole (1 mg per day for 5 days). Letrozole was associated with a significantly higher ovulation rate (84.4% vs 60.0%) and pregnancy rate (27.0% vs 16.6%) than anastrozole.

Comparison with other methods. A meta-analysis[73] of four prospective, randomized studies[68,74–76] revealed that the overall effects of letrozole in comparison with CC was not significant for ovulatory cycles (OR, 1.17; 95% CI, 0.66–2.09), pregnancy rate per cycle (OR, 1.47; 95% CI, 0.73–2.96) and pregnancy rate per patient (OR, 1.37; 95% CI, 0.70–2.71).

In a Cochrane review[77] on different ovarian stimulation protocols in intrauterine insemination treatment, five studies comparing CC with letrozole also found no significant difference in the pregnancy rate (OR, 1.2; 95% CI, 0.64–2.1).

Side effects. Letrozole is well tolerated. Fatigue, nausea, constipation, diarrhoea, headache, drowsiness and dizziness are common side effects.

The multiple pregnancy rate was significantly lower in letrozole, both 2.5 mg daily or 5 mg daily, compared with CC treatment, as the letrozole treatment gave more monofollicular development compared with CC as shown by earlier reports. However, in the recent RCT[78] on the pregnancy outcome after CC or letrozole treatment, the chance of twin pregnancies of letrozole was comparable to that of CC (8.3% vs 9.1%). There was also a case report of a triplet pregnancy resulting from ovulation induction in a PCOS woman resistant to CC treatment.[79]

The teratogenic effects of letrozole are well described in animal studies.[80,81] Biljan *et al*[82] in an abstract suggested that the use of letrozole for subfertility treatment might be associated with a higher risk of congenital cardiac and bone malformations in the newborns. In a retrospective study with a much larger sample size, Tulandi *et al*[83] could not show any difference in the overall rates of major and minor congenital malformations among newborns from mothers who conceived after letrozole or CC treatments.

Gonadotrophin-releasing Hormone

Mechanism of action. GnRH administered in a pulsatile fashion restores the normal pattern of gonadotrophin secretion of a spontaneous menstrual cycle, leading to the development of a single dominant follicle.

Regimen and monitoring. Pulsatile GnRH is given by the subcutaneous or intravenous route through a small butterfly cannula using a small battery-operated pump which delivers 2.5–20.0 µg per bolus at 60–120-minute intervals. The intravenous route is preferred by some, because more physiological LH profiles and higher ovulatory rates result when GnRH is administered intravenously.[84] Higher dosage (10 µg per bolus) given at lower intervals (120 minutes) are just as effective as lower dosage (2–5 µg per bolus) given at a higher rate (every 60–90 minutes).[85]

Treatment can be monitored by regular serum oestradiol measurements and pelvic ultrasound at regular intervals. Couples are advised to have regular intercourse during the treatment cycle. The luteal phase has to be supported, either by continuing with the same regimen of pulsatile GnRH administration or using exogenous hCG injections.

Results. Hypogonadotrophic patients of normal or low weight are the best candidates for this treatment. A cumulative pregnancy rate of 80% after six cycles and up to 93% after 12 has been reported.[86] It is recommended to continue this therapy for at least 12 cycles in the absence of other subfertility factors.

A Cochrane review did not find any evidence to show the effectiveness of pulsatile GnRH in women with PCOS.[87]

Side-effects. Multiple pregnancy rates ranged between 3.8–13.5%.[88–91] The risk of multiple pregnancy is predominantly present in the first cycle and is related to higher pulse dosages.[88] Therefore, this risk can be greatly reduced if lower pulse dosages are employed at a lower frequency for the first cycle.

OHSS has never been described with pulsatile GnRH administration.

Patients may be reluctant to use the pulsatile GnRH therapy because of inconvenience, worry about pump failure and the problems of the needle being left *in situ* for a long time (eg, displacement, local reaction, infection). As a result, it is used in

Table 2. Different gonadotrophin preparations

Preparation	Source of FSH	FSH activity (IU/ampoule)	LH activity (IU/ampoule)	Non-FSH urinary proteins
HMG	Urine	75	75	95%
Urinary FSH	Urine	75	< 0.7	95%
Urinary FSH – high purity	Urine	75	< 0.001	< 1%
Recombinant FSH	Chinese hamster ovary	50, 75, 100, 150, 200	None	None

FSH = follicle-stimulating hormone; HMG = human menopausal gonadotrophin.

very few patients for whom alternatives such as gonadotrophin treatment are available.

Gonadotrophin (Table 2)

Human menopausal gonadotrophins are extracted from urine of postmenopausal women. Besides the difficulty in collecting urine, urinary gonadotrophins contain other non-FSH urinary proteins and hence the higher incidence of local allergic reactions and batch-to-batch inconsistency. Recombinant human FSH is a pure FSH preparation, devoid of the disadvantages associated with urinary gonadotrophins and allows self subcutaneous injection, but is generally more expensive. There is no difference between urinary FSH and recombinant human FSH in ovulation and pregnancy rates, as well as in the incidence of miscarriage, OHSS, multiple pregnancy and duration of stimulation.[92]

Mechanism of action. The use of exogenous gonadotrophins is to overcome the FSH threshold required for the follicular development.

FSH is the key gonadotrophic hormone during the follicular phase and only minute amounts of LH are needed in different stages of follicular development and function. However, in women with hypogonadotropic hypogonadism, a preparation containing both FSH and LH gives better outcome than purely FSH[93] because of the fundamental role of LH in ovarian steroidogenesis to produce an adequate serum oestradiol concentration for optimal endometrial proliferation.

Regimens. ***(a) Chronic low-dose, step-up protocol.*** This is currently the recommended protocol in many centres worldwide. The principle is to determine the FSH threshold gradually, avoiding excessive stimulation and multifollicular development. FSH is commenced at a low starting dose (37.5–75 IU/day) for at least 10–14 days[27] and the daily dose is increased by 37.5 IU at weekly intervals up to a maximum of 225 IU/day if there is no evidence of ovarian response. The same dose is maintained once follicular growth is observed. Once one to two dominant follicles reach 18 mm in mean diameter, hCG is administered at a dose of 5,000–10,000 IU to induce ovulation. The couple is advised to have intercourse on the day of hCG injection and on the following day.

As it may take several weeks to achieve an ovarian response in those with a high FSH threshold, patients should be counselled about the time scale prior to the first treatment cycle. In subsequent cycles, the patient can then be started at a dose that gives rise to ovarian response in the first cycle and this will shorten the duration required.

An original approach was the 'conventional dose step-up' regime, where gonadotrophin is commenced at 150 IU/day and stepped up by increments of 75 IU every 4 to 5 days till ovarian response is evident.[94] Compared with the 'chronic low-dose step-up' approach, the duration of stimulation is shorter but the incidence of multiple pregnancy and ovarian hyperstimulation is higher, especially in patients with PCOS.

(b) Step-down protocol. The aim of this protocol is to mimic the physiological changes of normal cycles. Gonadotrophin injection is commenced at 150 IU/day starting on day 2–3 of the cycle, and the ovarian response is monitored by transvaginal scanning every 2–3 days. The same dose is continued until a dominant follicle ≥ 10 mm is seen on scanning, and is then reduced to 112.5 IU/day followed by a further decrease to 75 IU/day 3 days later, which is continued until hCG is administered to induce ovulation. Hence, it requires more intense monitoring than the step-up protocol.

According to the largest randomized trial,[95] the step-down regime has a shorter duration of stimulation compared with the step-up protocol but a higher rate of multifollicular development and OHSS, as well as a lower ovulation rate. The pregnancy rate is comparable between the two regimes.

Monitoring. Ovarian response is monitored during gonadotrophin treatment to allow for adjustment of the gonadotrophin dose, timing the hCG injection for ovulation trigger, and cancellation of cycles with excessive response. Both serum oestradiol concentrations and ultrasound examination are commonly used for monitoring purposes. Serum oestradiol concentration reflects the total amount of oestradiol secreted from growing follicles but not the precise number of follicles. Ultrasound examination gives an immediate result of the number of dominant follicles and their sizes. Sholam *et al*[96] has shown that oestradiol concentrations did not add any additional information to the monitoring solely based on ultrasound.

Concomitant use. ***(a) With GnRH agonists.*** High LH concentrations commonly found in the follicular phase of patients with PCOS are associated with an increased rate of spontaneous abortion. Premature luteinization may occur in some patients before the dominant follicle reaches 16–18 mm in mean diameter. The use of GnRH agonists (GnRH-a) prior to gonadotrophin administration will lower the tonic high LH concentrations during the follicular phase and prevents the occurrence of premature LH surges. This may be used in patients with a previous history of premature luteinization. However, a meta-analysis[97] of three randomized trials shows that there is no clear advantage in the routine use of GnRH-a in conjunction with gonadotrophin for ovulation induction in patients with CC-resistant PCOS. Common odds ratios for pregnancy per treat

The step-down regime has a shorter duration of stimulation compared with the step-up protocol but a higher rate of multifollicular development and OHSS, as well as a lower ovulation rate.

ment cycle and moderate to severe OHSS are 1.5 (95% CI, 0.72–3.12) and 1.40 (95% CI, 0.5–3.92), respectively. Moreover, the use of GnRH-a will further increase the cost of gonadotrophin treatment because of the GnRH-a and the increased amount of gonadotrophins used after using GnRH-a.

(b) With CC. A combination of CC and gonadotrophin has been used to lessen the overall cost by reducing the amount of gonadotrophin needed. CC is used initially (100 mg daily from days 2–6) for follicular recruitment, followed by gonadotrophin (150 IU daily or on alternate days) to promote follicular growth, thus reducing the gonadotrophin requirement by up to 50%. This regimen is only of use in anovulatory patients who have endogenous gonadotrophins.

Results. The 6-month cumulative pregnancy rate in non-PCOS patients is around 90% with a miscarriage rate of 25%, whereas the corresponding rate in PCOS is only 50–60% with a miscarriage rate of 30–40%. Conventional dose step-up protocol in PCOS patients leads to 5% severe OHSS rate and 34% multiple pregnancy rate. When chronic low-dose step-up protocol is used in these women, similar pregnancy rates are achieved but the rates of severe OHSS and multiple pregnancy can be reduced to < 0.1% and 6%, respectively.

Side-effects. Serious complications of gonadotrophin therapy include OHSS and multiple pregnancy. Other complications include local reaction at the site of the injection or, rarely, anaphylactic reaction, perhaps due to the protein content of the urinary products. Such patients should be switched to recombinant FSH preparations.

Surgical Induction of Ovulation

Laparoscopic ovarian drilling is the preferred surgical method of ovulation induction over ovarian wedge resection, which is associated with a higher risk of postsurgical adhesion formation, converting hormonal subfertility to mechanical subfertility.

Mechanism of action. The mechanism of action of LOD is thought to be related to the destruction of ovarian androgen-producing tissue and the decrease of the peripheral conversion of androgens to oestrogens. A fall in the serum concentrations of androgens and LH and an increase in FSH concentrations have been demonstrated after LOD.

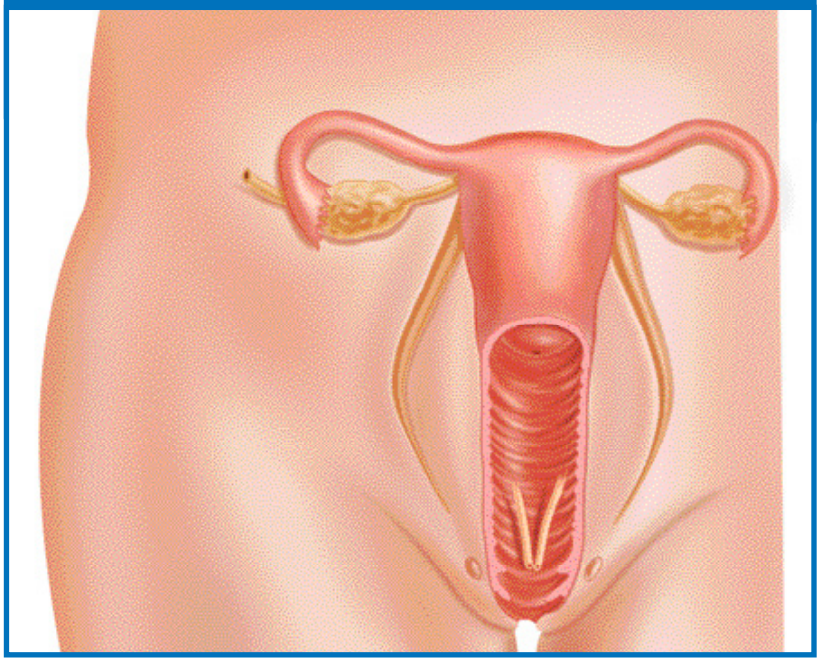
Regimen and monitoring. Electrocautery is commonly used in LOD. The procedure includes penetration of the ovarian capsule, making four punctures per ovary, and electrocautery is given at a power setting of 30 W applied for 5 seconds per puncture.[98,99] Another commonly used method is laser vaporization using carbon dioxide, argon or Nd:YAG crystal lasers.

Results. The ovulation rate after LOD in CC-resistant PCOS women was 52% to 67%.[100] The ovulation rate in PCOS women with LOD as the first-line treatment was 64%.[101] The pregnancy rate after LOD in CC-resistant PCOS women was 67%.[99]

Comparison with other methods. The theoretical advantages of LOD are multiple attempts of pregnancy allowed, monofollicular development, reduced miscarriage rate with the normalized hormonal profile, and assessment of the pelvic pathology and tubal status at the same setting.

LOD is usually the second-line treatment modality for PCOS women who fail to respond to CC, and so the comparison is usually with ovulation induction with gonadotrophins. In a Cochrane review,[100] the live birth rate of LOD is comparable to three cycles of gonadotrophins (OR, 0.68; 95% CI, 0.15–3.10) after 6 months of follow-up or six cycles of gonadotrophins at 12 months' follow-up (OR, 1.12; 95% CI, 0.60–2.08), with the pooled OR being 1.04 (95% CI, 0.59–1.83). There was no difference in the miscarriage rate between LOD and gonadotrophin therapy. The multiple pregnancy rate was reduced in the patients with LOD, with com

The incidence of spontaneous multiple pregnancies is increased in women taking clomiphene citrate and further increased in those with clomiphene citrate-resistant polycystic ovary syndrome treated with gonadotrophins.



parison of ovarian drilling with or without medical ovulation and gonadotrophins only (OR, 0.13; 95% CI, 0.03–0.59). There was no OHSS reported in the randomized trials in the LOD groups. There was no difference in ovulation rate and clinical pregnancy rate after unilateral or bilateral ovarian drilling.

Based on an economic evaluation by Farquhar *et al*,[102] the cost of a live birth in PCOS women resistant to CC using LOD would be one-third lower than using urinary or recombinant gonadotrophin treatment cycle.

LOD has been compared with CC treatment as the first-line treatment in a randomized study.[101] The pregnancy rate was higher in the CC group (44%) than the LOD group (27%), although the difference did not reach statistical significance (OR, 2.1; 95% CI, 0.7–5.8). The conclusion was that LOD was not superior to CC as a first-line method of ovulation induction in women with PCOS.

Side-effects. The main drawback of LOD is the need for general anaesthetic and surgery. Other complications such as adhesion formation and the risk of premature ovarian failure are of concern. The reported incidence of adhesion formation after LOD varied considerably in different studies from 0% to 100%.[103–105] Most of the studies reported mild to moderate adhesions in about 35% of cases, which did not seem to affect the pregnancy rate after LOD.[104]

RISKS OF OVULATION INDUCTION

Multiple Pregnancies

In the last two decades, significant increase in the incidence of multiple births is almost entirely the result of the use of gonadotrophins and other agents for ovulation induction or assisted conception.

Spontaneous multiple pregnancies occur in about 1–2% of women, which is increased to 7–10% of women taking CC and further increased to up to ~25% in women with CC-resistant PCOS treated with gonadotrophins.[106]

Multiple pregnancies carry extra risks for both the mothers and fetuses. Obstetric complications include increased incidence of pre-eclampsia and eclampsia, antepartum haemorrhage, preterm labour, and surgical or assisted delivery. The high incidence of prematurity and low birth weight in high-order multiple pregnancies result in a fourfold rise of perinatal mortality for twins and sixfold rise in triplets compared with singleton pregnancies. Multiple-gestation children may suffer long-term consequences of perinatal complications, including cerebral palsy and learning disabilities, as well as slow language development and behavioural problems.

In order to reduce the incidence of iatrogenic multiple pregnancies and its subsequent risks, ovu

lation induction should aim to restore the feedback system, which selects a single follicle for ovulation.

Hyperprolactinaemic women should be treated with dopamine agonists and women with hypogonadotrophic hypothalamic amenorrhoea should be treated with pulsatile GnRH if possible, which is associated with a high incidence of single ovulation.

For women with normogonadotrophic anovulation, including PCOS, the first-line treatment is CC and the ovarian response should be monitored by pelvic ultrasound especially in the first cycle or after the dose of CC has been stepped up. Incidence of twins is increased to 7–10% and that of triplets is 0.5–1%.[57]

Treatment with gonadotrophins should be confined to those who are resistant to CC, because multiple pregnancy is considerable (~25–36%) with the conventional 'step-up' regimens.[106] Low-dose 'step-up' or 'step-down' regimens should be encouraged, since they aim to maintain the physiological principle of follicle selection resulting in a high incidence of monovulation, though at the price of slightly lower pregnancy rates.[107]

Patients at risk of multiple follicular development, eg, patients with PCOS, should be identified. A lower starting dose of gonadotrophin should be used. Ovarian response should be carefully monitored with ultrasound examinations in terms of the size and number of developing follicles. Cycles with more than two dominant follicles should be cancelled and the starting dose should be reduced in subsequent cycles. Alternatively, the ovulation induction cycles could be converted to *in vitro* fertilization treatment with replacement of at most two embryos only. Supernumerary follicles could be aspirated and selective fetal reduction could be considered to help in reduction of multiple pregnancies. However, selective fetal reduction is not without complications, and it should never be considered a substitute for careful monitoring.

Ovarian Cancer

Epithelial ovarian cancer is the most life-threatening gynaecological cancer, with a low 5-year survival rate estimated at 30–35% when all stages are taken together.[108] Epidemiological studies have linked epithelial ovarian cancer with both nulliparity and subfertility.

Increasing concerns have been raised regarding the risk of ovarian malignancy during or after ovarian stimulation. A cohort study[42] indicated a RR of 11.1 (95% CI, 1.5–82) with long-term use of CC (12 months or more). A collaborative analysis of 12 US case-control studies[109] also showed an increased risk (OR, 2.8; 95% CI, 1.3–6.1) of invasive ovarian cancer in subfertile women who had used fertility drugs compared with women who were not subfertile.

Two hypotheses have postulated ovulation as potential biological promoters of ovarian cancer and thus increased risks of ovarian cancer with fertility drugs used in ovulation induction or stimulation. The most widely accepted hypothesis suggests that epithelial ovarian carcinoma results from repeated ovulations, where the cumulative effects of each minor trauma to the ovarian epithelium can lead to malignant transformation (Fathalla's incessant ovulation hypothesis). The second hypothesis suggests that persistent exposure of the ovary to endogenous and exogenous gonadotrophins in conjunction with secondarily elevated oestradiol concentration may be directly carcinogenic.[110]

A meta-analysis[111] including seven case-control studies and three cohort studies showed reassuring results. The pooled data showed a significantly elevated risk of ovarian cancer in subjects exposed to fertility medications when compared with general population controls (OR, 1.52; 95% CI, 1.18–1.97); such an increased risk was not ob

Levels of evidence and grading of recommendations

Weight loss	Weight loss is recommended as first-line therapy in obese women with and without PCOS seeking pregnancy.	Evidence 4; Grade D
Dopamine agonists	Dopamine agonists are an effective treatment for anovulation related to hyperprolactinaemia.	Evidence 1++, Grade A
	Bromocriptine remains the treatment of choice for women undergoing ovulation induction because of extensive experience with this drug, while cabergoline and quinagolide are acceptable second-line drugs in patients who are intolerant of bromocriptine.	Evidence 4, Grade D
CC	CC increases ovulation and pregnancy rates with no increase in spontaneous abortion or congenital abnormalities. It should be used as the first-line treatment in women with normogonadotrophic anovulation.	Evidence 1++, Grade A
	CC should be started at 50 mg daily for 5 days, at increments of 50 mg per cycle until ovulation occurs with a maximum dose of 150 mg daily. It should be continued for six cycles at ovulatory dose or until pregnancy occurs.	Evidence 4, Grade D
	Ovarian response should be monitored at least during the first cycle using pelvic ultrasound.	Evidence 4, Grade D
	There is no significant difference in pregnancy rate or ovulation rate between CC and tamoxifen.	Evidence 1++, Grade A
	CC in combination with dexamethasone (0.5–2.0 mg) and combined oral contraceptive pills improves pregnancy rate.	Evidence 1+, Grade A
Metformin	The routine use of metformin either alone or in combination with CC in fertility treatment appears to have limited efficacy.	Evidence 1++, Grade A
	In a subgroup of PCOS patients who are obese or CC-resistant, co-treatment with metformin and CC can be a second-line option before gonadotrophin induction or ovarian drilling is considered.	Evidence 1++, Grade A
Letrozole	Letrozole is as effective as CC in ovulation induction.	Evidence 1++, Grade A
	The use of letrozole in ovulation induction should be with caution in view of the possible teratogenic effects.	Evidence 2–, Grade D
Pulsatile GnRH	Pulsatile GnRH therapy is indicated in patients with hypogonadotrophic anovulation, but its use may be limited by the inconvenience of the pump.	Evidence 3, Grade D
Gonadotrophin	Women with normogonadotrophic anovulation with anti-oestrogen resistance or failure can be offered ovulation induction with gonadotrophin.	Evidence 3, Grade D
	Human menopausal gonadotrophin, urinary FSH or recombinant FSH are all equally effective and do not differ in ovulation and pregnancy rates and risk of complications.	Evidence 1++, Grade A
	For women with hypogonadotrophic hypogonadism, a preparation containing both FSH and LH should be used for ovulation induction.	Evidence 1++, Grade A
	The chronic low-dose step-up regime is the recommended approach, especially for women with PCOS.	Evidence 1+, Grade A
	Ultrasound scan should be the preferred modality of monitoring for ovulation induction with gonadotrophin.	Evidence 3, Grade D
	The use of GnRH agonist for pituitary downregulation should not be a routine but may be considered in patients with previous history of premature luteinization.	Evidence 1++, Grade A
LOD	LOD has a comparable outcome in terms of ovulation rate and pregnancy rate when compared with gonadotrophins, with a lower multiple pregnancy rate, as a second-line treatment for CC-resistant PCOS women.	Evidence 1++, Grade A
	LOD was not superior to CC as a first-line method of ovulation induction in PCOS women.	Evidence 1++, Grade A

CC = clomiphene citrate; FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinizing hormone; LOD = laparoscopic ovarian drilling; PCOS = polycystic ovary syndrome.

served when compared with subfertile controls not exposed to fertility medications (OR, 0.99; 95% CI, 0.67–1.45). Indeed, cohort data comparing outcome in treated infertile patients with untreated subfertile patients suggest that treated patients may tend to a lower incidence of ovarian cancer (OR, 0.67; 95% CI, 0.32–1.41). It suggested that subfertility itself rather than the use of fertility drugs is the risk factor for developing ovarian cancer. Successful fertility treatment, which results in pregnancy, may actually reduce the cancer risk.

Similar reassuring findings were also obtained from a recent large cohort study.[112] In 54,362 Danish women attending subfertility clinic during 1963–1998, 156 women with invasive epithelial ovarian cancer were identified during a follow-up period of up to 42.6 years (median, 16.0 years). The risk of ovarian cancer was 46% higher than that of the general Danish population after adjustment for parity. However, the overall risk of ovarian cancer was not significantly affected by the use of any fertility drug (RR, 1.03; 95% CI, 0.73–1.47), CC (RR, 1.14; 95% CI, 0.79–1.64), gonadotrophins (RR, 0.93; 95% CI, 0.50–1.37) or GnRH (RR, 0.80; 95% CI, 0.42–1.51) or in combinations. Risk did not differ according to the number of cycles of use and length of follow-up since first use of drug or parity. Potential confounders including various causes of infertility and any use of oral contraceptives had not been shown to affect the risk estimates.

In three studies[113–115] that have specifically examined the effect of fertility drug use on the risk of borderline tumours, a stronger association was observed than with the risk of invasive tumours. The plausibility of these results is heightened by the finding that oestrogen receptor expression is a common feature of ovarian borderline tumours.[114] And it may also suggest that the increased prevalence of borderline tumours compared to invasive cancer in a younger group of women. It should, however, be emphasized that the association between borderline tumours and ovulation inducing drugs was not a consistent finding among different studies.

The relationship between subfertility treatment and the risk of non-epithelial ovarian malignancies is even less clear with limited data showing conflicting results.[116,117]

In summary, findings to date on ovarian cancer risk associated with fertility drug treatment are reassuring but not definitive. A stronger association has been observed between fertility drug use and borderline tumours of ovary, though still not consistent.

RECOMMENDATIONS

The levels of evidence and grading of recommendations are given according to the Royal College of Obstetricians and Gynaecologists scheme (see the box on page 22).[118]

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.

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'Does My Child Have a Food Allergy?'

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Food allergy is an increasingly common problem that affects approximately one in 20 children in Australia.[1] Furthermore, the incidence of peanut allergy has undergone a 100% increase over the past 10 years.[2,3]

This article discusses the several food-related immune reactions that affect children, with emphasis on IgE-mediated allergies. Management strategies for the allergy and possible anaphylactic reactions are included, as is information about preventative strategies, the guidelines for which have changed over the past year.

DEFINING FOOD ALLERGY

A food allergy is an adverse reaction to a generally harmless substance within a food (usually a protein) that is mediated by the immune system. There are essentially three main types of food allergy: IgE-mediated; IgE- and non-IgE-mediated; and non-IgE-mediated.

IgE-mediated Food Allergy

IgE-mediated food allergy refers to immediate-type hypersensitivity reactions that occur, because specific IgE against that particular allergen is produced.

Theoretically, on first exposure to the allergen, the body recognizes this protein as foreign and plasma cells produce IgE directed against the allergenic component of that protein. The IgE then sits on the surface of mast cells that are located in various tissues of the body, including the skin, lining of the lungs and mucosa. On next exposure, the allergen cross-links the specific IgE molecules, resulting in a release of granules from the mast cell. The granules contain an inflammatory soup that includes chemicals such as histamine. These act on the end organs, such as blood vessels, bronchioles and mucosal

tissues, resulting in the symptoms and signs of an acute allergic reaction (Figure 1).

FOODS IMPLICATED IN FOOD ALLERGIES

Cow's milk, egg, peanut, tree nuts, fish, shellfish, soy and wheat cause more than 90% of food allergies in children. Sesame is also emerging as an increasingly prevalent allergen.

Cow's milk and egg are implicated as leading causes of anaphylaxis in young children.

It is important to note that any food is potentially allergenic. There are literally thousands of case reports that implicate a wide range of foods, from fruits and vegetables to different herbs and spices, as the cause of allergic reactions and even anaphylaxis. Around 90% of food-related anaphylaxis is caused by peanut, tree nuts or seafood. Cow's milk and egg are implicated as leading causes of anaphylaxis in young children.[4]

FOOD ALLERGIES

Oral Allergy Syndrome (IgE-mediated)

Some patients with seasonal allergic rhinitis/conjunctivitis experience itch and irritation of the tongue, mouth and throat after ingestion of some fresh fruits and vegetables. Most of these patients are allergic to cross-reactive proteins common to some pollen and foods, and the condition is known as oral allergy syndrome. It is usually a mild disorder but more severe symptoms may occur. Usually the treatment involves either avoiding the food or eating it in the cooked form (if tolerated).

Figure 1. Most children with food allergy have cutaneous symptoms such as urticaria before they develop more severe symptoms.

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Atopic Dermatitis and Food Allergy (IgE- and Non-IgE-mediated)

Many parents perceive that food allergy is the underlying cause of their child's atopic dermatitis and will try vigilantly to pinpoint the cause. Evidence would suggest that only about 40% of children with moderate to severe atopic dermatitis have a true food allergy.[5]

Delayed-type reactions to foods can occur in patients with atopic dermatitis and are not primarily IgE-mediated. A period of elimination of potentially allergenic foods may be trialled by specialists in conjunction with dietitians in these patients. However, these diets are difficult and may not yield results.

Severe allergic reactions have been reported on re-exposure of children to foods removed from

their diet for prolonged periods of time. It is important to remember that the child's underlying nutrition is of great importance and both physical and emotional problems can occur due to restricted diets.

In managing children with atopic dermatitis, treating the underlying skin disorder with emollients, appropriate topical corticosteroids and, in some cases, antihistamines and/or antibiotics is the most important intervention.

Eosinophilic Oesophagitis (Probably IgE- and Non-IgE-mediated)

In a population-based study performed from 2000 to 2003, Noel and colleagues reported that the annual incidence of paediatric eosinophilic oesophagitis was approximately 1 in 10,000 for patients aged up to 19 years. However, the rate of eosinophilic oesophagitis is increasing and it is probably underrecognized.[6]

The condition usually occurs in people with atopic diseases. In children, it tends to present as severe oesophageal reflux unresponsive to conventional medications. In older children, epigastric pain, dysphagia of solid foods or impaction is sometimes reported. The aetiology is unknown and diagnosis is based on characteristic microscopic abnormalities as well as history. Endoscopy is therefore necessary to confirm the diagnosis. Management is usually conducted in conjunction with gastroenterologists, immunologists and dietitians. It may involve dietary restriction as well as anti-inflammatory medications, including high-dose topical corticosteroids (such as fluticasone propionate aerosol) that are swallowed rather than inhaled for local application to the oesophagus.

Food Protein-induced Enterocolitis Syndrome (Non-IgE-mediated)

Food protein-induced enterocolitis syndrome (FPIES) is an increasingly recognized condition that usually presents in babies under 1 year of age. The most common foods that trigger FPIES are cow's milk and soy protein. In acute presentations, the child ingests the food and typically within 1.5 to 2 hours vomits profusely and may become shocked. It is frequently misdiagnosed as sepsis or bowel obstruction. In chronic forms, young infants exposed to these proteins on a daily basis typically manifest symptoms of daily vomiting, diarrhoea, failure to thrive and, occasionally, melaena. There is a high rate of reactivity to both cow's milk and soy in such infants. Symptoms resolve with substitution of the cow's milk or soy protein with an amino acid-based infant formula.

Solid food FPIES (such as to rice and other infant foods) usually has a more acute presentation and does not often occur on the first known exposure to the food.

The pathophysiology of FPIES is unclear, but skin tests are negative. Diagnosis is based on history, and management involves strict avoidance of the food. Cow's milk and soy FPIES usually resolve between the ages of 1 and 2 years, and resolution is established by formal supervised food challenge. The rate of resolution of solid food FPIES is variable.

Cow's Milk- or Soy-induced Proctocolitis (Non-IgE-mediated)

Cow's milk- or soy-induced proctocolitis is a condition of young babies exposed to cow's milk or soy either directly or through breast milk. Infants are irritable and have blood or mucous in their stool typically some hours after the ingestion of these proteins. Diagnosis is through history; skin tests are usually negative.

Treatment involves removing these foods from the infant's (or mother's) diet. Both cow's milk and soy must be removed because of the high rate of

Figure 2. Mild to moderate food allergy. a. Lip and mouth swelling. b. Urticaria.

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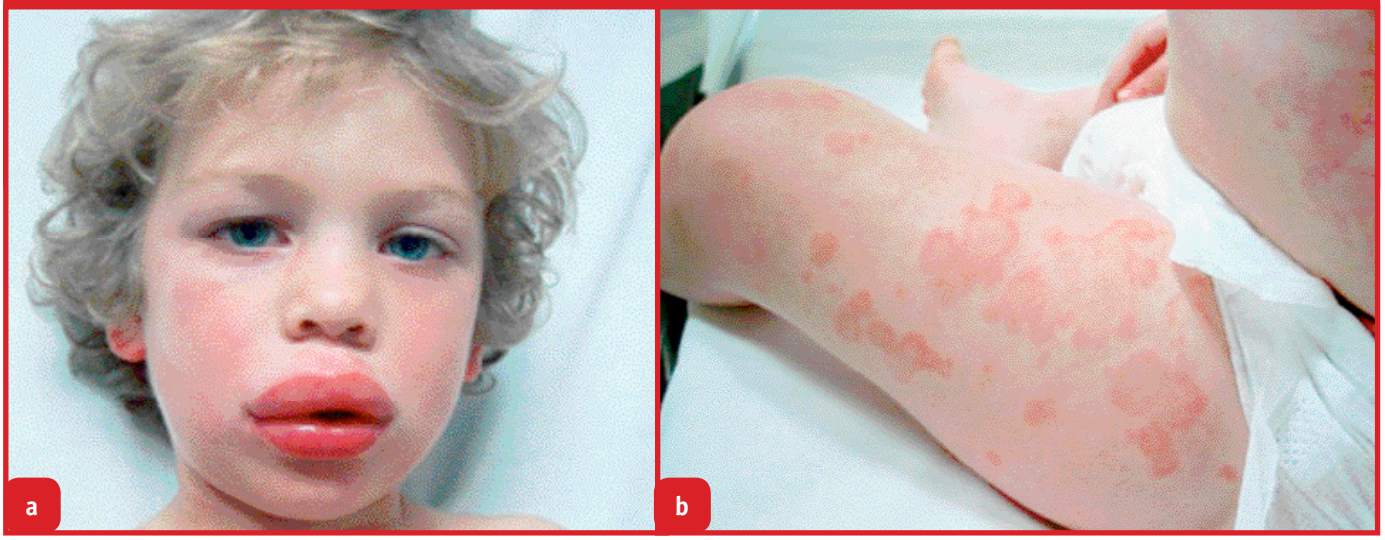


cross-reactivity. Amino acid-based infant formulas should be used if breastfeeding is discontinued. The condition usually resolves by the age of 1 year.

FOOD INTOLERANCE

Food intolerance is a general term describing any reaction to food that does not involve the immune system. Food intolerance can have the following causes:

- pharmacological mechanisms – for example, a reaction caused by particular chemicals in the food; these chemicals can be naturally occurring (such as caffeine) or additives (such as monosodium glutamate)
- metabolic mechanisms – for example, those caused by an enzyme deficiency, such as lactose intolerance
- toxic reactions – for example, caused by food poisoning
- idiopathic.

Although some symptoms of food intolerance are similar to those of food allergy, food intolerance usually is not life-threatening and results in milder symptoms than a true food allergy.

Food intolerance is often diagnosed by an elimination diet. The removal of suspect foods from a patient's diet to see if symptoms disappear and then the reintroduction of foods one at a time in an attempt to directly link symptoms with a specific food is often done under supervision (specialist and dieti

Table 1. Symptoms and signs of food allergy in children

Mild to moderate allergic reaction
- Urticaria
- Lip/mouth swelling (angioedema)
- Vomiting/diarrhoea/abdominal pain
- Rhinitis

Severe allergic reaction or anaphylaxis
- Difficulty breathing/noisy breathing
- Swelling of the tongue
- Swelling or tightness in the throat
- Difficulty talking and/or a hoarse voice
- Wheeze or persistent cough
- Loss of consciousness and/or collapse
- Young children may become pale and floppy

tian), depending on the original symptom complex.

Skin prick tests or specific IgE measurements are not appropriate or helpful for the diagnosis of food intolerance.

DIAGNOSING IgE-MEDIATED FOOD ALLERGY

Most cases of IgE-mediated food allergy are fairly easy to recognize. Symptoms generally appear within 30 minutes of ingesting the allergenic food and can occur on the first known exposure to that food.

Most food allergies are relatively mild. The symptoms and signs of a mild to moderate allergic reaction may include one or more of urticaria, lip/mouth swelling (angioedema), vomiting/diarrhoea/abdominal pain and rhinitis (Figure 2; Table 1).

Signs of a severe allergic reaction or anaphylaxis include any one or more of difficulty breathing, noisy breathing, swelling of the tongue, swelling or tightness in the throat, difficulty talking and/or a hoarse voice, wheeze or persistent cough, and loss of consciousness and/or collapse (Table 1). Affected young children may become pale and floppy. More than 90% of children will have cutaneous symptoms before they develop more severe symptoms; however, the reaction can evolve very rapidly.

The diagnosis may less obvious when the trigger food is not easy to identify on history or the symptoms are less defined. Food allergy is rarely a trigger for chronic rhinoconjunctivitis.

Tips for GPs about diagnosing food allergy are given in the box on this page.

Tips for GPs: Diagnosing food allergy in children

- Take a detailed history at the time of presentation – this is likely to be very helpful later.
- Recognize that not all food allergy is IgE-mediated.
- Counsel parents about the primary importance of treating the skin in atopic dermatitis rather than manipulating diets without evidence.
- Counsel parents about the relevance of allergy tests to their child's condition – this can help prevent unnecessary anxiety and investigations.
- If ordering *in vitro*-specific IgE tests, specify which allergen is to be tested; avoid ordering 'food panels'.

INVESTIGATING PATIENTS WITH FOOD ALLERGY

Several tests are available for identifying the likely cause of a food allergy.

Skin Prick Tests

Skin prick tests have the advantage of being more sensitive than blood tests for allergen-specific IgE. They provide immediate results, are usually well tolerated and rarely cause severe side effects. If an allergy to a fresh fruit, vegetable or a processed food is suspected, it is helpful for the patient to bring a sample of that food to the specialist appointment for fresh food testing. Antihistamines should be stopped for at least 3 to 5 days before testing.

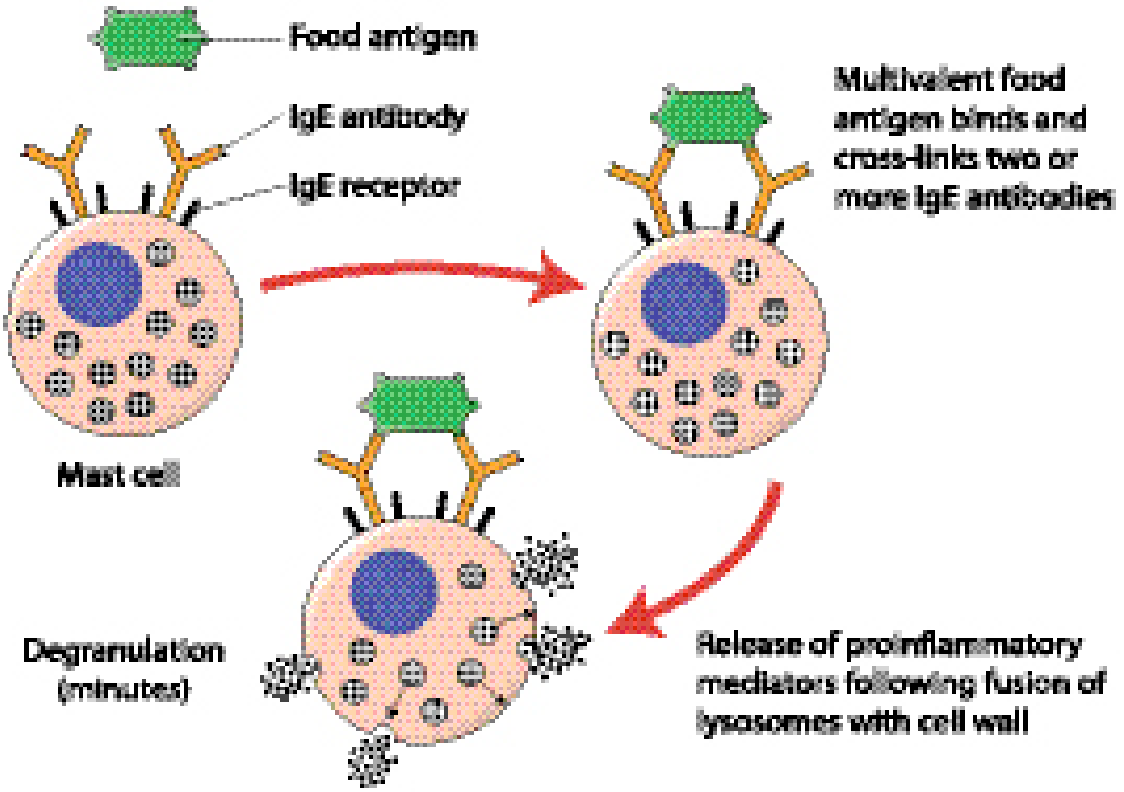
Skin prick tests can be performed in patients of any age but require careful interpretation in young infants. The risk of a more severe reaction to a skin test is higher in a young baby (under 1 year of age).[7]

Skin prick testing has no role in confirming suspected reactions to food additives.

Blood Tests for Allergen-specific IgE (RAST)

The original immunoassay technology for detecting allergen-specific IgE in the serum – radioallergosorbent testing (RAST) – has been superseded by enzyme and fluorescent-based assays, and the accepted term is now '*in vitro*-specific IgE

Symptoms of most cases of IgE-mediated food allergy generally appear within 30 minutes of ingesting the trigger food and can occur on the first known exposure to that food.



testing'.

If skin prick testing is not available or there is no clear skin on which to perform the test, or the patient cannot stop their antihistamines, an *in vitro*-specific IgE test may be useful. Specific antigens should be ordered rather than 'food panels'. Results of food panels are confusing, and parents often think that all the foods in the panel are to be eliminated from the diet if a result is positive.

It is important to note that the magnitude of a skin test reaction or blood test response correlates with the likelihood of the patient having a clinical allergy to that food but not with the severity of the reaction. A positive skin test or *in vitro* test signifies allergic sensitization and not necessarily clinical allergy.

Total IgE Levels

The total IgE value is often raised in people with allergies and/or eczema. However, measurement of the total IgE level does not help in the diagnosis of a food allergy.

Oral Food Challenges

The gradual feeding of a test food under close supervision and observation to see if it is tolerated is sometimes performed to prove a diagnosis of food allergy when the history is not entirely clear. An oral food challenge may also be used to determine if a food allergy has resolved.

Oral food challenges must always be performed by experienced clinicians who have the ability to recognize and manage anaphylaxis. Ex

Key points

- IgE-mediated food allergy usually presents within 30 minutes of exposure to the trigger food.
- Most food allergy reactions are mild.
- Most children with mild atopic dermatitis do not have a true food allergy. Treating the underlying skin condition is still the mainstay of treatment in these children.
- Dietary manipulation is complicated and should be managed in conjunction with a specialist and dietitian.
- Optimal treatment of atopic conditions should be ensured in children with food allergies.
- Asthma is a risk factor for a severe food-related allergic reaction.

Unfortunately, only around 20% to 25% of children will outgrow peanut, tree nut or seafood allergy

tensive resuscitation equipment should be readily available.

Unproven Methods

Examples of unproven methods of assessing food allergy include cytotoxic food testing, kinesiology, Vega testing, electrodermal testing, pulse testing, reflexology, and hair analysis. These tests have not been scientifically validated and may lead to dangerous avoidance strategies.[8]

A patient information sheet entitled *Food Allergy* and containing extensive information about these tests (under the heading 'Unorthodox so called tests for food allergy') is available from the Australasian Society of Allergy and Immunology (ASCIA) website (http://www.allergy.org.au/images/stories/aer/infobulletins/2010pdf/AER_Food_Allergy.pdf).

THE NATURAL HISTORY OF FOOD ALLERGY

The common wisdom is that most common childhood food allergies resolve before adulthood, and in the community this is still the most likely scenario. Between 70% and 80% of children will outgrow milk allergy by the age of 3 years, and egg allergy is commonly outgrown by the early school years (between 6 and 8 years of age). Unfortunately, only around 20% to 25% of children will outgrow peanut, tree nut or seafood allergy, and a number of these may lose their tolerance to the allergen if continued regular exposure to the allergen does not occur.

In patients managed in tertiary referral centres, it appears that the rate of outgrowing allergies is much slower than previously thought. However, most will still outgrow egg and milk allergies by their teenage years.

MANAGEMENT OF FOOD ALLERGIES

The management of patients with food allergy involves avoiding the food allergens. Accidental ingestions of the allergenic food are not uncommon, and other pitfalls of food avoidance include

Useful resources

Australasian Society of Clinical Immunology and Allergy (ASCIA) – http://www.allergy.org.au

The ASCIA website provides up-to-date resources for doctors and their patients, including information about anaphylaxis action plans, infant feeding advice and food allergies (general and to specific foods). The site also has an e-learning package for parents to provide information about the management of anaphylaxis.

- **Adverse food reactions.** All the available information sheets on adverse food reactions are listed at: http://www.allergy.org.au/content/view/290/235/
- **Anaphylaxis.** All the available information sheets on anaphylaxis, including action plans and information on adrenaline autoinjectors, are listed at: http://www.allergy.org.au/content/view/10/3

The Children's Hospital at Westmead – http://www.chw.edu.au/parents/factsheets/#allergy

The website of the Children's Hospital at Westmead, Sydney, provides fact sheets for parents on allergen avoidance and other useful advice about food allergy.

Anaphylaxis nurse educators
Nurse educators are available to visit schools in New South Wales, Western Australia and parts of Queensland to educate teachers about the management of anaphylaxis.

nutritional inadequacy as well as psychological difficulties.

If a major staple food such as cow's milk is removed from the child's diet, advice from a dietitian is important in order to assess adequate nutritional intake. Children with gross calcium deficiencies and even malnutrition are frequently seen in specialist clinics after being placed on restricted diets.

Providing clear written information to patients and their families about how to avoid allergens is helpful, because food labelling can be confusing (see the box on resources on this page).

Although there are many trials under way around the world seeking to find a better solution for the management of food allergies, these therapies are not yet ready for clinical use. These trial therapies include oral desensitization.

Situations when patients should be referred to an allergist or clinical immunologist are listed in Table 2. Some tips for GPs when managing children with food allergy are given in the box on page 34.

ANAPHYLAXIS

Anaphylaxis is a serious allergic reaction with rapid onset involving one or more systems of the body. Although the true prevalence of anaphylaxis is not known, in an Australian study published in 2000 parents reported that 1 in 170 preschool children had suffered at least one episode of anaphylaxis of any cause.[9] The rate of anaphylaxis appears to be increasing, but fatalities are extremely rare and the death rate has remained stable over the past 10 to 15 years.

There is currently no scientific evidence to suggest that anaphylaxis can occur from casual skin contact with an allergen.

Risk Factors for Anaphylaxis

There is no test that can predict which child with

Table 2. Referral of children with food allergy

- All cases of suspected anaphylaxis
- Any child at high risk of anaphylaxis, eg, children with asthma as well as food allergy
- Milder cases of suspected food allergy where the cause cannot be identified with certainty
- A suspicion of food protein-induced enterocolitis syndrome or eosinophilic oesophagitis
- Very young children (under 2 years of age) in whom tests are likely to be more difficult to interpret and nutritional issues are especially important
- If more than one staple food is to be eliminated (advice from dietitian also required)

Tips for GPs: Managing children with food allergy

- Identify the potential allergen or allergens.
- Provide the tools and knowledge to avoid the allergen.
- Ensure adequate nutrition.
- Prescribe emergency medications if appropriate and educate the family on how to recognize and manage an allergic reaction.
- Provide optimal treatment for the concurrent atopic diseases.

a food allergy will experience anaphylaxis. There are, however, several epidemiological factors that have been found to be associated with anaphylaxis fatalities and/or may favour the provision of a child with an adrenaline autoinjector. These include:

- a history of previous anaphylaxis
- asthma
- association with a particular allergen (peanut or tree nut, especially cashew)
- having a previous significant reaction to a very small amount of that protein
- the child's age – for example, the risk of fatality is higher in adolescents and young adults; very few deaths are reported due to anaphylaxis in children under 5 years of age
- access to emergency medical care.

There is also increasing evidence that concurrent presence of other atopic diseases is associated with increased severity of signs during a food-related allergic reaction.

Management of Anaphylaxis

If a child is considered at risk of anaphylaxis, then an emergency adrenaline autoinjector device should be prescribed. There are two devices currently available on the Pharmaceutical Benefits Scheme. ASCIA recommends that the lower-dose (0.15 mg adrenaline) junior versions of these devices be prescribed for children weighing between 10 and 20 kg and the higher-dose (0.30 mg adrenaline) versions for individuals weighing over 20 kg.[10] (Note that the approved product informations for the two autoinjectors state that the 0.15 mg adrenaline dose versions are intended for children weighing between 15 and 30 kg, and the 0.30 mg adrenaline dose versions for children and adults weighing more than 30 kg.) The two devices have different administration techniques, and patients should be specifically trained in the use of the device prescribed for them.

An action plan should be provided when an adrenaline autoinjector is prescribed (ASCIA Action Plan for Anaphylaxis, available from the ASCIA website, http://www.allergy.org.au/content/view/10/3). Details of these action plans and adrenaline autoinjector prescribing guidelines were

Preventing food allergy in children[12]

Infant feeding advice

The Australasian Society of Allergy and Immunology (ASCIA) guidelines for infant feeding to prevent food allergy, *Infant Feeding Advice*, are summarized below.[12]

- Breastfeeding is recommended for at least 6 months.
- If not breastfeeding or supplemental formula feeds are needed, partially hydrolysed cow's milk formulas (commonly referred to as hypoallergenic or HA formulas) are recommended for the first 4 to 6 months of life for infants at high risk of allergic disease (history of allergy in parents or siblings). These formulas are not suitable if the child already has a diagnosed cow's milk allergy. Standard cow's milk formulas may be used in infants not at high risk.
- Introduce solid foods from around 4 to 6 months of age. There is no convincing evidence to suggest that delaying the introduction of solid foods beyond 6 months of age will protect against the development of allergenic disease.
- Avoidance of potentially allergenic foods is not recommended. Previous guidelines suggested avoiding allergenic foods such as cow's milk and egg until 12 months of age, but there is no conclusive evidence to support delaying the introduction of foods beyond 6 months of age.

Other advice

- Children should not be exposed to cigarette smoke.
- Parents should not smoke during pregnancy.
- Mothers should not restrict their diets during pregnancy. Not only is this unhelpful in preventing allergic disease, but it may also cause nutritional difficulties in the mother and the child.

previously published.[11]

Although it is not within the scope of this article to discuss anaphylaxis management in detail, the first line of management in the acute setting is intramuscular adrenaline 1:1000 at a dose of 0.01 mL/kg to a maximum of 0.5 mL into the lateral thigh. This should be repeated after 5 minutes if the patient has not improved. The patient should be placed in a position of comfort with his or her legs elevated, and oxygen should be administered. They should not be allowed to stand.

ALLERGY PREVENTION

Prevention of allergic disease including food allergy remains an active but as yet unresolved area of research. In 2008, ASCIA published infant feeding guidelines that provide an approach to the prevention of food allergy in children at high risk (that is, those with a first-degree relative with atopy).[12] The introduction of solid foods at age 4 to 6 months is now recommended, as is also that no particular allergenic foods need to be avoided, rather than the previous recommendation to delay solid feeding and to restrict potentially allergenic foods. A patient information sheet on infant feeding is available from the ASCIA website (http://www.allergy.org.au/images/stories/aer/infobulletins/2010pdf/ascia_infant_feeding_advice_2010.pdf).

The current guidelines for infant feeding to prevent food allergy are summarized in the box on this page.

USEFUL RESOURCES

Sources of information sheets and other resources for both patients and GPs are listed in the box on page 33.

CONCLUSION

The rate of food allergy is increasing, as is the rate of anaphylaxis to food. Thankfully, most food allergy is mild and fatalities are rare.

GPs play a vital role in the management of food allergy, because they are often the first to see the child after an allergic reaction. It is important to take a detailed history and to provide this to the specialist if referral is appropriate. Treating coexisting atopic conditions is helpful in the overall management of the condition. Reassuring parents and discouraging unsupervised dietary restriction will help optimize the child's nutritional status. Recognizing anaphylaxis and the risk factors can be life-saving. Prescribing adrenaline autoinjectors appropriately and educating parents in using the devices is a service that GPs can provide in conjunction with a specialist.

Further Reading

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Management of Pregnancies With Previous Caesarean Section

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INTRODUCTION

Over the past few decades, there has been widespread concern about the increasing proportion of births born by caesarean delivery. The rising rate of primary caesarean section has led to the increased number of obstetric population with a history of prior caesarean delivery. Although this group of women may be offered planned vaginal birth after previous caesarean section (VBAC) or elective repeat caesarean section (ERCS), the VBAC rate is generally low particularly in well-developed countries. In the United States, the VBAC rate has decreased to 8.5% by 2006, while the total caesarean rate has increased to 31.1%.[1]

In this article, we review the recommendations on VBAC by different professional societies, the favourable and unfavourable factors in considering VBAC, the associated maternal and fetal benefits and risks, as well as the non-medical concerns that play a role in the decision-making process.



One of the obstetrician's roles is to identify women who are most likely to achieve successful vaginal birth after previous caesarean section.

WHO ARE SUITABLE TO ATTEMPT VBAC—WHAT DOES THE EVIDENCE SAY?

There have been numerous studies evaluating the risks and benefits of VBAC and ERCS. International authorities have published their guidelines to provide evidence-based obstetric care. Examples are guidelines from the American College of Obstetrics and Gynecology (ACOG) in 2010, the Royal College of Obstetrics and Gynecology (RCOG) in 2007, and the Society of Obstetricians and Gynaecologists of Canada (SOGC) in 2005. All three organizations emphasized that their data were limited by several factors: (1) there is no randomized controlled trial on VBAC versus ERCS; (2) adverse maternal and perinatal outcomes rarely occur; (3) there was selection bias in the published reports, as a woman's decision to attempt VBAC relies on the counselling by the health-care provider and local resources.[2]

The three societies share similar opinion on patient selection undergoing

planned VBAC. Previous uterine rupture and high vertical classical caesarean section are the contraindications, as they are associated with a substantial risk of scar rupture. For the other scar variants such as prior inverted T or J incision, lower vertical incision, previous myomectomy and prior complex uterine surgery, the available data are, however, insufficient and conflicting owing to the limited number of studies. Planned VBAC in such circumstances should be assessed by experienced obstetricians on an individual basis.

The risk of uterine rupture for women with one previous caesarean section of a low transverse incision is low. The risk figures by ACOG, RCOG and SOGC are < 1%, 0.2–0.7%, and 0.2–1.5%, respectively.

In some patients, the type of uterine incision of prior caesarean delivery cannot be confirmed. Although some have questioned the safety of offering VBAC under these circumstances, two case series reported a similar rate of successful VBAC and uterine rupture to known low transverse scar.[3,4] It is based on the fact that nowadays most caesarean incisions are low transverse. Therefore, the ACOG and SOGC guidelines suggest that VBAC is not contraindicated in women with one previous caesarean delivery with unknown type of scar unless there is a high clinical suspicion of a previous classical uterine incision. The RCOG states that the operative notes of previous operation should be reviewed where possible.

Although the risk of uterine rupture increases with the number of previous caesarean sections, the chance of achieving VBAC appears to be similar.[1] Both the RCOG and ACOG suggest that planned VBAC is contraindicated in women with more than two previous caesarean sections.[1,5] In clinical practice, most women undergoing planned VBAC have one prior caesarean delivery. The quoted success rates of planned VBAC by the ACOG, RCOG and SOGC are 60–80%, 72–76%, and 50–85%, respectively.

Maternal age alone should not be used to discourage women from attempting a vaginal delivery.

One of the obstetrician's roles is to identify women who are most likely to achieve successful VBAC. Prior vaginal birth, spontaneous onset of labour, prior caesarean section for a non-recurring condition and preterm labour are the favourable factors for successful VBAC.[1,5] On the contrary, recurrent indication for prior caesarean section (eg, labour dystocia), increased maternal age, maternal obesity, gestation greater than 40 weeks, increased neonatal birth weight, and short pregnancy interval are the negative predictor factors.[1]

Macrosomia has been recognized as a significant factor leading to failed VBAC, with a higher risk of uterine rupture in women with no previous vaginal delivery.[2,6,7] Peaceman *et al*[8] evaluated the effect of fetal size on VBAC. If prior caesarean delivery was performed for dystocia—defined as failed induction, cephalopelvic disproportion or failure to progress—or failed instrumental delivery, the VBAC success rate was reduced to 54% compared with 67% for other indications. If fetal weight of the current pregnancy exceeded the prior one by 500 g, the success rate was only 38%.[8] Other retrospective analysis showed that infants with birth weight of more than 4 kg were less likely to be delivered vaginally. However, obstetricians should be aware that so far there is a lack of reliable methods in estimating fetal weight with accuracy. Therefore, clinical suspicion of fetal macrosomia alone should not be a contraindication to offering planned VBAC.

Women's age might be considered during the counselling on planned VBAC. Although there were studies showing that the success rate decreased with advanced age,[9] maternal age alone should not be used to discourage women from attempting a vaginal delivery.

Maternal obesity adversely influences the success rate.[10] The available evidence consistently demonstrates a gradual reduction of vaginal delivery rate with increasing body mass index (BMI). Juhasz *et al*[11] evaluated 1,213 women in their study. The VBAC rate fell from 83.1% for BMI < 19.8, to 79.9% for BMI 19.8–26, further to 69.3% for BMI 26.1–29, and down to 68.2% for BMI > 29 ($P < 0.001$). Of interest, retrospective studies by Durnwald *et al*[12] found that women who gained weight between pregnancies had a lower VBAC

Table. Experience of Kwong Wah Hospital, Hong Kong, in the management of women with one prior caesarean delivery

	Year			
	2007	**2008**	**2009**	**2010**
Total no. of maternities	5,395	5,446	5,682	5,945
Women with prior caesarean deliveries (%)	9.1	9.9	9.7	9.4
Successful planned VBAC rate (%)	94.3	88.5	86.3	87.2
Total VBAC rate (%)	21.1	21.9	22.9	26.9
Uterine rupture (%)	0	0.8	0	0

VBAC = vaginal birth after previous caesarean section.

rate. Women with normal BMI who turned overweight (BMI 25–29.9) before their second pregnancy had a 56.6% success rate; which was in contrast to the 74.2% for women whose BMI remained normal ($P = 0.006$).[12]

Some authorities consider short inter-delivery interval as a risk factor for failed VBAC and uterine rupture. As uterine rupture is an uncommon complication, evidence from RCOG based on three small observational studies suggested a two- to threefold increased scar rupture risk with inter-delivery interval below 12–24 months.[5]

THE DELIVERY—INTRAPARTUM MANAGEMENT

Slight variations in opinion exist among authorities on the standard of an institution offering VBAC. Nevertheless, they are all in the direction that planned VBAC should be conducted in a suitably staffed and equipped delivery suite, with available resources for immediate laparotomy and neonatal resuscitation.

Early diagnosis of uterine scar rupture followed by expeditious laparotomy and resuscitation is essential to reduce adverse maternal and fetal outcome. Although there is no single pathognomonic clinical feature of the rupture, an abnormal tracing on cardiotocography is present in 55–87% of the cases.[5] The RCOG and SOGC recommend continuous electronic fetal monitoring for all women attempting VBAC.

Other associated features of uterine rupture include acute onset of scar tenderness, severe abdominal pain persisting between contractions, chest pain or shoulder tip pain, sudden onset of shortness of breath, abnormal vaginal bleeding or haematuria, cessation of previously efficient uterine activity, maternal tachycardia, hypotension or shock, and loss of station of the fetal presenting part.[5]

For women attempting VBAC, maternal and fetal condition should be regularly assessed once labour begins. The likelihood of vaginal delivery may be modified by intrapartum conditions. Studies reported that women admitted with a more favourable cervical status (eg, cervical dilatation > 4 cm, > 75% effacement) in spontaneous labour have a twofold increase in success rate.[13–15]

Induction of labour for maternal or fetal condition is increasingly common in obstetric practice. Labour induction and augmentation in women with previous caesarean delivery is associated with an increased risk of uterine rupture. The risk is highest with misoprostol (6%), followed by prostaglandin E_2 (2%) and lowest with oxytocin (1.1%).[16] All the three organizations discouraged the use of misoprostol and prostaglandins in most women with previous caesarean delivery.

Studies on mechanical cervical ripen-



Both planned vaginal birth after previous caesarean section and elective repeat caesarean section carry maternal and neonatal risks.

ing and labour induction with transcervical catheter were limited and retrospective. The risk on uterine rupture was inconclusive.[1]

Induced labour is also associated with lower success rate of VBAC compared with spontaneous labour. If oxytocin was used alone for induction or augmentation, the vaginal delivery rate was 62% (95% confidence interval, CI, 53–70%) and 68% (95% CI, 64–72%), respectively.[17]

Although induction of labour is not contraindicated in women with prior caesarean delivery, the fact of lower success rate together with higher rupture risk should be considered in the counselling.

Nonetheless, individual circumstances must be considered in all cases. For example, if a patient, who may not otherwise be a candidate for planned VBAC, presents in advanced labour, obstetricians may judge it best to proceed with vaginal delivery.

MATERNAL BENEFIT AND RISK

Both planned VBAC and ERCS carry maternal and neonatal risks. The risks of either approach include maternal haemorrhage, infection, operative injury, thromboembolism, hysterectomy, and death. The risk of uterine rupture is essentially limited to the VBAC group. As successful VBAC is associated with the least complications while a failed one with more complications, careful selection of women who would most likely deliver vaginally is the key to management of pregnancy after prior caesarean section.

Short term

Successful VBAC offers several distinct, consistently reproducible short-term advantages compared with ERCS, such as fewer hysterectomies, fewer thromboembolic events, lower blood transfusion rate, and shorter hospital stay. However, when VBAC fails, emergency caesarean section is associated with increased uterine rupture, hysterectomy, operative injury, blood transfusion, endometritis, and longer hospital stay.[18] At present, clinical prediction of the optimal candidate for planned VBAC remains imprecise.

Long term

It is well-known that caesarean delivery increases the risk of long-term problems. Chronic pain is a common condition experienced by some women after caesarean delivery. The risk appears to be higher with increasing number of operations performed. A group in Denmark followed up 244 women for chronic pain after caesarean section. Of those women, 18.6% had pain after 3 months and 12.3% still suffered from pain at 10 months after delivery. Furthermore, 5.9% of the women characterized their pain as being present daily or almost daily.[19] One of the causes of moderate to severe pelvic pain was neuropathic pain caused by entrapment of iliohypogastric or ilioinguinal nerves.[20]

As with chronic pain, pelvic adhesions increase with the number of caesarean sections. Dense adhesions make subsequent operation more difficult, and increase the operating time, blood loss and the risk of injury to the surrounding organs.[20] Adhesions were assessed in a cohort study involving 3,190 women in Saudi Arabia.[21] Adhesions were described as severe if they were dense or causing fusion of uterus to the abdominal wall or bladder. In that study, severe adhesions were present in 0.2%, 11.5%, 26.0%, 44.8%, 54.5% and 50.6% of women having their first, second, third, fourth, fifth, and sixth or more caesarean sections, respectively.

A strong association exists between previous caesarean delivery and abnormal placentation. A meta-analysis performed by Ananth *et al*[22] showed that a woman with at least one previous caesarean was at 2.6 times greater risk of placenta previa in her subsequent pregnancy. The risk increased with the number of prior

caesarean sections.

The most significant long-term risk of caesarean delivery is placenta accreta occurring in subsequent pregnancies. As the placenta does not properly separate from the uterus after delivery, it may result in massive bleeding, leading to disseminated intravascular coagulopathy, multi-organ failure and maternal mortality. Even if caesarean hysterectomy is to be performed as the life-saving procedure, the operation could be difficult with its own set of complications and results in permanent loss of fertility.[20] As with previa, it is certain that the risk of placental accreta increases with the number of prior caesarean sections. The combination of placenta previa and previous caesarean delivery dramatically increases the risk further. In a cohort study of 723 women with placenta previa, accreta occurred in 3%, 11%, 40%, 61% and 67% of those having their first, second, third, fourth, and fifth or more caesarean sections, respectively.[23]

FETAL BENEFIT AND RISK

Perinatal morbidity and mortality are other concerns when considering the option of delivery. The largest population-based evaluation of perinatal mortality was performed by Smith *et al.*[24] The rate of delivery-related perinatal death was significantly greater in the VBAC group than in the ERCS group (12.9 vs 1.1 per 10,000 births). The marked excess of perinatal deaths was mainly due to uterine rupture in the VBAC group. What further complicated the relative risk is that elective caesarean delivery at 39 weeks' gestation would prevent two fetal deaths per 1,000 live births compared with expectant management.

As with perinatal death, asphyxia-related injury in VBAC usually occurs after uterine rupture. In a study by Landon *et al*,[25] the incidence of hypoxic ischemic encephalopathy was 0.08% in the VBAC group compared with 0% in the ERCS group, at a background uterine rupture rate of 0.7%.

Sepsis is a frequent indication for admission to the neonatal intensive care unit. Both maternal fever and prolonged rupture of membrane greater than 18 hours are more common in the VBAC group. Neonates who were born after failed VBAC requiring emergency caesarean delivery had a significantly greater rate of suspected sepsis.[26]

Although the evidence suggests an increased perinatal risk for women undergoing VBAC, the absolute numbers of serious morbidity and mortality remain low. One should also note that a large proportion of women undergoing VBAC would deliver successfully. In fact, there are numerous beneficial effects of labour and vaginal delivery to the newborn. Even at term gestation, babies born vaginally are at lower risk of respiratory morbidity (respiratory distress syndrome or transient tachypnoea of newborn) compared with those born by prelabour caesarean section.[27,28] This finding was demonstrated by a large cohort study[29] in Denmark involving 34,458 babies over 9 years. The risk of respiratory morbidity for infants delivered by elective caesarean section was increased compared with that by the vaginal route at 37 weeks' gestation (odds ratio, OR, 3.9; 95% CI, 2.4–6.5), 38 weeks' gestation (OR, 3.0; 95% CI, 2.1–4.3) and 39 weeks' gestation (OR, 1.9; 95% CI, 1.2–3.0). A same pattern was observed for risk of serious respiratory morbidity at an even higher odds ratio at 37 weeks' gestation (OR 5.0; 95% CI, 1.6–16.0). This is the reason why most authorities recommend that ERCS be performed after 39 weeks' gestation. Other potential benefits of vaginal delivery are the lower risk of hypothermia and hypotension at birth, higher likelihood of successful breastfeeding, and lower incidence of asthma in childhood.[28]

NON-MEDICAL FACTORS

Despite the numerous research-based evidence on the safety of trial of labour after caesarean section, the VBAC rate remains low in some developed countries such as the United States (8.5% in 2006). It is apparent that some non-clinical factors play a role in the decision-making.

The factors which might affect VBAC rate in an institution include administrative policies, medicolegal pressures, professional society guidelines, and patient and obstetrician preferences.

According to a survey by Wells[30] in the United States, reasons for obstetricians not offering VBAC included (1) them being unwilling to accept the risk of adverse outcome, (2) them not believing that VBAC is safe, (3) medico-legal liability concerns, and (4) lack of immediate availability of facilities for laparotomy.

The decision may also be affected by non-clinical patient priorities, such as patient's desire for a vaginal delivery, her

wish to experience (or avoid) labour, her need for scheduling the delivery, and her positive or negative feeling about the previous delivery.[31] It is important to discuss with the women their risk perception and priorities when considering the mode of delivery.

COUNSELLING AND DECISION-MAKING

Depending on the clinical situation, either planned VBAC or ERCS is usually appropriate for most women with prior caesarean delivery. Understanding the women's beliefs and values of the process and outcome is essential in providing evidence-based, patient-centred care.[32] Discussing the options in early pregnancy allows the women and their family to evaluate the risks and benefits based on their own perception. While patient pamphlets play an important role in general information-giving, the obstetrician's advice should be more specific to the individual's condition. The decision made in early pregnancy should never be considered final, as medical and social circumstances continue to evolve. For instance, women who intend to deliver by ERCS might present with spontaneous labour before the scheduled date. If labour progresses well and the chance of a successful VBAC is high, she might change her preference to vaginal delivery. According to the international guidelines, ERCS should be scheduled after 39 weeks' gestation in an otherwise uncomplicated pregnancy.[1]

If a woman does not show any strong preference regarding the mode of delivery in early pregnancy, planned VBAC could be encouraged with the flexibility of a later change of plan. A local study has been conducted to assess the psychological impact of women being assigned to the mode of delivery.[33] It involved 298 women, who showed no preference for VBAC or ERCS, being randomly assigned to either option with flexibility. Women in the planned VBAC group achieved high success rate of vaginal delivery (73%) without an increase in the psychological stress and morbidity.

Successful VBAC carries the lowest risk, followed by ERCS, and the risk is highest with failed VBAC, requiring caesarean delivery.

EXPERIENCE FROM A PUBLIC OBSTETRIC UNIT

Kwong Wah Hospital is one of the eight public hospitals in the Hong Kong territory providing obstetric service. There are almost 6,000 deliveries annually. Women receive obstetric service at minimal personal cost, as the service is largely funded by the government. Obstetricians and midwives are salaried, and the advices given are therefore not influenced by personal financial gain. Women with history of prior caesarean deliveries are assessed by obstetricians at the booking visit. The previous operation records are traced via the electronic system of the public hospitals or by an enquiry letter to the corresponding obstetricians/hospitals. Planned VBAC is offered to women with one previous uncomplicated transverse lower segment caesarean delivery. Information pamphlets on planned VBAC and ERCS are given out during antenatal visits. The pregnancy conditions are continuously reviewed. The mode of delivery is discussed before 37 weeks' gestation and documented in the record. Women who have no strong preference for either option are encouraged to consider planned VBAC when the pregnancy conditions are favourable. Women who intend to undergo ERCS are forewarned of a possible re-evaluation of the mode of delivery if they present themselves in an advanced stage of labour. All women attempting VBAC receive electronic continuous fetal heart monitoring during labour. Labour progress is assessed regularly by the obstetricians. Facilities and expertise for emergency operation are available in the delivery suite. The authors' experience over a 4-year period is shown in the Table.

CONCLUSION

At present, there is no reliable formula to calculate the best mode of delivery in women with prior caesarean section. This should be a shared decision made by the obstetricians and the women, incorporating medical factors, social

circumstances and patients' preferences. Successful VBAC carries the lowest risk, followed by ERCS, and the risk is highest with failed VBAC, requiring caesarean delivery.

Although uterine rupture increases the risk of adverse outcome, it is still a rare complication in high-resource settings. The incidence has remained the same (< 1%) in UK, where the rate of primary caesarean section has increased over the past decade. Moreover, the resulting serious adverse outcome after uterine rupture is very low in absolute number.

Given the high success rate of VBAC in carefully selected pregnancies, obstetricians should not overstate the risk and consequence of uterine rupture so as to turn women away from attempting VBAC without balancing the short- and long-term complications of ERCS.

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CME Article

Management of Pregnancies With Previous Caesarean Section

Answer True or False to the questions below.

	True	False
1. Previous classical caesarean section is a contraindication to planned vaginal birth after previous caesarean section (VBAC).	○	○
2. Patients with unknown type of previous caesarean scar should not be offered planned VBAC.	○	○
3. Obese patients (body mass index, BMI, > 30) should not be offered planned VBAC, as high BMI is associated with a low success rate.	○	○
4. Spontaneous labour increases the likelihood of successful VBAC.	○	○
5. Continuous electronic fetal monitoring should be offered to all women attempting VBAC.	○	○
6. Labour induction and augmentation by oxytocin are associated with increased risk of uterine rupture in patients with prior caesarean delivery.	○	○
7. The risk of placenta previa/placenta accreta is directly related to the number of previous caesarean deliveries.	○	○
8. Perinatal mortality and asphyxia-related fetal injury are more significant in the VBAC group compared with the elective repeat caesarean section (ERCS) group.	○	○
9. Babies who are born vaginally are at lower risk of respiratory morbidity in both the short and long term.	○	○
10. Women who decline planned VBAC should be offered ERCS at 37 weeks' gestation in order to avoid spontaneous labour before the scheduled operation.	○	○

ANSWERS

1	2	3	4	5	6	7	8	9	10
T	F	F	T	T	T	T	T	T	F