Hormonal Contraception and Cancers
make CIMS your home page at the point of care

cimsasia.com

get connected
get addicted

cimsasia.com
Journal Watch

257 • Diagnosis of chlamydia in women: Self-taken versus physician-taken swabs
• Patient-taken swabs to diagnose gonorrhoea in women
• Bipolar disorder and increased risk of adverse pregnancy outcome
• Pre-eclampsia and later cardiovascular risk

258 • Genetic diagnosis antenatally and after stillbirth: Microarray versus karyotyping

International Editorial Board

Board Director, Paediatrics
Professor Pik-To Cheung
Associate Professor
Department of Paediatrics and Adolescent Medicine
The University of Hong Kong

Board Director, Obstetrics and Gynaecology
Professor Pak-Chung Ho
Head, Department of Obstetrics and Gynaecology
The University of Hong Kong

International Editorial Board

Professor Biran Affandi
University of Indonesia
Dr Karen Kar-Loon Chan
The University of Hong Kong
Associate Professor Oh Moh Chay
KK Women’s and Children’s Hospital, Singapore
Associate Professor Anette Jacobson
KK Women’s and Children’s Hospital, Singapore
Professor Rahman Jamal
Universiti Keladagan Malaysia
Dato/ Dr Ravindran Jegasothy
Hospital Kuala Lumpur, Malaysia
Associate Professor Kenneth Hiew
KK Women’s and Children’s Hospital, Singapore
Dr Sia Keong Lam
Kwang Wai Hospital, Hong Kong
Professor Terence Loo
Chinese University of Hong Kong
Dr Kwok Yin Leung
The University of Hong Kong
Dr Taky Young Leung
Chinese University of Hong Kong
Professor Tzu-Yue Lin
Chang Gung University, Taiwan
Professor Somsak Lolekha
Ramathibodi Hospital, Thailand
Professor Lucy Chai-See Lum
University of Malaya, Malaysia
Professor SC Ng
National University of Singapore
Professor Hextan Yuen-Sheung Ngan
The University of Hong Kong
Professor Carmencita D Padilla
University of the Philippines Manila
Professor Seng Hock Ooak
National University of Singapore
Dr Tanay Kastinman Samsi
University of Tarumanagara, Indonesia
Professor Perla D Santos Ocampa
University of the Philippines
Associate Professor Alex Sia
KK Women’s and Children’s Hospital, Singapore
Dr Raman Subramanium
Fetal Medicine and Gynaecology Centre, Malaysia
Professor Waltrud W Sumpaico
MCI DFT Medical Foundation, Philippines
Professor Cheng Lim Tan
KK Women’s and Children’s Hospital, Singapore
Professor Kok Hian Tan
KK Women’s and Children’s Hospital, Singapore
Dr Raman Subramaniam
Fetal Medicine and Gynaecology Centre, Malaysia
Professor Waltrud W Sumpaico
MCI DFT Medical Foundation, Philippines
Professor Cheng Lim Tan
KK Women’s and Children’s Hospital, Singapore

Indian Editorial Board

Obstetrics & Gynaecology
Editor
Dr. JB Sharma
Additional Professor, All India Institute of Medical Sciences, New Delhi
Dr. Asok Kumar
Professor, MAMC, New Delhi
Dr. Asha Pherwani
PD Hinduja Hospital & Research Centre, Mumbai

Pulmonology
Associate Professor Bharat J Parmar
BJ Medical College & Civil Hospital, Ahmedabad
Assistant Professor Despika Chauhe
Government Medical College & Hospital, Chandigarh
Dr. Sangeeta Sharma
LRS Institute of Tuberculosis & Respiratory Disease, New Delhi
Dr. Asha Pherwani
PD Hinduja Hospital & Research Centre, Mumbai
259 Gastro-oesophageal Reflux in Infancy

Gastro-oesophageal reflux is very common in infancy. This review summarizes the approach to infants with symptoms and signs of reflux, differential diagnosis, investigations with their limitations, and nonpharmacological, pharmacological and surgical treatment.

Hemant Bhavsar, Mick Cullen, R Mark Beattie

271 A 22 Year Old Lady with Post–tubectomy Wound Sepsis

VL Deshmukh, KA Yelikar, Krishna Pawar

272 Maternal Periodontal Disease as a Risk Factor for Low Birth Weight Babies

Various factors have been associated with the delivery of preterm lower birth weight babies. One of the major factors among these is infection, either sub-clinical or clinical. An association with maternal lower genitourinary tract infection, urinary tract-infection, cervical colonisation with microbes etc. has been demonstrated by a number of studies. Studies show that periodontitis may be a potential independent risk factor for preterm labour and/or lower birth weight infants when all other known obstetric risk factors are not dominant and the pathogenic mechanism is postulated to be the same as with other maternal infection.

Sumanlata Mendiratta, Prabha Kumar, Subodh Sharma, Sangeeta Popli, Renu Bhatia

278 Polycystic Ovary Syndrome: Diagnosis and Management of Related Infertility

Polycystic ovary syndrome is one of the most common complex and heterogeneous endocrine disorder in women with uncertain aetiology. This review describes the currently available evidence regarding the therapeutic challenges raised in these women.

Suresh Kini
290 In Practice (Answer)

Case Study

292 A Rare Case of Bilateral Granulosa Cell Tumours of both Ovaries of Differing Histopathological Variety
Saswati Mukhopadhyay

Continuing Medical Education

296 Hormonal Contraception and Cancers
This article reviews the evidence regarding the relationship between hormonal contraceptive use and the development of cancer, with the discussion focusing mainly on carcinoma of the breast and female genital tract.
Wong Yuen Kwan Alice

Erratum:
In the article “Knowledge attitude and perception of contraception in couples attending a tertiary care hospital”, featured on page 205 of the June 2013 issue (Vol. 4, No. 6) of JPOG, the name of the authors should be Dr Rina K Patel Assistant professor, Dr Parul T Shah Associate Professor, Dr Kruti Deliwala, Dr EV Gunawati and Dr Mohit A Dodiya are Resident, Department of Obstetrics and Gynaecology, Vadilal Sarabhai Hospital, Ahmedabad Gujarat.

The Journal of Paediatrics, Obstetrics and Gynaecology contains articles under license from UBM Medica India Pvt. Ltd.
Diagnosis of chlamydia in women: Self-taken versus physician-taken swabs

A study in Leeds, England, has shown that for the diagnosis of chlamydia at a sexual health clinic, a patient-taken vulvovaginal swab is more sensitive than a clinician-taken endocervical swab.

A total of 3,973 women were studied over a period of 10 months. They took their own vulvovaginal swabs before being examined by a clinician who took an endocervical swab. Samples were tested for chlamydia using the Aptima Combo 2 test, and positives were confirmed using the Aptima CT assay. Symptoms associated with a bacterial sexually transmitted infection (vaginal discharge, dysuria, intermenstrual or postcoital bleeding, deep dyspareunia, or lower abdominal pain) were complained of by 1,671 women (42%). Chlamydia infection was confirmed in 410 women (10.3% of the whole cohort). Risk factors for chlamydial infection were younger age, symptoms of infection, contact with someone recently diagnosed with a sexually transmitted infection, and a diagnosis of cervicitis or pelvic inflammatory disease. The sensitivity for the diagnosis of chlamydial infection (excluding wrongly taken or labelled swabs) was 97% for patient-taken vulvovaginal swabs and 88% for endocervical swabs, a highly significant difference. The sensitivities were 97% and 88% among women with symptoms and 97% and 89% among women without. The specificity, positive predictive value, and negative predictive value were all >99.5% for both methods of collection.

A vulvovaginal swab taken by the woman herself is the better method for the diagnosis of chlamydia. Taking an endocervical swab instead would miss 9% of chlamydial infections.

Patient-taken swabs to diagnose gonorrhoea in women

An article by the same team in Leeds (see above) addresses the question of swabs for the diagnosis of gonorrhoea in the cohort of 3,973 women.

Of the 3,973 women, 100 (2.5%) had gonorrhoea on testing with the Aptima Combo 2 (AC2) assay with positive results confirmed by Aptima GC. Fifty-five of these women also had chlamydial infection. The sensitivity was 96% for endocervical swabs and 99% for vulvovaginal swabs. Culture of urethral and endocervical swabs taken by clinicians showed a sensitivity of 81%. Using AC2 was significantly more sensitive than culture, and AC2 confirmed by Aptima GC was 100% specific. Vulvovaginal swabs taken by the patients were more sensitive than endocervical swabs or urethral samples taken by clinicians for the diagnosis of gonorrhoea in a sexual health clinic.

There have been reports of increased risk of adverse pregnancy outcomes in association with the use of mood stabilizers in pregnancy. Now, Swedish data have shown that there is increased risk among women with bipolar disorder whether treated or not.

The study included 332,137 women who gave birth in 2006–2009. There were 874 women with bipolar disorder, of whom 320 were treated during pregnancy with mood stabilizers (lithium, antipsychotics, or anticonvulsants). The risks of non-spontaneous delivery and of preterm birth were significantly increased among women with bipolar disorder whether treated (2.12-fold and 50% increases compared with other women) or untreated (57% and 48% increases) with no significant differences between treated and untreated women. The risks of infant microcephaly and of neonatal hypoglycaemia were increased significantly only among women with untreated bipolar disorder.

Women with bipolar disorder have an increased risk of adverse pregnancy outcome whether treated with mood stabilizers during pregnancy or not. The risk of infant microcephaly or hypoglycaemia is increased only with untreated bipolar disorder.

Bipolar disorder and increased risk of adverse pregnancy outcome

Women who have pre-eclampsia in a first pregnancy (especially preterm pre-eclampsia) have an increased risk of later cardiovascular death. A study using Norwegian national records has shown that this applies mainly to women who have no more pregnancies.

The study included 836,147 women who...
had a first singleton birth in 1967–2007. By 2009, more than 23,000 of these women had died, 3,891 from cardiovascular disease. Among women with preterm pre-eclampsia, the rate of cardiovascular death after 40 years was 9.2% if they had only one child and 1.1% if they had more than one. Among women with term pre-eclampsia, the corresponding rates were 2.8% and 1.1%. Overall, after pre-eclampsia in a first pregnancy, the risk of cardiovascular death was increased by 90% (3.7-fold after preterm pre-eclampsia and by 60% after term pre-eclampsia). Among women who only ever had one child the corresponding increases were 9.4-fold and 3.4-fold. Among women who had more children, the risk increases were 2.4-fold and 1.5-fold. Recurrent pre-eclampsia did not increase the risk appreciably. The husbands of women with pre-eclampsia were not at increased risk of cardiovascular death, suggesting that social status was not an important factor. It is suggested that factors leading to pre-eclampsia and later cardiovascular death may make women less likely to have further pregnancies and that these data do not point to a direct link between pre-eclampsia and later cardiovascular death.

The increased cardiovascular mortality among women who have pre-eclampsia (especially preterm pre-eclampsia) in a first pregnancy is highly dependent on having no more children.


Genetic diagnosis antenatally and after stillbirth: Microarray versus karyotyping

Chromosomal microarray analysis may improve genetic diagnosis. Now, this technique has been compared with standard karyotyping for prenatal diagnosis and for diagnosis after stillbirth in successive papers in the New England Journal of Medicine.

In a study at 29 US centres, chorionic villus or amniotic fluid samples from 4,406 women were analysed and the results of both microarray analysis and karyotyping for antenatal diagnosis were obtained from 4,282 women. Almost half of the women (46.6%) had been tested because of older age, 25.2% because of fetal abnormalities on ultrasound scanning, 18.8% because of the results of Down syndrome screening, and 9.4% for other reasons. Microarray analysis identified all the aneuploidies and unbalanced rearrangements found on karyotyping but did not detect balanced translocations and fetal triploidy. Among women who were tested because of fetal ultrasound abnormalities and in whom karyotyping was normal, microarray analysis revealed relevant abnormalities (deletions or duplications) in 6% of cases. This proportion was 1.7% among women who had been tested because of their age or an abnormal screening test for Down syndrome. It is suggested that invasive testing and microarray analysis might be offered to all women after appropriate counselling.

The stillbirths study included 532 stillbirths at 59 centres in five areas of the USA. In each case, standardized autopsy and karyotyping were performed, together with microarray testing on placental or fetal tissue. Copy-number variants were classified as benign, probably benign, pathogenic, or of unknown significance. A result was obtained more often with microarray analysis (87.4% vs 70.5%), and a genetic abnormality was detected in 8.3% of cases with microarray analysis and 5.8% with karyotyping. When stillbirth was associated with congenital abnormalities, microarray testing showed a genetic abnormality in 29.9% of cases and karyotyping in only 19.4%.

Microarray analysis is more sensitive than karyotyping for the detection of genetic abnormalities prenatally or after stillbirth. Some of the abnormalities detected may be of unknown significance but further experience may reduce their number.

WHAT IS GASTRO-OESOPHAGEAL REFLUX?

Gastro-oesophageal reflux (GOR) is the non-forceful regurgitation of milk and other gastric contents into the oesophagus (regurgitation). It should be distinguished from vomiting which is an active process requiring the forceful contraction of the diaphragm and abdominal muscles. It is a normal physiological phenomenon, particularly common in infancy. It is also seen in older children and adults less frequently and only pathological when it occurs in excess.

FUNCTIONAL REFLUX

More than 50% of normal infants regurgitate more than twice a day. Functional reflux is regurgitation without morbidity or clinical signs suggestive of gastro-oesophageal reflux disease (GORD).

Reflux is most common between 1 and 4 months. Major factors include the high fluid volume per kilogram ingested at that age compared with older children/adults, posture and the functional immaturity of the lower oesophageal sphincter. By 12–18 months, most symptomatic reflux will have resolved as the sphincter matures, the infant adopts an upright posture, and is established on a mixed rather than milk-predominant diet.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease is defined as ‘gastro-oesophageal reflux associated with troublesome symptoms or complications’. It refers to reflux with significant morbidity including faltering growth, respiratory disease, and oesophagitis or complications.
of oesophagitis such as stricture. Therefore, within
the umbrella term *gastro-oesophageal reflux*, there
is a considerable spectrum with a range of severity
from an intermittent nuisance to a life-threatening
disease.

Most children with GORD will present in the
first year, but there are some who present later with
symptoms including heartburn, acid regurgitation,
and dysphagia.

**REFLUX OESOPHAGITIS**

Severe GOR can cause oesophagitis. Oesophagitis
implies acid or, rarely, alkali-induced damage to the
lower oesophagus. Intake of food by mouth stimu-
lates gastric acid secretion. Reflux of this acid in
the lower oesophagus can be painful. GORD is the
most common cause of oesophagitis in children.

Crying and irritability may be symptoms of oe-
sophagitis in infants, similar to adults’ complaint of
heartburn and chest pain. Children with oesophagi-
tis can develop food aversion as a consequence of
experiencing pain when they eat, and food refusal
can be the presenting feature. This is likely to be
a significant factor in the faltering growth seen in
some children with reflux. This can be difficult to
diagnose and requires treatment of oesophagitis
before dealing with feeding issues.

**SYMPTOMS OF GORD**

GORD can be oesophageal or extra-oesophageal de-
pending on the presenting symptoms.

**Oesophageal**

1. Symptoms purported to be due to GORD
   - Especially in infants or younger children or old-
er children without cognitive ability to reliably
     report symptoms
2. Symptomatic syndrome

3. Syndromes with oesophageal injury
   - Reflux oesophagitis, reflux stricture, Barrett’s
     oesophagus and adenocarcinoma

**Extra-oesophageal**

1. Definite association
   - Sandifer’s syndrome, dental erosion
2. Possible association
   - Bronchopulmonary – asthma, pulmonary fibro-
sis, bronchopulmonary dysplasia
   - Laryngotracheal and pharyngeal – chronic
     cough, chronic laryngitis, hoarseness, pharyn-
gitis
   - Rhinological and otological – sinusitis, serous
     otitis media
   - Infants – pathological apnoea, bradycardia,
     apparent life-threatening events

Risk factors for GORD include obesity, neuro-
logic impairment, repaired oesophageal atresia or
other congenital oesophageal disease, cystic fibro-
sis, hiatus hernia, repaired achalasia, lung trans-
plantation, and a family history of GORD.

**DIFFERENTIAL DIAGNOSIS OF GORD**

- Infection, eg, urinary tract infection, gastroen-
teritis, peptic ulcer disease
- Intestinal obstruction, eg, pyloric stenosis,
  malrotation, intestinal atresia
- Food allergy and intolerances, eg, cow’s milk
  allergy, soy allergy, coeliac disease
- Eosinophilic oesophagitis (EO)
- Metabolic disorders, eg, diabetes, inborn er-
  rors of metabolism
- Psychological problems, eg, anxiety, irritable
  bowel syndrome
- Intestinal dysmotility, eg, primary achalasi sec-
Approach to the Management of GOR

1. Physiological reflux is common in infancy and is a clinical diagnosis. For most parents, reassurance that the condition will resolve without treatment is all that is needed. It is important to consider the differential diagnosis.
2. Full assessment of infants is essential, including a full feeding history, to explore the possibility of overfeeding or difficulty with feeding. Careful attention needs to be paid to severity of symptoms, faltering growth and relevant social factors, eg, parental anxiety and stress (Table 1).
3. Severe cases need further assessments and investigation. These include barium study, pH study, impedance study, milk scan, oesophagoscopy, and oesophageal biopsy (described below).
4. There is a step-up approach to management.
5. Difficult cases require assessment by a multidisciplinary team including dietitian, speech and language therapist, paediatric gastroenterologist and paediatric surgeon.

Indications for Investigation of Presumed GOR

- Need to confirm the diagnosis
- Faltering growth
- Excessive vomiting
- Features suggestive of oesophagitis
- Abnormal electrolytes/acidosis
- Unexplained or difficult-to-control respiratory disease

<table>
<thead>
<tr>
<th>Table 1. History in a child with suspected gastro-oesophageal reflux disease</th>
</tr>
</thead>
</table>

**Pattern of vomiting (predominant symptom)**
- Frequency/amount
- Associated pain/discomfort
- Is the vomit forceful?
- Does the vomit contain blood or bile?
- Are there any associated constitutional symptoms, eg, fever, lethargy, diarrhoea?

**Feeding and dietary history**
- Amount/frequency (overfeeding)
- Preparation of formula
- Recent changes in feeding type or technique
- Position during feeding
- Burping
- Behaviour during feeding
- Choking, gagging, cough, arching, discomfort, food refusal

**Medical history**
- Prematurity
- Birthweight, growth and development
- Past surgery, hospitalizations
- Respiratory illnesses, especially croup, pneumonia, asthma
- Other respiratory symptoms including hoarseness, hiccups, apnoea
- Features of atopy
- Other chronic conditions

**Medications**
- Current, recent, prescription, non-prescription

**Family psychosocial history and family set-up**
- Sources of stress
- Post-partum depression
- Maternal or paternal drug use

**Family medical history**
- Significant illnesses
- Family history of gastrointestinal disorders
- Family history of atopy

**Growth chart including height, weight, and head circumference**
HOW TO INVESTIGATE GOR?

Barium Radiology
Barium swallow assesses the patient over only a short period and can therefore either miss pathological reflux or overdiagnose physiological reflux. It is however an important test to rule out large hiatus hernia, oesophageal stricture or web, atypical pyloric stenosis, gastric web, duodenal web, malrotation, volvulus, or other anatomical causes of recurrent vomiting.

pH Study
This is considered by many to be the gold standard investigation test for acid reflux. It is a valid quantitative measure of oesophageal acid exposure, with established normal ranges.

Specific Indications for pH Study
- Diagnostic uncertainty
- Poor response to medical treatment
- If surgery is being considered
- Children in whom doing the test will lead to a change in management
- Symptoms suggesting occult reflux
- Unexplained or difficult-to-control respiratory disease

Physiological Basis and Technique of Using pH Probe
Acid reflux into the oesophagus occurs in all infants as a physiological phenomenon and is only significant when it occurs in excess. The pH probe is designed to measure acidity (ie, acid reflux) in the lower oesophagus. The test relies on the infant/child being off anti-reflux therapy in the 48–72-hour period running up to the test.

The pH probe is a microelectrode passed through the nose and down the back of the throat to sit above the lower oesophageal sphincter. An acid
Reflux episode is defined as an oesophageal pH of < 4 for a specified minimum duration, usually 15–30 seconds. A set period, usually 24 hours, is recorded, with a note made of the number of episodes, frequency of episodes, and the relationship of reflux to eating, position, sleeping or activity, and especially symptoms. The most sensitive marker of acid reflux on pH study is the reflux index, defined as the percentage of time that oesophageal pH is < 4. This has been validated in several studies. pH study reports are shown in Figures 1 and 2.

**Limitations of the Test**

There are several limitations to pH studies, as follows:

- pH studies are unable to detect anatomical abnormalities (e.g., stricture, hiatus hernia or malrotation) or aspiration.
- Non-acid reflux will not be detected. This should be borne in mind with non-acidic feeds, such as infant formula, and, in particular, when infants are continuously fed.
- The changes in environment, diet and behav-
Reproducibility is poor.

There is potential for technical difficulties.

pH studies provide no objective measures of inflammation and thus are less useful than endoscopy and biopsies for the diagnosis and grading of oesophagitis.

The severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications.

ALKALINE REFLUX

The pH study may be falsely negative in the presence of alkaline reflux (reflux of alkaline stomach contents, eg, during continuous feeding/duodenal contents). Either dual pH monitoring (electrode in stomach and oesophagus), oesophageal impedance or a radio-labelled milk scan is required to detect this.

MILK SCAN

This uses continuous evaluation for up to an hour after radio-labelled meal. It is independent of pH so it can detect alkaline reflux. It is performed over a period of up to an hour with a delayed 24-hour film to look for aspiration. The technique is useful for diagnosis of non-acid reflux. It also gives an assessment of gastric emptying which is a useful indicator of overall gut motility. Markedly delayed gastric emptying is common in children with cerebral palsy in whom vomiting may reflect an overall gut dysmotility rather than GORD. Sensitivity for detection of reflux is variable but can approach 95%.

IMPEDEANCE

This measures the changes in the electrical impedance (resistance) between multiple electrodes located along an oesophageal catheter. Oesophageal impedance tracings are then analysed for the typical changes caused by liquid, solid, air or mixed bolus. The impedance changes suggestive of retrograde bolus movement indicate reflux. This test is superior to pH monitoring alone for the evaluation of the temporal relation between symptoms and GOR.

OESOPHAGEAL MANOMETRY

This measures the pressure inside the lower part of the oesophagus. It may be abnormal in patients with GORD, but the findings are not sufficiently

Practice points

- Functional reflux is very common in infancy and generally resolves spontaneously.
- Gastro-oesophageal reflux disease is defined as ‘gastro-oesophageal reflux associated with troublesome symptoms or complications’.
- Physiological reflux is a clinical diagnosis and does not warrant further investigation. It is important to consider appropriate differential diagnoses during history taking and examination.
- Most reflux will respond to simple strategies, including reassurance and explanation, feeding advice, feed thickeners, and anti-reflux milk.
- Medical therapy is by a step-up approach with use of H2 blockers, prokinetics, proton pump inhibitors and consideration of a trial of hydrolysed formula.
- Surgery is required in cases resistant to medical treatment and in those with extra-oesophageal complications such as recurrent aspiration.
- Children with cerebral palsy are at increased risk of reflux, although many other factors are relevant in the assessment of feeding problems in children with neurodisability.
- It is important to carefully consider other conditions such as eosinophilic oesophagitis and cow’s milk protein allergy in cases not responding to medical therapy.
sensitive or specific to confirm the diagnosis, nor to predict response to medical or surgical therapy. It is useful to confirm a diagnosis of achalasia or other motor disorders of the oesophagus that may mimic GORD.

**OESOPHAGOSCOPY AND OESOPHAGEAL BIOPSY**

In children with suspected oesophagitis, upper gastrointestinal endoscopy is a useful investigation and should be considered in all children with severe symptomatic reflux. Biopsies need to be taken, as significant histological abnormality may not be obvious endoscopically. An eosinophilic infiltrate is a characteristic of reflux oesophagitis. However, an excess of eosinophils suggests cow’s milk allergic oesophagitis/EO.

Normal oesophageal histology does not exclude GOR.

In children with documented oesophagitis and normal pH study, other diagnoses should be considered.

**NON-REFLUX CAUSES OF OESOPHAGITIS**

- Cow’s milk allergic oesophagitis (see above)
- Eosinophilic oesophagitis
- Candidal oesophagitis
- Chemical oesophagitis from caustic ingestion
- Achalasia
- Crohn’s disease

**TREATMENT OF GOR**

Most patients with physiological gastro-oesophageal reflux are managed in primary care by the health visitor and general practitioner.

Simple measures are often effective, including:
- Explanation and reassurance about the natural history, particularly in the infant who is thriving.
- Review of feeding and feeding practice, eg, checking for overfeeding, trial of smaller more frequent feeds, and too small or too large a teat (both of which can cause air swallowing).
- Review of feeding posture – infants have significantly less reflux when placed in the prone position than in a supine position. However, prone position is associated with a higher rate of sudden infant death syndrome. In infants from birth to 12 months of age with reflux, the risk of sudden infant death syndrome generally outweighs the potential benefits of prone sleeping. In children > 1 year, it is likely that there is a benefit to right-side positioning during sleep and elevation of the head of the bed.
- Use of feed thickeners and use of anti-regurgitation milks – these are useful in reducing the symptoms of GOR and should be considered in children with persistent symptomatic reflux impacting on nutrient intake or through excessive vomiting on lifestyle. They should not be used for healthy children who regurgitate.
- Cow’s milk allergy is a potential differential and infants with persistent reflux may benefit from a 2–6 week trial of extensively hydrolysed formula. Soya formulae should not be used. There is a significant cross reactivity between cow’s milk and soya protein and because of the presence of phytoestrogens in soya milk, they are not recommended in infants < 6 months.

Drug treatment is indicated in children with severe symptomatic reflux or signs and symptoms suggestive of GORD.

The major pharmacological agents currently used for treating GORD in children are gastric acid–buffering agents, mucosal surface barriers,
Most children with gastro-oesophageal reflux disease will present in the first year.

and gastric anti-secretory agents. Acid suppressant agents are the mainstay of treatment for all but patients with occasional symptoms. The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and gastrointestinal infections, need to be balanced against the benefits of therapy.

**STEP-UP APPROACH TO MEDICAL TREATMENT OF GOR**

Step 1 – lifestyle changes

Step 2 – thickeners/H$_2$ receptor blockers

Step 3 – prokinetics

Step 4 – proton pump inhibitors (PPIs)

Step 5 – consider change in feed/feed regimen

Step 6 – surgery

**Compound alginates** are effective symptomatic treatment for GOR. Infant aluminum hydroxide/magnesium trisilicate works by reacting with gastric acid to form a viscous gel. It comes in a dual sachet and each half is a dose. One dose for under 4.5 kg and two doses for over 4.5 kg are given for a maximum of six times a day. In infants, aluminium hydroxide/magnesium trisilicate can be added to feed or, for breast-fed infants, dissolved in cooled boiled water and given by spoon after a feed. Chronic use of alginates is not recommended for GORD because some have absorbable components that may have adverse effects with long-term use.

**Acid Suppression Agents**

**Histamine H$_2$ receptor blockers** are widely used in the management of reflux. They are safe and well tolerated and can be considered before any further investigation in children who are thriving and in whom the diagnosis is robust. Ranitidine is the most commonly used H$_2$ receptor blocker. Oral ranitidine provides symptomatic relief and endoscopic improvement of oesophagitis in children with GORD. Dose is 2–4 mg/kg twice daily; the syrup can be used (75 mg/5 mL).

**Proton pump inhibitors** (eg, omeprazole, lansoprazole) increase the pH of gastric content, decrease the total volume of secretions, and facilitate emptying. For healing of erosive oesophagitis and relief of symptoms, PPIs are superior to histamine receptor blockers. Omeprazole is the most commonly used PPI and is shown to be effective in children with GORD resistant to ranitidine. It is available as dispersible tablets or capsules given once daily. The tablet can be gently mixed or dis-
persed (not crushed), or the capsule can be broken for ease of administration in children. Dosage is 0.7–1.4 mg/kg per day although higher doses can be used, at up to 3 mg/kg. In practice, twice daily doses are often used. Lanzoprazole is available as dispersible tablets and given in the dose of 0.5–1 mg/kg once daily.

**PROKINETIC DRUGS**

These drugs increase lower oesophageal spincture pressure, improve oesophageal clearance, and promote gastric emptying. Efficacy data are limited. Examples include metoclopramide, domperidone, cisapride and erythromycin. Cisapride has been withdrawn from use because of concerns about cardiotoxicity. Although the effectiveness of domperidone in children is unproven, it is often used with no serious adverse effects at 0.3–0.6 mg/kg three times daily in children. It can occasionally exacerbate reflux.

**OTHER AGENTS**

Buffering agents (magnesium hydroxide and aluminium hydroxide) and sucralfate are useful for occasional heartburn. Buffering agents carry significant risk of toxicity and are not recommended for long-term use. Sucralfate binds to inflamed mucosa and forms a protective layer that resists further damage from gastric acid.

**CHILDREN WITH SEVERE REFLUX RESISTANT TO MEDICAL MANAGEMENT MAY BENEFIT FROM:**

- Trial of hydrolysed protein formula feed
- Period of continuous feeding
- Trial of gastrostomy/gastro-jejunal feeding

**SURGERY**

**Indications**

- Failure of optimal medical therapy
- Dependence on long-term medical therapy
- Extra-oesophageal manifestations (asthma, cough, chest pain, recurrent pulmonary aspiration of refluxate)
- Complication of GORD (eg, Barrett’s oesophagus, peptic stricture)

Surgery is usually fundoplication with consideration of a pyloroplasty if there is delayed gastric emptying. A gastrostomy for feeding is often done at the same time, particularly if there are feeding problems, eg, neurodisability.

Most fundoplications are now done laparoscopically with good results in terms of reduced post-operative complications, reduced stay in hospital, and long-term outcome.

Children with underlying disorders predisposing to the most severe GORD are at the highest risk for operative morbidity and post-operative failure. Before surgery, it is essential to rule out non-GORD causes of symptoms and ensure that the diagnosis of chronic-relapsing GORD is firmly established. It is important to provide families with appropriate education and a realistic understanding of the potential complications of surgery, which include recurrence of reflux (10%), retching, bloating, dumping, and intestinal obstruction.

**Patient Groups at High Risk of Needing Surgery**

- Children with neurodisability
- Respiratory disease with intractable reflux (eg, oesophageal atresia, bronchopulmonary dysplasia)
- Children with complication of oesophagitis such as stricture
- Tracheo-oesophageal fistula repair
- Barrett’s oesophagus
Barrett’s Oesophagus

- This refers to the presence of metaplastic columnar epithelium in the lower oesophagus thought to be a consequence of long-standing GORD.

There is an increased risk of adenocarcinoma of the oesophagus.
- It is rare in childhood and requires aggressive medical treatment of the GOR and regular endoscopic surveillance.
- Surgery (fundoplication) is often considered.

GOR and Neurodisability

Children with cerebral palsy commonly suffer from feeding difficulties of which GOR is a component. Assessment of the contribution of GOR requires careful assessment.

There are many potential causes of feeding difficulties in children with neurodisability:
- Bulbar weakness with oesophageal incoordination
- Primary or secondary aspiration

Within the umbrella term gastro-oesophageal reflux, there is a considerable spectrum with a range of severity from an intermittent nuisance to a life-threatening disease

- Reflux oesophagitis
- Widespread gut dysmotility
- Mobility and posture, degree of spasticity
- Poor nutritional state
- Constipation

Children require careful multidisciplinary assessment by a feeding team including dietitian, speech and language therapist, occupational therapist, and the neurodevelopmental paediatrician. A video barium assessment of the swallow is often indicated. GORD, if present, should be treated aggressively.

Attention to nutrition is of key importance, and many children with feeding difficulties benefit from a feeding gastrostomy. A fundoplication is required if reflux is severe, although in some cases, improved nutritional status will result in improvement of the reflux.

The motility of the gut is a key factor in feed tolerance in children with cerebral palsy who may have delayed gastric emptying which impact significantly on the ability to feed, particularly if nutrition is dependent upon nasogastric or gastrostomy feeding. It is important to recognize this as a separate condition from reflux. Abdominal pain, bloating and constipation are common features of gut dysmotility. Therapeutic strategies include explanation and reassurance, prokinetic agent such as domperidone, laxatives and, occasionally (if there is a need for distal gut deflation), suppositories. It may be necessary to give feeds by continuous infusion. It may also be necessary to consider gastro-jejunal feeding. A milk-free diet for a trial period of 2–4 weeks can be helpful. Hydrolysed protein formula feeds may be given as a milk substitute.

GOR and Respiratory Disease

GOR has been associated with significant symptoms in infants and children. There is a complex relationship between asthma and GOR, manifested
by a bidirectional cause and effect.

One postulated mechanism for GOR-mediated airway disease involves micro-aspiration of gastric contents that leads to inflammation and bronchospasm. However, experimental evidence also supports the involvement of oesophageal acid-induced reflex bronchospasm, in the absence of frank aspiration. In such cases, GOR therapy using either H2 blockers or PPIs has been shown to benefit patients with steroid-dependent asthma, nocturnal cough, and reflux symptoms. Similarly, intrinsic lung disease may, through excessive coughing, result in reflux.

The association between GOR and apparent life-threatening events is somewhat controversial and probably only relevant if the infant vomits, chokes or turns blue during or immediately after feeds.

**Eosinophilic Oesophagitis**

In infants and young children, EO presents with symptoms similar to those of GORD but fails to respond to conventional acid blockade therapy. In older children, dysphagia and food impaction can occur.

EO is often seen in patients with atopy who have asthma, eczema or chronic rhinitis, or in those with family history of atopic disease. Multiple food antigens can also induce EO.

Endoscopy may reveal a ringed appearance or linear furrows. Standard biopsy findings reveal severe eosinophilic infiltration; more than 15–20 eosinophils per high-magnification microscopic field are necessary for diagnosis. In contrast to GORD, EO involves the mucosa, submucosa and, possibly, the muscularis.

EO is currently diagnosed based solely on endoscopic findings. Standardized skin prick testing and radioallergosorbent testing are not useful in the diagnosis of EO. About two-thirds of children with EO have an increased peripheral eosinophilic count. The exact pathophysiology of EO is unknown, but contact of the allergen with the oesophageal or intestinal mucosa is thought to be the initiating event.

Treatments include those for GOR, trial of dietary elimination, inhaled (swallowed) or oral steroids, anti-inflammatory, and immunosuppression. There is a natural history of relapse, remission and chronicity.

**CASE STUDY 1**

A 5-week-old, term, breast-fed baby presented unsettled in the evenings and at night. She was vomiting (not the whole feed), with episodes of arching. She has continued to gain weight appropriately. Mum was given advice on positioning and feeding, along with explanation and reassurance about the natural history of GOR. The symptoms, however, continued and infant aluminium hydroxide/magnesium trisilicate was started. She continued to thrive. Her reflux gradually improved with time. This infant presumably had functional GOR. There may have been a component of ‘infantile colic’. Infantile colic is poorly understood but, like reflux, generally improves. Symptoms may overlap and can cause considerable anxiety to parents.

**CASE STUDY 2**

A 3-month-old exclusively breast-fed baby was started on formula milk. He developed symptoms of retching (distress) with most feeds, constipation, and milk refusal. His symptoms failed to improve with anti-reflux therapy and he lost weight. Cow’s milk allergy was considered. He was referred to a specialist clinic where he was started on extensively hydrolysed formula. Weaning was delayed to 6 months, after which he was started on dairy-
free weaning solids, with dietetic support. His symptoms improved rapidly and he showed good catch-up growth. Cow’s milk was gradually introduced in his diet from the age of 12 months, after a day case challenge, which he tolerated well. His diet was subsequently normalized. Cow’s milk allergy is the commonest food allergy in infancy and usually resolves by 2 years of life and almost always by 5 years of age. GOR can coexist, but poor response to anti-reflux therapy should prompt consideration of cow’s milk allergy.

CASE STUDY 3

A 2-year-old boy with spastic quadriplegia and intractable epilepsy presented to hospital repeatedly with aspiration pneumonia and poor weight gain. He was nasogastrically fed at home, and parents reported frequent retching and vomiting associated with feeds in spite of being on ranitidine and domperidone. His pH study confirmed severe reflux. He failed to respond to PPIs at good doses and trial of hydrolysed formula feed. He underwent fundoplication with feeding gastrostomy. Post-operatively, his admissions to hospital were reduced. Parents reported good weight gain and improved feed tolerance.

CASE STUDY 4

A 15-month-old baby presented with history of poor weight gain, recurrent vomiting and food refusal from very early age. She was born at term and there was no significant antenatal or medical history. She was particularly distressed at meal times as if she was in pain. Further investigations revealed significant reflux (reflux index 14%) and endoscopic findings of oesophagitis. She was treated with PPIs, with improvement in her symptoms. Her symptoms were secondary to acid reflux in response to gastric acid secretion associated with meal times. Her feeding improved with reflux treatment.

FURTHER READING


About the Authors

Hemant Bhavsar is a Speciality Registrar in Paediatric Gastroenterology in the Paediatric Medical unit at Southampton General Hospital, Tremona Road, Southampton, UK. Mick Cullen is a Paediatric Gastroenterology Nurse Specialist in the Paediatric Medical unit at Southampton General Hospital, Tremona Road, Southampton, UK. R Mark Beattie is Consultant Paediatric Gastroenterologist in the Paediatric Medical unit at Southampton General Hospital, Tremona Road, Southampton, UK.
Case of the Month
A 22 Year Old Lady with Post-tubectomy Wound Sepsis
VL Deshmukh, KA Yelikar, Krishna Pawar

Case Report
A 22 years old woman (P_3L_3) underwent tubectomy operation at Primary Health Centre. She was referred as post-tubectomy, wound sepsis at a tertiary referral centre (Figure 1). She had no associate co-morbidity. Her tubectomy was uneventful and stitches removed on the 8th post-operation day. Wound had copious discharge. Dressing was done twice daily after stitches removal by the surgeon. However, the wound started rapidly progressing (extensive necrosis of tissue with copious collection seen) (Figure 2). Hence, patient referred to higher center. On examination the vital were stable and she was well oriented. Local examination reviewed irregular wound (of 7x8 cm) with watery discharge, oedema, cellulitis, profound pain was present (allodynia). The skin was inflamed too. Intravenous cefotaxion 1 gm IV BD and injection metrogyl 500 mg IV 8 hourly was started immediately. Initial blood investigation reviewed, TLC-15,300/mm³ of which neutrophils were 75%. Haemoglobin was 8.6, KFT, LFT, BSL were within normal limits. Urgent microscopy, gram staining and the culture of the fluid through the wound was sent. It revealed *Staphylococcus aureus* organism sensitive to gentamycin.

Figure 1. Post-tubectomy wound
Figure 2. Necrosis of tissues with copious collection

What is your diagnosis?

(Continued on page 290)
Maternal Periodontal Disease as a Risk Factor for Low Birth Weight Babies

Introduction

Periodontal diseases are a group of infectious diseases caused by predominantly Gram-negative, anaerobic and microaerophilic bacteria that colonise in the subgingival area resulting in inflammation of gingival and periodontal tissues and progressive loss of alveolar bone.

Low birth weight (LBW) (birth weight < 2.500 kg) is a major determinant of neonatal morbidity and mortality.1 Preterm lower birth weight is recognised as a major cause of neonatal mortality and of nearly one-half of all serious long term neurological morbidity.2 Various factors have been associated with the delivery of preterm lower birth weight babies. One of the major factors among these is infection, either sub-clinical or clinical. An association with maternal lower genitourinary tract infection, urinary tract-infection, cervical colonisation with microbes etc. has been demonstrated by a number of studies.3,4 Studies5–6 show that periodontitis may be a potential independent risk factor for preterm labour and/or lower birth weight infants when all other known obstetric risk factors are not dominant and the pathogenic mechanism is postulated to be the same as with other maternal infection. Inflamed periodontal tissues produce significant amount of pro-inflammatory cytokines mainly interleukin-1 beta (IL–1β), Interleukin-6 (IL-6), tumour necrosis factor–α (TNF-α)
and prostaglandin-E2 (PG-E2). It is known that prostaglandins and certain cytokines (IL-1β, IL-6, TNF-α) in appropriate quantities stimulate labour and these may be responsible for delivery of preterm lower birth weight babies in women with periodontal disease. These inflammatory cytokines may also cause placental tissue damage contributing to foetal growth restriction and lower birth weight at birth.

METHODS

Selection Criteria
Two hundred women of age between 20–35 years with singleton pregnancy in cephalic presentation and spontaneous onset of labour were included in the study. For statistical analysis all selected subjects were grouped into two groups:

- Group I (lower birth weight group): Group I was subdivided into Group IA and Group IB.
  - Group IA (Preterm-lower birth weight group): included women delivering babies weighing ≤ 2.500 kg before 37 completed weeks of gestation (n=50)
  - Group IB: (Term-lower birth weight group) included women delivering babies weighing ≤ 2.500 (kg) at or after 37 weeks of gestation (n=50)
- Group II (Normal birth weight group): included women with babies of birth weight 2.5 kg or more who delivered at term (n=100). As no preterm baby of birth weight 2.5 kg or more was found, Group –II was not subdivided.

  Group-IA (PT-lower birth weight) and group-IB (T-lower birth weight) represented study cases (n=100) and group-II (T-NBW) represented controls (n=100) in the present study.

Exclusion Criteria
Women aged < 20 years or > 35 years, having multiple pregnancies, malpresentation, stillborn infant and induced labour were excluded from the study. Exclusion criteria also included women with history of previous preterm and/or lower birth weight baby, history of medication such as current use of systemic corticosteroid, antibiotics etc. and history of smoking/alcohol intake. Those with history of medical/obstetrical problems that may affect the study outcome such as congenital heart disease, hypertension-gestational/essential, diabetes mellitus, bronchial asthma, chronic renal disease, genitourinary infection, threatened abortion and antepartum haemorrhage were also excluded from the study.

The subjects were selected by inspection of Hindu Rao Hospital’s birth records each weekday. They were examined within 24 hours of delivery. Detailed history was taken and complete examination was done. The risk factors for lower birth weight were established by examination of the hospital records and by a structured questionnaire. Pregnancy outcomes of lower birth weight babies were measured in terms of preterm or term delivery. Estimation of gestational age was based on the last menstrual period, antenatal ultrasound examination reports, sequential antenatal physical examination and postnatal examination of babies. All selected subjects were informed and consent was taken for participation in the study.

Measurement of Periodontal Status
The dental examination was carried out in the dental department. A specially designed 11.5 mm long, colour coded (black colour in 3.5 to 5.5 mm of the probe) periodontal probe (WHO CPITN Probe) with 0.5 mm ball tip was used to evaluate the probing depth (PD) of the dental sulcus i.e. the distance from gingival crest to the base of the dental pocket. Any bleeding after gentle probing was noted on sites at which probing depth was determined and deemed positive if it occurred within 15 seconds after probing.
### Table 1. The worst finding in each sextant

<table>
<thead>
<tr>
<th>Findings</th>
<th>Maximum score</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No signs of periodontal disease; healthy periodontium</td>
<td>0</td>
<td>No need for additional treatment</td>
</tr>
<tr>
<td>Gingival bleeding after gentle probing</td>
<td>1</td>
<td>Need to improve personal oral</td>
</tr>
<tr>
<td>Supragingival or subgingival calculus; entire black area of the probe visible</td>
<td>2</td>
<td>Need for professional cleaning of teeth and improvement in personal oral hygiene</td>
</tr>
<tr>
<td>Pathological pockets 4–5 mm deep; gingival margin situated on black area of the probe</td>
<td>3</td>
<td>Need for professional cleaning of teeth, and improvement in personal oral hygiene</td>
</tr>
<tr>
<td>Pathological pockets ≥ 6 mm deep; black area of the probe not</td>
<td>4</td>
<td>Need for more complex treatment to remove infected tissue visible</td>
</tr>
</tbody>
</table>

### Table 2. Measurement of periodontal status of mothers in different groups

<table>
<thead>
<tr>
<th>Dental parameters</th>
<th>Cases (n=100)</th>
<th>Cases (n=100)</th>
<th>Cases (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GrIA (PT-LBW)</td>
<td>Gr IB (T-LBW)</td>
<td>Gr II (T-NBW)</td>
</tr>
<tr>
<td><strong>Bleeding on probing (BOP)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>42(84%)</td>
<td>41(82%)</td>
<td>63(63%)</td>
</tr>
<tr>
<td>Negative</td>
<td>08(16%)</td>
<td>09(18%)</td>
<td>37(37%)</td>
</tr>
<tr>
<td><strong>Calculus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>42(84%)</td>
<td>39(78%)</td>
<td>60(60%)</td>
</tr>
<tr>
<td>Absent</td>
<td>08(16%)</td>
<td>11(22%)</td>
<td>40(40%)</td>
</tr>
<tr>
<td><strong>Probing depth in mm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>04(08%)</td>
<td>04(8%)</td>
<td>22(22%)</td>
</tr>
<tr>
<td>2</td>
<td>08(16%)</td>
<td>12(24%)</td>
<td>32(32%)</td>
</tr>
<tr>
<td>3</td>
<td>15(30%)</td>
<td>15(30%)</td>
<td>18(18%)</td>
</tr>
<tr>
<td>4</td>
<td>14(28%)</td>
<td>11(22%)</td>
<td>19(19%)</td>
</tr>
<tr>
<td>5</td>
<td>05(10%)</td>
<td>06(12%)</td>
<td>06(06%)</td>
</tr>
<tr>
<td>6</td>
<td>04(08%)</td>
<td>02(04%)</td>
<td>03(03%)</td>
</tr>
<tr>
<td>Mean probing depth ± SD</td>
<td>3.440±1.264</td>
<td>1.180±1.273</td>
<td>2.660±1.327</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0014</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cptin score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>00(0%)</td>
<td>04(08%)</td>
<td>23(23%)</td>
</tr>
<tr>
<td>1</td>
<td>08(16%)</td>
<td>07(14%)</td>
<td>17(17%)</td>
</tr>
<tr>
<td>2</td>
<td>16(32%)</td>
<td>20(40%)</td>
<td>32(32%)</td>
</tr>
<tr>
<td>3</td>
<td>22(44%)</td>
<td>17(34%)</td>
<td>25(25%)</td>
</tr>
<tr>
<td>4</td>
<td>04(08%)</td>
<td>02(04%)</td>
<td>03(03%)</td>
</tr>
<tr>
<td>Mean Cptin ± SD</td>
<td>2.440±0.8609</td>
<td>2.120±0.9823</td>
<td>1.710±1.149</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
teeth were examined for supragingival or subgingival calculus. The worst finding in each sextant was coded according to the table 1. Prevalence of periodontal disease was defined based on the CPITN score of all subjects. In the present study, score 0 denoted to healthy periodontium i.e., no periodontal disease; score 1 to 2 denoted to mild periodontal diseases; score 3 denoted to moderate periodontal diseases and score 4 denoted to severe periodontal diseases. The prevalence of periodontal disease in all groups was calculated and the possibility of relationship between periodontal disease and lower birth weight babies was explored. Data was analysed using Graphpad Prism-5 software. Analysis of Variance (ANOVA) test was done for statistical analysis.

RESULTS

There was no major difference in the mean age, socioeconomic status and educational level of women in the study groups almost 176 women (88%, n=200) never visited dental clinic even once prior to this study even if they had a history suggestive of periodontal disease. The examination of dental parameters like bleeding on probing (BOP), supra or subgingival calculus, probing depth and CPITN scoring was done (Table 2).

Periodontal disease was present in 173 women, at least in some form or other (CPITN scores ranging from 0–4), in the study population. Thus prevalence of periodontal disease was 86.50% (n=200) as shown in table 3.

The mean gestational age at the time of delivery was 33.16 ± 2.113 weeks in group IA (PT-lower birth weight), 38.44 ± 1.053 weeks in group IB (T-lower birth weight) and 38.78 ± 1.001 weeks in group II (T-NBW) respectively. Women delivering at lower gestational period had severe periodontal disease in all the groups.

The mean birth weight in group IA (PT-lower birth weight), IB (T-lower birth weight) and II (T-NBW) were 1.775 ± 0.3332 kg, 2.125 ± 0.1879 kg and 3.118 ± 0.2862 kg respectively. The means were significantly different with P value <0.0001. Women with severe periodontal disease had higher risk of having lower birth weight baby, both in preterm lower birth weight group (odds ratio [OR] 2.812, 95% confident interval [CI] 0.7234-10.93) and term lower birth weight group (odds ratio [OR] 1.347, 95% confident interval [CI] 0.2936-6.183) as shown in Table 4.

DISCUSSION

About 16% of the babies born in the world are lower birth weight babies.\(^1\) The determination of
risk factors for the delivery of lower birth weight babies represents a major public health priority. Ever since the pivotal study was performed by Offenbacher et al in 1996, there has been a considerable interest in identifying the association between periodontal disease and pregnancy outcomes. The present study was also an effort to determine maternal periodontal disease as a possible risk factor for lower birth weight in term and preterm babies. Similar study was carried out by Mokeem et al in 2004. To study the severity of periodontal disease clinically, there are a lot of potential measures available. CPITN scoring system was used in this study because it is a quick screening system which can be easily done in the ward also. This is an epidemiologic tool developed by the World Health Organization (WHO) in the year 1977 after an extensive field study by WHO and FDI (Federation Dentire Internationale) working group for the evaluation of periodontal disease and treatment recommendation in population surveys.

The prevalence of periodontal disease was high (86.5%, n=200) in the study population. The high prevalence of periodontal disease in the study population might be due to the lack of awareness about oral hygiene practices and utilisation of dental care facilities.

The present study suggests that women with severe periodontal disease (CPITN-4) had increased chances of having lower birth weight babies. This can be explained by the fact that periodontal disease might have influenced the pregnancy outcomes by direct and or indirect effect of periodontal pathogens on the developing foetus. Several investigators have reported that periodontal treatment during pregnancy

<table>
<thead>
<tr>
<th>Birth weight (Kg)</th>
<th>Cpitin score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01−1.49</td>
<td>0(0%)</td>
<td>2(4%)</td>
</tr>
<tr>
<td>1.50−1.99</td>
<td>0(0%)</td>
<td>1(2%)</td>
</tr>
<tr>
<td>2.00−2.49</td>
<td>0(0%)</td>
<td>5(10%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0(0%)</td>
<td>8(16%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>2.811</td>
<td></td>
</tr>
<tr>
<td>1.01−1.49</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>1.50−1.99</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>2.00−2.49</td>
<td>4(8%)</td>
<td>7(14%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4(8%)</td>
<td>7(14%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.347</td>
<td></td>
</tr>
<tr>
<td>2.50−2.99</td>
<td>6(6%)</td>
<td>1(1%)</td>
</tr>
<tr>
<td>3.00−3.49</td>
<td>11(11%)</td>
<td>16(16%)</td>
</tr>
<tr>
<td>3.50−3.99</td>
<td>6(6%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23(23%)</td>
<td>17(17%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth weight (Kg)</th>
<th>Cpitin score</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR-IA (PT-LBW) n=50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.01−1.49</td>
<td>0(0%)</td>
<td>2(4%)</td>
</tr>
<tr>
<td>1.50−1.99</td>
<td>0(0%)</td>
<td>1(2%)</td>
</tr>
<tr>
<td>2.00−2.49</td>
<td>0(0%)</td>
<td>5(10%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0(0%)</td>
<td>8(16%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>2.811</td>
<td></td>
</tr>
<tr>
<td>GR-IB (T-LBW) n=50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.01−1.49</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>1.50−1.99</td>
<td>0(0%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>2.00−2.49</td>
<td>4(8%)</td>
<td>7(14%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4(8%)</td>
<td>7(14%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.347</td>
<td></td>
</tr>
<tr>
<td>GR-II (T-NBW) n=100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.50−2.99</td>
<td>6(6%)</td>
<td>1(1%)</td>
</tr>
<tr>
<td>3.00−3.49</td>
<td>11(11%)</td>
<td>16(16%)</td>
</tr>
<tr>
<td>3.50−3.99</td>
<td>6(6%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>23(23%)</td>
<td>17(17%)</td>
</tr>
</tbody>
</table>

Table 4. Relationship between birth weight and maternal periodontal disease in different groups
leads to a reduction in preterm birth risk.13 Two recent meta-analyses of the association between maternal periodontal disease and preterm birth have been published.14,15

CONCLUSIONS

Most periodontal diseases are both preventable and treatable and would be of significant public health interest in pregnancy if a cause-effect relationship with preterm birth and lower birth weight can be demonstrated. Periodontal disease may be an independent risk factor for lower birth weight as almost all of the known risk factors for lower birth weight were excluded during the study. Maintaining good oral hygiene before and during pregnancy is crucial for preventing adverse effects on the foetus due to periodontitis. Hence routine periodontal examination and advice on good oral hygiene should be included as part of pre-conceptional care and antenatal check ups during pregnancy. Any dysfunction should be thoroughly investigated and treated for the sake of health of both mother and baby.

About the Authors

Dr Sumanlata Mendiratta is Senior Gynaecologist, Dr Prabha Kumari is Medical Officer, Dr Subodh Sharma is Head of Dental Department, Dr Sangeeta Popli is a Chief Medical Officer, Hindu Rao Hospital, Delhi and Dr Renu Bhatia is an Assistant Professor, Department of Physiology, AIIMS, New Delhi.

REFERENCES

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, yet its exact nature remains enigmatic. Women with PCOS can present with a wide range of features including reproductive (menstrual irregularity, hirsutism, infertility, and pregnancy complications), metabolic features such as insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes and cardiovascular disease, and finally psychological (poor self-esteem, anxiety, depression). Not all women demonstrate all symptoms, and there is considerable heterogeneity. Presentation can also vary across the lifecycle.

PCOS starts manifesting usually during adolescence with menstrual irregularity and symptoms of hyperandrogenism. Fertility problems manifest later on as PCOS remains the most common cause of anovulatory infertility (~75%). Despite its high prevalence (6–8% of women of reproductive age), there remains much controversy regarding its diagnosis, aetiology, and most appropriate treatment strategy. The pathophysiology of PCOS appears to be multifactorial, and although extra ovarian aspects have been suggested, ovarian dysfunction remains the central issue.

PCOS can be a frustrating experience for women, a complex syndrome for clinicians, and a scientific challenge for researchers, as well as being a major public health concern. This review will present an overview of PCOS, including a historical perspective, pathophysiology, diagnosis and various management options for PCOS.

HISTORICAL PERSPECTIVE

’Sclerocystic’ ovaries were recognized as early as the mid-18th century. The PCOS (originally called the Stein–Leventhal syndrome), was originally described by two Americans...
(Irving F Stein and Michael L Leventhal) in 1935. They described their treatment of this condition, by using wedge resection of the ovaries to induce ovulation with remarkable success. However, as medical treatment became available with the introduction of clomifene citrate (CC) (Greenblatt 1961), and subsequently the use of follicle-stimulating hormone (FSH) of pituitary (Kovacs and Norman 2012) and urinary sources (Wang and Gemzell 1980), surgical treatment became less often used. Interestingly, surgical treatment of resistant anovulation has had resurgence with the laparoscopic approach initially described by French gynaecologists, but popularized by Gjoanness (1984).

**PATHOPHYSIOLOGY**

Factors involved in the development of PCOS can be divided into the following groups.

**Aberration of Gonadotropin Secretion**

Compared with normally cycling women, those with PCOS generally exhibit increased serum luteinizing hormone (LH) concentrations, low-normal FSH levels and increased LH:FSH ratios. The increase in serum LH levels results from abnormal LH secretory dynamics, characterized by an increase in LH pulse frequency and, to a lesser extent, also in pulse amplitude. The decrease in FSH levels results from the increase in gonadotropin-releasing hormone (GnRH) pulse frequency, the negative feedback effects of chronically elevated oestrone concentrations (derived from peripheral aromatization of increased androstenedione), and normal or modestly increased levels of inhibin B (derived from small follicles). Increased circulating levels of oestrone may exert negative feedback effects on FSH, but probably do not have any important direct influence on LH secretion in women with PCOS. Whereas the lack of progesterone feedback resulting from anovulation undoubtedly contributes to the higher LH pulse frequency, as evidence suggests that the GnRH pulse generator is also less sensitive to the feedback inhibition of sex steroids. Studies suggest that excessive LH secretion or stimulation may be an important cause of disordered follicular development and anovulation, but is not the proximate cause of polycystic ovaries or of increased ovarian androgen production in women with PCOS.

**Genetics and PCOS**

PCOS appears to be inherited as a complex, polygenic trait. The familial clustering of PCOS cases and the accumulating evidence about the interaction between multiple genetic and environmental factors necessary for the development of the syndrome has led to the initiation of genetic studies on PCOS. These studies have focused on genetic polymorphisms and investigating their possible positive or negative correlation with the syndrome. Studies in large families have suggested an autosomal dominant inheritance, with premature balding as the male phenotype. Other studies of siblings and parents of women with PCOS have observed a high prevalence of hyperinsulinaemia and hypertriglyceridaemia, associated with premature balding of male trait. The syndrome clusters in families and prevalence rates in first-degree relatives are five to six times higher than in the general population. Nearly 50% of sisters of women with PCOS have elevated total or bioavailable testosterone concentrations, and approximately 35% of mothers are also affected. The first-degree relatives of women with PCOS also exhibit other metabolic abnormalities such as dyslipidaemia, which may predispose to an increased risk for cardiovascular disease. These observations further suggest a genetic predisposition or susceptibility. Although several genes have been postulated as responsible for the aetiology of this disorder, no single gene has been
confidently identified to play a predominant role in the pathogenesis of PCOS. Despite the progress that has been made in the elucidation of the genetic mechanisms of the PCOS, the genetic studies on the syndrome still face many challenges. Further studies are needed in order to shed new light on the pathogenesis of the syndrome.

Hyperinsulinaemia and Insulin Resistance
Insulin resistance is a condition in which endogenous or exogenously administered insulin has less than normal effects on fat, muscle and the liver. Decreased glucose utilization and increased hepatic gluconeogenesis (which insulin normally inhibits) result in increased blood glucose concentrations and a compensatory hyperinsulinaemia. The importance of insulin resistance and hyperinsulinaemia in the pathogenesis of PCOS was first suggested by a study conducted in 1980 and appears to be more common in obese PCOS patients. Increased circulating insulin levels cause or contribute to hyperandrogenism by stimulating ovarian androgen production and by inhibiting hepatic sex hormone–binding globulin (SHBG) secretion. Insulin also potentiates LH-induced androgen production by the ovarian stroma. High insulin concentrations also inhibit hepatic SHBG production, as do high androgen concentrations yielding increased free androgen concentrations, which then aggravate insulin resistance. Ultimately, these conditions foster a self-propagating positive feedback loop that can increase in severity over time. Insulin resistance and hyperinsulinaemia are undoubtedly an important part of the pathophysiology of PCOS. However, it is important to emphasize that 25–50% of women with PCOS have no demonstrable insulin resistance. Moreover, among all women with insulin resistance, the prevalence of PCOS is relatively low (approximately 15%). Therefore, insulin resistance and hyperinsulinaemia may not be the only pathogenic factors in women with PCOS.

**DIAGNOSIS**
Diagnosis of PCOS (Table 1) can only be made when other factors contributing to anovulation have been excluded (thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumours, and Cushing syndrome). Hyperandrogenic features are often most common among adolescents, whereas fertility issues are more prominent among women in their 20s–30s and metabolic challenges mostly have their effects in later years. The propensity to weight gain and psychological challenges affect all ages, and metabolic features can occur early, especially among those who are overweight.

**RACIAL DIFFERENCE IN EXPRESSION**
The highest prevalence of PCOS has been reported in around 52% women among South Asian immi-
grants in Britain, of whom 49% had menstrual irregularity. South Asians women with anovulatory PCOS have greater insulin resistance and more severe symptoms compared with anovulatory white Caucasians with PCOS, and tend to express symptoms at an earlier age. On the other hand, compared with Caucasians, Chinese women and Middle Eastern women with PCOS usually have a lower risk of metabolic syndrome.

**SIGNS AND SYMPTOMS**

PCOS has a variety of clinical manifestations, not all of which may be present, including:

**Menstrual Abnormalities**
The majority of women with PCOS (approximately 60–70%) exhibit gross menstrual dysfunction. The most common abnormalities are oligomenorrhoea and amenorrhoea. Polymenorrhoea is very uncommon, observed in less than 2%. Approximately 25% of the patients have regular periods.

**Symptoms of Hyperandrogenism**
These include hirsutism, acne persisting beyond adolescence, oily skin, and male-pattern alopecia. Hirsutism is the growth of terminal hairs on the face or body in a male pattern. Hirsutism is the most important feature of PCOS, affecting 65–75% of women and varies with ethnicity. The modified Ferriman–Gallwey score is the most common method for grading the extent of hirsutism. The prevalence of acne among white women with PCOS is 12–14% and, like hirsutism, varies with ethnicity. Androgenic alopecia, describing scalp hair loss in women in PCOS, affects less than 5% of patients.

**Sub-fertility**
Chronic oligo or anovulation is very common in women with PCOS, and PCOS accounts for approximately 75% women with anovulatory sub-fertility. Hypersecretion of LH is found in 40% of women with PCOS and is associated with a reduced chance of conception and an increased risk of miscarriage in both natural and assisted conception. Obese women with PCOS have increased rate of cycle disturbance and sub-fertility which is secondary to disturbance in insulin metabolism.

**Metabolic Symptoms**
Obesity is often associated with PCOS (approximately 35–60%), but many with PCOS are of normal weight. Women with PCOS have a greater truncal abdominal fat distribution as demonstrated by a higher waist to hip ratio, which is an indication of insulin resistance. Acanthosis nigricans is another marker of insulin resistance occurring in 1–3% of women and manifests as dark pigmented areas of skin commonly affecting axillae, perineum or extensor surfaces of the elbow and knuckles. Insulin resistance combined with abdominal obesity is thought to account for the higher prevalence of type 2 diabetes (~15%) in PCOS. Women with PCOS are also at increased risk of developing gestational diabetes and manifestations of dyslipidaemia.

**ENDOCRINOLOGICAL FEATURES**
The most frequently found endocrine abnormalities in PCOS include hyperandrogenism, elevated serum concentration of LH, LH:FSH ratio > 2, and hyperinsulinaemia. Increased testosterone > 2.5 nmol/L (~70%), increased free androgen index (FAI) > 5 (~75%), and decreased SHBG (~50%) may be seen in women with PCOS. A large proportion of circulating testosterone is bound to a protein called SHBG that is decreased in women with PCOS leading to increased free testosterone. The FAI is a simple method of estimating the circulating free testosterone and is calculated as: FAI = \[(\text{total testosterone})\]
Although raised LH more than 10 IU/L (~60%) with a normal FSH and LH:FSH ratio more than 2 (~95%) may be found in PCOS, it is important to note that the measurements of gonadotropins no longer form part of the diagnostic criteria. Some women with PCOS may demonstrate biochemical features of increased insulin (> 20 mU/mL) (~50%) and increased blood prolactin (~30%).

**ULTRASOUND FEATURES OF PCOS**

The ESHRE/ASRM Rotterdam consensus (2003) recommended that polycystic ovaries (PCO) should be considered as one of the possible criteria for PCOS. The criteria fulfilling sufficient specificity and sensitivity to define PCO are the following: ‘presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (> 10 cm³)’. Only one ovary fitting this definition is sufficient to define PCO (Figure 1). Although 35% women have PCO on transvaginal ultrasound, only 10% of these meet the criteria for PCOS.

**MANAGEMENT OF INFERTILITY IN PCOS**

**Lifestyle interventions:** lifestyle management (single or combined approaches of diet, exercise and/or behavioural interventions) for weight loss, prevention of weight gain or for general health benefits should be recommended in women with PCOS. Lifestyle management targeting weight loss (in women with a body mass index [BMI] ≥ 25 kg/m² [overweight/obese]) and prevention of weight gain (in women with a BMI 18.5–24.9 kg/m² [lean]) should include both reduced dietary energy (caloric) intake and exercise should be first-line therapy for all women with PCOS. Face-to-face, tailored dietary advice, including education, behavioural change techniques and ongoing support, should be provided to women with PCOS and a BMI ≥ 25 kg/m². Simple strategies, including self-monitoring, pedometers and time management techniques, should be encouraged. Exercise participation of at least 150 minutes per week should be recommended to all women with PCOS, especially those with a BMI ≥ 25 kg/m², given the metabolic risks of PCOS and the long-term metabolic benefits of exercise. Of these 150 minutes, 90 minutes per week should comprise aerobic activity at moderate to high intensity (60%–90% of maximum heart rate) to optimize clinical outcomes. Lifestyle management, including diet and exercise programmes, should be used throughout the lifespan in women with PCOS to optimize health benefits generally, and also to alleviate symptoms such as infertility. In women with PCOS and BMI ≥ 30 kg/m² (obese), due consideration should be given to age-related infertility, and intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be considered as the first-line therapy for 3 to 6 months duration to determine whether ovula-
 tion can ensue spontaneously. Weight loss of just 5–10% has been shown to reverse the deleterious effects of obesity on ovarian function and can restore reproductive function in a majority of women within 6 months of weight reduction. Pharmacological ovulation induction should not be recommended as first-line therapy in women with PCOS who are morbidly obese (BMI ≥ 35 kg/m²) until appropriate weight loss has occurred through diet, exercise, bariatric surgery or other appropriate means. Psychological factors should be considered and managed in infertile women with PCOS to optimize engagement and adherence to lifestyle interventions.

Anti-obesity pharmacological agents: the available literature supports the adjuvant use of pharmacological agents for weight loss treatment of obesity in PCOS. Orlistat blocks intestinal absorption of fat whereas sibutramine acts as an appetite suppressant, and both have been shown to significantly reduce body weight and hyperandrogenism in women with PCOS.

PHARMACOLOGICAL MANAGEMENT OF INFERTILITY IN PCOS

Clomifene

Clomifene citrate should be the first-line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility with no other infertility factors.

Mechanism of action: clomifene is a non-steroidal synthetic oestrogen that acts as a selective oestrogen receptor modulator, having both oestrogen agonist and antagonist properties. Structural similarity to oestrogen allows clomifene to compete with endogenous oestrogen for nuclear oestrogen receptors at the hypothalamic-pituitary level; clomifene blocks the negative feedback effect of oestradiol on GnRH secretion, thus triggering increased GnRH pulse amplitude leading to increase serum levels of both FSH and LH from the pituitary which, in turn, drives ovarian follicular development. In successful treatment cycles, one or more follicles emerge and grow to maturity.

Clomifene treatment regimens: CC administered orally, in the early follicular phase, can be used in different regimens; the most commonly used is administration of clomifene starting on day 2 of the menstrual cycle for 5 days after the onset of a spontaneous or progestin-induced menses. Ovulation and conception rates and pregnancy outcomes are similar when treatment starts anywhere between cycle days 2 and 5. Obese women often require higher doses of clomifene treatment, the results achieved ultimately are similar to those observed in lean women. Treatment usually starts...
with a single 50 mg tablet daily for 5 days, increases by 50 mg increments in subsequent cycles until ovulation is achieved. Lower oestrogen levels rise progressively, ultimately triggering an LH surge and ovulation. In addition to its desirable central actions, clomifene can exert less desirable anti-oestrogenic effects at peripheral sites: at endocervix which could lead to decreased quality and quantity of cervical mucus production, and at the endometrium where it could lead to impaired growth; but there is no compelling evidence to indicate that such effects have important clinical consequences in most doses. Most women who respond to clomifene will respond to either 50 mg (52%) or 100 mg (22%). It is recommended that at least the first cycle of ovulation induction with clomifene should be monitored with a combination of serial ultrasound scans and serum progesterone. Although the treatment with clomifene induces ovulation in 70–80% of patients but only 40–50% conceive. The cumulative conception rate is 67% over 6 months with multiple pregnancy rate of < 10%, and there is very small risk of ovarian hyperstimulation syndrome (OHSS). The response rate decreases with increasing age and BMI and with the extent of any associated hyperandrogenaemia in anovulatory women. There may be benefit in using CC for up to 12 cycles as cumulative pregnancy rates continue to rise after six treatment cycles before reaching a plateau, comparable to that of the normal fertile population. The treatment with doses up to 150 mg is reasonable before considering alternatives. Anovulatory women who do not ovulate while receiving the 150 mg dose of CC are considered to be resistant to the drug.

**Side effects of CC:** clomifene has cumulative side effects which occur as a result of its use in consecutive cycles. The main side effects of clomifene...
are related to its anti-oestrogen effects. Common side effects of clomifene include hot flushes, headaches, abdominal bloating and pain, nausea and vomiting, mood changes, and breast tenderness. Visual symptoms such as blurring, double vision or seeing spots occur in 1–2% of women, and usually resolve when treatment stops. Most studies do not show an increased risk of birth defects, miscarriage, or learning disability in children of women who took clomifene. There is no increased risk of breast cancer or uterine cancer. There may be a slightly increased risk of ovarian cancer if more than 12 cycles of clomifene are used. Cumulation of clomifene in hypothalamus-pituitary-ovarian-uterine-cervical axis causes irregularities in FSH secretion and follicular development, irregularities in LH secretion resulting in premature luteinization of the developing follicle (20–30%), and inappropriate endometrial development and dry secretions from the cervix.

Tamoxifen Citrate
Tamoxifen citrate is another non-steroidal selective oestrogen receptor modulator. It is a safe and effective alternative to CC for anovulatory infertility in women with PCOS. Unlike clomifene, tamoxifen acts as an agonist on the oestrogen receptors of the endometrium. It is used in a similar way to CC for 5 days in the early follicular phase at doses of 20 mg that can be increased to 40 mg and then 80 mg in subsequent cycles if ovulation is not achieved. There are no substantial differences in ovulation rates between tamoxifen and clomifene. Limited data on pregnancy rates and outcomes showed no significant differences between the treatments.

Letrozole
Aromatase inhibitors were first proposed as new ovulation-inducing agents in anovulatory women with PCOS (with an inadequate response to CC) in 2001. The most commonly used aromatase inhibitors in ovulation induction are letrozole and anastrozole, with letrozole being the most widely used.

**Mechanism of action:** the enzyme aromatase catalyzes the conversion of androgens to oestrogens. Therefore, aromatase inhibitors inhibit oestrogen biosynthesis, thereby releasing the hypothalamus/pituitary axis from oestrogenic negative feedback and increasing the secretion of FSH by the pituitary. The increasing oestradiol levels secreted by the multiple developing ovarian follicles which first appear on day 7 results in normal negative feedback on FSH secretion later in the follicular phase, resulting, in most cases, in single follicle ovulation.

**Usage:** letrozole is typically administered for 5 days in the early follicular phase at doses of 2.5–7.5 mg per day with 2.5-mg increments.

**Advantages:** letrozole may be very effective for ovulation induction in cases of CC resistance. When used together with FSH injections, letrozole resulted in a significant reduction in the FSH dose needed for controlled ovarian hyperstimulation. Aromatase inhibitors likely increase ovarian sensitivity to FSH and may be useful in poor responders and in women undergoing ovarian stimulation for *in vitro* fertilization (IVF). Letrozole avoids some of the adverse effects of CC including the peripheral anti-oestrogenic effects on the endometrium and cervical mucus and the increased risk of multiple pregnancies. Letrozole is not licensed for use in UK and Europe owing to controversial reports of fetal anomalies; further large randomized trials are needed to confirm this.

Metformin
The association of insulin resistance contributing to anovulation in PCOS has led to the introduction of insulin-sensitizing drugs in an attempt to restore
ovulation and enhance pregnancy. The early studies examining its effects on the reproductive system effects in women with PCOS showed promising results but most of these studies had relatively small sample sizes. An extremely variable large target dose of 1,500–2,550 mg per day in divided doses was proposed. If one is considering using metformin alone to treat women with PCOS who are anovulatory, have a BMI $\geq 30$ kg/m$^2$ (obese), and are infertile with no other infertility factors, CC should be added to improve fertility outcomes. In women with PCOS who are CC-resistant, metformin can be combined with CC to improve fertility outcomes. The recent Cochrane review showed that metformin was associated with improved clinical pregnancy rate, but there was no evidence that metformin improves live birth rates whether it was used alone or in combination with clomifene, or when compared with clomifene. Therefore, the role of metformin in improving reproductive outcomes in women with PCOS appears to be limited.

There is no good evidence available on the long-term use of statins (alone or in combination) for the management of PCOS.

The role of metformin in improving reproductive outcomes in women with PCOS appears to be limited

Gonadotropins
Gonadotropins may be used as a second-line treatment in patients with clomifene resistance or for those who fail to conceive despite ovulating with clomifene. Human menopausal gonadotropin is a purified extract from human postmenopausal urine; it contains both FSH and LH. FSH alone is available in a variety of preparations, which are either derived from human menopausal urine or as a recombinant peptide produced by cultured cells. These are equally effective in achieving pregnancy, and consideration should be given to minimizing cost when prescribing.

Regimens: the therapy is based on the physiological concept that initiation and maintenance of follicle growth may be achieved by a transient increase in FSH above a threshold dose for sufficient duration to generate a limited number of developing follicles.

- ‘Step-up’ regimen: this regime involves commencing therapy with 50 or 75 IU per day of FSH for 7–10 days and then increasing the dose incrementally by 37.5 IU every week if there is no development of a follicle $\geq 12$ mm in size. Once follicle growth is observed, then FSH is administered in the same dose until follicular selection is achieved. Ovulation is triggered when there is development of a solitary follicle $\geq 18$ mm in size in the absence of any other follicles in excess of $14$ mm in size.
- ‘Step-down’ regimen: this is used with a usual starting dose of 150 IU of FSH until a dominant follicle develops and then the dose of FSH is decreased until the triggering of ovulation with human chorionic gonadotropin. The success of this regime is comparable to that of the ‘step-up’ regimen, although it is believed that a step-up approach is safer with regard to the induction of monofollicular ovulation and potentially easier to monitor.
- ‘Sequential’ regimen: this is a combined approach with step-up and step-down regimens, which has shown to help reduce the risk of over response.
The ‘step-up’ gonadotropin regimen is well-established in fertility practice. This approach results in a monofollicular ovulation rate of ~70%, a pregnancy rate of 20% per cycle and low incidence of multiple pregnancies (~5%) and OHSS (<1%).

**Risks:** The sensitivity to gonadotropin therapy is increased in PCOS with multiple follicular development and cycle cancellation. Ovulation induction with gonadotropins is expensive, requires regular monitoring, and often results in the development of multiple mature follicles with a potential risk of multiple pregnancies and OHSS.

**SURGICAL MANAGEMENT OF INFERTILITY IN PCOS**

**Laparoscopic Ovarian Drilling**

Laparoscopic ovarian diathermy (LOD) or ‘ovarian drilling’ was first described in 1984, with minor variations in the procedure described since then. LOD carried out with either electro surgery (Figure 2) or laser has been demonstrated to lead to a resumption of menstrual cycles and ovulation in a significant proportion of women. This is also associated with a fall in serum androgen and LH levels.

**Indication:** LOD is a second-line of therapy for women with PCOS, who are either CC-resistant or do not conceive. LOD can also be considered first-line treatment if laparoscopy is indicated for another reason in infertile women with PCOS.

The mechanism of the effect of LOD is believed to be due to the damage to the ovarian androgen producing tissue leading to a correction in the pituitary–ovarian feedback mechanism, since treatment of only one ovary is believed to be as effective as treating both. A fall in serum concentrations of androgens and LH and an increase in FSH concentrations have been demonstrated after LOD. Several factors have been found to influence the response to LOD. The presence of pre-treatment elevated LH (in excess of 10 IU/L) has been associated with favourable response to LOD while the presence of an increased BMI (≥35 kg/m²), marked hyperandrogenism (testosterone ≥4.5 nmol/L or FAI ≥15) and long duration of infertility (>3 years) have been found to predict resistance to treatment. Response to LOD has been found to be dependent on the amount of energy delivered to the ovary where ovulation rates increase with an increase in the dose of energy. Obviously, this needs to be balanced against the potential harm that can result from the use of excess energy levels leading to ovarian damage. The procedure includes penetration of the ovarian capsule by monopolar electrocautery making four punctures per ovary at a power setting of 30 W (150 J) applied for 4 seconds per puncture (600 J/ovary). The site of application should be away from the ovarian hilum and fallopian tube.

**Outcome:** The ovulation rate after LOD in CC-resistant PCOS women was approximately 80%. Approximately two-thirds of PCOS women treated with LOD respond to treatment, with resumption of regular cycles for a variable length of time. Live
**Practice points**

- PCOS is the most common endocrine disorder affecting 6–8% of women of reproductive age
- PCOS is the most common cause (~75%) of anovulatory infertility
- The pathophysiology of PCOS appears to be multifactorial and polygenic
- The diagnosis is based on Rotterdam ESHRE/ASRM revised 2003 criteria (2 out of 3)
  - Oligo- and/or anovulation
  - Clinical and/or biochemical signs of hyperandrogenism
  - Polycystic ovaries
- Life style management targeting weight loss (in women with BMI *≥* 25 kg/m²) and prevention of weight gain (in women with normal BMI) should be the first line therapy for all women with PCOS
- More patient-tailored approaches should be developed for ovulation induction based on initial screening characteristics of women with PCOS
- The recommended first-line treatment for ovulation induction remains the anti-oestrogen CC. The cumulative conception rate with CC continues to increase until 12 cycles, then plateaus
- Recommended second-line intervention should CC fail to result in pregnancy is either exogenous gonadotrophins or LOD
- The use of gonadotrophins is associated with increased chances for multiple pregnancy and intense monitoring of ovarian response is therefore required
- LOD can lead to monofollicular development and has the advantage of being associated with a lower risk of multiple pregnancies
- Recommended third-line treatment is IVF
- Metformin use in PCOS should be restricted to women with glucose intolerance. The role of metformin in improving reproductive outcomes in women with PCOS appears to be limited as there was no evidence that metformin improves live birth rates whether it is used alone or in combination with other ovulation induction
- Insufficient evidence is currently available to recommend the clinical use of aromatase inhibitors for routine ovulation induction

Births were reported in 34% of women in the LOD groups. In patients remaining anovulatory 8 weeks after LOD or those who subsequently became anovulatory, adjuvant therapy with CC or gonadotropins was required to achieve equivalent pregnancy and live birth rate. A recent Cochrane review found that there was no evidence of a significant difference in rates of clinical pregnancy, live birth or miscarriage in women with clomifene-resistant PCOS undergoing LOD compared with other medical treatments. Compared with gonadotropin therapy, LOD can lead to monofollicular development and has the advantage of being associated with a lower risk of multiple pregnancies. An economic evaluation has shown that the cost of a live birth after LOD is approximately one-third lower than the equivalent cost of gonadotropin treatment. In contrast, ovulation induction with gonadotropins is expensive and requires regular monitoring, with risks of multiple pregnancy and OHSS. However, laparoscopic surgery, especially in overweight women, is associated with intra-operative risks (ie, difficulty with access to abdominal cavity and manipulation of surgical instruments, reduced operative field exposure) and postoperative risks (ie, bleeding, infection, thromboembolism, pulmonary atelectasis/hypoxaemia, and wound complications). LOD can be associated with the occurrence of adhesions in a significant number of patients. Furthermore, there is also a concern that LOD may damage the ovarian reserve as evidenced by lower concentrations of antimullerian hormone and lower antral follicle counts following the procedure. However this evidence is not conclusive and there is little research addressing the long-term complications of LOD. These potential risks suggest minimizing ovarian trauma during the procedure.

**Bariatric Surgery**

Bariatric surgery could be considered as a second-line therapy to improve fertility outcomes in adult women with PCOS who are anovulatory, have a body mass index *≥* 35 kg/m², and who remain infertile despite undertaking an intensive structured lifestyle management programme involving reduced dietary energy intake, exercise, behavioural and/or drug interventions for a minimum of 6 months. A structured weight management programme should...
continue even postoperatively. The patient should be made aware of the risk of pre- and postoperative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a bariatric surgeon, a dietician and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery. Pregnancy should be avoided during periods of rapid weight loss, and patients should be counselled to avoid pregnancy for at least 12–18 months after bariatric surgery.

ASSISTED REPRODUCTION TECHNIQUES: IVF

IVF treatment is recommended either as a third-line treatment or in the presence of other infertility factors. IVF is a reasonable option because the number of multiple pregnancies can be kept to a minimum by transferring small numbers of embryos. The optimal stimulation protocol is still being debated. At present, there are no randomized controlled trials upon which to base any practice recommendations regarding in vitro maturation of immature oocytes before IVF for women with PCOS. The available published data is reassuring that the pregnancy rates in women with and without PCOS are similar. The increase in the cycle cancellation rate in women with PCOS appears to be due to absent or limited ovarian response or due to increased OHSS. The Cochrane review found no evidence that metformin treatment before or during assisted reproductive technique cycles improves live birth or pregnancy rates. However, the risk of OHSS was reduced with metformin.

CONCLUSION

PCOS is the most prevalent endocrine disorder in women of reproductive age and by far the most common cause of anovulatory infertility. Lifestyle change alone is generally considered as the first-line treatment for the management of infertile anovulatory women with PCOS who are overweight or obese. CC should be considered as a first-line pharmacological therapy to improve fertility outcomes. Second-line medical treatments may include ovulation induction with gonadotropins (in CC-resistant or CC-failure women) or laparoscopic ovarian drilling (in CC-resistant women) or possibly with metformin combined with CC (in CC-resistant women). IVF treatment is recommended either as a third-line treatment or in the presence of other infertility factors.


FURTHER READING


About the Authors

Suresh Kini is a Consultant in Obstetrics & Gynaecology in the Assisted Conception Unit at Ninewells Hospital & Medical School, Dundee, UK. Conflicts of interest: none declared.
IN PRACTICE

Introduction
Necrotising fasciitis is progressive fulminating bacterial infection of the subcutaneous tissue that spreads rapidly through the facial planes causing extensive tissue destruction. Prompt recognition and intervention is essential.1 Although rare, it is frequent enough that surgeries will likely have case of necrotising fasciitis but, infrequent enough to achieve complete recovery of the disease. Knowledge of all the available tools is the key to early and accurate diagnosis.2

Management and Follow up
Microscopy, gram staining and the culture of the fluid through the wound revealed Staphylococcus aureus organism sensitive to gentamycin. After 72 hour of injectable antibiotics, patient was taken in the OT and debridement of the wound was done. Wound was washed thoroughly and packed with betadine pack was soaked. Patient was taken to the OT again after 48 hour for re-examination. Debridement and washout was again done. Further, washout was repeated after 48 hours till no further progression of necrosis was seen.

Injection of gentamycin and Injection cloxacillin was started for 14 days followed by oral vitamin C, multivitamins, proteins. Blood transfusion was given to build up of haemoglobin patient remain stable systematically and responded well to the treatment as by the wound, decreasing WBC count and ESR.

After built of haemoglobin, improvement of malnutrition and multidisciplinary approach involving surgeon microbiologist and gynaecologist, patient started recovering dressing of the wound was done till secondary granulation tissue seen at the base which was reference and healthy (Figure 3). Patient was posted for skin grating and wound closure after 1 month of her admission (Figure 4). Patient made an amazing recovery from this life threat-
ening condition and discharged after 45 days of her admission. Final follow up 1 month later, she had full recovery.

Discussion
Necrotising fasciitis is characterised by soft tissue involvement extending down to fascia superficialis. Inflammation induces venous micro thrombi, arterial vasculitis, local haemorrhage and secondary skin infection oedema rapidly progresses due to release of bacterial toxins. When liquefactive necrosis of superficial fascia and fat to less place it produces a watery thin fluid K/as dishwater pus.3

Necrotising fasciitis is also said to be due to flesh eating bacteria. Anaerobic bacteria are present in most necrotising soft tissue infection, usually in combination of aerobic gram–ve organisms. Anaerobic organisms proliferate in an environment of local tissue hypoxia in those patient with trauma, recent surgery or medical compromise. The neutrophils exhibit decreased function under hypoxic wound conditions. This growth further lowers the oxidation/reduction potential, enabling more a anaerobic proliferation, and, thus, accelerating the disease process. Septicemia, multiorgan failure and death is the course of necrotising fasciitis in uncared and neglected patients. Hence early diagnosis is important.4

Risk factors for necrotising fasciitis include diabetes mellitus, NSAID use, HIV positive patient, cancer, alcoholism.4

In this case, the wound was just 2–3 cm in length (incision). Patient had no risk factors. Necrotising fasciitis is extremely rare as a post-tubectomy complication. It is a life threatening infection which can lead to septicaemia and mortality also. Mortality in necrotising fasciitis is said to be 25 to 60%.5

Recognition of signs of local skin and tissue damage in early stage is crucial for early diagnosis and surgical intervention emergency incision and drainage, combined with selective debridement and skin graft could improve the prognosis and can save the life of patient.6

References

About the Authors
Dr VL Deshmukh is an Associate Professor and Unit Head, Dr KA Yelikar is Professor and Head of Department and Dr Krishna Pawar is Resident, Department Obstetrics and Gynaecology, Government Medical College, Aurangabad, Maharashtra.
INTRODUCTION

Granulosa-theca cell tumours, more commonly known as granulosa cell tumours (GCTs), belong to the sex cord–stromal category. Although granulosa cells normally occur only in the ovary, granulosa cell tumours occur in both ovaries and testicles.

GCTs account for approximately 2% of all ovarian tumours and can be divided into adult (95%) and juvenile (5%) types based on histological findings.

Inhibin, the specific tumour marker for GCT, is used for diagnosis and tumour surveillance after treatment to assess for residual or recurrent disease. Although inhibin A and inhibin B levels can both be elevated in patients with granulosa cell tumours, inhibin B level is usually elevated in a higher proportion of these tumours.

GCTs are tumours of low malignant potential. Most of these tumours follow a benign course, with only a small percentage showing aggressive behaviour. Metastatic disease can involve any organ system, although tumour growth is usually confined to the abdomen and pelvis.

CASE REPORT

A 53 year old postmenopausal lady, (P1+0), presented to gynaecology OPD with pain in abdomen, flatulence and loss of appetite for 3 months. Abdominal examination revealed a hard, nontender mass with restricted mobility, measuring 15X12 cm extending from symphysis pubis upto umbilicus. On pelvic examination, a solid mass was palpated in right fornix, extending into the pouch of douglas. Uterus was not felt separately from the mass and left fornix was free.

Routine haemogram, urinalysis, liver and renal function tests were within normal levels. CA125 value was raised to 265.6 IU/ml. Sonography indicated a highly vascular SOL of heterogenous nature measuring 170X151 mm arising from right pelvic wall, extending into the abdominal cavity. A subserous myoma of 35X31 mm size was seen in uterus; small amount of ascitic fluid was found in peritoneal cavity. FNAC report of the mass revealed clusters of discreet atypical cells in papillary and glandular pattern, with nucleomegaly, clumped chromatin and hyperchromasia, consistent with the picture of adenocarcinoma.

Intraoperatively, moderate amount of clear fluid was found and sent for cytology. A mass was seen, arising from the right adnexa, occupying the whole abdominal cavity, having a partly cystic partly solid consistency, with a haemorrhagic, irregular surface, severely adherent to the small intestine and caecum (Figure 1). The right fallopian tube was stretched across the
surface of the tumour. After adhesiolysis, the mass was removed intact; the uterus, left ovary and left tube appeared normal, exploration of abdominal viscera revealed no metastatic deposits except for a 3X2.5 cm size nodule on the pylorus of stomach. Total abdominal hysterectomy, left salpingo-oophorectomy and excision of the tumour mass was done. Pelvic and para-aortic lymph nodes were palpated but were not found to be enlarged. Patient had an uneventful postoperative period, stitches were removed on 7th postoperative day. The tumour was clinically staged at stage IIIc.

Histopathology report showed adult granulose cell tumour of microfollicular, macrofollicular and insular pattern in the right ovary; and adult granulosa cell tumour of diffuse pattern in the left ovary; uterus showed subserous fibroid. Inhibin level done postoperatively, showed normal values (Inhibin A 1.3 Pg/ml), CA125 levels fell to 20.8 U/ml. Immunohistochemistry of the ovarian mass was negative for inhibin.

Post-operatively, patient administered 6 cycles of chemotherapy with bleomycin, etoposide and cisplatin. Vigilance was kept on toxicity features of chemotherapy like pulmonary toxicity, haematologic toxicity and GI toxicity. While on chemotherapy, patient showed neutropenia, which was corrected by Granulocyte Stimulating Factor-Filgrastin. There was no pulmonary toxicity; moderate amount of nausea and epigastric tenderness was found, corrected by antacids and antiemetics.

Follow-up
Patient followed up by chest X-ray, inhibin levels and abdomino-pelvic CT scan to look for recurrences. The follow up will be at 2 monthly and 6 monthly intervals, for first 2 years and next 3 years respectively; thereafter, it will be lifelong, since GCTs are known to recur many years later.

DISCUSSION
GCTs are part of sex cord stromal tumours arising from the granulose cells of the ovaries; very rarely from granulose cells of the testes. Sex cord stromal tumours account for 8% of all ovarian neoplasms, of which GCTs make up only 2%. GCTs can be classified into adult (95%) and juvenile (5%) types based on histological findings. The peak age incidence is 50–55 years. GCTs can occur in the juvenile and adult male testes, albeit very rarely.

Almost 70% of GCTs are functioning tumours, producing oestradiol. In menopausal patients, the usual manifestation is postmenopausal bleeding; in women of reproductive age, menometrorrhagia is the presenting symptom. Children with GCTs manifest features of precocious pseudopuberty. Pelvic mass is the most consistent finding on pelvic and rectal examination in patients of all ages. This was so in this particular our patient whose presenting feature was a huge abdominal swelling due to abdomino-pelvic mass and mild ascitis. Rarely, there can be acute abdominal pain due to adnexal torsion, rupture of a partially cystic GCT, or haemorrhage within tumour or into the peritoneum.

The specific tumour marker for GCTs is inhibin. Both subunits of inhibin i.e., inhibin A and inhibin B are raised in GCTs; inhibin B is elevated in a higher proportion of GCTs. Inhibin levels return to normal after removal of the tumour and becomes elevated if there is recurrence. Mullerian-inhibiting substance (MIS) is another tumour marker of GCT. Normally, it is undetectable in postmenopausal women but its elevated value is highly specific for ovarian granulosa cell tumour. An elevated CA 125 level is not specific for GCTs since it is raised in all malignant ovarian tumours. Both inhibin and Ca125 levels (inhibin–27.8 Pg/ml and CA125–265.6 IU/ml) were raised in this patients preoperatively; follow-
After removal of the tumor, inhibin level fell to 1.3 Pg/ml and CA125 value became 20.8 IU/ml. Inhibin levels are useful to detect recurrences, as their values become raised before detection of recurrent pelvic masses.

Grossly, GCTs can be solid, cystic or of mixed variety. Cut section appears yellowish if they are steroid producing; and greyish if they are non-steroidogenic. In this patient, the tumor was solid, with a few small cysts, cut section appeared greyish- white.

Microscopically, GCTs are composed of granulosa cells, theca cells, and fibroblasts in varying amounts and combinations. Young and Scully proposed a system in which a tumor must have at least 25% of theca cells for a tumor to be designated as a true granulosa-theca cell tumor. Adult granulosa cell tumor (making up 95% of GCTs) has two categories—well-differentiated and less well-differentiated. The well-differentiated group has 4 patterns—microfollicular, macrofollicular, trabecular and insular. Microfollicular is the commonest pattern, with characteristic call-exner bodies (Figure 2). These are rings of granulose cells surrounding eosinophilic fluid and basement membrane material. The less well-differentiated group includes diffuse and watered-silk or gyrfilar patterns. In this case, the histopathology showed mixture of microfollicular, macrofollicular and insular pattern in the granulosa cell tumor of right ovary, with nuclear grooving (Coffee-Bean nucleus) while the left ovary showed diffuse granulose cell tumor. Juvenile granulose cell tumor (accounting for 5% of GCTs) occur in children and adults below 30 years of age. They grossly resemble adult type GCTs but are different microscopically with no nuclear grooves, hyperchromatic nuclei, more mitotic figures. Cytoplasm is more abundant and dense in JGCTs.

GCTs are staged clinically during laparotomy, in a similar fashion as ovarian carcinoma. These tumors are of low malignant potential and approximately, initially 90% of GCTs are at stage I at the time of diagnosis. However, in this patient, the clinical staging during laparotomy was put at stage IIIc since multiple nodules were found in the omentum, single nodule was found on the stomach and malignant cells were present in peritoneal fluid; this evidently proves that presented patients do not seek medical consultation at early stages of disease.

Standard care for initial management is surgery which allows staging, tissue diagnosis and excision of tumour mass for patients with family completed, bilateral salpingo-oophorectomy with total abdominal hysterectomy is performed. In younger patients, who desire future fertility, unilateral salpingo-oophorectomy is sufficient if the tumour is at stage I.

Adjuvant chemotherapy is reserved for patients with advanced or recurrent disease. Current multidrug regime includes bleomycin, etoposide and cisplatin (BEP)-bleomycin at 20U/m² IV q3wk for 4 courses, etoposide at 75mg/m² IV on D1-5 q3wk for 4 courses, and cisplatin at 20mg/m² IV on days 1–5 q3wk for 4 courses. This patient was staged at IIIc by laparotomy, thus BEP regime chemotherapy was given (6 courses).

Prognosis for granulosa-theca cell tumors generally is very favourable. GCTs are considered to be tumors of low malignant potential. The 5 year survival rate for stage I tumors in adults is 90–96%. GCTs of more advanced stages are associated with 5 and 10 year survival rates of 33–44%. The overall 5 year survival rates for patients with AGCTs or JGCTs are 90% and 95–97%, respectively. The 10 year survival rate for AGCTs is approximately 76%. Tumour stage at the time of initial surgery is the most important prognostic variable. Other features
associated with a poorer prognosis include high mitotic rates, moderate-to-severe atypia, preoperative spontaneous rupture of the capsule, and tumours larger than 15 cm. The presence of bizarre nuclei and tumour rupture intraoperatively does not appear to affect prognosis.

Recurrences in patients with AGCTs tend to be later than in patients with JGCTs. Average recurrence for the adult type is approximately 5 years after treatment, with more than half of these occurring more than 5 years after primary treatment.6 These tumours tend to follow an indolent course, with a mean survival of 5 years after the recurrence is diagnosed. The 10 year overall survival after an AGCT recurrence is in the 50–60% range. JGCTs recur much sooner, with more than 90% of recurrences occurring in the first 2 years. Recurrence in these patients is rapidly fatal.

Research is going on to include taxanes in treating GCTs, particularly for recurrence in patients previously treated with BEP.7 For non-responders to chemotherapy, hormonal therapy using medroxyprogesterone acetate, GnRH agonists is under trial in a small number of patients.

Several recent reports have documented the use of the aromatase inhibitor anastrozole, which inhibit the conversion of androstenedione to estrone, in the management of patients who previously received surgery and chemotherapy. Several patients with recurrent disease demonstrated normalisation of their serum inhibin, decrease in tumour size, and an increase in disease-free survival. Serum antimullerian hormone was undetectable in normal postmenopausal women and was < 5 micrograms/L in premenopausal women.

About the Author
Dr Saswati Mukhopadhyay is an Assistant Professor, Department of Obstetrics and Gynaecology, ESI PGIMSR, Joka, Kolkata,

REFERENCES
Hormonal Contraception and Cancers

Wong Yuen Kwan Alice, MBBS, FRCOG, FHKAM(O&G), FHKCOG, Cert HKCOG(Reprod Med)

INTRODUCTION

The use of hormones has provided great convenience to a woman’s life, be it for therapeutic use or as a lifestyle drug, ie, contraceptives. However, the duration of hormone use is frequently long, in terms of years. Concerns have been raised about the possibility of a relationship between cancer development and long-term hormonal influence. This article reviews the evidence regarding the relationship between hormonal contraceptive use and the development of cancer, with the discussion focusing mainly on carcinoma of the breast and female genital tract.

HISTORICAL EVIDENCE

The first report dated back to 1972 when combined oral contraceptive pills (COC) containing mestranol and norethynodrel appeared to cause a case of metastatic breast cancer in a female rhesus monkey. Soon after, there were further similar reports of development of breast cancer in beagles and rodents after exposure to hormones contained in today’s COC.

In June 2005, the International Agency for Research on Cancer (IARC) Working Group of the World Health Organization (WHO) met in Lyon, France, and classified combined oral contraceptives and combined oestrogen-progestogen hormone therapy as ‘carcinogenic’ to humans.

THEORY OF ‘CARCINOGENESIS’

Carcinogenesis involves two steps, namely, initiation and promotion. Most of the studies on the relationship between hormones and cancer development involved the latter step. In 1989, Anderson et al reported that nulliparous women who took COC had a significantly higher rate of breast cell division. It was also found that COC caused a rise in epithelial cell proliferation of the glandular breast, leading to an increase in accumulation of random genetic errors.

However, whether these proliferating effects on normal epithelia, as a result of replication error, may cause malignant transformation has not yet been proven, although DNA repair is hampered by activated proliferation. With the end point being ‘chromosomal mutation’, numerous chromosomal aberrations have been
observed with natural and synthetic oestrogens and progestogens. There was no proof of sufficient strength to show that these proliferative effects could induce tumours. Hormonal tumour promotion also cannot be discriminated from a causal relation with breast tumour induction.

Moreover, toxicity studies used animal models. Species-specific effects might not allow for extrapolation of the effects to humans. Supraphysiological doses had been used in animal studies and this might not reflect actual clinical use. Possibility of genetic predisposition and other environmental factors were not taken into account.

CARCINOMA OF THE BREAST

In 1981, Pike et al reported that women who took COC for 4 years or more prior to their first full-term pregnancy experienced a 125% increased risk of developing carcinoma of the breast and a 250% increase in risk with 8 years or more of COC use.9 Similarly, in 1989, Chilvers et al reported that women under the age of 36 who used COC for at least 4 years before their first full-term pregnancy had at least 44% increased risk of breast cancer.10

However, the Cancer and Steroid Hormone Study (CASH), which was one of the largest case-control studies in the 1980s, found no association between breast cancer and COC use for women up to the age of 54. Risk was found only among a subgroup of women who underwent menarche before age 13 and used COC for more than 10 years before their first birth.11

In the 1990s, the Collaborative Group on Hormonal Factors in Breast Cancer in Oxford, UK, analysed individual data of 53,297 women with breast cancer and 100,239 women without breast cancer from 54 studies conducted in 25 countries. The results provided two strong conclusions. First, while women are taking COC and in a period of 10 years after stopping, there is a small increase in the relative risk (RR) of having breast cancer: RR of 1.24 (95% CI, 1.15–1.33) for current users; RR of 1.16 (95% CI, 1.08–1.23) 1–4 years after stopping; and RR of 1.07 (95% CI, 1.02–1.13) 5–9 years after stopping. Second, there is no significant excess risk of having breast cancer diagnosed 10 or more years after stopping use (RR, 1.01 [95% CI, 0.96–1.05]). The cancers diagnosed in women who had used COC were less advanced clinically than those diagnosed in never-users; the RR for tumours that had spread beyond the breast compared with localized tumours was 0.88 (95% CI, 0.81–0.95). There was no pronounced variation in the results for recency of use between women with different background risks of breast cancer, including women from different countries and ethnic groups, women with different reproductive histories, and those with or without a family history of breast cancer. Other features of hormonal use, such as duration of use, age at first use, and the dose and type of hormone
within the contraceptives, had little additional effect on breast cancer risk, once recency of use had been taken into account.12

Other important studies worth mentioning include the Nurses’ Health Study (1997),13 Women’s Lifestyle and Health Cohort Study (2002),14 Oxford-Family Planning Association study (1981),15 Mayo Clinic Meta-analysis (2006),16 and Royal College of General Practitioners study (2007).17 There were some inconsistencies among their findings, and the increase in RR shown by some of these studies was modest. Possible confounders that may be related to the use of high-dose COC include the clinical practice during the time of these studies and the possibility of the nature of recall bias. The study by the Collaborative Group on Hormonal Factors in Breast Cancer12 also shared a similar problem. Another weakness of this study was that it analysed pooled data from studies which examined women with breast cancer from as far back as the early 1970s. Taking data from studies which interviewed women before the 1980s might underestimate the risk of breast cancer development because the latent period for cancer development was too short and few women had used COC for significant periods of time prior to their first full-term pregnancy in the late 1960s and early 1970s as compared with women of the late 1970s and 1980s.

In 2005, the IARC classified COC and combined oestrogen-progestogen hormone therapy as carcinogenic to humans. The Working Group mentioned a ‘slightly increased risk of breast cancer in current and recent users of hormonal contraceptives’. This risk disappears 10 years after cessation of COC use and will be similar to that in never-users.18 The Working Group also acknowledged that their statement does not meet the overall net public health outcome, be this of a beneficial or adverse effect other than cancer, and there is no reason to change the current clinical practice, particularly when the risks of unwanted pregnancy are taken into consideration.18

For BRCA mutation carriers, who already have a 50–80% increase in risk of breast cancer, the use of COC will be of concern. Among BRCA1 mutation carriers, those who first used COC before 1975, who used them before age 30, or who used for 5 years or more might have an increased risk of breast cancer in BRCA2 carriers; however, data to support this are limited.19

On the use of depot medroxyprogesterone acetate (MPA), pooled analysis of two major case-control studies (one in New Zealand20 and the other under the auspices of the WHO21) found no increase in risk for breast cancer. A currently unexplained pattern of increased risk in recent users mimics that seen with COC.22

In a study involving completed ques-
tionnaires from 17,360 levonorgestrel-releasing intrauterine system (LNG-IUS) users, there was no apparent association between the length of time elapsed from the LNG-IUS insertion up to 10 years and yearly incidence of breast cancer in the Finnish female population (data from the Finnish Cancer Registry). A causal relationship between LNG-IUS use and occurrence of breast cancer was not supported.23

CARCINOMA OF THE UTERINE CORPUS

A meta-analysis of 10 case-control studies (published up to 1996; 1,728 cases and 6,243 controls) and another cohort study (440,000 woman-years of observation) both showed statistically reduced RR for carcinoma of endometrium in COC users. This RR was negatively associated with the duration of COC use; the risk reduction was 56% with 4 years’ use, 67% with 8 years’ use, and 72% with 12 years’ use.24

The Oxford-Family Planning Association (Oxford-FPA) contraceptive study, which took place in 1968–2004, involved 540,000 woman-years of observation. There were 50 women with carcinoma of the uterine corpus in the control group and 27 women in the COC user group. The RR for ever-users versus never-users was 0.3 (95% CI, 0.2–0.6). The risk was further found to be negatively related to the duration of COC use, ie, a RR of 0.6 (95% CI, 0.3–1.1) for up to 48 months’ use, 0.4 (95% CI, 0.2–0.5) for 49–96 months’ use, and 0.1 (95% CI, 0.0–0.4) for > 97 months’ use.25 The Royal College of General Practitioners oral contraceptive study also showed similar findings.17

Another meta-analysis of 11 epidemiological studies found that the more recent the use of COC, the lower the risk for carcinoma of the uterine corpus. Such protective effect from the previous use of COC would attenuate with time after discontinuation. The RR was 0.33, 0.41 and 0.51 for 5, 10, and 20 years of ceasing, respectively. Even after more than 20 years of cessation of use, the protective effect is still significant, ie, at 50% less than non-users.24

Prolonged and unremitting mitotic activity of the endometrium due to unopposed oestrogenic stimulation has been proposed to be the cause of development of the majority of cases of endometrial adenocarcinoma. COC suppress endometrial mitotic activity, leading to apoptosis, thus reducing the risk of endometrial cancer.

The use of depot MPA is associated with an 80% risk reduction of endometrial adenocarcinoma, a level of protection even greater than that observed with COC. The effect was also found to be long-term.22

CARCINOMA OF THE OVARY

The Collaborative Group on Epidemiological Studies of Ovarian Cancer published a collaborative reanalysis of data from 45 epidemiological cohort and case-control studies (published up to 1996; 1,728 cases and 6,243 controls) and another cohort study (440,000 woman-years of observation) both showed statistically reduced RR for carcinoma of endometrium in COC users. This RR was negatively associated with the duration of COC use; the risk reduction was 56% with 4 years’ use, 67% with 8 years’ use, and 72% with 12 years’ use.24

The Oxford-Family Planning Association (Oxford-FPA) contraceptive study, which took place in 1968–2004, involved 540,000 woman-years of observation. There were 50 women with carcinoma of the uterine corpus in the control group and 27 women in the COC user group. The RR for ever-users versus never-users was 0.3 (95% CI, 0.2–0.6). The risk was further found to be negatively related to the duration of COC use, ie, a RR of 0.6 (95% CI, 0.3–1.1) for up to 48 months’ use, 0.4 (95% CI, 0.2–0.5) for 49–96 months’ use, and 0.1 (95% CI, 0.0–0.4) for > 97 months’ use.25 The Royal College of General Practitioners oral contraceptive study also showed similar findings.17

Another meta-analysis of 11 epidemiological studies found that the more recent the use of COC, the lower the risk for carcinoma of the uterine corpus. Such protective effect from the previous use of COC would attenuate with time after discontinuation. The RR was 0.33, 0.41 and 0.51 for 5, 10, and 20 years of ceasing, respectively. Even after more than 20 years of cessation of use, the protective effect is still significant, ie, at 50% less than non-users.24

Prolonged and unremitting mitotic activity of the endometrium due to unopposed oestrogenic stimulation has been proposed to be the cause of development of the majority of cases of endometrial adenocarcinoma. COC suppress endometrial mitotic activity, leading to apoptosis, thus reducing the risk of endometrial cancer.

The use of depot MPA is associated with an 80% risk reduction of endometrial adenocarcinoma, a level of protection even greater than that observed with COC. The effect was also found to be long-term.22
studies, which included 23,257 women with ovarian cancer and 87,303 controls from 21 countries. It was found that 7,308 (31%) of the women with ovarian cancer and 32,717 (37%) of the controls had used COC, and the average duration of use was 4.4 and 5.0 years, respectively. The overall RR for ever-users versus never-users was 0.73 (95% CI, 0.70–0.76). The longer the duration of use, the lower the risk for ovarian cancer development. The overall RR decreased by 20% for each 5 years of use. For women who had used COC for 15 years, the risk was almost halved. The protective effect started after at least 1 year of COC use. The RR for < 1 year, 1–4 years, 5–9 years, 10–14 years, and ≥ 15 years of use were 1.0, 0.78, 0.64, 0.56, and 0.42, respectively.26

This reanalysis also found that the more recent the use of COC, the lower the RR of ovarian cancer. The proportional decline in RR per 5 years of cessation of use was 29% for < 10 years of cessation of use, 19% for 10–19 years, and 15% for 20–29 years. The longer the duration of use, the higher the protective effect irrespective of the time elapsed from ceasing. The start age of COC use and age of last use seemed to have no effect on the protective effect of COC use. Low-dose pill use was found to have an identical RR compared with high-dose pill use.26

The Oxford-FPA contraceptive study, which included 17,032 women aged 25–39 recruited at 17 family planning clinics in England and Scotland between 1968–1974 with a long follow-up till 2004, analyzed a total of 540,000 woman-years of observation and 58 ovarian cancer cases in the control group and 48 cases in the COC group.25 The overall ovarian cancer RR for ever-users versus never-users was 0.5 (95% CI, 0.3–0.7). The risk of ovarian cancer was significantly lower in women on oral contraceptives for more than 4 years.

The Royal College of General Practitioners oral contraceptive study, which started in 1968, collected data from 23,377 COC users and 23,796 never-users over a period of 14 months, with 339,000 woman-years of observation for never-users and 744,000 woman-years for ever-users.17 It was found that the RR was 0.51 for ever-users as compared with never-users. Similarly, a statistically significant gradual decrease in risk with increasing duration of COC use was observed. The protective effect was found to last for at least 15 years after stopping COC.

In the early 1970s, it was proposed that defective cellular repair after ovulation represents the major risk factor for ovarian cancer development.27 More recent theories assume that ovarian cancer development is attributed to either activated proto-oncogenes or inactivated tumour-suppressor genes,27,28 which seem to point to abnormalities of genomic DNA quality and quantity, with the resulting defects in post-ovulatory ovarian cellular repair being the causative factor for ovarian cancer. Thus, the protective effect of COC against ovarian cancer may be attributed to the resulting anovulation during their use, which prevents genetic predisposing cellular repair defects to be expressed.

Although depot MPA also suppresses ovulation and would theoretically lower the risk of ovarian cancer, a hospital-based WHO case-control study failed to uncover such a protective effect.22

The protective effect of COC against ovarian cancer may be attributed to the resulting anovulation during their use

CARCINOMA OF THE CERVIX

There is evidence suggesting that long-term use of COC for 5 years or more may be associated with an increased risk of cervical cancer.29 A meta-analysis of 28 studies, involving 12,531 women with cervical cancer, suggested that the risk of cervical cancer may decrease after stopping the use of COC.30 Another IARC analysis which included eight studies found a fourfold increase in risk among women with over 5 years of COC use. The risk was also increased in women who started using COC before the age of 20 and in those who had used COC within the previous 5 years.31

The mechanism for increased risk of cervical cancer in COC users is uncertain. Human papillomavirus (HPV) has been recognized to be the major cause of carcinoma of the cervix. Steroid contraception has been postulated to be able to bind to specific DNA sequences within transcriptional regulatory regions on the HPV DNA, either to increase or suppress the tran-
scription of various genes. It was suggested that the regulatory region of HPV type 16 viral genome indicates transcriptional control of the HPV genome and might contain enhancer elements that are activated by steroid hormones.32

In COC users, the cervical mucus becomes scanty, thick, and highly viscous. It has been hypothesized that such mucus may modulate and prolong the effect of carcinogenic agents and pathogens (including HPV), which might have been carried by coitus, on the cervical squamocolumnar junction, causing them to become difficult to be removed.33

However, the majority of studies did not analyse the HPV status of COC users and controls. Moreover, early use of COC might be related to early onset of sexual activity, which is itself a significant risk factor for HPV infection and development of cervical cancer. The lower use of the barrier method of contraception in COC users might be another accountable factor for the increase in risk of HPV infection. However, with the development of HPV vaccines, the observed association of increased risk of cervical cancer in COC users might be changed, and fear of cervical cancer should not be a reason to avoid COC use.

A large, population-based, case-control study in Costa Rica, a hospital-based WHO case-control study in Thailand, Mexico and Kenya, and a study in New Zealand found that the risk of cervical cancer did not appear to be affected by depot MPA use.22

**CONCLUSION**

The majority of studies on the relationship between hormonal contraceptive use and development of cancer have focused on COC and breast cancer, albeit with conflicting results. From the cumulative experience and meta-analyses of large epidemiological studies with a long follow-up duration, the present evidence suggests an increase in risk of breast cancer development mainly in current COC users, with
the risk decreased on stopping therapy. By 10 years of cessation of use, the risk is similar to that in never-users. Similarly, the risk of carcinoma of the cervix is found to be increased in current COC users. However, COC use confers a strong and prolonged protective effect against carcinoma of the endometrium and ovary, which will last even after over 20 years of cessation of therapy (Figure 1).

Depot MPA was observed to cause a plausible increased risk of breast cancer in current or recent users, similar to that observed in COC users. It does not seem to affect the overall breast cancer risk. However, there is strong evidence of prolonged decreased risk for carcinoma of the uterine corpus. No strong association has been noted for carcinoma of the cervix and ovary.

When counselling women regarding hormonal contraception, the issue of potential carcinogenic effect from its use is to be included. However, its prescription should be based on an individual risk-benefit assessment, provided contraindications are taken into account and regular visits to doctors or health-care professionals are made.

**About the Author**

Dr Wong is Consultant in the Department of Obstetrics and Gynaecology, Kwong Wah Hospital, Hong Kong.

**REFERENCES**