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Physical activity interventions in children

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

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

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

High-sugar drinks and body weight in children and adolescents

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

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

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

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


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

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

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

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

Urinary urge incontinence in women: Anticholinergics vs onabotulinum toxin A

Urinary urge incontinence may affect up to 20% of older women. The most commonly used medication is with anticholinergic drugs. In a multicentre US trial, oral anticholinergic treatment has been compared with onabotulinum toxin A injected into the detrusor muscle.

A total of 249 women with idiopathic urge incontinence (five or more episodes per 3-day period) entered the trial, and complete data were analysed for 241. Randomization was to daily oral solifenacin plus a single injection of intradetrusor saline (placebo) or a single intradetrusor injection of onabotulinum toxin A plus daily oral placebo. Follow-up was for 6 months. The mean number of episodes of urge incontinence at baseline was 5.2 per day in the anticholinergic group and 4.8 per day in the onabotulinum toxin A group; at 6 months, the mean reduction in daily episodes was 3.4 and 3.3, respectively, a non-significant difference. The rate of complete resolution of urge incontinence was significantly greater with onabotulinum toxin A (27% vs 13%), but onabotulinum toxin A was associated with a significantly greater risk of urinary infection (33% vs 13%). Self-catheterization was more frequent in the onabotulinum toxin A group and dry mouth in the anticholinergic group. Quality of life was similar in the two groups.

Intradetrusor injection of onabotulinum toxin A, compared with an oral anticholinergic drug, was more likely to produce complete resolution of urge incontinence but was associated with a greater risk of urinary infection and transient urinary retention. Dry mouth was more common with the anticholinergic drug. These researchers do not recommend one treatment over the other but suggest that the pros and cons be discussed with each patient.


Cervical intraepithelial neoplasia: Post-treatment risk of cervical cancer and cost-effectiveness of HPV surveillance

Dutch registry data have been used to assess the risk of cervical cancer after treatment for cervical intraepithelial neoplasia (CIN). Women in the Netherlands with CIN have to have three consecutive normal smear tests before returning to routine screening every 5 years.

Data were analysed for 38,956 cases of CIN with completed follow-up and for 7,096,816 women with normal primary smear test results. The rate of diagnosis of cervical cancer was 35.1 per 100,000 woman-years after completed treatment and follow-up for CIN and 6.4 per 100,000 woman-years after a normal primary smear test result, giving a hazard ratio of 4.2 with the risk not dependent on grade of CIN.

A Markov modelling study based on data from England (the NHS Sentinel Sites Study) showed that the sentinel sites protocol (post-treatment follow-up with human papillomavirus [HPV] testing and cytology at 6 months) was more effective and less costly than annual cytological follow-up over 10 years.

After completed follow-up following treatment for CIN in the Netherlands, the risk of cervical cancer was four times that of women without CIN. In an English study, HPV testing for cure after treatment for CIN was cost-effective. It is recommended that after treatment for CIN, women should have combined HPV testing and cytology at 6 months and 24 months and then return to the routine national screening programme.

INTRODUCTION: SLEEP IS IMPORTANT IN CHILDREN

Interest in paediatric sleep disorders is increasing worldwide. There is evidence that there are significant short- to long-term consequences on the development, growth, and health in children with poor/insufficient sleep or sleep-disordered breathing. More caregivers are recognizing the importance of good sleep and are seeking medical advice for sleep problems in their children.

Table 1 summarizes the wide range of physical and psychosocial health deficits that can be found in children with poor/insufficient sleep or sleep-disordered breathing.

Normal Sleep

Sleep and wakefulness is regulated by the (1) circadian rhythm, which is entrained by the light–dark cycle, and (2) homeostatic process, which builds up the need for sleep during the waking hours.

Normal sleep comprises two states: non-rapid eye movement (NREM) sleep, also known as ‘quiet sleep’ (with stages N1, N2 and N3), and rapid eye movement (REM) sleep, otherwise known as ‘active sleep’. These states alternate cyclically across a sleep episode. NREM sleep is characterized by synchronized electroencephalography activity, muscle relaxation, and decreased heart rate, blood pressure and tidal volume. REM sleep resembles wakefulness with desynchronized electroencephalography activity, phasic events such as episodic bursts of rapid eye movement, but muscle atonia (a highly activated brain in a paralysed body).

Sleep in children differs from sleep in adults in its architecture, sleep pattern, and behaviour. This is related to the maturation of the central nervous system and developmental changes that take place when one ages through the years.
The cycling of NREM and REM sleep is established by 3 to 4 months of age. Sleep usually begins in NREM sleep and progresses through deeper NREM sleep stages (N2 and N3) before the first episode of REM sleep occurring about 50 minutes later in children and 80 to 100 minutes later in adults. Thereafter, NREM and REM sleep cycles with a period of between 50 to 70 minutes in infants to 90 to 120 minutes in adults. Stage N3—also called slow wave sleep (SWS)—concentrates in the early NREM cycles, and REM sleep episodes lengthen across the night. An example of a sleep histogram is illustrated in Figure 1.

Most children have sleep requirements that fall within a predictable range of hours based on their age, but each child is a unique individual with distinct sleep needs. There is no fixed number required by all children in a certain age group, but a guide to the approximate number of hours needed is as follows:

- **Newborns** usually sleep in stretches of about 3 to 5 hours (shorter in breastfed babies) and are awake for 1 to 3 hours in between. This adds up to 16 to 20 hours in a 24-hour period. Day–night differentiation only develops between 6 weeks to 3 months old, with most babies being able to sleep through the night by 9 months old.
- **Infants** typically take two naps in the day (mid morning and afternoon) and do away with the morning nap by 18 to 24 months old. Average sleep duration over a 24-hour period at this stage ranges between 13 and 15 hours in infants below a year old to 12 hours in a 2-year-old toddler.
- **At 3 to 5 years old**, most children do away with naps and sleep an average duration of 11–12 hours.
- **School-going children** require about 10 to 11 hours of sleep.
- **Adolescents** tend to have irregular sleep schedules. Most sleep less than 6 to 7 hours a night, although the ideal requirement should be 9 hours for their age. At the onset of puberty, they develop a 2-hour phase delay in their circadian rhythm, leading to a natural tendency to sleep late and, therefore, rise late.

**Good Sleep Hygiene Advice for Children**

- Keep consistent sleep and wake times daily, including over the weekends.
- Do not use the bed for any activity other than sleeping (eg, watching television, playing, eating). Avoid placing the computer, television, mobile phones, and other personal electronic devices in the bedroom.
- Do not use the bedroom for time-out or punishment.
- The child’s bedroom should be conducive for sleeping at bedtime—cool, quiet, and comfortable. A dim nightlight is acceptable for children afraid of the dark.
- Establish a predictable, relaxing pre-bedtime routine such as brushing teeth, changing into pyjamas, and reading a story. Avoid stimulating

### Table 1. Impact of poor/insufficient sleep and sleep-disordered breathing in children

<table>
<thead>
<tr>
<th>Daytime somnolence</th>
<th>Reduced immune function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired memory and concentration</td>
<td>Increased risk of obesity/metabolic conditions</td>
</tr>
<tr>
<td>Impaired motor skills</td>
<td>Cardiopulmonary complications</td>
</tr>
<tr>
<td>Poor academic performance</td>
<td>Poor growth</td>
</tr>
<tr>
<td>Mood disturbances (mood lability, poor emotional control, irritability)</td>
<td></td>
</tr>
<tr>
<td>Disruptive behaviour (aggressiveness, impulsivity, hyperactivity)</td>
<td></td>
</tr>
<tr>
<td>Negative parent–child relationships</td>
<td></td>
</tr>
</tbody>
</table>
activities before sleep, such as watching exciting television programmes and playing games on personal electronic devices.

- Go to bed only when tired or sleepy; avoid spending too much time awake in bed. If the child is awake and unable to fall asleep after 20 minutes, consider letting him/her get out of bed to do low stimulation activity (eg, quiet reading) then return to bed later. This prevents the bed from being associated with sleeplessness.

- ‘Transitional’ objects, like a toy, blanket or doll, are useful for young children who need to feel safe and secure when their caregiver is not physically present, and may aid in independent settling and self-soothing.

- Checks on the infant or toddler at night should be ‘brief’ and non-stimulating.

- Avoid caffeine (coffee, tea, chocolate, energy drinks, and sodas) close to bedtime, as caffeine can lead to difficulty falling asleep, shallow sleep, or frequent nocturnal awakenings.

### Sleep Disorders

Sleep disturbances are common in children of all ages and have been described in up to 45% in the population of healthy preschool and school-going children. These figures may even be an underestimate, as many parents do not voice their concerns about their child’s sleeping habits unless asked.

It is therefore vital for all physicians managing the paediatric population to be vigilant in screening for potential sleep problems in their patients. In particular, the physician should actively seek to identify sleep disorders in children presenting with behavioural/learning difficulties and in high-risk populations (eg, trisomy 21, attention deficit hyperactivity disorder).

A screening tool that has been used widely to

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**Figure 1. Sleep histogram.**
identify major sleep disorders in the paediatric population is the BEARS questionnaire. This comprises a set of parent- and child-directed questions which is age-appropriate (toddler/preschool, school-aged, and adolescence). The questions cover five major sleep domains: B = bedtime problems, E = excessive daytime sleepiness, A = awakenings during the night, R = regularity and duration of sleep, and S = snoring.1

In this article, we will discuss paediatric insomnias, sleep-related breathing disorders, circadian rhythm sleep disorders, and parasomnias.

INSOMNIAS IN CHILDHOOD

The term ‘insomnia’ is a descriptive one and involves difficulty initiating or maintaining sleep. A child with insomnia can affect the sleep of not just the main caregiver but also the entire family.

There are many causes of insomnia in children. They include behavioural insomnia of childhood and delayed sleep phase disorder, both of which are further discussed below. Medical conditions with nocturnal symptoms that disrupt sleep (eg, obstructive sleep apnoea [OSA], eczema, allergic rhinitis, asthma), psychological conditions (eg, stress, anxiety), or medications/stimulants (eg, β₂ agonists, caffeine) can also cause insomnia.

Behavioural insomnia of childhood
In behavioural insomnia of childhood, there are unique features characterized by the interplay of child temperament and maturity, parental style, and child–parent interactions.

Sleep-onset Association Disorder
Sleep-onset association disorder is a condition characterized by reliance on specific stimulation, objects or conditions for initiating sleep or returning to sleep following an awakening.
Epidemiology. Onset is usually at 4 to 6 months old, and it has been estimated to affect 25–50% of infants at 6–12 months old and 15–20% of toddlers.1

Presentation. It is normal for infants to wake intermittently in the night, but when they are unable to return to sleep without external factors like parental presence or rocking, recurrent or prolonged night awakenings can result. Persistent night awakenings can continue up to mid-childhood, but the negative sleep associations developed during infancy tend to taper off with age (eg, pacifier usage till 3 to 4 years old, parental help to fall asleep till 6–7 years old).

Risk factors. Factors that may increase the likelihood of night awakenings include breastfeeding, co-sleeping, colic, intercurrent illness, parental anxiety, and when the child has achieved new motor/social milestones (eg, pulling to stand, separation anxiety).

Management. The first step of management is to examine the details of the family set-up and bedtime habits, and to reinforce a strict bedtime and good sleep hygiene. The use of a ‘transitional’ object like a blanket or stuffed toy can help to act as a positive sleep association and aid in ‘self-soothing’.

Self-soothing is a skill that usually develops beyond the age of 3 to 6 months old, but parents can help to encourage their babies to fall asleep independently early. They can put their babies down to bed drowsy but still awake so that he can learn to fall asleep on his own. Continuous patting of a child till he/she falls asleep or allowing him/her to fall asleep with a bottle in his mouth is also not advisable.

Methods including ‘extinction’, ‘graduated extinction’, and ‘fading’ have been used widely. Extinction involves the parent putting the child to bed at a fixed time and ignoring the child’s cries completely till the next morning. Graduated extinction involves the parent responding to the child briefly, but after progressively longer periods of time to allow the child to fall back to sleep independently. This method is usually chosen in preference to the first because it is less emotionally taxing for both the child and parent. In fading, the parent physically distances himself/herself from the child each night, such that the eventual aim is to have the parent outside the child’s room.

Parents–child interaction is a very important influencing factor in a child’s sleeping behaviour, and there is no one best method for every family. Any change would require consistency and perseverance of the caregiver(s) to work.

Limit-setting Sleep Disorder

Limit-setting sleep disorder describes children who resist or refuse bedtime. Parents who are too lenient in enforcing a strict bedtime may encourage this behaviour.

Epidemiology. Bedtime resistance has been found in up to a third of preschoolers. About 15% of children between 4 to 10 years old may still continue to have significant limit-setting sleep issues.

Presentation. Bedtime refusal may manifest as refusal to go to bed or refusal to stay in bed. Attempts by the child to stall bedtime include screaming and crying, requesting for another drink of water, or bedtime story.

Risk factors. In addition to over-lenient parenting, conflicting parental disciplinary styles, inconsistency in limit-setting (eg, allowing the child to fall asleep while watching television or spend some nights in the parents’ bed), and family tension can increase the occurrence of limit-setting disorder.

Management. This includes good sleep practices mentioned earlier, and the importance of consistency in parental limit-setting cannot be
emphasized more. The method of bedtime fading may be practised, in which the bedtime is gradually brought forward from the existing bedtime to the intended bedtime. Clear bedtime rules must be set, and positive reinforcement like rewards or star charts can help motivate children.

CIRCADIAN RHYTHM DISORDERS

Delayed Sleep Phase Disorder

Epidemiology. Delayed sleep phase disorder is a disorder of timing that has been described in between 7% and 16% of adolescents and young adults.6

Presentation. Individuals with delayed sleep phase disorder go to bed much later than desired (eg, 4 AM) and find it very difficult to wake up in the morning. Daytime alertness decreases, and many teenagers report waking up tired and exhibit daytime somnolence,7 thus affecting school performance.

Risk factors. Exact pathophysiological mechanisms remain largely unknown. Up to 40% of patients have a positive family history, and polymorphisms in the clock gene PER3 have been described.6

Management. Polysomnography is not routinely indicated unless there are symptoms suggestive of sleep-disordered breathing. Sleep logs are useful to demonstrate the habitually late sleep onset and late awakening.6 Catch-up sleep on weekends should be documented as well.

The main aim of management is to gradually adjust the sleep/wake schedule such that the typical school-going adolescent would still receive an adequate duration of sleep. Sleep hygiene must be reinforced. To reset the sleep rhythm earlier, it is important to get morning sunlight and avoid exposure to bright light late at night. Success has been shown to be largely dependent on patient and environmental factors (such as patient and parental motivation).

SLEEP-RELATED BREATHING DISORDERS

Sleep-related breathing disorders describe a spectrum of abnormalities in breathing patterns during sleep in which snoring is the predominant symptom. Primary snoring and OSA are at either ends of the continuum, and upper airway resistance syndrome falls in between (Figure 2).8

Primary Snoring

Primary snoring is defined as snoring during sleep without associated apnoea, hypoventilation, hypoxaemia, or hypercarbia, and with no associated sleep disturbance or associated daytime symptoms.
Upper Airway Resistance Syndrome
Upper airway resistance syndrome is defined as partial upper airway obstruction sufficient to cause sleep disruption and daytime symptoms, but not gas exchange abnormalities.

Obstructive Sleep Apnoea
OSA is characterized by prolonged partial upper airway obstruction (obstructive hypoventilation) and/or intermittent complete or partial obstruction (apnoea/hypopnoea) that disrupts normal ventilation during sleep and normal sleep patterns.9

Epidemiology. OSA is a condition that was once thought to be rare in the paediatric population in the 1970s, but newer studies have estimated the incidence to be 2–3% in children below the age of 10 years.10 There is a familial tendency, but the relative role of genetics versus environmental factors has yet to be determined.

The peak age is between 4 to 7 years old, usually in children with enlarged tonsils and/or adenoids. With increasing rates of obesity in children, there is a second peak seen in older children above 8 years old.

Causes. The most common aetiology of OSA is adenotonsillar hypertrophy. This group of children may have a typical ‘adenoidal face’, with a dull expression, allergic shiners, and mouth breathing.

Obesity is another important cause of OSA in children. An adult study has shown that a 10% increase in body mass increases the subject’s odds of developing moderate to severe OSA by sixfold.11

Risk factors. OSA tends to be worse during REM sleep as upper airway tone falls, allowing obstruction to manifest. Children with craniofacial syndromes like Pierre Robin sequence have fixed anatomical variations that predispose them to upper airway obstruction, while in children with neuromuscular disease like cerebral palsy, obstruction is caused by abnormal muscle tone. Children with trisomy 21 or those with a positive family history of sleep problems also have higher risks of OSA. A severe upper respiratory tract infection or severe allergic rhinitis may produce ‘transient’ OSA, especially in young children.

Symptoms. Snoring is the most commonly reported symptom of OSA. However, as explained above, not all children with snoring have OSA. The converse is also true in that in some children with OSA, the history of snoring may not always be elicited. This may be due to the snoring being unnoticed because it occurs more during REM sleep, which predominates in the later half of the night, especially in a child who sleeps alone in his/her own room.

In general, symptoms of OSA may be divided into night-time and daytime symptoms (Table 2).

Complications. The impact of OSA is great, as recurrent obstruction leads to repeated desaturations, arousals, and sleep fragmentation.10 The secretion of growth hormone occurs during SWS and the consolidation of memory during REM sleep. If sleep is fragmented, a detrimental effect on growth and learning may arise. Cardiopulmonary complications (pulmonary hypertension, cor pulmonale) and metabolic conditions (insulin resistance, impaired

<table>
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<th>Table 2. Symptoms of obstructive sleep apnoea</th>
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<td><strong>Sleep symptoms</strong></td>
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<td>Snoring</td>
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<td>Apnoeas</td>
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<td>Snorting</td>
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<td>Gasping</td>
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<td>Paradoxical breathing</td>
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<td>Enuresis</td>
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<td>Restless sleep</td>
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<td>Frequent arousals</td>
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<td>Unusual body positions</td>
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<tr>
<td><strong>Wake symptoms</strong></td>
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<tr>
<td>Poor school performance</td>
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<tr>
<td>Aggression</td>
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<tr>
<td>Hyperactive behaviour</td>
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<td>Inattention</td>
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<tr>
<td>Excessive daytime sleepiness</td>
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<td>Morning headaches</td>
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glucose tolerance, hypertension) may arise if OSA is untreated or, rarely, even death can occur in severe untreated cases.

**Diagnosis.** Snoring, mouth breathing, and daytime sleepiness often prompt parents to seek medical attention for their children. Clinical history and physical examination cannot always differentiate a primary snorer from a child with OSA. An overnight polysomnography is the gold standard test and involves continuous monitoring and recording of the child’s sleep and breathing parameters. The aim is to look for sleep disruption, laboured breathing, airflow limitation or cessation, hypoxaemia, and hypercarbia.

**Clinical history and physical examination cannot always differentiate a primary snorer from a child with OSA.**

**Treatment.** In 2002, the American Academy of Pediatrics issued an evidence-based clinical practice guideline with recommendations for the management of OSA in children. Adenotonsillectomy is curative in most children, and postoperatively, repeat polysomnograms may be done in some to document resolution. Continuous positive airway pressure is an option for those who are not surgical candidates or who respond poorly to surgery. Weight loss measures must be undertaken in those who are obese.

**PARASOMNIAS**

Parasomnias are sleep-related phenomena that disrupt normal sleep and can take place during sleep-wake transitions, NREM sleep, or REM sleep. As symptoms generally appear in early childhood and undergo spontaneous resolution, the aetiology has been proposed to be maturational in nature. Parasomnias can generate great anxiety as some can be very bizarre and even violent, causing much distress to the caregivers.

**Confusional Arousals**

In a confusional arousal, the child may awake from typically SWS in the first third of the night or in the morning (on attempted awakening), frightened and crying.

**Epidemiology.** The prevalence is estimated to be 5–15%, with the natural course being benign. The onset usually begins before 5 years of age, peaks during mid-childhood, and then undergoes spontaneous remission.

**Presentation.** The child appears awake but is actually disorientated in time and space, and responds very poorly to commands and is slow in speech and mentation. He may sit up in bed and say words like ‘no… no… no…’ or ‘go away!’ or even appear to be talking to an object. These episodes can last from a few minutes to a few hours with no recollection of the event thereafter.

**Somnambulism (Sleepwalking)**

Somnambulism has been described as partial arousal from sleep during SWS, and most occur during the initial third of the sleep period.

**Epidemiology.** An estimated 15–40% of all children will sleepwalk on at least one occasion, with only 3–4% having frequent episodes that occur weekly to monthly. Peak age is usually between 4 to 8 years old. The majority settle by adolescence,
and a significant familial pattern is associated. Sleepwalking can commonly co-occur with sleep-talking and night terrors.14

**Presentation.** Episodes often begin with sitting up in bed and looking around in a confused manner before ambulation. Routine behaviours like opening of the window or door and leaving the house can occur. Some may exhibit vocalization, but speech is usually meaningless and inappropriate. Children are usually difficult to wake during the episode and would appear confused and disorientated if awakened.

**Night Terrors**

Night terrors also transpire during the SWS cycle, in the first third of sleep.

**Epidemiology.** Typical onset is in early childhood between 2 to 4 years old, and spells are rare after adolescence.15,16 A familial pattern has been described, and more males than females are affected.

**Presentation.** Episodes are sudden and are usually associated with intense autonomic arousal (like flushing, tachycardia, diaphoresis) and inconsolable screaming or crying. They are usually brief, lasting only a few minutes, and the child will return to sleep on his/her own.12 The child will appear confused and disorientated if awakened.

Factors that may increase the likelihood of occurrence of sleep terrors in susceptible children include periods of febrile illnesses, sleep deprivation (when naps are restricted or eliminated),18,19 or medications like antihistamines, stimulants and sedatives.20

Sleep terrors can usually be identified through information provided by parents but, in the rare, more complex cases, may warrant investigation with polysomnography or electroencephalography for seizure evaluation.21

**Nightmare Disorders**

These attacks, as opposed to the conditions mentioned above, tend to occur in the last third of the night when REM sleep predominates.

**Epidemiology.** Nightmares can occur in all ages but peaks in children between 6 to 10 years old. Nearly all children experience nightmares, and there is no clear familial pattern.

**Presentation.** They are recurrent episodes of awakenings from REM sleep with recall of intensely disturbing dream mentation, usually involving fear or other intense emotions. Autonomic manifestations are usually mild, and vocalization is rare. Movements are also rare during nightmares because of normal REM sleep hypotonia.

Trigger factors include sleep deprivation, stress, and traumatic events.14

**Management of Parasomnias**

The arousal disorders are generally self-limiting, and the mainstay of management is conservative.
Management is based on reassurance and education, with reinforcement of appropriate sleep hygiene.

In cases in which there is potential danger (e.g., unlocking of windows or doors in somnambulism), interventions should be in place to prevent injuries (e.g., gates at the top of the stairway, padlocking of doors and windows, or an alarm bell on the door-knob of the child’s room). Parents are advised not to wake the child up during episodes, but to gently guide them back to bed.

When the events are predictably recurrent, scheduled awakening just before the typical time of the episode on a nightly basis for a few weeks has been shown to be effective.

Pharmacotherapy has been used rarely and would first require consultation with a sleep specialist and detailed counselling of the parents.

CONCLUSION

Paediatric sleep is an area of growing interest, and there is an increasing awareness of the need for good sleep in children. Different sleep disorders are prevalent in the different age groups, but for all children, poor/insufficient sleep and sleep-disordered breathing can have mild to serious sequelae.

Screening for sleep disorders for all children should be part of routine health care, with onward referral to a paediatric sleep specialist for symptomatic, complex, or high-risk patients.

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INTRODUCTION

Puerperal sepsis is one of the leading causes of maternal deaths globally (Latin word ‘puer’ means child). It is also called ‘Childbed fever’. It is severe form of septicemia. The infection is contracted by women during or shortly after childbirth, miscarriage or abortion leading to septicemia and death. Along with pre-eclampsia and obstetrical haemorrhage it has formed the lethal triad of causes of maternal deaths for many decades. Puerperal sepsis is defined in the International Classification of Diseases (ICD–10) as a temperature rise above 38.0°C (100.4°F) maintained over 24 hours or recurring during the period from the end of the first to the end of the tenth day after childbirth or abortion.1 Alternatively, the United States Joint Commission on Maternal Welfare, uses a standard definition for puerperal fever used for reporting puerperal morbidity as an oral temperature of 38.0°C (100.4°F) or more on any 2 of the first 10 days postpartum. While puerperal infection is most commonly encountered within the first 2 weeks after delivery, the definition extends to 42 days postpartum. Further, the World Health Organization (WHO)2 defines puerperal sepsis as infection of the genital tract occurring at any time between the rupture of membranes or labour and the 42nd day post partum in which 2 or more of the following are present: pelvic pains, fever (that is oral temperature 38.5°C or higher on any occasion), abnormal vaginal damage (example presence of pus), abnormal smell or foul odour of discharge, delay in the rate of reduction of the size of the uterus (less than 2 cm per day during the first 8 days). Inflammatory markers such as interleukins (IL) and C reactive protein (CRP) are extremely useful prognosticators besides increase in WBC. Recognition of prognostic factors in an early stage of the treatment and influence further treatment. Risk
assessments can help physicians to improve the efficiency of treatment, with optimal monitoring of high-risk patients preventing unnecessary complications, ICU admissions or deaths. Therefore, it is important to identify these prognostic factors.

**History**
In the 1600s to late 1800s, majority of the childbirth fever was caused by doctors themselves due to little knowledge of antisepsis and the importance of hand washing. In 1865, J. Lister (United Kingdom) demonstrated antiseptic principles in prevention of infection. In 1871, Dr. Ignaz Semmelweiss (Vienna, Austria) noticed a difference in women giving birth in maternity wards to homes. He identified puerperal sepsis as a wound infection caused by Streptococcus. Elizabeth of York, mother of Henry VIII of England and his two wives Jane Seymour and Katherine Pasa, Suzanne Barnard, mother of Philosophy, Jean Jacques Rousseau and Phyllis Wheatling, African American poet were few among the many renowned people who had died of Childbed fever. From olden to the more recent times, the cause of sepsis has changed from hand washing to contaminated medical equipment or unhygienic medical staff during delivery. Other infections leading to sepsis include urinary tract infection, breast infection and respiratory tract infection.

**Material and Methods**
Appropriate epidemiological studies were identified by internet sources Wikipedia, Google, Google scholar and PubMed search, using the key words ‘puerperal sepsis’, ‘inflammatory markers’ and by tracking references from these papers case reports were also identified. Also, experts from the field were consulted (Dr. JB Sharma’s textbook on Gynaecology and Obstetrics was referenced further).

**Incidence**
Over the decades, from pre-antibiotic era, the incidence has decreased with antibiotics, obstetric care, and improved general health of women and decreased virulence of the *Streptococcus B haemolyticus*. It is the single most common cause of maternal mortality.

In the United States, puerperal infection ranges between 1–8% of the deliveries. About three women die from puerperal sepsis for every 1,00,000 deliveries. The single most important risk factor is cesarean section.

In United Kingdom, from 1985–2005, the number of direct deaths associated with genital tract sepsis per 1,00,000 maternities was 0.40–0.85 %. In 2003–2005, genital tract sepsis accounted for 14% of direct causes of maternal deaths. Puerperal fever or childbirth fever in the 18th and 19th centuries, 6–9 women in every 1000 deliveries killed on an average 2 to 3 women with peritonitis or septicemia (approximately 250,000–500,000 deaths).

**Predisposing Factors**
Certain factors may influence the pathogenicity of the vaginal flora like introduction of the organism from outside during delivery, lowered general or local host resistance, multiplication of organisms in the devitalised tissues and relative increase in the drug resistant organisms.

The most common predisposing factors to puerperal sepsis are:
- Anaemia in pregnancy
- Non-adherence asepsis during delivery/ prolonged rupture of membrane
- Frequent vaginal examination during labour
- Obstructed/prolonged labour
- Caesarean section
- Retained products of conception
- Preterm labour
Medical conditions like diabetes, obesity other chronic illnesses
Immune-suppressive states, like HIV, AIDS patients with renal transplant
Antepartum haemorrhage

Aetiology
The organisms responsible for puerperal sepsis are typically those which normally colonise the genital tract and are of low virulence but can cause infection in the presence of above mentioned predisposing factors. Normal vaginal flora in late pregnancy and during labour are as follows:
- Doderlein’s bacilli (lactobacilli)
- Yeast like fungi
- Staphylococcus albus and aureus
- Anaerobic streptococci
- Escherichia coli
- Bacteroides groups
- Streptococcus beta haemolyticus
- Clostridium welchii

Human nasopharynx is the main reservoir for Streptococcus pyogenes in winter and rarely is found in normal vaginal flora. The most common causative organisms for puerperal sepsis are Staphylococcus aureus, Streptococcus group B (GAS specifically Strept. pyogenes) B, C, D and

G. Group B Streptococcus causes pneumonia and meningitis in neonates and systemic bacteremia in elderly. Microorganisms that commonly cause puerperal sepsis are given in Table 1.

Source of infection
The source of infection may be:

- Endogenous: Causative organism are from within the patient, the mixed flora colonising the women’s own genital tract, usually S. faecalis in anus and perineum, anaerobic Streptococci, Clostridium welchii.
- Autogenous: Infection is carried to the genital tract from other body parts directly or through blood stream, e.g., Streptococcus haemolyticus from sore throat, E. coli from bowel, Streptococcus albus from abdominal skin.
- Exogenous: Infection is contracted from outside sources like hospital or attendants, bed, blankets, etc. Streptococcus beta haemolyticus can be acquired from nasopharynx of maternal and child health care providers. Staphylococcus aureus is an important nosocomial infection.

Risk Factors
Septic risk factors for each aetiologic condition are listed in order of the postpartum day (PPD)
on which the condition generally occurs and are enumerated in Table 2.

Pathogenesis
Infection may be localised to the site (perineum, vagina, cervix, uterus) or generalised (systemic). Lacerations in the lower genital tract get infected easily with microorganisms in presence of blood clots and dead space. This leads to local inflammation and a high risk of developing puerperal sepsis.

CLINICAL FINDINGS AND MANAGEMENT

The illness begins in the postnatal, period 3–4 days after delivery and lasts for about 10–12 days and the severity of the symptoms depends on the underlying infection. The symptoms include abnormal vaginal discharge with foul smell, pelvic pain, fever, increased heart rate, cough, increased respiratory rate. The patients may have symptoms of septic shock and leucocytosis. The clinical outcomes, findings and management of puerperal sepsis are highlighted in Table 3.

Prevention
Almost all predisposing factors leading to sepsis and maternal mortality are preventable. It needs proper implementation of protocols for antenatal, intranatal and postnatal care, count swab before cesarean section, treatment of respiratory infection before/during delivery/surgery and operative techniques, continuing perinatal education programs for midwives, trained birth attendants (TBAs) and doctors for proper management during labour, aseptic measures, prophylactic antibiotics, proper hand washing, avoiding unnecessary repeated vaginal examinations, unnecessary catheterisation of bladder, prolonged labour, observing partograms, avoiding unnecessary interventions in premature/pre-labour rupture of membranes, proper and timely referrals to health facility. Nutrition is an important part of prevention and treatment of sepsis especially foods that are rich in protein and vitamins should be taken during pregnancy. Gross inspection of placenta and membrane to ensure its completeness in all deliveries should be done compulsorily.

TREATMENT

General Care
Sepsis in pregnancy is often insidious in onset but can progress very rapidly. Regular monitoring of pulse, blood pressure, respiratory rate may assist with early identification. If sepsis is suspected,
urgent referral to hospital is indicated and close monitoring of fluid balance may be required, early involvement of critical care staff may also be required. Correction of anemia and antibiotics should be started immediately after obtaining appropriate cultures.

Specific Treatment
Antibiotics are the mainstay of treatment. Broad spectrum intravenous antibiotics according to culture sensitivity should be started immediately.

The various combination regimes are as follows:
- Inj. ampicillin 1 gm IV 6 hourly or Inj. amoxicillin n 1 gm 8 hourly for gram positive bacteria.
- Inj. gentamicin 2 mg/kg IV 8 hourly followed by 1.5 mg/kg 8 hourly for gram negative bacilli.
- Inj. metronidazole 500 mg or Inj. clindamycin 600–900 mg 8 hourly for anaerobes.

Intravenous cefotaxime 1 gm 8 hourly with

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Table 3. Clinical outcomes, findings and management of puerperal sepsis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atelectasis</td>
<td>Mild to moderate fever</td>
<td>Pulmonary exercises and ambulation</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>High fever, malaise, costovertebral tenderness</td>
<td>Antibiotics per culture</td>
</tr>
<tr>
<td>Wound infection</td>
<td>Persistent spiking fever despite antibiotics</td>
<td>• Antibiotics for cellulites&lt;br&gt;• Open and drain wound&lt;br&gt;• Saline soaked packing and closure</td>
</tr>
<tr>
<td>Septic pelvic thrombophlebitis</td>
<td>Persistent wider fever swings despite antibiotics, benign localized venous cord with pain tenderness, swelling, redness along the entire course</td>
<td>• Broad spectrum antibiotics, associated abscesses&lt;br&gt;• Incised and drained.&lt;br&gt;• Surgical excision of involved vein&lt;br&gt;• Anticoagulant not routinely used until thrombosis is extensive</td>
</tr>
<tr>
<td>Mastitis</td>
<td>Unilateral localized erythema, tenderness</td>
<td>• Antibiotics for cellulitis&lt;br&gt;• Open and drain abscess</td>
</tr>
<tr>
<td>Endometritis</td>
<td>Moderate fever, exquisite uterine tenderness, minimal abdominal pain</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Parametritis</td>
<td>General malaise, weakness, chills, rise in body temperature to 38° or 39°C, mild pain in the lower abdomen</td>
<td>• Bed rest&lt;br&gt;• Cooling of the lower abdomen&lt;br&gt;• Broad spectrum antibiotics, fluoroquinolones and anti-inflammatory agents</td>
</tr>
<tr>
<td>Pelvic peritonitis</td>
<td>Swelling of the abdomen, severe pain and tenderness in the lower abdomen, nausea, vomiting, rapid pulse, chills and fever, rapid breathing</td>
<td>• Antibiotics: IV metronidazole to be included for anaerobic coverage and after clinical improvement switch over to oral antibiotic therapy&lt;br&gt;• Appropriate analgesia&lt;br&gt;• Surgery (laparotomy if required)</td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>Pelvic pain and tenderness, fever, increased urination frequency, diarrhoea</td>
<td>• Surgical drainage of abscess through posterior colpotomy or laparotomy, dead tissue removal, bed rest, fluid electrolyte balance.&lt;br&gt;• Broad spectrum antibiotic for anaerobic coverage duration of which depends on severity of the condition.&lt;br&gt;• Other treatment depends on sign and symptoms of the disease</td>
</tr>
<tr>
<td>General peritonitis</td>
<td>Pain, bloating and tenderness in the abdomen, diarrhoea, nausea, vomiting, rapid pulse, chills and fever, rapid breathing, fatigue, unable to pass stool</td>
<td>• Pain medication&lt;br&gt;• IV fluids/oxygen supplement—if required.&lt;br&gt;• Bed rest</td>
</tr>
</tbody>
</table>
metronidazole or clindamycin can be given. Piperacillin 100–150 mg/kg/day IV in 3 divided doses or imipenem with cilastatin can be used for more serious infections. The treatment is given for about 7–10 days. However, if the patients do not respond to the treatment, antibiotics should be changed according to repeat culture sensitivity.

**Surgical Treatment**
Surgery has limited role and is indicated only in resistant cases and where ever there is blood or pus collection can be performed.

- Removal of stitches from infected episiotomy for pus drainage and for pain relief. Local antiseptic dressing should be done and if needed a secondary suturing can be performed.
- Evacuation of retained bits of placenta should be carried out after 24 hours of intravenous antibiotics to avoid septicemia.
- Vaginal posterior colpotomy for pus drainage in pelvic abscess should be done under anaesthesia cover.
- Laparotomy is rarely indicated for peritonitis or tubo-ovarian abscess resistant to antibiotics. Hysterectomy is rarely performed for uterine rupture or perforation, multiple abscesses and gangrenous uterus.

**CASE REPORTS OF Puerperal Sepsis and Inflammatory Markers**

- In a study, at Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, 45 women with preterm premature rupture of membranes were assessed at 24–34 weeks and IL–6 levels were measured. These women were followed till puerperium and foeto-maternal outcome. The data was analysed using ‘t’ test and ‘Chi’ square test. Histopathology of the placenta and umbilical cord was done for all the outcomes. Chorioamnionitis and funisitis was done found in 48.8% and 13.3% women respectively and correlated significantly with increased IL–6 levels and foeto-maternal infection. A cut-off value of IL–6 ≥8 pg/ml was associated with puerperal sepsis and neonatal sepsis. This was found more sensitive (82.6%) and specific (86.3%) as compared to TLC and CRP in diagnosing preterm premature rupture of membrane (PPROM). Therefore, this study concluded that maternal serum IL–6 having a good sensitivity and specificity and it can be used as a biomarker to predict preclinical asymptomatic infection.

- A 33 years old woman with PPROM at 37 weeks gestation and breech had heart rate deceleration and was delivered. Postoperatively, she had increased fatigue, pain in muscles and increased CRP. She had massive peritonitis and the organism isolated was *Strep. pneumonia*. This old woman was admitted 16.5 hours after delivery and was diagnosed as an emergency case in shock postpartum with acute respiratory distress syndrome. It seemed she was a case of septicemia and her laboratory reports showed increased WBC and CRP. *Staphylococcus aureus* was cultured from lochia. She was put on corticosteroids and protease inhibitors and recovered fully in the intensive care.

**Differential diagnosis of puerperal sepsis:**

- Lower genital tract infection
- Wound infection
- Urinary tract infection
- Acute pyelonephritis
- Pneumonia
- Atelectasis
- Mastitis
- Appendicitis
- Thrombophlebitis
Complications associated with puerperal sepsis:
- Septicemia
- Endotoxic shock
- Peritonitis
- Abscess formation often requiring surgery

**DISCUSSION**

Puerperal sepsis is a preventable condition. With necessary and adequate prevention steps in terms of educating the patient, staff and good hygiene practices of the doctor, the incidence of septicemia can be reduced considerably. Prophylactic antibiotics reduce the risk of high risk cases. Inflammatory markers are raised as a result of the infection and the outcome can be measured to prognosticate a better outcome of the disease. Prophylactic antibiotics can be started sooner for a better outcome and faster recovery. IL-6 can be used as a biomarker to predict preclinical asymptomatic infection in PPROM with good sensitivity and specificity.

In the recent case reports, it has been documented and proved that inflammatory markers are helpful in prognosis of puerperal sepsis and useful in starting antibiotics so that severe septicemia can be avoided and prevented. CRP and ILs are both found to be increased in separate case reports indicating that these are prognosticators for puerperal sepsis. Therefore, it is important to use useful laboratory tests including inflammatory markers for the prognosis of puerperal sepsis to avoid complications and mortality.

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An Analytical Study to Evaluate the Accuracy of HPV DNA Screening in Comparison to Liquid PAP Smear and Visual Inspection with Acetic Acid

Neetu Sareen, Ratna Rao, Neeta Misra

INTRODUCTION

India cervical cancer is the commonest malignancy in women in India and the second most common in the world with approximately 400,000 new cases diagnosed every year.1 The world wide mortality is 2.9 per 100,000 population. Human papilloma virus (HPV) infection is aetiologically linked to invasive cervical carcinoma. HPV infection is a common sexually transmitted disease. Most infections resolve spontaneously. It is the persistent infection with HPV which results in pre-invasive lesions.2,3 Almost all high grade lesions and cancers contain HPV. The cervical carcinogenesis model comprises of three steps:

- HPV infection
- Progression to high grade pre-invasive lesion and
- Invasion

There are more than 30 HPV types, however only 13 have been implicated in the causation of cancer of the cervix.

Infection with high risk HPV is associated with a relative risk of 8–11 for the development of squamous intraepithelial lesion (SIL) and only low grade SIL containing high risk HPV type progress to high risk SIL.4 The risk of developing cervical intraepithelial neoplasia (CIN) after two years of having HPV DNA positivity is 28% and only 3% if the patient is tested negative.5 Prevalence rate of HPV is 20% in women under 30 and
declines to 10% in the age group 60 and above.\textsuperscript{6,7} Conventional Pap has sensitivity rates varying from 40 to 68.1% whereas liquid based cytology has sensitivity rates of up to 87.8%. Negative Pap and negative HPV DNA test\textsuperscript{8} confers 100% assurance of not having CIN II and III and squamous cell carcinoma of the cervix. The Pap test has been the mainstay of cervical cancer detection and prevention. The new carcinogenesis model suggests that sensitive HPV testing maybe useful in cancer prevention. Because of this, there is immense increase in interest in using HPV DNA detection either alone or in addition to cytology as a tool for early detection of pre-invasive lesions and cancer of the cervix. HPV DNA testing in cervical scrapes offers a potentially automatic and cheap diagnostic assay without the sampling errors and subjectivity of cytology. HPV DNA has been reported to have 90–98% sensitivity for diagnosing CIN.\textsuperscript{6,8,9} HPV DNA is being tested by PCR, Hybrid capture I test and the more recent Hybrid Capture II test.

Various studies have tried to establish whether testing for HPV DNA if combined with other screening test like Pap smear improves the sensitivity and specificity of the individual test. However the exact role of HPV testing in wide scale screening programs remains to be established and the ideal single or combination screening test needs to be decided. A study was conducted to screen for pre-malignant and malignant lesions of cervix using visual inspection with acetic acid (VIA) and liquid based cytology, to assess whether the addition of HPV testing improves sensitivity and specificity of these tests.

Material and Methods
This analytical study was undertaken after taking ethical clearance. One hundred and twenty two sexually active women between 25–50 years of age, attending the gynecology OPD were included in the study after taking informed consent, over the time period from April 2005 to April 2006. All sexually active females 25–50 years of age attending the gynaecology OPD, with or without symptoms like discharge per vaginum, post coital bleeding, recurrent genital tract infections, were included. Pregnant females, patients with a history of hysterectomy, immunocompromised patients (e.g., HIV +ve) and known cases of cervical cancer were excluded.

Patients were required to fill a standard questionnaire, which included demographic profile, reproductive, sexual history and symptoms if any. General and pelvic examinations were performed. Perspeculum examination was performed to assess cervix. Exfoliated cervical cells were collected with cytobrush. This cytobrush was placed in universal collection medium (UCM). The vials were capped with brush inside. HPV DNA testing (by Hybrid capture II method) and cytology by liquid Pap test was performed. Smear was classified by Bethesda system, and was considered positive when there was finding of ASCUS (atypical squamous cells of unknown significance)/AGUS (atypical glandular cells of unknown significance) or higher grade on Pap smear.

PRINCIPLE
The Digene HPV test using Hybrid Capture II technology is a signal amplified hybridisation antibody capture microplate assay that uses chemiluminescent detection and detects a pool of 13 high risk HPV types (16,18, 31, 33, 35, 39, 45, 51, 5, 56, 58, 59, or 68). Specimens containing the target DNA hybridise with a specific RNA probe cocktail. The resultant RNA-DNA hybrids are captured on to the surface of a microplate well, coated with antibodies specific for RNA-DNA hybrids. Immobilised hybrids are then reacted with alkaline phos-
phatase antibodies specific for RNA-DNA hybrids and detected with a chemiluminescent substrate. Several alkaline phosphatase molecules are conjugated to each antibody. Multiple conjugated antibodies bind to each captured hybrid resulting in substantial signal amplification. As substrate is cleaved by the bound alkaline phosphatase, light is emitted which is measured as relative light units (RLUs) on a luminometer. The intensity of the light emitted denotes the presence or absence of target DNA in the specimen.

An RLU measurement equal to or greater than the cutoff value indicates presence of HPV DNA sequences in the specimen (>1pg/ml). An RLU measurement less than the cutoff value indicates absence of specific HPV DNA sequences tested or HPV DNA levels below the detection limit of the assay.

Liquid based cytology (LBC) was done using DNA Citoliq system which is composed of an aluminium instrument, the pregene developed to hold the duogene (which has two components, a slide holder and a filter holder). After obtaining smears, 5% acetic acid was applied and cervix was examined after one minute under adequate light source. On VIA (visual inspection of the cervix with acetic acid) thickened, raised, acetowhite areas or ulceration or significant friability were considered positive. All patients were subjected to colposcopy and if needed, biopsy. Colposcopy was done using a videocolposcope. Mucous was removed with saline, leukoplakic areas were noted. Five percent acetic acid was liberally applied over the cervix, and the entire cervix specially the transformation zone was examined thoroughly under magnification (10x–20x). Then the cervix was painted with Lugol’s Iodine so that any abnormal areas would stand out as yellow areas against the mahogany brown colour of the normal squamous epithelium. All colposcopic findings were noted according to the International colposcopic nomenclature. Scoring was done using the Reid’s combined colposcopic index. All negative patients were reassured that they need no further screening for at least 3 years. Patients positive on colposcopic examination and biopsy were managed according to the protocol followed depending upon the stage and grade of the disease. Histology and/or colposcopy report were considered as the gold standard to compare the performance of the different tests. Cervical tissue was obtained from the abnormal areas with a punch biopsy forceps. The specimen was fixed in 10% formalin and was analysed by the pathologist. Biopsies revealing ASCUS/AGUS or worse lesions on histopathology were considered as true positives (cases), Biopsies showing chronic cervicitis or other benign changes were considered negative.

Statistical analysis
All results were compiled and subjected to statistical analysis using SPSS version 15. To calculate sensitivity and specificity, tables were generated using results. The sensitivity, specificity, positive predictive value, negative predictive value, and prevalence of HPV infection were calculated for VIA, LBC and HPV DNA testing with colposcopy and/or biopsy as the gold standard.

Observations and Results
Mean age was 36.1 years amongst the total screened population and 40.1 years amongst the cases. In study 69.6% of the population attended the general OPD as opposed to 30.4% who attended the private OPD. The general OPD patients represented the lower socioeconomic class and 90% of the cases (ASCUS or higher lesions) belonged to the general OPD group. Mean parity in screened population and cases was 2.21 and 3.1 respectively.

Five women (4.1%) were nulliparas. Fifty seven (46.7%) were para 2 with 3 cases of CIN belong-
ing to this parity. Twenty seven women (22.1%) were para 3 with 5 cases of CIN belonging to this category. Six (4.9%) women each belonged to para 4 and para 5 group. Majority of study population 48/122 (39.3%) used barrier methods of contraception. The next most frequently used were natural methods 26/122 (21.3%).

Most common presenting complaint in the study population was discharge per vaginum (80/122 = 65.6%), followed by pain abdomen/back ache seen in 32/122 (26.2%) of the study population. Post menopausal bleeding was observed in 2 (1.6%) patients. One of these had HSIL while the other had cervical cancer. Most common finding on per speculum examination was cervical erosion seen in 57/122 (46.7%) patients followed by a normal looking cervix in 39/122 (32%). Chronic cervicitis was seen in 23/122 (18.9%) patients. One patient had an irregular growth over the cervix.

Amongst the study population 65/122 (53%) had a normal cytology report. Inflammation was the most common abnormality detected in 34/122 (27.9%). Seventeen out of one hundred and 22 (13.9%) patients were found to have ASCUS/LSIL or higher lesions on cytology and out of these 2 showed features highly suggestive of malignancy. Seven (5.7%) had LSIL on cytology. Four patients (3.3%) had HSIL on cytology. Only 1 patient was found to have cells highly suspicious of malignancy. Present study showed that 13/122 (10.7%) were VIA positive and 109/122 (89.3%) were VIA negative. Nineteen (15.5 %) patients were positive for high risk HPV DNA, thus giving a prevalence rate of 15.5% amongst the study population. Amongst patients with ASCUS or higher lesion the prevalence of HPV DNA positivity was 8/10 (80%).

In this study, 25/122 (20.5%) screened women were found to have abnormal colposcopic findings (Reid’s 0–8), whereas 97/122 (79.5%) had a normal colposcopy. Amongst patients with abnormal colposcopic findings, 13/122 (10.6%) patients had a Reid’s score of 0–2, whereas 7/122 (5.73%) patients had a score of 3–5. A score of 6–8 was seen in 5/122 (4.09%) patients. All patients with abnormal colposcopic examinations were subjected to cervical biopsy. Results of the cervical biopsies are shown in figure 1. Total number of true positives was 10 out of total of 122 patients. The prevalence of CIN in the screened population was found to be 7.37% (9 out of 122) and prevalence of cervical cancer was found to be 0.8% (1 out of 122). The sensitivity, specificity, PPV and NPV of Pap smear, HPV DNA test, VIA and combined tests is tabulated in table 1.

**DISCUSSION**

Cytological screening of the cervix using Pap smear, with appropriate treatment and follow up is the only proven strategy for the prevention of cervical cancer. However Pap smear has several limitations. It has a low sensitivity ranging from 51%–84% in various studies. To overcome this problem, LBC was introduced in the mid 1990’s to improve its performance. Specimen adequacy and the detec-
tion of HSIL were found to be much higher with LBC. Also the residual material can be used for HPV DNA testing. Visual inspection of the cervix with acetic acid is an inexpensive screening method with high sensitivity and specificity and provides immediate result.\textsuperscript{12,13} The main drawback of this technique however stems from the inter observer bias. Association between high risk HPV and the development of cancer cervix is well established. Prevalence of HPV infection in reproductive age group is 5–40\%,\textsuperscript{6,7,14,15} and HPV DNA is found in 80–99\% cases of cancer cervix hence it’s utility as a screening tool for cervical cancer.

In the present study, 15.5\% women were found to be positive for high risk HPV DNA, thus giving a prevalence rate of 15.5\% amongst the study population. Amongst patients with ASCUS or higher lesions, the rate of HPV DNA positivity was 80\%. Kulasingam (2002)\textsuperscript{7} reported that in patients with HSIL and LSIL, positivity rates for HPV DNA were 82\% and 64.4\% respectively.

In this study, the sensitivity and specificity for LBC is found to be 70\% and 91\%, comparable to the 70\% and 91\% found by Longatto \textit{et al} (2005).\textsuperscript{16} In present study, the sensitivity, specificity, positive predictive value, and negative predictive value for VIA was calculated as 80\%, 95.5\%, 61.5\% and 98.2\% respectively. Sankarnarayanan \textit{et al} (2004) calculated sensitivity and specificity to be 77\% and 86\% respectively.\textsuperscript{17} The sensitivity, specificity, positive predictive value, and negative predictive value for HPV DNA testing was calculated as 80\%, 90.2\%, 42.1\% and 98.1\% respectively in this study. Its comparison to other studies is shown in table 2. It is thus seen that sensitivity of HPV DNA testing in the present study is less as compared to the other studies while the positive predictive value is higher. The specificity and negative predictive value are comparable when seen in reference to various previous series.

Pap smear and HPV DNA testing were studied as a combined test for screening. The combination

| Table 1. Showing the comparison of individual and combined testing |
|-------------------|----------------|----------------|----------------|----------------|
|                  | Pap            | VIA            | HPV            | Pap+HPV        | Pap+VIA        |
| Sensitivity (%)   | 70             | 80             | 80             | 100            | 90             |
| Specificity (%)   | 91             | 95.5           | 90.2           | 81.2           | 87.5           |
| PPV (%)           | 41.2           | 95.5           | 42.1           | 32.3           | 39.1           |
| NPV (%)           | 97.1           | 48.7           | 98             | 100            | 98.8           |

PPV: Positive predictive value; NPV: Negative predictive value

| Table 2. Table showing the performance of HPV DNA testing in various studies |
|-------------------|----------------|----------------|----------------|
|                  | Clavel \textit{et al} (2001)\textsuperscript{6} | Belinson \textit{et al} (2001)\textsuperscript{18} | Cuzick \textit{et al} (2003)\textsuperscript{20} | Present study |
| Sensitivity(%)    | 100            | 95             | 97.1           | 80             |
| Specificity(%)    | 88.4           | 85             | 93.3           | 90.2           |
| PPV (%)           | 8.7            | 23             | 15.8           | 42.1           |
| NPV (%)           | 100            | 99             | –              | 98.3           |

PPV: Positive predictive value; NPV: Negative predictive value
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14. Franco EL, Villa L, Villa M, McGeechan E, Adam F, Bolognesi P, et al. DCS liquid-based system is comparable whereas the specificity is lower when compared with previous studies.18,19

CONCLUSION

HPV DNA test has better sensitivity and comparable specificity, when compared to pap smear and VIA, but HPV DNA test and pap combined together gives excellent specificity and negative predictive value. However combination test cannot be used as a universal screening method because of cost constrains. Increase in sensitivity is greater than the decrease in specificity when the two tests are combined. Such a trend has been substantiated by various other authors as well.18,19

Acknowledgement

We thank Holy Family Hospital for providing all the necessary support for carrying out this study. Also we would like to thank Digene Lab where HPV DNA testing was carried out, without their help this study would not have been possible.

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INTRODUCTION

Fibroids or leiomyomas are the commonest benign tumour of the uterus and are the most common pelvic tumours in women, with a clinical incidence of 20–25%. They mostly occur during the late child-bearing age beyond 30–35 years. The paucity of smooth muscle in the cervical stroma makes leiomyomas in the cervix uncommon. Though a rare entity, 1–2% of uterine fibroids may be located in the cervix usually to its supra-vaginal portion. Fibroids may be anterior, posterior, lateral or central in location involving either the vaginal or supravaginal portion of the cervix. Central cervical fibroid expands the uterus equally in all directions and the cavity of the pelvis is more or less filled by a tumour, elevated on top of which is the uterus like ‘Lantern on the dome of St. Paul’. Sometimes fibroids arising from the body of the uterus may burrow downwards to lie in the position of the cervix and may form pseudocervical fibroid but is very rare. Large fibroid arising from the vaginal part of the cervix is often confused with chronic inversion of uterus.

Cervical fibroids with excessive growth may cause pressure symptoms. They may also cause bladder symptoms (such as retention, frequency etc.) or bowel symptoms (such as constipation depending on whether they are anterior or posterior, respectively). Usually there is no evident menstrual abnormality associated with cervical fibroid. A large cervical fibroid may cause obstruction during labour.

Cervical fibroids prove to be a challenge to the clinician in view of their close proximity to important pelvic structures and of their likelihood to cause complications and difficulty in removal e.g., ureters. The typical diagnostic features of cervical fibroids are firm, fixed, pelvic position and cervical attachment in clinical examination. Ultrasonography proves to be a very effective tool for its diagnosis and treatment. Intravenous pyelography is essential to see the location of ureter.

Cervical fibroids may be managed by myomectomy alone or enucleation followed by hysterectomy depending upon the need for fertility of the patient and/or its location and size. However the newer modalities of treatment such as medical therapy with GnRH, uterine artery embolisation (UAE), focused ultrasound, hysteroscopic and laparoscopic myomectomy tend to decrease the mortality and morbidity of the patient and preserve the fertility. Ten selected cases of cervical fibroids are presented, describing different aspects like location of fibroids in cervix, patient profile, mode of presentation and methods of management in relation to the age and fertility outcome with brief discussion of review of literature.
CASE REPORTS

Case 1
A 42 years old female, fourth gravida with last child birth 10 years back complained of something coming down per vagina which occurred suddenly 14 days ago. She complained of retention of urine since then. She was having irregular bleeding per vagina for the last one and half years. On examination multiple fibroids were found in the vaginal part of the cervix, of which two of them were of very large size, along with cystocele and rectocele. She was treated with vaginal hysterectomy and pelvic floor repair (Figure 1a, b).

Case 2
A 35 year old nullipara attended GOPD with complain of something coming down per vagina for 7 years duration with difficulty in urination and defecation. Her husband had left her soon after the marriage. On examination there was complete uterine prolapse with cystocele and rectocele. There was a fibroid in the anterior portion of the cervix which was most probably the cause of the prolapse. There were pigmentation over the prolapsed mass and the mass was infected as well. After controlling infection and oedema, the prolapsed mass was reduced under anaesthesia, without removing the fibroid. Vaginal pack was given which was changed every 24 hours for about a week. The mass came out again after the packing was removed. In this case, the leiomyoma was enucleated from the anterior wall of cervix under spinal anaesthesia and the prolapsed mass was reduced. (Figure 2a, b).

Case 3
A 41 years old female, [P, (5+1) all delivered vaginally], was referred as a case of uterine inversion. She complained of something coming down per vagina for past five years. She also complained of excessive white discharge but had no menstrual abnormality. On examination under anaesthesia, fibroid was found to be situated on the vaginal part on the posterior lip of the cervix. She too had associated cystocele and rectocele. This case was managed by vaginal hysterectomy with pelvic floor repair (Figure 3a, b).
Case 4
An unmarried 39 years old female complained of lump over the lower abdomen with retention of urine. On examination huge lump was found in the lower abdomen, vaginal part of the cervix was flushed and the mass was palpable through all the fornices. Ultrasonography revealed a large cervical fibroid of 20 cm x 16 cm. Laparatomy showed the typical Lantern on the dome of St. Paul’s appearance where uterus, tubes and ovaries are normal in size and shape and are situated over the hugely enlarged cervix due to the presence of central cervical fibroid. Enucleation was done leaving a large defect and only a narrow posterior wall of cervix. As the patient was elderly and expressed her strong desire for hysterectomy during preoperative counseling total abdominal hysterectomy was performed without attempting a difficult repair (Figure 4a, b).

Case 5
A 49 years old female, third gravida, with the last child birth 18 years ago, had severe bleeding per vagina following menopause for 11 months. She had also complain of retention of urine and pain lower abdomen. There was suprapubic fullness on abdominal examination and vaginal examination showed uterus of 14 weeks size enlargement, mostly palpable through the anterior fornix. On laparotomy, body of the uterus was found to be of normal size and both sided tubes and ovaries looked healthy. However, cervix was found to be enlarged with large central fibroid (8 inches X 6 inches). This was another case of Lantern on the dome of St. Paul’s. As she had attained menopause and her family was completed, enucleation was done followed by total abdominal hysterectomy with bilateral salpingo-oophorectomy (Figure 5a, b).

Case 6
Another case was 21 years old nullipara, married for 6 months and she attended with complaint of lower abdominal pain for more than 1 year duration. Per abdominal examination showed a just palpable mass on the left iliac fossa and bimanual examination a firm mass was palpable on the left fornix with deviation of vaginal cervix and uterus towards the right side. Ultrasonography revealed a mass on the
left adnexal region with mild hydronephrotic change in the left kidney suggesting broad ligament fibroid. On laparotomy this was found to be a case of pseudo broad ligament fibroid, arising from the left wall of cervix. Intracapsular enucleation was done taking precaution not to injure the ureter. Stitches were given in the bed and cervix was repaired keeping a dilator inside the canal vaginally (Figure 6a, b).

Case 7
This was a case of pseudo cervical fibroid where a 45 years old female with completed family complained of discomfort in the vagina and occasional difficulty in urination. Vaginal examination showed a mass in the vagina which seemed to be arising from the cervix. Ultrasonography confirmed it to be a cervical fibroid polyp. On laparotomy, after incising the utero-vescical fold of peritoneum and retracting the bladder downwards, a longitudinal incision was given on lower anterior part of the uterus and the fibroid was found to be arising from the lower portion of the uterine body with a thick but long stalk, and not from the cervix. This fibroid was approached by abdomino-vaginal route, stalk of the fibroid was cut with scissors through the uterine cut wound and the fibroid mass was then removed vaginally with the help of a vulsellum (Figure 7). And then abdominal hysterectomy was completed. This approach avoided the difficult removal of the mass abdominally along with uterus and thus avoiding the chance of vault injury during removal and also minimising the chance of intra-abdominal infection.

Case 8
32 years old woman, mother of three children was referred as a chronic case of uterine inversion. She complained of something coming down per vagina for past seven days with retention of urine. A huge mass (20cm X 15cm) was seen coming out from the vagina which was irreducible and infected. After the infection had subsided examination was done under general anesthesia. A mass was found to be emerging from antero-lateral part of the cervix (vaginal). Per rectal examination showed that the uterus was normal in size and normal in location, thus the mass seems to be arisen from cervix suggesting it to be a cervical fibroid. The mass was excised (myomectomy) vaginally and cervix reconstructed (Figure 8 a, b, c).

Case 9
A 41 years old woman with completed family presented with pelvic discomfort and occasional urinary retention. Per vaginal examination also confirmed a large pelvic mass central in position that is nonseparated from uterus. Sonography examination showed also confirmed a large central fibroid. Following laparotomy, hemisection of uterus...
(Figure 9a) was done, then the myoma was enucleated followed by hysterectomy (Figure 9b). By this method injury to the ureter is prevented during clamping of uterine vessels.

Case 10
A 36 years old female with completed family had complain of pelvic discomfort, menorrhagia and retention of urine. On examination, there was just a palpable suprapubic lump and on bimanual examination supra vaginal part of the cervix felt, bulky occupying almost the whole pelvis with vaginal part of the cervix flushed with vagina. Ultrasonography showed the presence of central cervical fibroid. She was treated with total abdominal hysterectomy without enucleation with difficulty, of course avoiding the injury to the ureter. The specimen showed typical Lantern on the dome of St. Paul’s (Figure 10). Ideally, this type of hysterectomy should be performed after enucleation of myoma to avoid ureteric injury.

DISCUSSION
Uterine fibroids are benign clonal tumours arising from the smooth muscle cells of the uterus and contain an increased amount of extracellular matrix for which they are also referred as leiomyoma. Their location in the cervix is not common and cervical fibroid belongs to Type 8 category in the new FIGO fibroid classification system.

All types of uterine leiomyoma usually occur in reproductive age group. In this series of ten cases of cervical fibroid five women were of either forty or more than 40 years of age and among them one woman was postmenopausal for 11 months. Four women were between 30–39 years of age, only one presented at 21 years.

Majority were multiparous (seven out of ten). Three were nulliparous, of them one was unmarried at 39 years, one married for 6 months only at the age of 21 years and other one was infertile.

Clinical presentation of cervical fibroids is different from that of body fibroid, and they present more with features of obstruction than with menstrual abnormalities as found in body fibroid. Urinary problem (retention of urine and difficulty of micturition) was the commonest symptom (seven out of ten patients) in this series irrespective of the site of fibroid, supravaginal or vaginal. Defaecation problem was complained only by one patient. Something coming down per vagina was complained by four patients, those who had fibroids in portio vaginalis. One patient complained of discomfort inside the vagina, that was the case of pseudocervical fibroid (case 7).

Two cases were referred as chronic uterine inversion (case 3 and 8) and diagnosis could not be reached till the patient was examined in operation theatre. Menorrhagia was found only in one case (case 10). One patient presented with postmenopausal bleeding (case 5). However, all cases of vaginal variety of cervical fibroid including pseudocervical fibroid had some sorts of white discharges and blood mixed discharges (case 1, 2, 3, 8 and 7). Only four patients had pain lower abdomen, but not of severe variety. Abdominal lump was palpable in three cases (case 4, 5 and 10), all were of supravaginal varieties.

Cervical fibroids are usually found to occupy the supravaginal portion of the cervix thus causing more difficulty in its treatment. In the present series, five cases were supravaginal variety and four developed in vaginal part of the cervix.
cervix and other one was pseudocervical fibroid arising from the body but presenting as cervical fibroid. Of the supravaginal varieties two were of anterior type (case 4, 5), two central (case 9, 10) and one lateral encroaching to broad ligament (case 6). Of the vaginal varieties two (case 2, 8) developed in anterior lip, one arose from posterior lip (case 3) and in one there were multiple fibroids (case 1). Typical Lantern on the dome of St. Paul’s appearance was observed in three cases (case 4, 5 and 10).

In this series, conservative surgery was performed in three cases (case 2, 6 and 8). Case 2 presented with procidentia due to cervical fibroid on anterior lip in an unmarried female which was treated with myomectomy alone and did not require hysterectomy. Case 8 which was referred as chronic uterine inversion had actually a large anterior fibroid and was treated by vaginal myomectomy. Another important case (case 6) was lateral cervical fibroid (pseudobroad ligament fibroid) found in a nullipara. Lateral cervical fibroid poses a greater difficulty during laparotomy due to its close proximity or rather its tendency to alter the position of important structures of the pelvis such as the ureter. It may cause hydronephrotic changes in the kidney due to its compression over the ureter. Intracapsular enucleation a before hysterectomy was found to be help in proper placement of the uterine clamps and also provides space for visualisation of the operative field.

A fibroid polyp arising from the uterine body may occupy and distend the cervical canal, thus mimicking a cervical fibroid therefore called pseudocervical fibroid. Pseudocervical fibroid which arises from the lower part of the uterus with a thick stalk is difficult to confirm without laparotomy as was in case 7 of the series which was wrongly diagnosed as a cervical fibroid. It was dealt in a way different from the remaining cases i.e., the abdomino-vaginal route where the stalk of the fibroid was cut through an opening made on anterior uterine wall during abdominal hysterectomy and the fibroid was removed vaginally. Ultrasonography is the basic investigation to reach at diagnosis. CT scan, MRI are also very useful. Sometimes, preoperative intravenous pyelography is mandatory to visualise the ureteric course. Cystoscopy with peroperative ureteric catheterisation may be helpful to identify the ureter and to protect it from inadvertent injury during surgery.

There are case reports of cervical fibroids in the literature. A case of central cervical fibroid was reported by Basnet N et al., where a 35 year old woman with 3 living issues presented with an abdominal swelling reaching upto the umbilicus. Ultrasound and CT scan showed a normal sized uterine cavity while exploratory laparotomy under GA revealed a 5 kg single cervical fibroid of size 45 cm X 35 cm, with normal sized uterus and bilateral ovaries. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done in that case.

In management of fibroids newer methods of treatments are gradually coming up. UAE is such a minimally invasive therapy. Although it seems to be safe and effective, major complications and adverse outcomes have been reported. A case has been reported where a patient treated with UAE for a huge cervical fibroid presented with an infected, necrotic cervical mass 4 weeks after the procedure. Vaginal expulsion of the infected cervical fibroid from the left lateral cervical fistula tract occurred
CASE STUDY

spontaneously 3 weeks later while the patient was receiving antibiotic therapy. After 6 months of intervention, an approximately 99% regression rate in the fibroid volume was achieved. The patient gave birth to a healthy, female infant following a spontaneous, uneventful pregnancy and uncomplicated vaginal delivery. Thus UAE is associated with a significant reduction in fibroid volume though expulsion of the infected, necrotic parts of the fibroid which may be accepted as a natural process. Warning the patient about this potential risk, early recognition of infective complications and close follow up is crucial to avoid potentially fatal septic shock following UAE. Recently, cervical myomectomy is being performed through laparoscopy. In a study12 laparoscopic cervical myomectomy was found to be performed in twelve women with cervical myomas and menorrhagia. The uterine artery was ligated at its origin from the internal iliac as an initial step to reduce the blood loss. Myomectomy was subsequently performed safely and the outcome was good.

Takeda A et al13 has reported a case where a nulliparous woman with a large cervical myoma was found to be successfully treated with minimal blood loss by laparoscopic-assisted myomectomy combined with prophylactic temporary endovascular balloon occlusion of the bilateral internal iliac arteries. Fertility preservation was achieved with minimal blood loss.

Reproductive outcome in cervical fibroid is not well studied. In uterine body fibroid, there may be infertility, abortion, pain abdomen during antenatal period due to red degeneration, preterm premature rupture of membranes, malpresentation, increased cesarean delivery rate, and postpartum endomyometritis. In cervical fibroid, where there is large fibroids in portio vaginalis infertility may be due to difficult intercourse, whereas in supravaginal variety there is more chance of obstructed labour and retained placenta. In this series, only one woman out of ten cases has infertility, but in the parous women no history of obstructed labour could be elicited. A case report was made describing the obstetric outcome in a patient with multiple uterine and supravaginal cervical fibroids.14 A 36-year-old, third gravida, (para 0+2) with multiple uterine and cervical fibroids presented with inevitable abortion at 17 weeks gestation after 10 years of secondary infertility. She had a spontaneous rupture of membranes followed by expulsion of foetus as breech with entrapment of after coming head by a cervical fibroid. Oxytocin infusion and digital traction delivered the foetus but the placenta was trapped and could not be delivered even under general anesthesia as a result of mechanical obstruction by the fibroid. Expectant management was successful in expulsion of the placenta within 7 days without complication.

Retained placenta is a known complication associated with multiple uterine and cervical fibroids.5 It is more frequent when fibroids are present in the lower segment of the uterus and cervix representing some degree of mechanical obstruction.15

CONCLUSION

Though incidence of fibroids in cervix uteri is less it is not uncommon in clinical practice in a Gynaecologist’s life. Sometimes its diagnosis is difficult and very often it poses a great challenge in its management. Here, are the few selected varieties of cervical fibroids have been presented with detailed discussion. Thorough preoperative evaluation is thus the most important step in the management of cervical fibroids. One should be able to anticipate the operative challenges while dealing with cervical fibroids. Every case should be individualised regarding the mode and the selection of the route of surgery. Judicious and rational approach to decide the route makes the surgery safer and results in good outcome.

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REFERENCES

Imaging in Ectopic Pregnancy—Revisited

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INTRODUCTION

An ectopic pregnancy (EP) occurs when the implanted embryo is outside the endometrial cavity. EPs remain a significant threat to women of childbearing age despite advances in imaging and treatment, and are one of the leading causes of pregnancy-related first-trimester death. EPs represent approximately 2% of all pregnancies.1,2

Morbidity and mortality from EPs have dropped precipitously with improved diagnostics and management techniques. Nonetheless, EPs remain a significant gynaecological emergency, and delay in diagnosis and treatment can be catastrophic.

RISK FACTORS

Fertilization of the ovum occurs in the fallopian tube, and the blastocyst then arrives in the endometrial cavity and begins implantation on day 6 after fertilization. Anything that hampers or delays the tubal migration of the embryo to the endometrial cavity will result in an ectopic gestation. More than 95% of EPs are tubal in location.

Some of the factors contributing to the relative risk of EP are

• gynaecological infections and pelvic inflammatory disease in which there is a direct co-relation with tubal damage.3
• History of salpingitis increases the risk by fourfold.
• history of prior EP4
• history of tubal surgery or disease
• previous caesarean section
• use of fertility drugs or assisted reproduction.

It is unclear why the incidence has increased with the last factor listed above, but postulations include high hormone levels and multiple eggs implanted disturbing the milieu of implantation. Other risk factors include intrauterine contraceptive device, increasing age, smoking, previous abdominal surgery, and variant anatomy of the uterus. Most patients do not have any risk factors.5–7

PRESENTATION

The classical clinical triad of EP is pain, amenorrhea, and per vaginal bleeding. Only around 45% of patients present with such features. The diagnosis can be challenging, because the presentation in EP can vary significantly. Common physical findings include abdominal and adnexal tenderness, with either a change in vital signs (eg, tachycardia, hypotension) or unremarkable findings. EPs can mimic other conditions such as spontaneous abortions, early pregnancy failure, ruptured corpus luteal cyst, and infection.
LOCATION

Over 95% of all EPs occur in the fallopian tubes (Figure 1), with the rest occurring in the ovary (3.2%), abdomen (1.3%), or cervix (< 1%). Of the tubal pregnancies, the ampulla is the most common site (70%), followed by isthmus (12%), fimbria (11%), and interstitium/cornua (2.4%).

IMAGING

High-resolution transvaginal ultrasonography (TVUS) has enabled one to visualize normal and abnormal embryonic development at an earlier stage and with greater clarity. The reliable diagnosis of EP depends on one’s ability to recognize the normal intrauterine pregnancy (IUP) and the wide spectrum of ultrasonographic features of EPs. This, combined with serum β human chorionic gonadotrophin (hCG) measurements and the clinical presentations, is the best way to diagnose an EP with high accuracy. A completely normal pelvic sonogram may be present in up to 20% of patients with EP.

Identification of an IUP virtually excludes an EP, as the frequency of heterotopic pregnancy is very low (1 in 10,000 to 1 in 50,000 pregnancies) in women who conceive normally. In patients undergoing assisted reproductive therapy, the risk is increased.

Recognizing Normal and Abnormal Early IUP

TVUS can identify early gestation of 5.5 menstrual weeks at nearly 100% accuracy. The double sac sign found with an early IUP can be difficult to distinguish from the pseudogestational sac seen in 20–50% of EPs. The early IUP is located in an eccentric position, within the decidua of the endometrial lining, and consists of two concentric hyperechoic rings (Figure 2)—the intradecidual sign. This is in contrast with the pseudogestational sac (decidual cast which is central and consists of fluid in the endometrial cavity) surrounded by a single hyperechoic layer (Figure 3).

It is possible to make a diagnosis of pregnancy failure based on gestational sac
characteristics. The most reliable gestational sac criteria for poor outcome is the size. The mean sac diameter is measured using the sum of three orthogonal dimensions of the fluid sac wall interface divided by three. A cut-off of 18 mm was proposed by Filly in which an embryo should be seen. Lindsay et al. reported that non-visualization of the yolk sac in patients with a mean gestational sac diameter of greater than 8 mm is associated with poor outcomes. An irregular yolk sac has also been associated with poor outcomes by some authors, although this remains controversial.

Use of Colour Doppler in Diagnosis of EP
A ring of fire has been described as characterizing the appearance of flow around an EP (Figure 4); however, the corpus luteum is also very vascular and can have similar appearances (Figure 5). Colour Doppler is most helpful when an extraovarian mass has not yet been found, and allows for detection of an ectopic surrounded by loops of bowel. Luteal flow can be helpful in identifying an ectopic, because about 90% of ectopic occur on the same side as the luteal flow.

An extraovarian adnexal mass is one of the most common sonographic finding in an EP. A method of assessing whether the adnexal mass is ovarian or extraovarian can be demonstrated by gentle probing of the ultrasound transducer and observing if the mass moves in tandem with the ovary or separately. If it moves in tandem, the mass in question is likely ovarian and may be a complex ovarian cyst. If the mass moves independently, an extraovarian mass is suspected and an ectopic is more likely, and this helps differentiate from an exophytic corpus luteal cyst.

IMAGING THE EP

Tubal EP
A ring adnexal mass, seen separate from the ovary, is considered the most common feature of tubal EP. Finding an adnexal mass containing a live embryo is the only definitive diagnosis of an ectopic gestation. This is present in 8–26% of EPs on TVUS (Figure 6). The second most common specific sign, ‘an extraterine gestational sac containing a yolk sac with or without an embryo’, carries the risk of being confused with a haemorrhagic cyst containing debris, mimicking a yolk sac or embryo. Adnexal findings, other than a live embryo, need to be differentiated from a haemorrhagic corpus luteal cyst arising from the ovary. A sonographic clue is the echogenicity of the wall of the corpus luteum, which is more hypoechoic when compared with the wall of the tubal ring and endometrium. Sometimes, a haematoma can surround the small EP and obscure the EP.

Free Peritoneal Fluid
This is detected in 28–56% of EPs. There is no quantitative amount of fluid that is diagnostic, but the greater the amount, the greater the likelihood of EP. Occasionally, small amount of peritoneal fluid may be seen in normal pregnancies owing to exudation from the normal corpus luteum. The fluid in EP can be simple (anechoic), or complex with floating echoes or a layering appearance. Complex fluid suggests haemoperitoneum and sometimes even blood clots.
The site of ectopic implantation characterizes the ectopic gestation.

**Interstitial EP**

Interstitial EP accounts for 2–3% of all EPs. The interstitial portion of the fallopian tube is the proximal segment that is surrounded by the muscular wall of the uterus. These pregnancies are associated with a higher morbidity and mortality than other tubal pregnancies because of their ability to grow till the early second trimester before rupturing. Some have referred to these as cornual pregnancies, but the term is best reserved for pregnancy in a bicornuate uterus. In scanning for ectopic locations, the operator needs to inspect the cornua of the uterus, as this may be overlooked and an early interstitial EP can be missed (Figure 7). The ectopic gestational sac is covered only by a thin layer of myometrium (< 5 mm) or this is absent laterally,\(^{27-29}\) and not the endometrium. Whilst both thinning of the myometrium and the eccentric position are features of a more advanced interstitial EP (Figure 8), both features may also be seen in an eccentrically located IUP. Another ultrasound feature, the interstitial line sign, which is an echogenic thin line extending from the central endometrial echo to the gestational sac, was found to be more sensitive and specific than the other signs.\(^{30}\) The line probably represents the tubal canal.

**Cervical EP**

Cervical EP occurs in fewer than 1% of all EPs. Risk factors include previous dilatation and curettage, Asherman’s syndrome, and cervical or uterine surgery. The sonographic diagnosis is made when a gestational sac is identified within the cervix. The implantation can cause cervical dilatation relative to the corpus, giving an hourglass configuration.\(^{31,32}\) Differentiation from a low but normal IUP or a spontaneous abortion in progress can be made using the sliding sign test.\(^{33}\) The transducer is applied to the pregnancy, and gentle pressure is used to see if the pregnancy moves. If the pregnancy is complicated by an abortion in progress, the pregnancy would move; whereas if the pregnancy is implanted at the cervix, no movement is detected. Colour Doppler sonography to detect peritrophoblastic blood flow can aid to differentiate between the two conditions. Patients who have cervical EPs tend to bleed profusely, because the cervix does not have contractile tissue. The most reliable sonographic finding

Transvaginal sonography remains the only and most effective radiologic modality in the diagnosis of ectopic pregnancy.
of a cervical EP is identification of a gestational sac with peritrophoblastic flow or a live embryo within the cervix (Figure 9).

**Scar Pregnancy**

Scars in the uterus can be sites for implantation, and caesarean scar pregnancy is the most common. Myomectomy scar pregnancy has been described as well. In caesarean scar pregnancy, the gestational sac is embedded in the myometrium, and this becomes thinner when the pregnancy advances. Soon, only the serosal layer surrounds the pregnancy. This predisposes the patient to uterine rupture.34

This can be suspected when the sac is located anteriorly in the lower part of the lower uterine segment (Figure 10).

**Ovarian and Abdominal EPs**

Primary abdominal EP is less common than secondary abdominal EP in which the tubal EP ruptures into the peritoneal cavity with subsequent implantation. It most often occurs in the pouch of Douglas and posterior uterine wall but could occur anywhere in the peritoneal cavity (eg, broad ligaments, ovaries). Most obtain the blood supply from the omentum and abdominal organs. ‘Lithopedion’ is the name given to an extrauterine pregnancy that evolves to fetal death and calcification.35

Ovarian pregnancy develops as a result of retention of the ovum in the ovarian operculum and its continued entrapment within the ruptured ovarian follicle, which eventually is fertilized by the sperm, resulting in pregnancy. Ovarian pregnancies usually appear on the surface or within the ovarian parenchyma as a cyst with an echogenic ring. This is difficult to distinguish from a haemorrhagic ovarian cyst or corpus luteal cyst (Figure 11), and the diagnosis is usually confirmed histopathologically.

**Pregnancy of Unknown Location**

Pregnancy of unknown location (PUL) can be defined as a situation in which there is a positive pregnancy test with no signs of intra- or extrauterine pregnancy on transvaginal sonography. The woman should have no signs of intra-abdominal bleeding or evidence of haemoperitoneum on ultrasound scan.

The rate of PULs in different studies ranges from 8% to 31%. The prevalence of PULs is determined by the quality of TVUS scanning.35 The higher the quality of scanning, the better the detection of EPs using ultrasound as a single diagnostic test, resulting in fewer women classified with a PUL. Up to 90% of EPs can be detected at the initial ultrasound scan. Most PULs are not aggres-
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