Management of Eating Disorders in Children and Adolescents

Methods of Induction of Labour—Critical Review of Literature (Part II)

Bacterial Vaginosis

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Management of Eating Disorders in Children and Adolescents

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32  Intrauterine Foetal Growth Restriction
Intrauterine foetal growth restriction is a placental function disorder in which Doppler ultrasound has a major role in foetal surveillance. Sequential changes in Doppler velocimetry of the umbilical artery, middle cerebral artery and ductus venosus can be seen in progressively worsening placental dysfunction. Management requires balancing the risk of prematurity and the risk of intrauterine asphyxia.
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Hormonal contraception and cardiovascular risk

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

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

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


Midurethral sling during vaginal prolapse surgery to reduce postoperative incontinence

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

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

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


Effect of contraception on maternal mortality rates

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

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

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

The treatment of eating disorders in childhood and adolescence presents different challenges from the treatment of adults with eating disorders. These include the medical concerns specific to periods of increased growth; the fact that children and adolescents are usually brought for treatment, which will influence motivation; statutory responsibilities in relation to the protection of children and adolescents; and the importance of family context as the primary provider of care and the need, therefore, to engage families rather than individuals in treatment.

The majority of the literature pertaining to this age group relates to anorexia nervosa, reflecting both the frequency and severity with which eating disorders present at this age. In addition, bulimia nervosa is often perceived as the less severe condition. In fact, it can often be even more distressing both to sufferers and to their carers, clouded as it is in secrecy, and associated with a number of multi-impulse and maladaptive behaviours, including self-harm, substance misuse and depression. There is often a gap of several years between the onset of symptoms and diagnosis. Hence, bulimia nervosa generally presents to clinicians in the older adolescent population, giving a false reflection of its prevalence. In addition, adolescents with bulimia nervosa may be reluctant to engage with services that expect involvement of family members.1

ASSESSMENT AS INTERVENTION

A comprehensive assessment not only forms the basis for treatment planning for a child with an eating disorder, but the experience of having concerns recognized and the sharing of anxiety can be a powerful first step in regaining strength for the battle ahead. The assessment process initiates the therapeutic alliance between the treating team, and the child and family, ensuring a shared understanding about the nature of the eating difficulties and factors influencing them. Assessment will inform diagnostic formulation, taking into consideration predisposing, precipitating and perpetuating factors. Emphasis is placed on assessing the
child in the context of both their family system and their developmental stage at onset. An open discussion about the history and development of the eating problems ensures transparency, as well an opportunity for young people to hear the reflections of others. For the therapist, it is an opportunity to begin recognition of patterns of anxiety and communication that have become established around the problem.

A detailed family tree helps establish the systemic context and sources of support. Individual psychopathology is best assessed through a structured interview such as the Eating Disorders Examination (EDE) or child EDE for those under 13 years of age, and an individual mental state examination is needed to assess co-morbidity and contribute to the assessment of risk. It is important to clarify, with the child, issues around confidentiality in relation to individual components of the assessment, both in terms of the need to share aspects of risk, but also the benefit of conveying some of the young person’s hopes and anxieties to the rest of the family. The use of timelines and Likert scales, for example, to rate mood, can help to establish a collaborative relationship with the young person and his or her family.

Through this process, the family has an opportunity to review the context in which the eating disorder has arisen, its severity and impact, and can begin to take on its role as the primary source of support. Motivations and expectations of each family member are laid out from the start of treatment and lines of communication established. This is especially important when parents are no longer living together. Barriers to intervention, both practical (eg, access to treatment facilities) and psychological (eg, parental guilt about causing the problem), need to be addressed directly.

The provision of information is a key component of collaborative working and forms the core of intervention at this stage. Families need to be given verbal and written information about diagnosis, physical and psychological risks, course, potential complications and treatment options. It is important to acknowledge that although the majority of patients will make a good recovery, up to one-third of young people do not, and a significant proportion (around 40%) will have a second co-morbid Axis 1 diagnosis on follow-up. A resource list, books and helplines for parents and young people are very helpful; some examples are given below.

**TREATMENT**

The aims of treatment are threefold:
- To address eating behaviour and related cognitions directly, including nutritional deficiencies.
- To facilitate emotional communication and problem-solving skills.
- To address developmental issues and promote individuation.

Addressing issues of control and responsibility is central to successful intervention, as is the development of good collaborative relationships with the young person and his or her parents. A collaborative stance is facilitated if the therapist is able to adopt a directive, client-centred style, which aims to help explore and resolve ambivalence about behaviour change, and empowers decision making by the young person and his or her family. This may be difficult in the face of considerable anxiety about a young person’s nutritional status, but can be facilitated by good risk management protocols. Like most safety nets, these protocols are less likely to be needed if everyone knows they are there.

A number of recommendations have been made in the UK National Institute for Clinical Excellence (NICE) 2004 guidelines specifically regarding the management of children and adolescents with anorexia nervosa, based on a combination of research evidence and expert opinion. The importance of clarifying areas of responsibility and lines of communication between professionals in writing is highlighted throughout the guidelines, with an emphasis on ongoing risk assessment.
Medical and Nutritional Management

The medical management of anorexia nervosa is discussed in greater detail elsewhere in this issue. However, it is important to highlight differences between children and adults. Firstly, the increased medical risks associated with food restriction in young people are well documented, as is the increased risk associated with the tendency for younger patients to restrict fluid as well as food intake. The implications in terms of the need for close partnership with paediatric services are clear, with ongoing medical assessment as a core component of treatment. Weekly weighing and physical review are standard practice in outpatient treatment, with 3-monthly measurement of height by a clinician skilled in growth assessment for those who have not completed pubertal development.

Secondly, calorie requirements are age-dependent, but may be much higher (up to 3,000 kcal per day) during the weight-gain phase, especially in adolescents who are in puberty or very active. Views differ on the benefits of structured meal plans, because they imply a ‘correct’ way to eat when the aim ultimately is to empower parents to re-establish authority over eating. Nevertheless, involvement of a dietician in giving nutritional information and adjusting meal plans can be helpful and should involve parents as well as the young person. Weight gain of between 0.5 and 1 kg per week in an inpatient setting, or 0.5 kg in an outpatient setting, is considered optimal.

Finally, the use of body mass index (BMI) in children and adolescents is not appropriate as a measure of nutritional status. BMI centiles, which adjust for age and sex, are more helpful, although they do not take delays in growth and development into consideration. However, BMI centile charts facilitate discussion of healthy weight ranges, and determinants of healthy weight status can be clarified. For post-menarcheal adolescents, this will usually be the resumption of menses, but for pre-menarcheal girls, and for boys, resumption of growth, advances in pubertal development and maturation of pelvic ultrasonographic appearances are more appropriate. Bone density is measured annually in patients with chronic anorexia nervosa, with adjustment for bone size being important to take developmental delay into account with interpretation. Although vitamin D and mineral supplements may be helpful, oestrogen preparations or dehydroepiandrosterone (DHEA) should not be used because of the risk of premature fusion at the epiphyses.

Special considerations in younger people with binge–purge behaviours include the risk of aspiration pneumonia when they vomit, and an increased risk of primary pneumomediastinum, pneumothorax, subcutaneous emphysema and rib fractures. Menstrual dysfunction including oligomenorrhea or amenorrhoea may also occur, but can be hard to differentiate from the natural inconsistency of menses following menarche.

Psychological Treatments

Family Therapy

The evidence in young people supports a family-based approach (NICE Category B recommendation), with a model in which parents help their child fight the eating disorder, reinforcing their role as experts on their child and the primary source of support. This can be a challenge in the inpatient setting, where the unintentional effect of skilled nursing care can be to reduce parental confidence and skills, but can be overcome if acknowledged and addressed. The model is specific in exonerating parents of blame for the eating disorder. Externalization helps the family to see the illness as a distinct entity, rather than purposeful misbehaviour.

Separated family therapy, where the parents and child are seen separately, is most helpful when significant criticism and negative expressed emotion are apparent. Multi-family group interventions have also been shown to be helpful and may provide an alternative to inpatient admission in some cases. An approach emphasizing that the responsibility for change lies with young people, for example, cognitive-be-
behavioural therapy (CBT), is appropriate for some older adolescents or where, for whatever reason, family factors make a family-based approach difficult.

Cognitive–behavioural therapy for young people with bulimia nervosa is more effective than a family-based approach in reducing symptoms.14

Individual Work

In the treatment of anorexia nervosa, there is modest evidence in adults for the use of a range of individual therapies: cognitive analytical therapy, CBT and psychodynamic psychotherapy (NICE Category C recommendations). For young people, it can be more helpful to tailor individual work to the motivation, developmental stage and cognitive style of the young person. For example, a child who is very rigid and anxious may respond well to a more structured approach, whereas a child who is struggling with verbal communication may respond well to an explorative play-based approach. Those with more entrenched difficulties may benefit from psychodynamic approaches.

The evidence base for CBT approaches in young people with anorexia nervosa and bulimia nervosa is limited, although randomized controlled trials are under way. In adults with bulimia nervosa, there is excellent evidence (NICE Category A) to support the use of self-help manuals and CBT. Adolescents with bulimia nervosa may be treated with CBT-BN, adapted as needed to suit their age, circumstances and level of development, and including the family as appropriate (NICE Category C recommendations).

Inpatient vs Outpatient Treatment

Most adolescents with anorexia nervosa and bulimia nervosa should be managed as outpatients. Nevertheless, the likelihood of children and young people with anorexia nervosa needing an inpatient admission to either a paediatric or a psychiatric inpatient ward are around 50% or higher, depending on the healthcare system. Successful admission to paediatric wards is facilitated by the use of documented treatment protocols, agreed between paediatric and mental health teams.

Admission to a psychiatric or specialist eating-disorders inpatient unit is a serious decision, given a likely length of stay on average of 6 months, and often longer. It should be considered when there has been a failure to progress psychologically as an outpatient or when there are indications based on a paediatric admission that outpatient work carries too high a risk. This may be in terms of physical or psychological risk presented by the young people themselves or because of the degree of support available on an outpatient basis, due to either family factors or health service resources. In other words, many young people are treated in inpatient settings for reasons of context rather than the severity of their illness.15 This should be reflected in the aims of admission. In an inpatient setting, the therapeutic goals should be clearly agreed and documented. Role identification for staff and regular reviews to avoid splitting is essential. Consistency between therapists, between parents and over time should be maintained, if this is not possible, recovery may be hampered.

Consent to Treatment

Consent in young people is a complex issue and beyond the scope of this article to explore in full. Differences between consent, assent and refusal vary with age and competence, and it is important to remember that consent is specific to each treatment decision. The current UK NICE guidelines state that when essential treatment is refused, clinicians may treat the child or adolescent under the Children Act 1989 up to the age of 17 years, with the responsible parent’s permission, or under the Mental Health Act 1983, which has no lower-age limit. However, the Mental Health Act 2007, to be fully implemented in October 2008, now states that it is no longer appropriate to admit informally a 16- or 17-year-old refusing admission for treatment of a mental health disorder, even if his or her responsible parent consents to
admission. In these cases, it is now recommended that the Mental Health Act should be used. This recommendation is made to ensure that these young people do not end up detained in hospital against their will, but without the protections offered to those formally detained under the Mental Health Act. Which of these Acts is used is a matter for individual judgement, with pros and cons for each. The status of a young person in terms of his or her consent to treatment should be documented, and opportunities for appeal or advocacy provided to young people being treated against their consent. Relying indefinitely on parental consent to treatment of the child who continues to refuse should be avoided. Clinicians have statutory responsibilities in relation to children's well-being that override consent, but which can impact on the therapeutic alliance.

Psychopharmacology

No medication is used in the first-line treatment of anorexia nervosa or bulimia nervosa, but appropriate drugs can be effective in the treatment of co-morbid diagnoses and symptoms, especially anxiety. In anorexia, symptoms of depression and obsessive compulsive disorder often resolve with weight restoration. Fluoxetine may be prescribed to weight-restored adolescents with anorexia nervosa, and supplementary vitamins, folate, zinc and calcium can be used. In adult patients, there have been increasing case reports and retrospective studies on the use of atypical antipsychotics, such as olanzapine. Given the risks of metabolic syndrome in children, a short trial of risperidone may be more appropriate in treatment-resistant patients where there is significant psychological rigidity and anxiety. As drugs may prolong the QTc interval, some authors suggest that medication in young people should be used only in a healthy weight range. If medication is used, this needs to be alongside careful electrocardiogram monitoring.

Antidepressant drugs have been used for the treatment of bulimia nervosa in young people, but there is no evidence to support this approach. In adults, they have been shown to reduce the frequency of binge eating and purging.

CONCLUSION

The management of eating disorders in children and adolescents is a fascinating and challenging area that requires further research. Working collaboratively with the child within the context of their family and the professional system, in the right therapeutic setting, is crucial to recovery. The organization of services aimed at young people with eating disorders also is an area that merits further work, given the challenges of working on the interface between paediatrics and mental health, inpatient and outpatient care, and for transition to adult services.


About the Authors

Dr Barton is Consultant in Child Psychiatry at St Ann’s Hospital, London, UK. Dr Nicholls is Consultant Child and Adolescent Psychiatrist at Great Ormond Street Hospital for Children NHS Trust, London, UK.

Further Reading


Lask B, Bryant-Waugh R. Anorexia Nervosa and Related Eating Disorders in Childhood and Adolescence. 3rd ed. Hove, UK: Brunner–Routledge; 2007. (Clearly written, concise chapters with a wide range of experts in the field contributing to the book, offering practical advice on assessment and management based on the authors’ experience of outpatient and inpatient work at Great Ormond Street Hospital.)

A list of references can be obtained upon request from the editorial office.
Case Report

A female patient about 22 years old, para 1 admitted with history of passing menstrual blood through urethra cyclically (menouria/cyclical haematuria) for past 2 years. She used to pass maximum menses through urethra, and only few ml of through cervix. She had no complains of pain abdomen and incontinence. She had undergone caesarean section 21/2 years back at rural hospital during second stage labour. Post operative period was uneventful. Following 6 months of caesarean, she developed passing blood through urethra once she got her periods. During work up of the patient, when she became pregnant of 8 weeks gestation, she was given tablets for medical termination of pregnancy. She expelled most products of conception through urethra only.

On examination of the abdomen, pfannenstiel incision was noticed, and speculum examination revealed normal cervix and vagina, but obliterated anterior fornix. Examination per vagina showed uterus normal, antverted and fornices free. Cystoscopy showed a large fistula of about 2 cm in supratrigonal region, away from ureteric orifices. Hysterosalphingography (HSG) showed flow of contrast from uterus to bladder (Figure 1 a,b,c). Ultrasound of abdomen and pelvis were unremarkable. Other investigations were normal.

Intraoperatively, bladder was seen densely adherent to uterus. On separating bladder, large fistulous tract was observed between lower segment of uterus and bladder. Uterus and bladder were separated and bladder was closed in two layers. Omentum graft was put over bladder surface. Uterus opening closed. Catheterisation has done for 4 weeks. The patient’s menstruation, was postponed for 2 months with medroxy progesterone. After 2 months she had regular menstruation normally through cervix and vagina.

Figure 1. (a) Fistula post-caesarean delivery (b) Separated fistula (c) HSG (lateral view) showing spillage of dye from uterus to bladder
Misoprostol (PGE₁)
Recent interest in inducing agents has been focused on misoprostol, a synthetic PGE₁ analogue which was first used as treatment of gastric and duodenal ulcers. Misoprostol is about 50 times cheaper than dinoprostone gel and as opposed to dinoprostone gel, is stable at room temperature.

Although misoprostol can be administered vaginally/rectally/orally/sublingually, vaginal route at present offers most benefits in terms of efficacy and minimising side-effect profile.⁸²

Different Routes of Administration
Vaginal
In 1987, Rabe T et al.⁸¹ first reported the use of misoprostol on pregnant uterus in the first trimester of pregnancy. In a randomised controlled by Margulies et al.⁸² in 1992, 64 women beyond 28 weeks gestation undergoing indicated induction in the third trimester of pregnancy, were given 50 µg doses of misoprostol vaginally or oxytocin intravenously. Intravaginal misoprostol was found to be as effective as oxytocin and without differences in neonatal outcomes.

Sanchez-Ramos et al.⁸² described their experience with intravaginal misoprostol 50 µg given every 4 hours compared to intravenous oxytocin in 129 subjects with undilated and uneffaced cervices. There was reduction in induction delivery interval in those with misoprostol (11 vs. 18 hours). However the frequency of uterine tachysystole in the misoprostol treatment arm was 3 times that in oxytocin treatment arm (34.4%
No differences were found in mode of delivery or neonatal or maternal morbidity. The authors concluded that misoprostol was safe and effective for labour induction, and recommended further investigation to detail the optimal route, dose and dosing regimen.

Hofmeyr et al in a Cochrane database systematic review concluded that although vaginal misoprostol is more effective than other inducing agents, the apparent rise in uterine hyperstimulation is a cause of concern. However, dosing regimen less than 25 µg, 4 hourly is comparable to traditional methods of induction in terms of hyperstimulation. In dosages of 25 micrograms three hourly or more, vaginal misoprostol is more effective than conventional methods of cervical ripening and labour induction. However, uterine hyperstimulation with foetal heart rate changes is increased. Although no differences in perinatal outcome were shown, it states that the studies are not sufficiently large to exclude the possibility of uncommon serious adverse effects. The trend to an increase in meconium-stained liquor also requires further investigation. Anecdotal reports of uterine rupture following labour induction with misoprostol are cause for concern.

Misoprostol currently is approved by the US Food and Drug Administration (FDA) for the prevention of peptic ulcers. The manufacturer of misoprostol had issued a cautionary letter to health care providers against the use of misoprostol in pregnant women. This stand was maintained despite a large body of evidence supporting efficacy and safety of misoprostol for induction of labour in term pregnancy. This prompted a response by the American Congress of Obstetricians and Gynecologists (ACOG) which endorsed its previous conclusions regarding the efficacy of intravaginal misoprostol tablets for labour induction in women with unfavorable cervixes. Debate continues as to the optimal dosing regimen of vaginally administered misoprostol. ACOG committee opinion stated that if misoprostol is used for cervical ripening and labour induction, 25 mg should be considered for the initial dose to be repeated 3–6 hourly.

FDA has now approved a new label on the use of misoprostol during pregnancy for cervical ripening and for the induction of labour. This labeling does not contain claims regarding the efficacy or safety of misoprostol, nor does it stipulate doses or dose intervals. It is now on the WHO essential drug list for labour induction. Recently generic forms of misoprostol have become available. Misoprostol has been approved by Drug Controller General of India (DCGI) in December for 25 µg, 100 mcg and 200 µg for cervical ripening, prevention of postpartum haemorrhage and first trimester of abortion with mifepristone with additional strength approval for 50 µg for same approved indications in August 2008.

### Table 4. Pharmacokinetics of misoprostol

<table>
<thead>
<tr>
<th>Route</th>
<th>Onset of action (minutes)</th>
<th>Peak concentration (minutes)</th>
<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>8</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Sublingual</td>
<td>11</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Vaginal</td>
<td>20</td>
<td>70–80</td>
<td>4</td>
</tr>
<tr>
<td>Buccal</td>
<td>15</td>
<td>75</td>
<td>4</td>
</tr>
<tr>
<td>Rectal</td>
<td>15–20</td>
<td>20–65</td>
<td>4</td>
</tr>
</tbody>
</table>

vs. 13.8%).
Thus, use of misoprostol for induction of labour is associated with decrease in induction to delivery interval, decreased need for oxytocin augmentation, increased chances of successful induction, decrease in incidence of caesarean section; but with increased rates of uterine hyperstimulation, both with and without associated foetal heart rate changes and no differences in perinatal or maternal outcome. Though misoprostol shows promise as a highly effective, inexpensive and convenient agent for labour induction, the lack of global registration for this purpose, and thus of well-established regimens, is problematic.

Comparative Studies of Vaginal Misoprostol

Vaginal Misoprostol vs. Vaginal Dinoprostone Tablets

Fletcher et al. compared 32 cases of intravaginal misoprostol (100 µg) with 31 cases of intravaginal dinoprostone tablets (3 mg). The mean change in Bishop’s score was significantly higher in the misoprostol arm (5 vs. 3.3) and there were no significant differences in labour outcome. The author concluded that misoprostol was as effective as dinoprostone for inducing labour at term.

Chang et al. in 1997 compared vaginal dinoprostone tablets (3 mg) with vaginal misoprostol tablets (200 µg) in a group of 60 women with term singleton pregnancy. After 12 hours of induction, the mean Bishop score was 9.7 in Group II compared with only 7.3 in Group I. The mean time from insertion of the drug to delivery was shorter in group II (16.5 hours) than in group I (25.7 hours). There were no significant differences in the spontaneous labour rate, need for oxytocin augmentation, type of delivery, and Doppler flow velocity waveforms of the umbilical artery. The average number of required doses per patient was 1.8 in group II and 2.7 in group I. The spontaneous vaginal delivery rate was 88% in group I and 80% in group II; 6% and 10%, respectively, were delivered by caesarean section.

Thus it was concluded that inexpensive drug misoprostol, is associated with higher Bishop scores and a shorter interval to vaginal delivery than dinoprostone tablets.

Vaginal Misoprostol vs. Vaginal Dinoprostone Gel

Danielian et al. studied the efficacy of vaginal misoprostol (50 µg 4 hourly) in comparison with vaginal dinoprostone gel (1 mg 6 hourly) for induction of labour. The misoprostol group had a highly significant reduction in median induction-delivery interval compared with the dinoprostone group. There were no adverse neonatal outcomes associated with the use of misoprostol. Women in the misoprostol group experienced more pain in the interval between induction and being given analgesia in labour, but this did not reach statistical significance. The authors concluded that misoprostol 50 µg vaginally is a more effective induction agent than 1 mg dinoprostone vaginal gel, with no apparent adverse effects on mode of delivery, or on the foetus. The higher pain scores in the misoprostol group must be balanced against the reduction in time spent having labour induced, and the reduction in need for intravenous oxytocin augmentation.

Van Gemund compared the efficacy of vaginal misoprostol (25 µg 4 hourly) with vaginal dinoprostone gel (1 mg 4 hourly). The median induction-delivery interval was longer in the misoprostol group compared with the dinoprostone group (25 vs. 19 hours). The caesarean section rate was lower in the misoprostol group: 16.1% vs. 21%, but this difference was not statistically significant RR = 0.8 (95% CI 0.6–1.04). 'Adverse neonatal outcome'
was found to be similar in both groups: 21% in the misoprostol and 23% in the dinoprostone groups. Significantly fewer neonates were admitted to neonatal ICU in the misoprostol group compared with dinoprostone 19% vs. 26% (RR = 0.7, 95% CI 0.5-0.98). The authors concluded that misoprostol in this dosing regimen is a safe method of labour induction.

Gregson et al\textsuperscript{88} conducted a single-blind randomised controlled trial comparing the efficacy of vaginal misoprostol tablet (25 µg 4 hourly) with vaginal dinoprostone gel (1–2 mg 6 hourly). There were no significant differences between the two groups in induction-to-vaginal delivery interval, mode of delivery, number of women delivering within 24 hours and neonatal outcomes. The incidence of uterine contraction abnormalities (tachysystole and hyperstimulation) and the incidence of abnormal CTG recordings were also similar for both groups. Thus both the drugs are equally effective, misoprostol being much less costly.

Thus, misoprostol in doses 25–50 µg 4 hourly is having comparable safety and efficacy when compared to 1–2 mg dinoprostone gel 6 hourly.

**Vaginal Misoprostol vs. Vaginal Dinoprostone Insert**

Garry et al\textsuperscript{89} in 2003 compared the safety and efficacy of vaginal misoprostol tablets (50 µg 3 hourly) with vaginal dinoprostone gel (12 hourly) for induction of labour. The authors concluded that intravaginal misoprostol and dinoprostone were safe and effective medications for use in cervical ripening before labour induction. Misoprostol resulted in a shorter interval from induction to delivery. However, Caesarean delivery for a non-reassuring foetal heart rate tracing was more common with misoprostol.

Wing et al\textsuperscript{90} in October 2008 compared the efficacy of dinoprostone vaginal insert to misoprostol vaginal insert for induction of labour. A total of 1,308 women requiring cervical ripening (modified Bishop score less than or equal to 4) before induction of labour were randomly assigned to receive misoprostol vaginal insert 100 µg (n=428), misoprostol vaginal insert 50 µg (n=443) or 10 mg dinoprostone vaginal insert (n=436). The misoprostol vaginal insert 100 µg and the dinoprostone vaginal insert had similar median time intervals to vaginal delivery, whereas the misoprostol vaginal insert 50 had a significantly longer time to vaginal delivery. The three products had similar cesarean rates and safety profiles.

Ozkan et al\textsuperscript{91} in 2008 compared the efficacy and safety of vaginal misoprostol with dinoprostone vaginal insert for labour induction in term pregnancies. The subjects were randomised to receive either [i] 50 µg misoprostol intravaginally every 4 hour to a maximum of five doses or [ii] 10 mg dinoprostone vaginal insert kept for a maximum of 12 hours. Time interval from induction to vaginal delivery was found to be significantly shorter in misoprostol group when compared to dinoprostone subjects (680 min vs. 1070). More subjects required oxytocin augmentation in dinoprostone group (62.5% vs. 35.7%). Cardiotocography tracings revealed early decelerations occurring more frequently with misoprostol induction (10.7 vs. 0%). Tachysystole and uterine hyperstimulation, mode of delivery, rate of caesarean sections due to foetal distress and adverse neonatal outcome were not demonstrated to be significantly different between groups. The authors concluded that using vaginal misoprostol is an effective way of labour induction, misoprostol and dinoprostone being equally safe.

**Vaginal Misoprostol vs. Endocervical Dinoprostone Gel**

Varaklis et al\textsuperscript{92} compared 25 µg misoprostol every 2 hours to commercially available endocervical
preparation containing 0.5 mg of PGE₂ gel administered at 6 hour intervals for a maximum of two doses. Women who received misoprostol experienced a significantly reduced mean time from drug administration to onset of three contractions in 10 minutes (6.7 vs. 12.4 hours). Mean time to rupture of membranes was also shorter in the misoprostol group (9.7 vs. 13.6 hours), as was the mean time to delivery (16 vs. 22.4 hours). Three patients in the misoprostol group experienced uterine hypertonus but not related foetal morbidity. Thus, they concluded that misoprostol is more effective than endocervical PGE₂ in bringing about labour and delivery.

Krithika et al. conducted a prospective randomized controlled trial to compare the efficacy and safety of intravaginal misoprostol with endocervical dinoprostone gel for induction of labour in cases of unfavourable cervix. One hundred women with an unfavourable cervix requiring induction of labour were randomised to receive either 25 µg vaginal misoprostol 4 hourly or 0.5 mg of endocervical dinoprostone 12 hourly. The improvement in Bishop’s score at 12 hours was significantly better in the misoprostol group. Induction to delivery interval was shorter in the misoprostol group, 16.59 +/- 5.13 hours vs. 27.77 +/- 12.71 hours. The rate of complications was comparable. Thus, it was concluded that vaginal misoprostol 25 µg 4 hourly is safe and effective for induction of labour with shorter induction to delivery interval.

Shivarudraiah and Palaksha conducted a prospective randomised controlled trial to compare the efficacy and safety of intravaginal misoprostol with endocervical dinoprostone gel for induction of labour in women with unfavorable cervix. Three hundred and twenty women with an unfavourable cervix requiring induction of labour were randomised to receive either 25 µg vaginal misoprostol 4 hourly or 0.5 mg of endocervical dinoprostone 6 hourly. Median induction to active phase interval was similar in both groups (465 vs. 457), but there was no significant difference in median induction to delivery interval in misoprostol and dinoprostone groups (684 vs. 690). The proportion of women delivering in 24 hours was similar, requirement of oxytocin augmentation was similar. No difference was noted in overall incidence of caesarean section, vaginal/instrumental delivery rate.

Similar study was carried out in Government Medical College and Hospital (GMCH), Aurangabad, Maharashtra by Sonali D, Kanan Y and Pradeep I in 2012 to compare safety and efficacy of intravaginal misoprostol tablet as compared to endocervical dinoprostone gel for induction of labour in women with unfavorable cervix. Primary outcome measure was induction to delivery interval while secondary outcome measures were labour characteristics, maternal and neonatal outcomes. Of 100 women randomised, 50 received tab misoprostol 25 µg every 4 hourly (maximum 6 doses) and 50 received dinoprostone gel 0.5 mg every 6 hourly (maximum 4 doses). Both groups were found to be comparable with respect to primary and secondary outcome measures except the cost of misoprostol was 50 times cheaper than dinoprostone gel.

Thus, misoprostol tablet is having comparable safety, efficacy and side effect profile when compared with the established agent dinoprostone gel thus may be used as a cost effective alternative to dinoprostone gel for induction of labour.

Vaginal Misoprostol vs. Mechanical Methods

Perry et al. studied the efficacy of vaginal misoprostol (25 µg 4 hourly) to intracervical Foley’s catheter and intravaginal dinoprostone. They found Foley’s catheter/dinoprostone to have lesser induction ripening interval (7.5 vs. 12.0 hours) as well as induction delivery interval (17.4 vs. 21.2 hours).
Chung et al\textsuperscript{96} studied efficacy of combination intravaginal misoprostol and intracervical Foley catheter for prelabour cervical ripening. Women were assigned to one of three groups:
• Intravaginal misoprostol 25 µg every 3 hours,
• Intracervical 16F Foley catheter, or
• Combination misoprostol-Foley catheter

They concluded that intravaginal misoprostol and intracervical Foley catheter are comparable for preinduction cervical ripening. The combination of the two methods did not provide additional efficacy.

Prager et al\textsuperscript{97}, included 588 subjects and randomised them for induction of labour using intravaginal dinoprostone (2 mg once every 6 hours) or misoprostol (25 µg once every 4 hours) or a transcervical balloon catheter. The shortest mean induction-to-delivery interval was obtained with the catheter (12.9 hours) vs. 16.8 and 17.3 hours for dinoprostone and misoprostol, respectively. The efficacies of the two prostaglandins were similar. The maternal and neonatal outcomes associated with each of the three procedures were similar. The researchers concluded that induction of labour with a transcervical balloon catheter is effective and therefore safe and can be recommended as the first choice.

Thus, transcervical balloon catheter can be used as a safe and cost effective alternative to prostaglandins. Though combination of catheter with dinoprostone gel is found to be more effective, similar efficacy could not obtained using catheter with misoprostol tablet. The two prostaglandins, dinoprostone and misoprostol, were shown to be equally effective and safe, while misoprostol costs significantly less and is easier to store.

Oral

Ngai et al\textsuperscript{98} investigated the effectiveness of oral misoprostol as a cervical priming agent for patients presenting with pre-labour rupture of membranes at term. Eighty patients were randomised to receive either 200 µg of misoprostol or 50 mg of vitamin B\textsubscript{6} orally 1 hour after admission. The cervical score was significantly improved and the induction rate was also reduced in the misoprostol group when compared with the control group. The interval from recruitment to onset of labour, duration of labour, and the interval from recruitment to delivery were significantly shorter in the misoprostol group. The mode of delivery and the perinatal outcome were similar for the two groups. The authors concluded that oral misoprostol is an effective agent for cervical priming and labour induction in patients with pre-labour rupture of membranes at term.

Thus, oral misoprostol is simple and noninvasive. Onset of action is most rapid by this route and there is almost complete absorption, peak levels reached by 30 minutes. It might reduce the incidence of chorioamnionitis (associated with repeated vaginal examinations) particularly in the presence of prelabour rupture of membranes.

Comparative Studies of Oral Misoprostol

**Oral Misoprostol vs. Vaginal Misoprostol**

Wing et al\textsuperscript{99} compared 50 µg of oral misoprostol every 4 hourly with 25 µg vaginal misoprostol every 4 hourly for maximum 6 doses. Overall mean time to delivery (hours ± SD) was 29 ± 14.1 in oral group and 23.2 ± 12.8 in vaginal group. Mean number of doses required were 3.3 ± 1.7 in oral group and 2.3 ± 1.3 in vaginal group. There was no significant difference in maternal and perinatal morbidity. Thus, they concluded that oral administration of 50 µg dose of misoprostol appears less effective than vaginal administration of 25 µg dose of misoprostol for cervical ripening and labour induction.

Nopdonrattakoon L\textsuperscript{100}, studied 106 pregnant women at term with unfavorable cervix with
Bishop’s score less than 4 to receive intravaginal misoprostol 50 µg every 4 hourly or oral misoprostol 50 µg every 4 hourly. It was found that time interval from induction to delivery in oral group was significantly longer than intravaginal group (881 ± 443 min vs. 637 ± 373 min respectively). The number of dosage required was higher in oral group but there was no difference between both groups with regard to failure of induction and maternal and neonatal complications.

In cross sectional comparative study by Bano et al, 200 term women were recruited and allotted to receive 50 µg of misoprostol every 4 hourly either vaginally or orally. Mean induction to delivery interval was similar in both groups (9.09 vs. 9.08 hours). This study concluded that oral route was as effective as vaginal route in terms of induction to delivery interval, number of dosage, caesarean section rate, maternal complications and neonatal outcome.

RCOG committee opinion states that in women with an unfavorable cervix, oral misoprostol 50 µg is less likely than vaginal misoprostol 25 µg to achieve vaginal birth within 24 hours. Oral misoprostol has similar efficacy to vaginal PGE2 gel in terms of vaginal birth within 24 hours.

Thus oral misoprostol is having comparable efficacy when compared with vaginal misoprostol but rise in the incidence of uterine contraction abnormalities is the cause of concern.

**Oral Misoprostol vs. Vaginal Mechanical Methods**

Abramovici et al compared oral misoprostol (50 µg 4 hourly) with cervical Foley catheter and intravenous oxytocin infusion. In multiparous patients the percentage delivered of their neonates within 24 hours and the median induction-to-delivery times were similar in the 2 groups. In nulliparous patients, however, delivery within 24 hours was significantly less likely in the misoprostol group (53.4% vs. 82.5%; p<0.001), and the median induction-to-delivery time was longer (23.3 hours vs. 17.2 hours; p<0.01). The incidence of hyperstimulation was higher in the oxytocin-Foley group (4.1% vs. 13.1%; p=0.02). They concluded that oral misoprostol is as effective as oxytocin-Foley’s catheter for inducing labour in multiparous women, but appears less efficacious in nulliparous patients.

**Oral Misoprostol vs. Endocervical Dinoprostone Gel**

Bartha et al compared the efficacy, safety, and tolerance of oral misoprostol with endocervical dinoprostone for cervical ripening and labour induction. They concluded that a single dose of 200 µg oral misoprostol was more effective for cervical ripening and labour induction than 0.5 mg of dinoprostone endocervically every 6 hours.

Nagpal et al from New Delhi conducted a study in April 2009 comparing the efficacy of oral misoprostol (50 µg 4 hourly) with endocervical dinoprostone gel (0.25 mg 6 hourly). Twenty women in the misoprostol group (n=31) delivered within 12 hours compared with 5 in the PGE2 group (n=30). The induction-to-delivery interval in the misoprostol group was shorter than in the PGE2 gel group (615 vs. 1070 min). The mode of delivery was comparable between the 2 groups. Abnormalities in uterine contractions and neonatal outcomes were also comparable. The requirement for oxytocin was lower and patient satisfaction was better in the misoprostol group.

Oral misoprostol is more effective than endocervical dinoprostone gel for induction of labour.

**Titrated oral misoprostol**

This is the latest method of administration being studied for induction of labour with misoprostol.
The rationale behind this is the short half-life of misoprostol when administered by oral route (peak concentration at 34 minutes and half-life of 20–40 minutes. This method is designed to reduce the risk of hyperstimulation which is seen with misoprostol, especially by the oral route. The principle used is 200 µg of misoprostol tablet with dissolved in 200 ml of water (1µg/ml), initial administration of 20 µg/hour till adequate contractions are achieved. Dose is increased to 40 µg/hour if sufficient contractions are not reached in 4 doses. When adequate contractions are achieved, no further misoprostol is given if contractions decrease; hourly doses of misoprostol are restarted at 10 µg/hour and increased to 20 or 40 µg/hour if necessary. Induction failure is defined as inability to reach active phase by 36 hours.

Hofmeyr et al. compared titrated oral misoprostol solution with 2 mg vaginal dinoprostone for induction of labour. They found similar efficacy and hyperstimulation rates.

Cheng and Chen evaluated the efficacy of titrated oral misoprostol in a study group of 77 women. The mean interval from induction to vaginal delivery for all the women was 9.7 hours, with a 2.3 hour active phase. The mean misoprostol dosage was 206 µg, with eight women (10.4%) requiring oxytocin augmentation. There was no uterine hyperstimulation or induction failure, except for seven cases of uterine tachysystole (9.1%). They concluded that titrated oral misoprostol is a safe and effective method of labour induction because the dosage can be adjusted according to individual response.

**Comparison of Titrated Oral Misoprostol with Other Methods of Induction of Labour**

Cheng, Ming and Leo compared titrated oral misoprostol vs. vaginal misoprostol (25 µg 4 hourly) for induction of labour in women between 34 and 42 weeks with unfavorable cervix (Bishop’s score ≤ 6). Completed vaginal cervix occurred within 12 hours in 75 (74.3%) women in the titrated oral group and 27 (25.5%) women in the vaginal group (relative risk [RR] 8.44, 95% confidence interval [CI] 4.52–15.76). The incidence of hyperstimulation was 0.0% in the titrated oral group compared with 11.3% in the vaginal group (RR 0.08, 95% CI 0.01–0.61). Although more women experienced nausea (10.9%) in the titrated oral group (RR 27.07, 95% CI 1.57–465.70), fewer infants had APGAR scores of less than 7 at 1 minute in the titrated oral group than in the vaginal group (RR 0.10, 95% CI 0.01–0.76).

Kundodyiwa and colleagues conducted a review of the use of low dose oral misoprostol for induction of labour. They concluded that low-dose oral misoprostol solution (20 micrograms) administered every 2 hours appeared to be as effective as both vaginal dinoprostone and vaginal misoprostol, with lower rates of caesarean delivery and uterine hyperstimulation, respectively.

Though, titrated oral misoprostol has proven effective in few studies, it is considered that future studies this area may give us definitive word regarding its safety and efficacy.

**Oral Misoprostol on Outpatient Basis**

Kipikasa et al. evaluated the use of oral misoprostol outpatient basis for pre-induction cervical ripening and induction of labour. Forty nine subjects followed in an outpatient obstetrical clinic with pregnancies of at least 40 weeks’ gestation, and an unfavorable Bishop’s score were assigned randomly to receive oral misoprostol 50 or 25 µg every 3 days for a maximum of three doses.

Twenty three subjects received misoprostol 25 µg and 26 received 50 µg. The mean interval (+/-standard deviation) from start of cervical ripen-
ing to delivery was 2.4 days +/-0.3 vs. 3.9 days +/-0.7 for the 50 and 25 µg. No adverse events were noted.

Gaffney et al110 studied the use of oral misoprostol 100 µg given orally on outpatient basis. Subjects received either oral misoprostol 100 µg or placebo daily for 3 days unless the subject developed significant cervical change or began labour spontaneously. Study drug was repeated every 24 hours for a maximum of three doses if subjects did not develop significant cervical change or enter labour. A significant difference was noted in reduction of time from study entry to both active phase and delivery in the misoprostol group. Fewer women remained undelivered after the 72 hours study period in the misoprostol group. There were no differences in route of delivery or neonatal outcomes between groups.

RCOG committee2 opinion states that induction of labour in the outpatient setting should only be carried out if safety and support procedures are in place and the practice of induction of labour in an outpatient setting should be audited continuously.

**Endocervical**

Srisomboon et al111 compared the efficacy of intracervical misoprostol with vaginal misoprostol. No significant differences were noted between intracervical and intravaginal misoprostol in terms of Bishop’s score change, (score 7.2 vs. 7.5), interval from gel insertion to vaginal delivery (17.0 hours vs. 16.4 hours), route of delivery and perinatal outcome. Uterine tachysystole occurred in 24% and 32% in the intracervical and intravaginal groups respectively which did not significantly differ. No evidence of foetal distress was noted in these events. The authors concluded that the two routes of misoprostol application appeared to be safe and equally effective in ripening cervix and inducing labour, however, the intravaginal application was more convenient to administer practically as compared with the intracervical.

Liu et al from Taiwan112 also evaluated the safety and efficacy of intracervical misoprostol (50 µg 4 hourly). They concluded that misoprostol as a single 50 µg intracervical dose is safe and effective. However, they advised caution in repeated doses as might be required in an unfavorable cervix.

Chang et al113 compared the safety and efficacy of intracervical misoprostol (50 µg 4 hourly) with intracervical dinoprostone (0.5 mg 4 hourly). They concluded that as compared to dinoprostone, intracervical misoprostol was more effective in cervical ripening and labour induction at term. The higher frequency of uterine hypercontractility associated with the use of misoprostol did not increase the risk of adverse intrapartum and neonatal outcomes.

Although intracervical misoprostol has been found to be effective some studies, the intravaginal application is more convenient to administer practically as compared to intracervical.

**Buccal and sublingual**

With these routes there is rapid increase in concentration and higher $C_{max}$ than oral route, as first pass metabolism is avoided. RCOG committee2 opinion states that there is insufficient data to determine the effectiveness of buccal/sublingual misoprostol as compared with oral and vaginal misoprostol.

**Misoprostol for Labour Induction with Prior Caesarean Births**

The only randomised controlled trial by Wing et al114 comparing vaginal misoprostol with oxytocin in women with prior caesareans was terminated prematurely because of 2 uterine scar disruptions in subjects who had received multiple doses of vaginal misoprostol 25 µg.
Aslan et al\textsuperscript{115} in a retrospective report compared labour induction with vaginal misoprostol in previous caesarean delivery vs. that in unscarred uteri. Uterine rupture occurred in 4 out of 41 patients in the prior caesarean group compared to none in 50 patients without scarring. Thus, use of misoprostol in prior caesarean deliveries, is not recommended.

Oxytocin

Use of oxytocin drip was described by Theobald and Helman in 1948. Oxytocin, an octapeptide neurohormone that originates in the hypothalamus is secreted by the posterior lobe of the pituitary gland. This is secreted in a pulsatile manner. The uterus becomes increasingly responsive to oxytocin as pregnancy progresses; there is a gradual increase in response from 20–30 weeks of gestation, followed by a plateau from 34 weeks of gestation until term, when sensitivity increases.

It seems that oxytocin has direct stimulatory effects on the myometrium in addition to stimulating decidual prostaglandin production. An increased level of prostaglandin F2\textalpha metabolite was demonstrated in women who underwent successful oxytocin induction of labour, whereas this increase was not present in failed inductions.

The intravenous route is used almost exclusively to stimulate the pregnant uterus because it allows precise measurement of the amount of medication being administered and a relatively rapid discontinuation of the drug when side effects occur. Oxytocin is administered as a dilute solution, with the flow rate into the intravenous line precisely regulated by an infusion pump.

ACOG states that each hospital’s obstetrics and gynaecology department should develop guidelines for the preparation and administration of oxytocin. One United States Pharmacopoeia unit being equivalent to 2 mg of oxytocin. Uterine response ensues after 3–5 minutes of infusion, and a steady level of oxytocin in plasma is achieved by 40 minutes.

Several trials (Blackmore et al\textsuperscript{116}, Mercer et al\textsuperscript{117}, Chua et al\textsuperscript{118}, Satin et al\textsuperscript{119}, Muller et al\textsuperscript{120}) have compared options in oxytocin dosage increases and time intervals between dose increases. Starting doses have ranged from 0.5 to 2 mU/min, with some as much as 6 mU/min. Increments of dose increase have ranged from as low as 1–2 mU/min to as much as 6 mU/min, with adjustments for increased uterine activity. Time intervals between increases have ranged from 15 to 40 minutes. Although low-dose regimens (initial dose 0.5–2 mU/min, with incremental increases of 1–2 mU/min every 15–40 min) are commonly used in the United States, high-dose regimes (initial dose 6–8 mU/min, with incremental increases of 6 mU/min every 15–40 min) have been shown to be safe and effective for labour induction in patients with viable pregnancies (Merrill and Zlatnic\textsuperscript{121}). A meta-analysis of 11 trials by Crane and Young\textsuperscript{122} compared low-dose with high-dose oxytocin for labour induction. They found that greater increases and shorter intervals were associated with shorter labour and lower rates of intra-amniotic infections and cesarean delivery for dystocia, but more hyperstimulation was noted. Based on recent pharmacokinetic data, many obstetricians have moved to a regimen whereby the dose of oxytocin is increased by 1–2 mU/min every 40 minutes. Advantages of this regimen derive from not increasing the oxytocin dose before steady-state levels of oxytocin have been reached. This approach should lead to a lower total dosage of oxytocin required in addition to a lower incidence of hyperstimulation that can result from increasing the oxytocin dose before steady-state is reached. A potential disadvantage is that women who are relatively insensitive to oxytocin may have a prolonged course before adequate
labour is achieved. Nearly 90% of patients respond to 16 mU/min or less, whereas it is most unusual for a patient to require more than 20–40 mU/min.

In 1978, Pavlou et al. were the first to describe a protocol of pulsatile infusion. More recently, several randomised trials compared the safety and efficacy of pulsatile oxytocin administration with continuous infusion. Most authors (Salamalekis et al., Reid and Helewa, Wellcourt et al.) concluded that though there does not seem to be a shortening of the intervals to delivery, pulsatile administration of oxytocin reduces the amount of oxytocin required for successful labour induction. The concentration of oxytocin administered, the rate of infusion, and the interval between dose increments are subjects of study and debate.

**Mifepristone**

Mifepristone, also known as RU-486, is an anti-progestin and has been developed to antagonise the action of progesterone. Mifepristone now has an established role in the termination of pregnancy and has been approved by FDA, in combination with prostaglandins, for the first trimester abortion. Some studies have used in post term pregnancies and is probably a new field of research for labour induction.

Cochrane database of systematic review by Neilson JP (7 RCTs, 594 women, mixed parity and Bishop score < 6) that evaluated the effects of mifepristone vs. placebo/no treatment in women at term, found insufficient information to support the use of mifepristone to induce labour. However, there is recent evidence of serious neonatal side effects involving renal function in the form of ischemic hypoxic changes in the foetal kidney ultrastructure when labour was induced by mifepristone between 16 and 28 weeks of gestation. The smaller is the foetus, more obvious the changes.

RCOG committee opinion states that at present there is insufficient information to support the use of mifepristone to induce labour in a women with live foetus.

**Hyaluronidase**

The level of hyaluronic acid increases markedly after the onset of labour. Cervical injection of hyaluronidase was postulated to increase cervical ripening.

Kavanagh et al. in Cochrane database of systematic reviews assessed the effects of intracervical hyaluronidase in women undergoing induction of labour. Women given hyaluronidase were reported to achieve significant improvement in cervical status (RR 0.62, 95% CI 0.52 to 0.74) and there were significantly fewer caesarean births (RR 0.37, 95% CI 0.22 to 0.61) when compared with placebo. No side effects for mother or baby were reported. Thus, intracervical hyaluronidase is likely to improve cervical ripening and reduce caesarean rates when compared with placebo. Although intracervical hyaluronidase may be effective in improving cervical ripening and reducing caesarean birth rates, it is an invasive procedure that women may find unacceptable when alternative available methods, such as vaginal PGE2, are less invasive.

RCOG committee opinion states that hyaluronidase should not be used for induction of labour.

**Corticosteroids**

Corticosteroids are postulated to have a promoting effect in induction of labour but their role in the process of labour is not well understood. Kavanagh et al. in Cochrane database of systematic reviews (one RCT involving 66 women, and unfavorable cervix) assessed the effects of corticosteroids versus intravenous oxytocin in cervical priming and induction of labour. Vaginal birth within 24 hours was not reported. There were no reports of uterine hyperstimulation, APGAR score < 7 or maternal...
fever in either group and caesarean birth rates were not significantly different (RR 0.40, 95% CI 0.08 to 1.92).

The available evidence relating to the effects of corticosteroids for cervical priming and induction of labour is limited thus RCOG committee (2008) opinion states that corticosteroids should not be used for induction of labour.  

**Oestrogen**
The increase in the serum oestrogen-to-progesterone ratio that occurs before the onset of labour is believed to activate prostaglandin production, which in turn stimulates cervical ripening. One systematic review by Thomas et al (6 RCTs involving 341 women, Bishop’s score < 3) assessed the effects of oestrogen in women undergoing induction of labour. The included studies compared oestrogen (intravenous, oral, vaginal or extra-amniotic) versus placebo (four RCTs); versus vaginal PGE$_2$ (one RCT); versus intracervical PGE$_2$ (one RCT); versus oxytocin (one RCT); and versus extra-amniotic PGF2α (one RCT). It reported no significant differences between the oestrogens and the placebo groups in the rates of caesarean births, instrumental vaginal births or uterine hyperstimulation with or without foetal heart rate (FHR) changes. There were insufficient data for the remaining comparisons. Overall, there were insufficient data to make any meaningful conclusion. Limited evidence suggested that oestrogen and placebo achieve similar maternal and foetal outcomes. There was insufficient data available for the comparisons between oestrogen and vaginal PGE$_2$, oxytocin alone or extra-amniotic PGF2α.

RCOG committee, 2008 opinion stated that oestrogen should not be used for induction of labour.

**Vaginal Nitric Oxide Donors**
Nitric oxide is considered a fundamental mediator of cervical ripening without causing uterine contractions or adverse effects on the mother and foetus.

Studies by Chanrachakul and Bullabo state that vaginal glyceryl trinitrate and nitric oxide donors have not been shown to be of any particular benefit when compared with vaginal PGE$_2$ as induction agents, although they seem to be associated with less uterine hyperstimulation. However, there are significant side effects associated with its use. RCOG committee 2008 opinion states that vaginal nitric oxide donors should not be used for induction of labour.

**Relaxin**
Relaxin is a protein formed by two amino acid chain. Its role in pregnancy and parturition is not clear. Because of difficulty in using human, relaxin bovine or porcine relaxin is used with controversial results. Controlled studies indicate improvement in cervical status with no case of uterine hyperstimulation, however further studies are required to assess its safety and efficacy.

**Homoepathy and Herbal Supplements**
Homoepathy involves the administration in dilution of substances aimed at the alleviation of symptoms, that the same substances generally cause in their undiluted form. It has been suggested that the herbs belonging to the Caulophyllum genus are useful in establishing labour, when uterine contractions are short and/or irregular or when they stop.

RCOG committee 2008 opinion states that in the absence of sufficient evidence to prove either effectiveness or harm, homeopathy as a method of induction is not recommended to be offered.  

The use of herbal supplements to promote health has become popular. It is believed by some that drinking herbal beverage teas while pregnant nourishes and tones the uterus, supporting optimal health in pregnancy.
RCOG committee 2008 opinion states that no evidence was identified relating to the effects of herbal supplements in cervical priming or induction of labour.2

CONCLUSION

Amongst the numerous methods of induction, prostaglandins are the preferred for induction of labour. Dinoprostone gel used endocervically is found to be both, safe and effective method, but its cost and need of refrigeration limit its universal use. Misoprostol vaginal tablet is rapidly becoming a cost effective alternative to dinoprostone gel, but lack of global consensus regarding its safety and thus absence of global registration for this purpose is a problem.

Oxytocin induction is not found to be as effective as prostaglandins. Though mifepristone was found to be effective, there is inadequate data on its safety profile. Other methods like use of hyaluronidase, steroids, oestrogen, herbal supplements, homeopathy are not found to confer any advantage over the established methods of labour induction.

Even with the availability of the armamentarium of inducing agents, simple methods like membrane sweeping should be offered whenever opportunity exists, so as to decrease the rate of formal induction.

About the Authors

Dr Varsha Deshmukh and Dr Sonali Deshpande are Associate Professor, Dr Kanan Yelikar is Professor and Head and Dr Pradeep Ingale is Assistant Professor, Department of Obstetrics and Gynaecology, GMCH, Aurangabad, Maharashtra.

The complete list of references is available on request to the editorial office.
Bacterial vaginosis is the most common cause of abnormal vaginal discharge in women of childbearing age. It is a syndrome of unknown cause characterized by depletion of the normal *Lactobacillus* population and an overgrowth of vaginal anaerobes, accompanied by loss of the usual vaginal acidity. In 1983, the term ‘bacterial vaginosis’ replaced the older term ‘*Gardnerella* vaginitis’. This recognized the fact that many anaerobic or facultative anaerobic bacteria are present and that classical signs of inflammation are absent.¹

Women with symptomatic bacterial vaginosis report an offensive, fishy-smelling discharge that is most noticeable after unprotected intercourse or at the time of menstruation. The diagnosis can be confirmed by microscopy ± additional tests. About 50% of cases are asymptomatic. Bacterial vaginosis is associated with infective complications in pregnancy and following gynaecological surgery, and is a risk factor for the acquisition of sexually transmitted infections (STIs) including human immunodeficiency virus (HIV).

**EPIDEMIOLOGY**

In unselected populations in the UK, the prevalence of bacterial vaginosis is 10–20%, but it may be as high as 36% in women attending STI clinics and 28% in those seeking elective termination of pregnancy.² A prevalence of more than 50% was reported in rural Uganda.³ The debate about whether bacterial vaginosis is an STI or merely sexually associated continues. A meta-analysis has concluded that bacterial vaginosis has the characteristics of an STI: being associated with partner change and other STIs.⁴ The strongest evidence against it being an STI has come from studies reporting similar rates in self-reported virgin and non-virgin women.⁵–⁷ This has been chal-
Challenged by a detailed study that reported no bacterial vaginosis in women denying any oral or digital genital contact. In many studies, it is associated with black race and intrauterine device use. The condition often arises spontaneously around the time of menstruation and may resolve spontaneously in mid-cycle. It is not known how often bacterial vaginosis occurs in post-menopausal women.

**AETIOLOGY AND PATHOGENESIS**

Lactobacilli dominate the normal vaginal flora, although other organisms may be present in small numbers. When bacterial vaginosis develops, the lactobacilli reduce in concentration and may disappear whilst there is an increased concentration of anaerobic and facultative anaerobic organisms. Lactobacilli produce inhibitory mediators including lactic acid, H$_2$O$_2$, defensins, and bacteriocins. The triggers for bacterial vaginosis are probably multiple. An increase in vaginal pH from the normal 3.5–4.5 to as high as 7.0 is observed, which reduces the inhibitory effect of H$_2$O$_2$ on anaerobic growth. Hormonal changes and inoculation with organisms from a partner might also be important.

The organisms classically associated with bacterial vaginosis using culture and those more recently identified using molecular techniques are shown in Table 1. The description of the biofilm that develops in bacterial vaginosis by Swidsinski and colleagues places *Gardnerella vaginalis* once again at the centre of pathogenesis of bacterial vaginosis. In some women, the biofilm covered the entire biopsy; in others, it was more patchy. *Gardnerella* accounted for 90% of bacteria seen in the biofilm, with *Atopobium vaginae* the only other numerically important organism. Lactobacilli predominated in women with normal flora but did not form a biofilm.

**Table 1. The organisms classically associated with bacterial vaginosis using culture are shown in the first column and those more recently identified through molecular techniques in the second**

<table>
<thead>
<tr>
<th>Organism Name</th>
<th>Organism Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Gardnerella vaginalis</em></td>
<td><em>Atopobium vaginae</em></td>
</tr>
<tr>
<td><em>Bacteroides (Prevotella)</em></td>
<td><em>BVAB1-3 (Clostridiales)</em></td>
</tr>
<tr>
<td><em>Mycoplasma hominis</em></td>
<td><em>Megasphaera</em></td>
</tr>
<tr>
<td><em>Mobiluncus species</em></td>
<td><em>Sneathia</em></td>
</tr>
<tr>
<td></td>
<td><em>Leptotrichia</em></td>
</tr>
</tbody>
</table>

**Table 2. Composite (Amsel) criteria for the diagnosis of bacterial vaginosis**

- Vaginal pH > 4.5
- Release of a fishy smell on addition of alkali (10% potassium hydroxide)
- Characteristic discharge on examination
- Presence of ‘clue cells’ on microscopy of vaginal fluid mixed with normal saline

At least three of the four criteria must be fulfilled to make a diagnosis of bacterial vaginosis.

**DIAGNOSIS**

Bacterial vaginosis should be suspected in any woman presenting with an offensive, typically fishy-smelling vaginal discharge. Speculum examination shows a thin, homogeneous, white or yellow discharge adherent to the walls of the vagina. Amsel criteria (Table 2) have been the mainstay of diagnosis in settings such as genitourinary medicine clinics where microscopy can be performed. Epithelial cells covered with so many small bacteria that the border is fuzzy are termed ‘clue cells’ because their presence is a clue to the diagnosis. Any of the Amsel criteria can, however, be misleading:

- The appearance of vaginal secretions may be
Figure 1. Gram-stained vaginal smear from a woman with normal flora. Epithelial cells and their nuclei can be seen clearly. Gram-positive rods are typical of lactobacilli.

Figure 2. Gram-stained vaginal smear from a woman with bacterial vaginosis. There are many small bacteria present, some Gram-positive and some Gram-negative. Large, curved rods, typical of *Mobiluncus mulieris*, are present. Clue cells are not part of most scoring systems for bacterial vaginosis, and none are seen in this field.
altered by factors such as recent intercourse and douching.

- Both *Candida* and trichomoniasis can give a similar clinical appearance.
- A positive potassium hydroxide test may be found in the presence of semen.
- Vaginal pH may be elevated during menstruation or by the presence of semen.
- Detection of clue cells is the single most sensitive and specific criterion, but the interpretation of microscopy is subjective. Debris or degenerate cells can be mistaken for clue cells, and lactobacilli sometimes adhere to epithelial cells in low numbers.

Recent studies have concluded that there is a continuum from normal *Lactobacillus*-dominated flora to ‘severe bacterial vaginosis’. This is recognized in Gram-stain scoring systems but not with Amsel criteria. When the history is highly suggestive of the condition but the tests are negative, offer further testing if symptoms return.

**Gram Staining**

Examination of a Gram-stained vaginal smear is a quick and relatively simple means of diagnosis. It enables recognition of intermediate flora, and stored slides can be subsequently evaluated independently in research studies.

Typical lactobacilli are large, Gram-positive rods with blunt ends. *Gardnerella* is usually a Gram-negative coccus. The normal flora includes plentiful lactobacilli (Figure 1), whereas in bacterial vaginosis there are large numbers of Gram-negative cocci and small rods (Figure 2). Curved rods (*Mobiluncus* species) may be present. Recognition of intermediate categories can be more difficult and entails subjective assessment of the morphotypes. Scoring systems (eg, the Nugent) have attempted to reduce interobserver variability. A simplified scoring system (Hay–Ison criteria) has been recommended for use in genitourinary medicine clinics in preference to the Amsel criteria.14

**Other Tests**

Commercially available tests detect biochemical changes in vaginal fluid associated with bacterial vaginosis. However, the relatively high cost of the currently available tests compared with use of the Gram stain or Amsel criteria has limited their uptake. In routine practice, vaginal pH can be measured using pH-sensitive paper. A pH of less than 4.5 almost excludes bacterial vaginosis. If the pH is high, a high vaginal swab can be sent to the microbiology laboratory for examination by wet mount or Gram staining.

**DIFFERENTIAL DIAGNOSIS** (TABLE 3)

Other common causes of vaginal discharge are cervicitis caused by *Chlamydia* or gonorrhoea, candidiasis and trichomoniasis, all of which can also coexist with bacterial vaginosis. In cervicitis, there may be contact bleeding, and purulent discharge may be visible in the external os. *Candida* typically causes a curd-like discharge and is associated
with itching. Trichomonas causes a more purulent discharge and is associated with soreness and erythema. These organisms can be sought using specific diagnostic tests.

**MANAGEMENT**

Bacterial vaginosis is sometimes distressing and must be managed with sensitivity. Because it has a relapsing–remitting course in many women, the value of treating asymptomatic bacterial vaginosis has not been established. There is also no evidence that treatment reduces the prevalence in the community. Treatment should therefore be prescribed for control of symptoms and in situations in which it might prevent complications of a procedure (eg, termination of pregnancy) or in pregnancy.

**Antibiotics**

Antibiotics targeting anaerobic organisms should be effective in bacterial vaginosis. Metronidazole and clindamycin are obvious choices. The standard treatment for bacterial vaginosis is metronidazole, 400 mg orally 12-hourly for 5–7 days. An alternative is a 2-g single dose, or tinidazole 2 g which is more expensive. The cure rate immediately after treatment with metronidazole is up to 95%, but after 4 weeks this declines to 80% in open-label studies and less than 70% in blinded studies.

Topical treatments with intravaginal 2% clindamycin cream or 0.75% metronidazole gels are licensed for the treatment of bacterial vaginosis. They are more expensive than oral metronidazole but have similar efficacy and can be useful when systemic treatment is not desirable.

**Adverse Effects of Treatment**

Oral metronidazole is associated with nausea, a metallic taste, and alcohol intolerance. Allergic rashes occur occasionally. Initial concerns about potential teratogenicity have not been substantiated, and metronidazole can be used in pregnancy. Oral clindamycin can induce rashes and occasionally pseudomembranous colitis. About 10% of women develop symptomatic candidiasis following
treatment of bacterial vaginosis.

**Male Partners**
Four double-blind, placebo-controlled trials have failed to show any difference in bacterial vaginosis relapse rates following treatment of male partners with metronidazole, tinidazole or clindamycin. Many physicians advocate screening for STIs in the partners of women with recurrent bacterial vaginosis, but this is not based on prospective studies.

**Alternative Treatments**
Probiotics and prebiotics have been studied as a treatment for gastrointestinal conditions. Vaginal lactobacilli differ from those considered optimal for the gut, but several vaginal strains are now available. Another approach is to use lactic acid gel to acidify the vagina. Both approaches have been evaluated in small studies of variable quality, so there is insufficient evidence to support their routine use in current guidelines.19,20

**Relapses**
In some women, bacterial vaginosis recurs frequently following treatment. Management of such cases is difficult. It is reasonable to screen the sex partner for infections. If available, the probiotics or lactic acid gel may help to prevent relapse, otherwise regular antibiotic treatment is the only option. One study showed that use of metronidazole gel twice weekly reduced the rate of relapse, although it was associated with increased rates of candidiasis.21 The author usually prescribes metronidazole in the dosage and preparation preferred by the woman to self-treat at the first sign of relapse, accompanied by an antifungal agent if there is a history of candidiasis.

**Patient Advice and Self-help**
Vaginal douching and the use of shower gel and bubble bath should be avoided. If the woman washes her hair in the shower, she should avoid contact between the shampoo and the vulval area. It is sensible to use condoms with new sex partners to protect against infections, possibly including bacterial vaginosis.

**COMPLICATIONS**

**Pregnancy**
Bacterial vaginosis is associated with second-trimester miscarriage and preterm birth. The reported odds ratio is 1.4–7.0. It is thought that women with bacterial vaginosis are at increased risk of chorioamnionitis, which can stimulate preterm birth through the release of proinflammatory cytokines.22 Several studies have assessed the value of screening for and treatment of bacterial vaginosis in preventing adverse outcomes in pregnancy. The results have been variable; some studies showed a benefit with treatment in terms of reducing preterm birth
rates, but the largest study to date showed no benefit from treatment with short courses of metronidazole.23 On the basis of these studies, it cannot be concluded that antibiotic treatment of bacterial vaginosis in pregnancy will universally reduce the incidence of preterm birth. This was confirmed by the most recent Cochrane review.24

Termination of Pregnancy
Women infected with *Chlamydia trachomatis* who undergo elective termination of pregnancy are at high risk of endometritis and pelvic inflammatory disease. Bacterial vaginosis also confers an increased risk and may be present in almost 30% of such women. A double-blind, placebo-controlled trial in Sweden showed that the risk of endometritis in women without *Chlamydia* was 12.2% in a placebo-treated group and 3.8% in those prescribed oral metronidazole before termination.25 A more recent randomized controlled trial in Sweden found a fourfold reduction in infective complications with clindamycin cream compared with placebo.26

Other Gynaecological Surgery
Bacterial vaginosis has been associated with vaginal cuff cellulitis, wound infection and abscess formation after hysterectomy. No randomized trials have been performed to investigate the value of screening and treatment before such surgery. The potential role of bacterial vaginosis in infections following intrauterine device insertion, hysteroscopy, and dilatation and curettage has not been systematically studied.

HIV and STIs
HIV has spread rapidly through sub-Saharan Africa
and South East Asia in the last two decades. Initial reports identified genital ulcer STIs as co-factors for transmission. Bacterial vaginosis emerged as a cofactor for HIV acquisition in the Rakai study in rural Uganda. A study of pregnant women in Malawi reported bacterial vaginosis to be associated with HIV acquisition during pregnancy and the postnatal period. Potential mechanisms by which bacterial vaginosis might increase HIV transmission include effects on local immune mediators. Additionally, hydrogen peroxide produced by lactobacilli can inhibit HIV in vitro and is absent in most women with bacterial vaginosis. If bacterial vaginosis is established as an important risk factor for HIV spread, its control will become an important public health issue in many countries.

Bacterial vaginosis has also been associated with an increased incidence of non-gonococcal urethritis in male partners.

PREVENTION

Because the aetiology of bacterial vaginosis is not fully understood, it is not known how to prevent it. Antibiotics inhibit growth of the anaerobes but do not necessarily eliminate the factors that led to the development of bacterial vaginosis; therefore, relapse is relatively common. In the Rakai study, intermittent ‘mass treatment’, which included a course of metronidazole, did not reduce the prevalence of bacterial vaginosis, except in pregnant women.

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About the Author

Phillip Hay is Reader in Genitourinary Medicine at St George’s University of London, UK.
IN PRACTICE

Case of the Month
Large Fistula in Supratrigonal Region after Lower Segment Caesarean Delivery

Mallazzar Masaarapa Vijaykumar, Shivappa Prasanth, Madhusudan, Shobana Bhojaraj

VESICOUTERINE FISTULA

Introduction

Vesicouterine fistula (VUF) is a rare type of fistula accounting for only 1–4% of all cases of urogenital fistula. However, the incidence of VUF has been on the rise due to increasing incidence of lower segment caesarean section. Fistulas are common following caesarean section done for obstructed labour, deep transverse arrest and other neglected labour cases. VUF can be prevented if care is taken to separate the bladder from the uterus during caesarean sections.

Discussion

Most cases of VUF occur after lower segment caesarean delivery, and accounts for about 80% of VUF. Other causes include endometriosis, contraceptive device, malignant tumours, inflammations, rupture of the uterus, radiation therapy, iatrogenic trauma and intermittent or self-catheterisation of bladder. The classical Youssef’s syndrome is characterised by menouria, amenorrhoea, and VUF. In this case, the patient was having hypomenorrhoea and not amenorrhoea.

Symptoms of VUF depend on the level of the fistula and can be explained by the sphincteric mechanism of the uterine isthmus and the different pressure gradients. The shape and the diameter of the isthmus lumen change during the menstrual cycle. The menstrual blood accumulates in the uterine cavity, and when the pressure rises above 25–30 mm Hg, the sphincter of the isthmus relaxes and a bloody discharge occurs.

When a fistula is present above the isthmus, the menstrual blood passes directly from the uterine cavity into the bladder. No distention of the uterine cavity takes place, and the sphincter of the uterine isthmus fails to relax because the pressure in the uterine cavity does not increase.

When the fistula is located below the isthmus, the menstrual blood accumulates normally in the uterine cavity, and when the sphincter of the isthmus relaxes, the menstrual blood passes as it should through the cervix into the vagina and not through the fistula into the bladder. Conversely, when submitted to high pressure in the bladder, urine leaks through the fistula from the bladder into the uterine cervix and the vagina. The symptoms of urinary leakage through the vagina are similar to those of the more common vesico-vaginal fistula.

Diagnosis can be achieved by cystoscopy, hysteroscopy, cystography or excretory urography. Methylene blue instilled into the uterine cavity or through the urethra or through catheterisation of a visible lesion in the bladder wall can confirm the fistula. This test, however, does not show directly the fistulous tract and its specific location. Moreover, this test can be negative in patients with a long and tortuous tract. VUF following caesarean section may heal spontaneously with involution of uterus in 5% cases. In this case, approach was to separate the bladder from the uterine wall, excise the fistula tract and close bladder and uterus separately.

The bladder was suggested to be closed in two layers. Omentum had been interposed. Successful pregnancy and delivery has been reported by caesarean section after fistula repair.

References


About the Authors

Dr Vijaykumar MM is Associate Professor, Department of Obstetrics and Gynaecology, SS Institute of Medical Sciences & Research Centre and RC, Davangere, Karnataka. Dr Prasanth S is Associate Professor, Department of Obstetrics and Gynaecology and Dr Madhusudan is an Assistant Professor, Department of Surgery, SS Institute of Medical Sciences & Research Centre, Shimoga, Karnataka and Dr Shobana Bhojaraj is a Consultant Gynaecologist, Vinayaka Hospital, Shimoga, Karnataka.
CASE REPORT

Buschke Lowenstein tumour (BLT) or giant condyloma acuminatum is a rare sexually transmitted disease with an incidence of 0.1% in the general population. These are slow growing, cauliflower like destructive lesions that histologically have benign appearance. It is characterised by invasive growth and recurrence after treatment, and malignant transformation is possible.

22 years G2P1L1 at 24 weeks of pregnancy presented in the outpatient department of North Eastern India Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, with history of rapidly increasing lesion in the vulva and perianal region. The mass rapidly grew over one month and resulted in itching, bleeding and pain. The patient also gave history of weight loss and presence of multiple warts on the hands. The patient gave history of similar growth present on the penoscrotal area of the husband. The general examination was within normal limits. On abdominal examination, the uterus corresponded to 24 weeks gestation. Examination of perineal area of the patient revealed a warty cauliflower like growth involving labia majora and perianal region (15X12 cm²) (Figure1). Speculum examination showed thick curdy white discharge. Cervix and vagina seemed apparently healthy. On doing blood investigations, the complete blood picture was within normal limits. Venereal Disease Research Laboratory test (VDRL) and human immunodeficiency virus tests (HIV) tests were negative. Ultrasonography showed a single live foetus of 24 weeks gestation. Biopsy of the growth confirmed it as BLT (Figure 2 and 3). Human papilloma virus (HPV) testing could not be done due to in availability of the test in the institute. A dermatologist was consulted for further line of management. A combined decision to excise the growth was taken. Viral therapy was deferred as the patient was pregnant. The husband was also referred to the dermatologist for further management. The growth was surgically excised along with electrocautery. The recovery period was uneventful and the patient got discharge with an advice to follow up but was lost to follow up.

Giant condyloma acuminatum is an aggressive fungating variant of condyloma. It is a rare sexually transmitted
disease, triggered by HPV, usually genotype 6 or 11. It can be associated with congenital or acquired immunodeficiency including alcoholism, diabetes or immunosuppressive therapy.2

Giant condyloma acuminatum presents with 2.7:1 male to female ratio. For patients younger than 50 years, this ratio is increased to 3.5:1. The most common symptoms are perianal mass (47%), pain (32%), abscess or fistula (32%) and bleeding (18%).3

Chu et al analysed 42 known cases of giant condyloma acuminatum in English literature and reviewed their behaviour and management. They concluded it as highly aggressive tumour with propensity for recurrence and malignant transformation but without metastatic potential.4

Surgery is considered the treatment of choice for this disease.5 Complete excision is the preferred initial therapy when feasible. Wide local excision, faecal diversion or abdominoperineal resection have been used. Chemotherapy with 5 fluorouracil and focused radiation therapy may be used in certain cases of recurrence or extensive pelvic disease.

For unknown reasons, genital warts frequently increase in number and size during pregnancy. Acceleration of viral replication by the physiological changes of pregnancy might explain the growth of perineal lesions and progression of some to cervical neoplasm.6 Since our patient was pregnant so probably the genital wart grew into gigantic size. These lesions sometimes grow to full vagina or cover perineum, thus making vaginal delivery or episiotomy difficult. Therapy in pregnancy is mainly directed towards debulking symptomatic large growths.

Giant condyloma acuminatum or BLT of anorectal region and perineal region is an uncommon entity that has not been extensively reviewed hence more multi-institutional studies are necessary to further elaborate the nature and treatment of this rare disease.

Acknowledgement
I would like to thank Professor Vandana Raphel, Department of Pathology, NEIGRIHMS, Shillong for providing histopathological pictures of Condylomata acuminatum and Dr. Sharat Agarwal, Department of Orthopaedics and Trauma, NEIGRIHMS, Shillong for providing the help in preparing this manuscript.

About the Authors
Dr Manika Agarwal, Dr Rajlaxmi Mundhra, Dr Santa Singh is MD, Department of Gynaecology and Obstetrics and Dr Kalkambe A Sangma is a MD, Department Dermatology, North Eastern India Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya.

REFERENCES
**INTRODUCTION**

Placental insufficiency leading to intrauterine growth restriction (IUGR) in the fetus affects up to 15% of pregnancies. IUGR can present diagnostic and management challenges. The suspicion of IUGR arises when fetal biometry indicates small for gestational age (SGA), variously defined as abdominal circumference below 2 standard deviations, abdominal circumference at the 5th or 10th percentile, or estimated fetal weight less than the 10th percentile. SGA fetuses represent a heterogeneous group comprising constitutional smallness and pathological smallness. When pathologies, such as chromosomal aberration and genetic syndrome, are excluded, placental insufficiency is implied.

Management challenge lies in timely intervention especially when IUGR complicates a preterm pregnancy. On the one hand, the obstetrician wants to avoid unnecessary preterm delivery, which puts the neonate at risk for complications of prematurity such as cerebral palsy, neonatal death, respiratory distress, necrotizing enterocolitis, and intraventricular haemorrhage. On the other hand, there is the burden of possible *in utero* fetal demise from delaying delivering. Surveillance tools, such as electronic fetal heart monitoring and Doppler velocimetry, have been evaluated for their predictive strength of adverse perinatal outcomes which may guide decision regarding timing of delivery.

A synopsis of fetal growth regulation and fetal responses to placental insufficiency will first be presented. This is followed by a discussion on Doppler surveillance, with attention to clinical significance of the various arterial and venous waveforms. Finally, a suggested approach to management of IUGR is presented.

**REGULATION OF FETAL GROWTH**

The placenta acts as a conduit for transfer of nutrients and oxygen from mother
to fetus. Adequate substrate delivery depends on normal uterine perfusion, normal fetoplacental exchange area, and normal umbilical–placental perfusion. The placenta, being a metabolically active compartment, utilizes approximately 70% of the glucose and 45% of the oxygen being transferred. Placental growth follows a sigmoid-shaped curve, while fetal growth is exponential at 1.5% per day to term. The development of the matched fetoplacental unit from early pregnancy is critical in ensuring optimal fetal growth and development throughout pregnancy.

Following fertilization, cytotrophoblast migration occurs, leading to the establishment of placental adherence through anchoring the villi to the decidua and uterus. The process is complete when a low-resistance, high-capacitance placental compartment is achieved. Nutrient-rich blood entering the fetal circulation is delivered via the umbilical vein to the heart and liver. The ductus venosus (DV) acts as a shunt to direct a larger proportion of that blood to the liver and the remaining to the heart. Differential directionality of blood entering the right atrium ensures that well-oxygenated blood is distributed to the left ventricle, myocardium and brain. Low-nutrient venous return is forwarded to the placenta for re-oxygenation and nutrient-waste exchange via the umbilical arteries. Through autoregulation, various organs modify blood flow to meet the oxygen and nutrient demands.

FETAL RESPONSES TO PLACENTAL INSUFFICIENCY

In placental insufficiency, fetal responses are seen in various systems. Metabolically, fetal hypoglycaemia leads to blunting of pancreatic insulin responses, which in turn allows hepatic gluconeogenesis. As the situation worsens, there is inability to maintain oxidative metabolism. The ensuing anaerobic metabolism leads to the production of lactate, which is metabolized by the liver and used as an alternative substrate by fetal heart and brain. Acid-base balance will be maintained as long as fetal haemoglobin buffering capacity is sufficient with a matching removal rate by the liver, heart and brain. To maintain oxygenation of the vital organs such as the heart and brain, there is preferential shunting of blood from the umbilical vein through the DV. To facilitate preferential distribution of cardiac output to the left ventricle and thus coronary circulation and brain, there is an increase in peripheral vascular and placental blood flow resistance (increased right ventricular afterload) and a decline in cerebral flow resistance (decreased left ventricular afterload).

Fetal growth is exponential at 1.5% per day to term whereas placental growth follows a sigmoid-shaped curve.
Reduced liver perfusion from the increased shunting through the DV to the heart leads to the accumulation of blood lactate, thus acidaemia. As hypoxaemia and acidaemia worsen, the metabolic demands of the heart can no longer be maintained and myocardial dysfunction supervenes. With declining cardiac function, there is failure to accommodate the venous return and so the central venous pressure rises. Progressively, forward cardiac function fails. As cardiac dysfunction reaches a critical state, there is cardiac dilatation, indicative of loss of cardiovascular homeostasis. Typically, this starts in the right heart, manifesting as dilated tricuspid annulus, tricuspid regurgitation and reversed a wave in the DV flow. Characteristic responses are seen in the fetal behaviour when there is hypoxaemia. There is delayed central nervous system maturation and delayed central integration with the fetal heart, resulting in reduced short- and long-term fetal heart variation. As the hypoxaemia worsens, fetal activity slows down and fetal heart decelerations are observed.

**Fetal Surveillance**

There are multiple methods of fetal assessment in IUGR. The biophysical profile score, which incorporates fetal tone, fetal movement, fetal breathing, amniotic fluid volume and non-stress test, has been shown to predict fetal status and to produce improvement in outcomes when employed in high-risk pregnancies. Doppler ultrasound, which provides information about placental vascular resistance, preferential cerebral blood flow and filling capacity of fetal heart, allows the tracking of progression of placental insufficiency. The evidence for Doppler velocimetry in clinical management has been evaluated more thoroughly and more systematically than evidence for any other techniques in modern obstetrics. Doppler has been applied to various vessels including umbilical artery (UA), middle cerebral artery (MCA), uterine artery, DV, aorta (isthmus) and umbilical vein to predict placental dysfunction, to assess fetal cardiovascular status in response to hypoxia, and to predict adverse perinatal outcomes. Cardiotocography of the fetal heart also plays an important role in assessing the fetal condition in IUGR pregnancies, although it is considered a late-stage disease when there is abnormality such as deceleration in the tracing.

UA velocimetry gives information about placental function. There is abundant data linking abnormal UA Doppler and adverse outcomes in IUGR pregnancies. This is hardly surprising because
histological analysis has confirmed placental vascular pathology in the presence of abnormal UA velocimetry, such as reduction in volume of the intervillous space, reduction in the elaboration of distal villi, smaller exchange surface area, and thicker trophoblastic epithelium. The categories of abnormal UA waveforms—increased pulsatility index (PI), absent end-diastolic flow (AEDF) or reversed end-diastolic flow (REDF)—represent progressively worsening placental dysfunction. Hence, fetuses can be assigned varying degrees of risk according to these waveforms. The risk stratification can help inform the obstetrician on the level of fetal monitoring required.

McCowan et al. found raised UA PI to be associated with fetuses of smaller proportions in terms of birthweight, head circumference, and length. The utilization of UA PI for predicting adverse perinatal outcome has been widely practised for many years. The sensitivity and specificity for any adverse outcome have been reported to be 44.7% and 86.6%, respectively. Comparing pregnancies with positive end-diastolic flow, those with AEDF or REDF have been shown to be associated with lower birthweight, earlier gestation at birth, and higher frequency of severe respiratory distress syndrome, cerebral haemorrhage, hypoglycaemia and anaemia. The temporal changes on Doppler ultrasound in IUGR are well documented. Pregnancies with raised UA PI have been seen to sequentially deteriorate to UA AEDF and UA REDF. Perinatal mortality rates of up to 28% are reported in such cases. It is generally accepted that the finding of these waveforms indicates that the condition is severe and indeed should prompt the obstetrician to reassess management, in particular, to make a decision regarding delivery.

Decision on the timing of delivery should be considered with gestational age in mind. Baschat et al. investigated the outcomes of fetuses with abnormal Doppler velocimetry in arterial and venous circulations. The outcome parameters evaluated were perinatal mortality, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular haemorrhage, and circulatory insufficiency. Although fetuses with abnormal venous circulation generally fared the worst, gestational age at delivery was the most significant contributor to short-term outcomes after multivariate analysis. Although fetuses with abnormal venous circulation generally fared the worst, gestational age at delivery had a significant impact on short-term morbidity. One recommendation by Hartung et al. is that delivery should be considered if the pregnancy is greater than 32 weeks’ gestation as morbidity is low. In the ascertainment of gestation-specific survival and complication rates, Baschat et al. showed that the median survival gained per day in utero was 2% between 24 and 27 weeks’ gestation. With more advanced gestation, major morbidity fell from 56.6% at 24 weeks to 10.5% at 32 weeks, leading to significant neonatal survival and intact survival.

‘Brain-sparing’ is a compensatory fetal response seen in placental insufficiency whereby blood is preferentially distributed to cerebral structures by autoregulation to maintain delivery of oxygen and nutrients. MCA is the vessel of choice because it is the most accessible and there is a high degree of observer agreement in terms of PI measurement. MCA velocimetry is expressed as either MCA PI or a ratio such as MCA/UA PI (cerebroplacental ratio [CPR]). CPR is thought to be a better index because it allows detection of blood flow redistribution from two potential mechanisms. As well as detecting decreased cerebral blood flow resistance due to brain-sparing, CPR may be the first sign of elevated placental blood flow resistance. Longitudinal studies have shown brain-sparing to be an early phenomenon in placental dysfunc-
tion. Persistent dilation of MCA was seen in > 50% of fetuses 2 to 3 weeks before any fetal heart tracing abnormality. The consensus that cerebral redistribution is a marker for early hypoxaemia is also supported by findings of Dubiel et al who demonstrated that fetuses with brain-sparing effect still had reserves to cope with the stress of normal labour.

In IUGR, understanding of the vascular dynamics is enhanced by the incorporation of venous Doppler on vessels such as umbilical vein, DV, inferior vena cava, and portal vein. Abnormal DV velocimetry has been shown to correlate with acidaemia at cordocentesis and a significant predictor of perinatal morbidity and mortality. Longitudinal studies have demonstrated abnormal DV to be a sign of advanced stages of fetal compromise and be indicative of the need for delivery within the subsequent 7 days. Bilardo and colleagues showed that at 2–7 days before delivery, abnormal DV was present in 79% of fetuses with adverse outcome. On the day before delivery, this increased to 93%. The significance of DV velocimetry is supported by the work of Baschat et al. Having corrected for birthweight and gestation at delivery, DV velocity was the only statistically significant predictor of intact survival of IUGR babies.

Doppler velocimetry at the level of aortic isthmus has been evaluated as a monitoring tool in IUGR. The isthmus is the area between the origin of the left subclavian artery (perfused by the left ventricle) and aortic end of the ductus arteriosus (perfused by the right ventricle). Its unique position means that it is influenced by both downstream impedance in the lower body and that of the upper body especially the brain. Waveform abnormalities are classified as decreased, absent or reversed flow. Reversed flow through the aortic isthmus results in low-oxygen blood from the right heart being directed to the brain. This has been shown to be associated with long-term neurodevelopmental impairment. The current thinking is that aortic isthmus flow velocimetry has a low sensitivity although it appears to be highly specific as a sign of decompensation.

Late-onset IUGR is associated with a lesser degree of placental vascular abnormality and hence the lack of abnormal umbilical artery Doppler findings. There is increasing recognition of the entity of late-onset IUGR. In contrast to early-onset IUGR, late-onset IUGR is associated with a lesser degree of placental vascular abnormality and hence the lack of abnormal umbilical artery Doppler findings. The progressive cardiovascular deterioration observed in early-onset IUGR is also not seen. Oros et al monitored the longitudinal Doppler changes in a cohort of fetuses with suspected IUGR diagnosed at a mean gestation of 34.1 weeks until delivery at 38.7 weeks. They found no significant difference in UA PI. There was, however, progressive decrease in MCA PI and CPR until delivery. The utility of MCA Doppler as a prognostic indicator in late-gestation IUGR is supported by findings from studies showing abnormal neurobe-
bavioural performance in the neonatal period and early childhood in fetuses with abnormal MCA Doppler antenatally.30,31,32

**SUGGESTED APPROACH TO MANAGEMENT**

A suggested management approach is as described in the Figure. It is useful to bear in mind the time frame of progression. In early-onset IUGR, the anticipated progression rate is defined by the rate of progression of UA Doppler. Loss of UA end-diastolic flow within 2 weeks is suggestive of a rapidly progressive picture with venous flow abnormality within the subsequent 4 weeks. If, however, loss of UA end-diastolic flow is more gradual over 4 weeks, there will be a longer latency period of about 6 weeks to venous deterioration.21 Delivery threshold needs to be high if gestational age is less than 26 weeks owing to a high chance of mortality. Up until 28 weeks, each day in utero potentially increases survival by 2% per day. Abnormal DV is the most significant predictor of neonatal mortality.

CTG = cardiotocograph; IUD = intrauterine fetal demise.
In late-gestation IUGR, there is no good evidence to guide the best management. The clinician needs to balance the risk of intrauterine fetal demise from not delivering and the risk of delivery by either labour induction or caesarean section. The choice of delivery to avoid stillbirth is, however, considered rational.

CONCLUSION

IUGR is associated with significant risk of mortality and morbidity, which extends into adult life. Doppler ultrasound is the mainstay of fetal surveillance in these pregnancies. There are sequential changes in Doppler velocimetry, which can provide clues to worsening of condition and hence guide decision-making regarding delivery.

About the Authors
Dr Lim is Consultant, Dr Kwek is Head and Senior Consultant, Dr Tan is Clinical Associate Professor and Senior Consultant, and Dr Yeo is Chief of Obstetrics, Adjunct Professor and Senior Consultant, Department of Maternal Fetal Medicine, KK Women’s and Children’s Hospital, Singapore.

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