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Editor  
**S.S. Ratnam**

# *Obstetrics and Gynaecology Communications*

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### Erratum

The recent report on the 4<sup>th</sup> National Conference of the Indian Menopause Society (*Obstet Gynaecol Communications* 2000;2(4):52-56) did not convey clearly that Dr Urvashi Jha is Secretary General of the Indian Menopause Society. Accordingly, the Journal apologises for any confusion that may have arisen as a result of this.

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Please direct all submissions for publication to:

**Dr Manju Purohit, Managing Editor**

*Obstetrics and Gynaecology Communications*

3/A/F Indira Apartments

Banganga, Govandi Station Road

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Fax: + 91 22 558 4253

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**Dr James E. Frampton, Publication Manager**

Scientific Communications (NZ) Ltd

P.O. Box 13929, Christchurch, New Zealand

Phone: + 64 3 365 8787

Fax: + 64 3 365 8388

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- 500 copies circulated internationally

## Salivary Oestriol a Useful Marker for Preterm Birth

(USA) A prospective multicentre study has highlighted the potential of salivary oestriol measurements in predicting the risk of preterm delivery.

Weekly saliva samples were collected from 601 pregnant women from 22 weeks' gestation, and tested for unconjugated E3 using enzyme-linked immunosorbent assay. One hundred and fifty-two women were judged to be at high-risk for preterm delivery (Creasy score  $\geq 10$ ).

A single elevated sample (E3  $\geq 2.1$  ng/mL) identified 50% of the women in the low-risk group who delivered before 37 weeks, and as many as 64% in the high-risk group of women. Test specificity and positive predictive value were greatly increased with two consecutive elevated measurements incurring only a modest reduction in test sensitivity. In addition, evaluation of women presenting with symptomatic preterm labour found that a salivary E3 threshold of 1.4 ng/mL identified 61% of those who delivered within 2 weeks.

*"Serial measurement of oestriol in saliva appears to be useful for assessing the risk of preterm birth before physical symptoms are manifest. These tests could greatly aid decision-making, particularly for those women previously deemed at high risk for preterm labour,"* concluded researchers.

Source: *Obstet Gynecol* 2000;96:490-497.

## Abortion Pill Approved in US

(New York, USA) The abortion pill RU-486 (mifepristone) has been approved by the Food and Drug Administration (FDA) for use in the United States, despite prolonged and fierce lobbying from anti-abortion groups.

*Obstetrics and Gynaecology Communications* 2000;2(6):11-11

## Briefly...

### MEA Effective for Menorrhagia

(UK) A clinical trial comparing microwave endometrial ablation (MEA) and transcervical resection of the endometrium (TCRE) has indicated that results are similar after 1 years' follow-up, but that MEA operation time is faster and associated with fewer complications.

Source: *Curr Opin Obstet Gynecol* 2000;12:293-295.

### Pasteurising HIV-infected Breast Milk — An Alternative to ART?

(Denmark) A solar-powered breast milk pasteuriser has been developed by a Danish specialist in tropical and infectious diseases, Dr Jorgensen (Kolding Hospital). According to recent research trials, the device — which can be operated by the nursing mother — inactivates human immunodeficiency virus (HIV) as well as pathogenic bacteria. Importantly, antibodies in the breast milk are preserved in the process.

*"Compared with antiretroviral therapy (ART), pasteurising HIV-infected milk offers a more manageable and cost-effective solution for HIV-infected mothers,"* says Dr Jorgensen.

Source: <http://www.obgyn.net>

Mifepristone has specifically been approved for the termination of early pregnancy, which has been defined as no more than 49 days after the last menstrual period. The terms of approval allow for mifepristone to be available to doctors with access to ultrasound in order to date the pregnancy and to identify ectopic pregnancies, the latter being a contraindication for RU-486 use.

The FDA reported that the safety and efficacy of mifepristone has been demonstrated in clinical trials undertaken both in the United States and in France where the drug was first released in 1988. It is estimated that more than half a million women in Europe have used mifepristone to date.

Source: *BMJ* 2000;321:851.

## Medical Accountability Under the Spotlight

(New Delhi) Many medical facilities in India currently do not have complaints procedures in place for patients and their relatives — that is if a recent survey conducted in Delhi, Hyderabad, and Lucknow is representative.

The survey, carried out by the Voluntary Organisation in the Interest of Consumer Education, with support from the Indian Health Ministry and the World Bank, found that patients generally tried to resolve their grievances initially with the doctors and hospitals concerned, rather than the consumer courts. However, more than half of the medical facilities surveyed (large hospitals and small clinics) were without an organisational mechanism to process such complaints.

Source: *BMJ* 2000;321:588

## Women's Health Report Highlights Indian Gains

(Washington, USA) The triennial report on the state of women's health recently released by the International Federation of Gynecology and Obstetrics (FIGO) makes dismal reading overall. However, a few countries have shown some gains, notably India which was seen to have an increasing rate of safe labour and delivery.

*"If women's health is improving, it is in a very small number of places. In the developing world there are still a thousand miles to go,"* said Dr Shirish Sheth, FIGO president, speaking in an interview.

Key factors contributing to poor health outcomes for women outlined in the report include a culture of stigma surrounding women's sexuality which, in combination with poverty, prevents their seeking disease prevention or treatment. Lack of

education for women was also highlighted, particularly with respect to lack of awareness of contraceptive choices.

Source: <http://www.obgyn.net>

## CS Rate Questioned

According to a report published in the National Medical Journal of India, caesarean section (CS) rates may be as high as 45% in some private hospitals in India.

The trend to increased CS rates was first seen in western countries, but has been noted in many parts of the world since. In China, for example, the CS rate rose from 4.7% to 22.5% in the last 30 years.

The World Health Organisation is concerned over the trend and suggests CS should comprise approximately 10-15% of all deliveries. In India, the dramatic increase in rates has been labelled by international experts as unjustified and an inappropriate use of scarce medical resources.

Source: <http://www.indiatimes.com>

## Ca Breast and Tumeric

(Calcutta) Researchers at the Bose Institute investigating potential anti-cancer properties of the traditional Indian spice haldi (tumeric) have obtained promising results. Following positive results in mice with induced malignancies, the research team applied the alkaloid compound curcumin, extracted from tumeric, to an established breast cancer cell line isolated from patients.

The results were very positive and suggested that curcumin may have selective killing properties, since effects were seen only on cancerous and not on normal cells tested.

*"Perhaps this (tumeric) is one of the reasons Western countries have more breast cancer cases than Asians in China, India, and Japan who thrive on a predominantly tumeric-rich diet,"* hypothesised Dr Gauri Sankar Sa, one of the lead researchers.

Source: <http://www.newsindia-times.com>

# Should Ultrasound Scanning in Pregnancy be Performed by Indication Only?

L. Chitty

*Institute of Child Health and University College Hospital,  
London, United Kingdom*

## Routine Screening

### **Advantages**

Routine ultrasound examination is offered to many women at around 20 weeks of gestation to examine the foetal anatomy in detail with the objective of identifying foetal abnormalities. There are several arguments in favour of such a policy.<sup>1</sup> These include:

- The option of prenatal treatment.
- Planning the time and place of delivery in cases which may need expert neonatal care and/or early surgery.
- Allowing parents the option to terminate a pregnancy where the foetus has a lethal or severely handicapping condition.

Such interventions, it is argued, can potentially decrease perinatal mortality and morbidity rates. In addition, it can be argued that it is helpful for the parents to be prepared for the birth of a child with some degree of problem. However, there has been little formal evaluation of routine foetal anomaly scanning and there is little scientific evidence for these arguments. In addition, there is wide variation in detection rates in routine screening programmes, varying from 16-85%.<sup>1</sup>

## Key Points

- There is little scientific support for routine foetal anomaly scanning using ultrasound.
- Detection of foetal abnormalities during the second trimester depends in part on the sonographer having sufficient time (and skill) to examine the foetus in detail.
- Compared with routine scanning, there are several advantages to select screening of women identified by other prenatal tests as having risk factors for foetal abnormalities.
- Serious consideration should now be given to a selective screening policy.

## Disadvantages

There are also many disadvantages to routine foetal anomaly scanning. These include false-positive diagnoses with concomitant parental anxiety and the risk of unnecessary abortion. Conversely, the fact that anywhere between 1 to 5 out of 6 abnormalities are not detected at the time of a second trimester scan means that many parents are falsely reassured that their baby is normal. This may be because the sonographic feature associated with an underlying abnormality is not evident at 20 weeks (e.g. duodenal atresia, microcephaly, hydrocephalus etc.), or because the sonographer has insufficient time or skill to examine the foetus in detail. Finally, when scanning the low-risk population, there can be considerable difficulty in defining the prognosis for many anomalies, some being normal variants. When screening a woman with a previously affected child, the outcome following de-



***Detection rates  
vary widely  
between screening  
programmes***

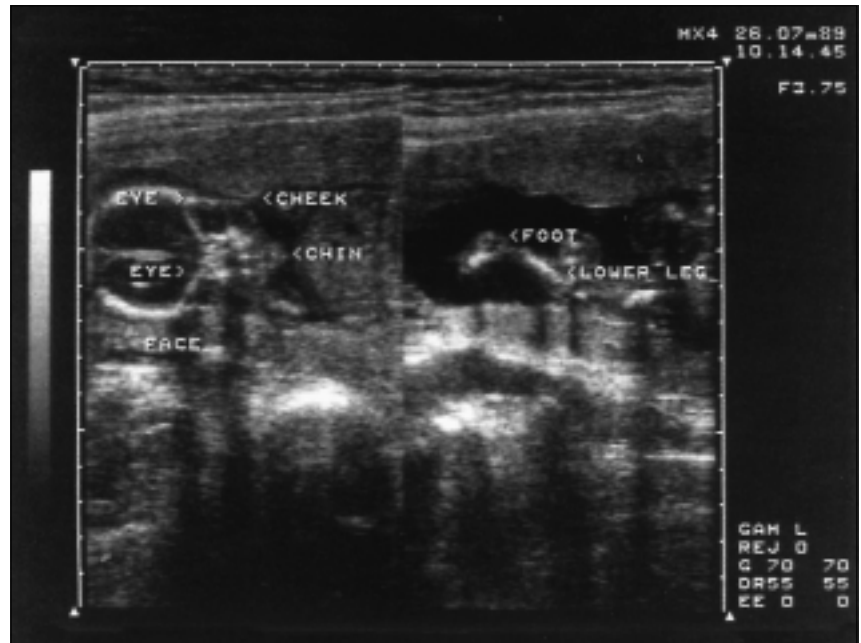
tection of such an abnormality is usually clear, but when screening the low-risk population there can be considerable difficulty in giving a confident prognosis. This results in further parental anxiety, and in some cases the unnecessary termination of pregnancy.

### Select Screening

An alternative to offering a detailed scan to all women is to selectively scan those at increased risk. This would include all women with a relevant medical or family history. However, most foetal abnormalities occur in pregnancies at low risk and so just scanning those with a relevant history would not detect the majority of anomalies. If, however, select screening were offered to all those with risk factors identified by other prenatal screening tests (e.g. second trimester serum screening, first trimester measurement of nuchal translucency), a far greater proportion of affected foetuses would be identified.

Chambers *et al.*<sup>2</sup> reported the audit of such a screening programme based on a dating scan in the first trimester (nuchal translucency was not measured as this was not a recognised screening tool at that time) and second trimester serum screening. Detailed anomaly scanning was only offered if there was a relevant history or maternal alpha-foetoprotein (MSAFP) was raised. Further scanning was done later in pregnancy if there was a clinical indication (e.g. small for dates, polyhydramnios, etc.). There were a total of 255 abnormalities in this study, of which 51% were diagnosed prenatally (37% prior to 24 weeks' gestation). The majority of anomalies not detected were chromosomal or cardiac.

It is of note that screening for aneuploidy in this population was done on the




*Routine ultrasound scanning has both advantages and disadvantages.*

basis of maternal age and MSAFP. Introduction of triple or quadruple serum screening in the second trimester would considerably improve detection of aneuploid foetuses.<sup>3</sup> With the recognition that an increased nuchal translucency is a marker for cardiac<sup>4</sup> and other abnormalities,<sup>5</sup> if this were added to the first trimester dating scan and used as a further indicator for detailed scanning at 20 weeks, detection of cardiac anomalies as well as some other abnormalities (and aneuploidy) could be improved.

### Advantages

Selective screening as discussed above would have several advantages:

- The overall false-positive rate would be decreased.
- Detailed second trimester scans would be targeted and likely to be performed by highly skilled operators with more time allowed for scanning, thereby reducing the false-negative rate in women scanned.
- There would be fewer interpretational difficulties.
- The majority of cases requiring early



**Selective screening would reduce the false-positive rate**

postnatal intervention would still be detected in time to plan delivery.

- Intestinal obstruction and diaphragmatic herniae usually present with polyhydramnios and would be detected in the third trimester following a scan for that indication.
- Anterior abdominal wall and neural tube defects cause elevation in MSAFP; therefore, the majority should be detected at 20 weeks.
- The majority of lethal abnormalities would still be detected in time to give parents the option to terminate pregnancy. Even if other anomalies were detected later, time would still be available for parental preparation.

### Concluding Comments

Ultrasound technology and knowledge has advanced considerably in recent years. Unfortunately there has been little formal evaluation of population screening programmes, but with advances in first trimester screening and screening for aneuploidy, serious consideration should now be given to a selective screening policy.

#### Acknowledgement

*This editorial feature — taken from OBGYN.net (The Obstetrics and Gynaecology Network) at: [www.obgyn.net/](http://www.obgyn.net/) — has been modified to suit the style of the journal.*

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## What the Experts Say About Routine Ultrasound in Pregnancy...

***“Based on existing evidence, routine Doppler ultrasound in low-risk or unselected populations does not confer benefit on mother or baby”***

**Cochrane Review**

***“[We] do not recommend routine [ultrasound] screening [in pregnancy]. At the moment, the best research shows no benefit from routine ultrasound scanning and the real possibility of a serious risk”***

**World Health Organisation**

***“[We] reject routine ultrasound scanning [in pregnancy]”***

**American Food and Drug Administration (FDA)**

***“[We] recommend ultrasound [in pregnancy] only for specific indications”***

**National Institutes of Health, United States**

***“No well-controlled studies have shown a benefit [of ultrasound screening] in the outcome of pregnancy”***

**American College of Obstetricians and Gynaecologists**

***“There should be a ‘clinical indication’ for an ultrasound technique to be used (in pregnancy)”***

**New Zealand Ministry of Health**

# Surgery for Recurrent Cervical Carcinoma

**Andreas J. Papadopoulos** (*Subspecialty Fellow*)  
**Omer Devaja** (*Subspecialty Fellow*)  
**Rahul Nath** (*Research Registrar*)  
**George D. Wilbanks** (*Visiting Professor*)  
**K. Shanti Raju** (*Consultant and Director of Department*)

*Department of Gynaecological Oncology, Guy's and St Thomas' Hospital NHS Trust, London, England*

## Introduction

The incidence of cervical cancer in developed countries has decreased considerably over the last half century. This has been due to national screening programmes based on the pioneering work of Papanicolaou and Traut.

The concept of cervical intraepithelial neoplasia (CIN) and the role of human papillomavirus (HPV) infections in this process has been discussed in this journal previously.<sup>1</sup> In the majority of cases, squamous cell carcinoma of the cervix is a slow-growing, locally-invasive tumour which can be treated by radical surgery in the early stages prior to distant spread. As such, the treatment of cervical cancer is traditionally

## Summary

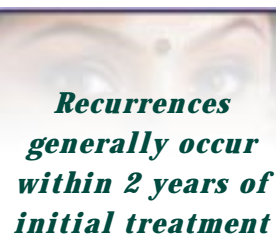
- Recurrent disease occurs in approximately 35% of cervical cancer cases.
- Evaluation of the patient includes assessing the extent of disease and performance status for surgery.
- Exploratory laparotomy determines the extent of disease and the appropriateness of planned surgery.
- The choice of exenterative procedure varies according to the site and extent of recurrence.
- Exenteration is associated with a significant number of complications, but has achieved 5 year survival rates of between 19-50% in selected patients.

based on localised pelvic treatment – either surgery or radiotherapy – the choice being dependent on clinical stage of the disease. But, despite new modality treatments in the form of neoadjuvant chemotherapy with either radiation or surgery, recurrent disease is still a significant problem.

The overall recurrence rate in patients with cervical cancer is approximately 35%, with more than 80% recurring within 2 years of the initial treatment.<sup>2</sup> If disease is detected soon after primary treatment (< 3 months), then this is considered as persistent disease. Recurrent disease, however, is defined as tumour after a period of complete clinical and radiological remission. Presentation of recurrent carcinoma varies in different studies: for example, minimal symptoms (with as many as 50% of patients being asymptomatic)<sup>3</sup> were reported in one study compared with 80% of patients being symptomatic (e.g. weight loss, leg swelling, vaginal discharge or bleeding and bone pain) in another.<sup>4</sup>

## Editor's Comment

*The benefits and limitations of surgical approaches to recurrent cervical cancer are carefully appraised in this detailed review. Along with well-established procedures, experimental techniques are reported for pelvic sidewall recurrences which traditionally are associated with a particularly poor prognosis.*



**Recurrences generally occur within 2 years of initial treatment**

*Correspondence to:  
 Miss K. Shanti Raju  
 Dept. of Gynaecological Oncology  
 Guy's and St Thomas' Hospital NHS Trust  
 London, SE1 7EH, UK  
 Tel: + 44 207 928 9292 ext. 2068  
 Fax: + 44 207 960 2739  
 Email:  
 andreasjp@yahoo.com*

## Risk Factors for Recurrence

A variety of risk factors increase the likelihood of a recurrence in cervical cancer (see table 1). Risk factors for recurrence in early-stage disease (IB/IIA) relate to:

- Depth of tumour invasion.
- Tumour grade.
- Lymphovascular space involvement.
- Presence/absence of bilateral tumour extension.

Table 1. Risk factors for recurrence of cervical cancer

Risk factor	Risk of recurrence	
	Present (%)	Absent (%)
Nodal metastasis <sup>5,6</sup>	24-53	1-6
Tumour volume > 4-5 cm <sup>5,7</sup>	40-78	1-6
Parametrial involvement <sup>8</sup>	35-54	25
Stage of disease ≥ III <sup>9</sup>	20-40	15

Additional factors influencing recurrence include the type and adequacy of the initial treatment provided, tumour susceptibility, and host resistance.

Cervical cancer recurrence occurs in approximately 15% of patients treated surgically for stage IB/IIA disease, approximately 10-40% in stage IIIA, and 17-45% in stage IIIB.<sup>9</sup>

Other investigators have examined the recurrence rate for different histological types of cervical cancer — squamous cell, adenocarcinoma, and adenosquamous — and found no differences.<sup>8,10,11</sup> As a general guideline, 25% of recurrences will be local (vaginal apex), 25% will be pelvic (in the pelvis or along the sidewall), with the remaining 35-50% beyond the pelvis.

## Management

Key principles underlying the management of recurrent cervical cancer are outlined in table 2. The most important considerations are assessment of the extent of

Table 2. Principles of management for recurrent cervical cancer

1. Adequate assessment of patient
  - Age
  - Performance status
  - Psychological/social aspects
2. Adequate assessment of extent of disease (noninvasive and invasive techniques)
3. Design appropriate treatment programme [surgery, RT, chemotherapy, or combination therapy]
4. Minimise potential for complications and maximise potential for long-term QOL
5. Maximise palliative control of patient's symptoms

*Abbreviations:* QOL= quality of life; RT = radiotherapy.

disease, followed by appropriate treatment of each individual patient.

## Patient Assessment

Evaluation of the patient includes assessing the extent of the disease and performance status for surgery. Pre-treatment evaluation tools are presented in table 3.

It is important to investigate the urological tract, as traditionally the probability of good margins at tumour resection is linked to the degree of abnormality on intravenous pyelogram (IVP). Unre-

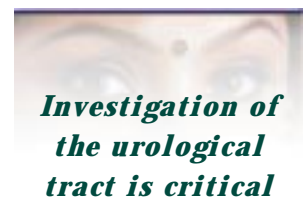


Table 3. Pretreatment patient evaluation techniques

Clinical assessment	General examination (e.g. lymphadenopathy) Abdominopelvic examination Rectal plus bimanual examination Examination under anaesthesia (can be performed at laparotomy)
Blood investigations	Full blood count Urea, creatinine, electrolytes Liver function tests Coagulation profile
Urological disease	Intravenous urography Cystoscopy
Bowel/rectal disease	Barium enema Sigmoidoscopy + colonoscopy
Abdomino-pelvic	CT (lymph node involvement + tumour extension) MRI (local tissue plane involvement) PET (lymph node disease; distinguish disease from fibrosis)
Distant disease	Chest X-ray Bone scan
Tissue biopsy	Needle biopsy (Trucut®) or FNAC
Surgical assessment	Laparoscopy Exploratory laparotomy

*Abbreviations:* CT = computer tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; FNAC = fine needle aspiration cytology.

sectable disease occurs in as many as 60% of patients with unilateral ureteric obstruction, rising to 90% with bilateral involvement on the IVP. Those with an abnormal IVP but resectable disease tend to have a poorer long-term prognosis than those without an IVP abnormality.

MRI has been evaluated as a tool to select patients for exenteration, with an accuracy rate of 83%, a positive predictive value of 56%, and a negative predictive value of 100%.<sup>12</sup> MRI identified bladder extension of the tumour in 81%, and rectal involvement in 85%. These areas can be biopsied under radiological guidance.

Nodal involvement can be detected on CT scan, provided the nodes are > 1 cm in diameter.<sup>13</sup> Spinal metastases have to be excluded: up to 6% of patients present with, or develop these after initial treatment (4% for stage I to 22% for stage IV disease).<sup>14</sup> Age is also an important factor, as the operative-associated mortality is 0% if the patient is younger than 40 years, but rises to 12.2% if the patient is older than 60 years.

In general, 50% of patients referred for exenteration are rejected. In addition, a further 33-50% of patients undergoing a laparotomy do not have an exenteration.<sup>15,16</sup> This leaves only approximately 25% actually undergoing the procedure. In an attempt to reduce the failure rate of proceeding with an exenteration at laparotomy, the laparoscope has been investigated in a small study of 3 patients, and shown to be able to select patients for surgery with a mean operating time of 146 minutes.<sup>17</sup> Currently, laparotomy is the final method of selection.

Once the patient has been assessed for distant disease and (pre-operative) contraindications to surgery (see table 4)

Table 4. Pre-operative contraindications to surgery

#### Absolute

- Extrapelvic disease
- Tumour pelvic sidewall fixation
- Triad (unilateral leg oedema, ureteric obstruction, nerve pain)
- Severe medical illness
- Inadequate facilities
- Lack of specialised skilled staff
- Bilateral ureteric obstruction (due to 2° spread)

#### Relative

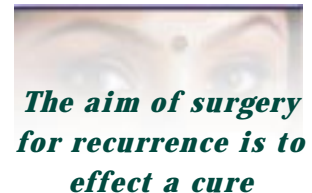
- Age > 75 years
- Unilateral ureteric obstruction
- Large tumour volume > 4 cm
- Metastases to lower vagina

excluded, he/she has to be advised by the relevant specialised personnel before embarking on a surgical procedure. The risks and complications of the surgery, as well as the long-term chances of survival, should be discussed. Details concerning vaginal reconstruction, urinary and bowel diversion procedures, the post-operative recovery period, as well as the possible abandonment of the procedure (if needed), should be outlined to the patient. The colostomy/urinary diversion nurse must visit the patient if there is a chance that this procedure may be performed.

### Choice of Surgery

The objective of the surgical procedure for recurrence should be a cure. This equates to complete resection of the entire recurrent tumour. If complete surgical resection with clear margins is not possible, the prognosis is poor. However, not treating these recurrences surgically also has a poor prognosis, as has been illustrated by Haas *et al.*<sup>15</sup> In that study, 41% of unresected cancer patients died within 6 months, 25% lived for > 1 year, and 5% for > 2 years. Results reported by Morley *et al.*<sup>18</sup> demonstrated only a 13% survival at 1 year.

The patient deemed suitable for an exenterative procedure will, at laparotomy, have a small (< 3 cm), mobile, and central recurrence – with a good likelihood of



achieving 2 cm clear margins – and no lymph node involvement evident. Approximately 15-25% of patients referred meet these criteria. Preferably, these patients should not have received any form of pelvic radiotherapy during at least the previous 12 months. The decision is then between a partial or total exenterative procedure. An indication of the type of surgery would have been anticipated from the pre-operative examination and investigations as discussed earlier. However, in some cases, the extent of disease may not become apparent until after the exploratory laparotomy has been performed and the type of surgery altered or abandoned.

Table 6 (see page 21) provides a summary of the surgical procedures that can be considered.

### **Simple Hysterectomy**

Simple hysterectomy is rarely performed and (consequently) the literature is very scarce concerning this procedure. Several authors dismiss this procedure because of the increased rate of urinary complications, as well as the high recurrence rate associated with incomplete clearance due to inappropriate patient selection. This procedure may be considered *only* with a microscopic or very small localised recurrence when sufficient clear tumour margins can be achieved – however, this is rarely possible with such a procedure.

### **Radical Hysterectomy (RH)**

RH following RT is performed in only a few patients, namely those with a small-volume central recurrence. This procedure is associated with a 20-50% complication rate including: ureteric damage (22%); bladder dysfunction (20%); vesicovaginal, ureterovaginal or rectovaginal fistulas (28%); and strictures and other complications.<sup>21-23</sup>

## Exploratory Laparotomy

The initial incision is a subumbilical midline incision, which will be extended for complete exploration, provided no contraindication to surgery is found in the pelvis. Assessment of the pelvis and abdomen is paramount to determine disease extent and the possibility of complete tumour resection. Exploration of the abdomen includes the diaphragm, liver, stomach, pancreas, spleen, small and large bowel, and lymph node chains. Any lesion or suspicious nodes should be removed and analysed intra-operatively by frozen section. Needle biopsy may be useful for suspicious areas not readily accessible to open biopsy or resection.

The pelvic exploration must include the retroperitoneal avascular spaces (prevesical - Retzius, paravesical, and pararectal). The vesicouterine or vesicovaginal and rectovaginal spaces are not examined *unless* an anterior or posterior exenteration is being performed. Through appropriate exploration of these spaces, sidewall fixed disease can be excluded and, if necessary, the procedure abandoned. Table 5 lists reasons for abandoning the exenteration procedure and the frequency with which they occur.

It is imperative to exclude lymph nodal disease, because if this is present in patients undergoing exenteration, then the 5-year survival rates are significantly reduced to 5-10%.

The indications for a surgical procedure include locally-advanced pelvic tumours, with no bone or sidewall involvement, and no lymph node metastasis or distant spread. The goal is to have at least 2 cm tumour-free margins. Surgery, therefore, is mainly reserved for central recurrent disease.

Patients with signs and symptoms indicating pelvic sidewall involvement, i.e. leg oedema, sciatic pain, and/or hydronephrosis, do not benefit from surgery.<sup>20</sup> The presence of weight loss, obesity (> 95-100 Kg), or previous radiotherapy (> 6000 cGy) to the pelvis, increases the morbidity and mortality associated with surgery.

Table 5. Intra-operative contraindications to surgery

Contraindication	% <sup>a</sup>
Macroscopic peritoneal disease (pelvic or upper abdomen)	44
Lymph nodal metastasis (pelvic or paraortic)	40
Parametrial fixation	13
Hepatic/subdiaphragmatic lesions or small bowel adhesions/serosal involvement	4.5
Malignant ascites/positive washings	
Tumour invasion of major vessels	

<sup>a</sup>Relative percentages for termination of procedure at exploratory laparotomy.<sup>16,19</sup>

Table 6. Standard<sup>a</sup> and new, non-standard<sup>b</sup> surgical options


Procedure	Recurrence (site, size)	Previous treatment	Organs removed	Reconstruction procedures
<i>Standard</i>				
RH	Small, central (< 2 cm)	RT	Uterus, tubes, vaginal cuff ± ovaries	
Anterior exenteration	Small, central, anterior	RT	Uterus, tubes, ovaries +	Urinary diversion procedures
		RH ± RT	Bladder, vagina	
Posterior exenteration	small, central, posterior	RT	Uterus, tubes, ovaries +	Colostomy
		RH ± RT	Rectum, vagina	
Total exenteration	< 5 cm central recurrence, extends to lower vagina, fibrosis	RT	Uterus, tubes, ovaries +	Urinary + bowel diversion
		RH ± RT	Bladder, rectum, vagina	
Abandon (standard treatment)	Sidewall recurrence, lymph node or peritoneal spread	RT		
		RH ± RT		
<i>New, non-standard</i>				
Surgery above + CORT	Inadequate tumour margins or sidewall recurrence	RT	As above	As above
		RH ± RT		
LEEPRT	Infra-iliac pelvic sidewall recurrence	RT	As above + <i>en bloc</i> procedure removing parietal endopelvic fascia, pelvic wall muscles ± internal iliac vessels	Urinary + bowel diversion ± TRAMP
		RH ± RT		
LEEPRT + CORT	As above with inadequate tumour margins	As above	As above with intra-operative RT	As above
<sup>a</sup> Providing adequate margins are attainable.				
<sup>b</sup> Under investigation.				
<i>Abbreviations:</i> RH = radical hysterectomy; CORT = combined operative RT; LEEPRT = lateral extended endopelvic sidewall resection technique; TRAMP = transversus and rectus abdominus musculoperitoneal procedure.				

The recurrence rate following RH is 48%.<sup>22</sup> Coleman *et al.*<sup>22</sup> reported that of the patients studied, those with larger lesions (> 2 cm) and those with positive lymph nodes had a poorer survival rate. Median survival for the subgroup of patients with positive nodes (n = 5) was only 13 months. Five-year survival rates in selected patients with minimal disease are 70-85%.<sup>22,23</sup> RH for cervical recurrence is, therefore, only offered to a small, carefully-selected, group of patients.

### ***Pelvic Exenteration***

It has been over 50 years since Brunschwig

first described exenteration of the pelvic organs, with an operative mortality rate of 23% and a median survival of 1.3 months.<sup>24</sup> This procedure was initially used as primary treatment for advanced cancer of the cervix, but is now reserved for patients with central recurrences following prior radiation or surgical treatment. As intra-operative and post-operative care has improved, the mortality rate has fallen to 5-10%, with the 5-year survival rates improving to 30-50%. Recurrent cancer of the cervix is now the main indication for this surgery.



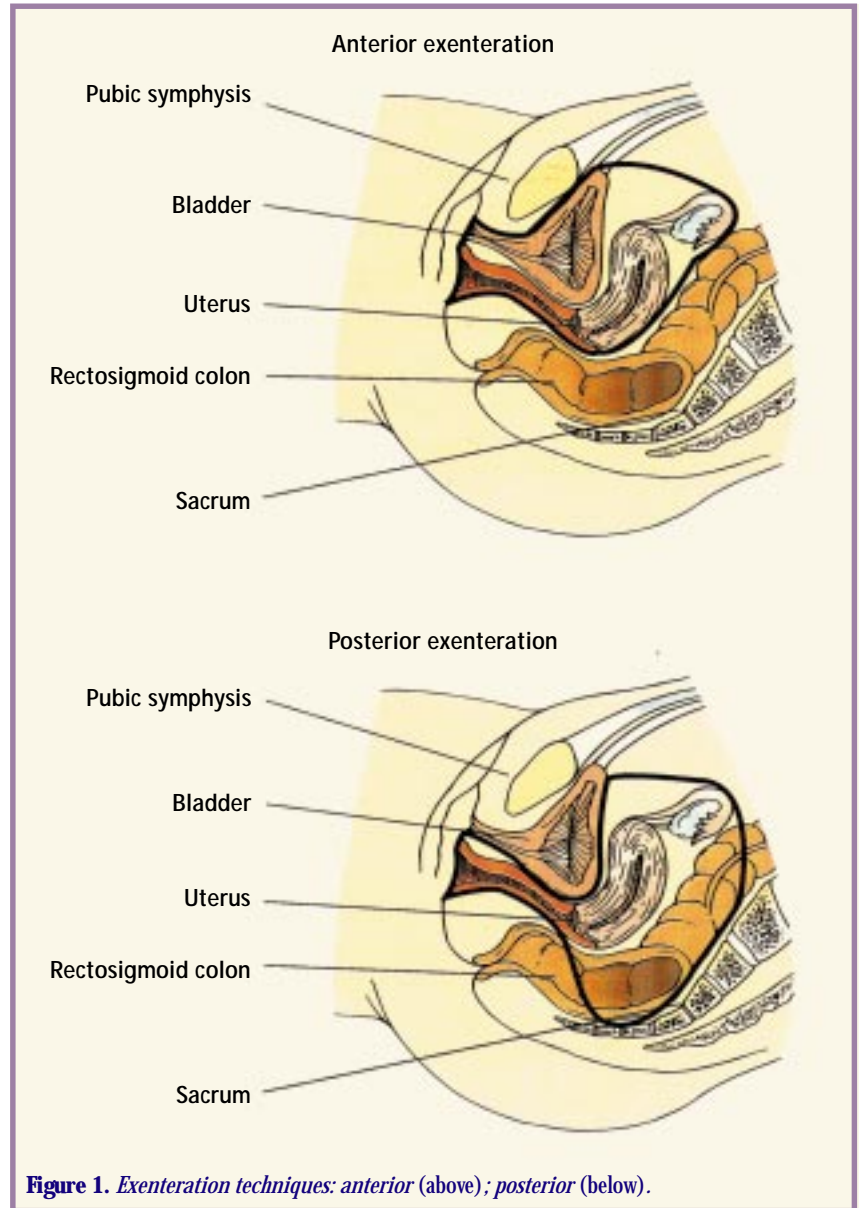
***Exenteration is reserved for patients with central recurrences***

The site and extent of the cancer recurrence determines the choice of the exenterative procedure. The exenteration can be anterior, posterior, or total.

**Anterior exenteration** — (see figure 1) this involves resection of the uterus, vagina, and urinary bladder, with preservation of the rectosigmoid colon and anus. It is indicated if the lesion is small and anterior in location, with minimal tumour extension vaginally, and laterally. Usually, these are cases which were early stages at diagnosis (I-IIb). To ensure adequate tumour margin clearance, it is preferable that a deep posterior cul de sac and no posterior tumour is present when this procedure is performed.

**Posterior exenteration** — (see figure 1) this involves resection of the uterus, vagina, rectum, and anus, with preservation of the urinary bladder. It is indicated when the recurrence extends into the posterior compartment and adequate margins can be achieved with sparing of the bladder and ureters. In practice, posterior exenteration is not a common procedure due to the close approximation of the cervix and bladder, and post irradiation fibrosis. The risk of ureteric fistula complications is significant in this group of patients.

**Total exenteration** — this involves resection of the uterus, vagina, urinary



**Figure 1.** Exenteration techniques: anterior (above); posterior (below).

bladder, rectum, and anus. Adequate resection margins are imperative as this procedure is still aiming for cure; only in rare surgery planned as palliation would close margins be acceptable. It is performed in cases with: bladder and rectal extension of tumour or fibrosis; vaginal extension greater than the upper third; posterior lateral vaginal extension; and minimal parametrial involvement.

**Complications**

There are a significant number of complications associated with the exenteration procedure (see table 7).

**Potential complications include infection and bowel obstruction**

Table 7. Postoperative complications associated with exenteration procedures	
Complication	%
Infections	30-70
- Febrile morbidity	75-85
- Wound infections	5-30
- Pyelonephritis	5-20
- Respiratory infections	10
Bowel fistulae	3-26
Small bowel obstruction	4-18
Urinary fistula	1-14
Pulmonary embolus	1-5
Mortality rate	4-5

In a study of 50 patients (including 32 with cervical cancer) who underwent a total pelvic exenteration, the morbidity rate was 62%. Forty percent required a second procedure, 18% had pelvic sepsis, 6% a small bowel fistula, and 6% a urinary fistula.<sup>25</sup> Complication rates can be reduced if transverse colon conduits are used instead of ileal conduits, as the former has been exposed to less radiation. For example, small bowel fistula are reduced from 9.7% with ileal conduits to 1.9% with transverse colon conduits; small bowel obstruction is reduced from 8.7% to 0%, respectively.

The exenterative procedure results in a large denuded area and subsequent adhesion of small bowel can result in significant morbidity — from bowel obstruction to fistula formation, and possible dehiscence. A variety of procedures have been described to prevent small bowel adhesion and its sequelae. These include the use of omental J flaps as well as Vicryl® meshes.

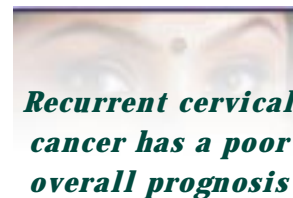
Postoperatively, these patients require intensive nursing care and experienced specialist medical care. Massive fluid shifts can occur in association with large areas of peritoneal denudation. Hence, central pressure monitoring is essential via the pulmonary arterial wedge catheter, or the less accurate central venous pressure lines. Blood loss can result in several unit blood transfusions, with resultant abnormalities in coagulation. Thromboembolic complications require anticoagulation and active antiembolic supportive care. Psychological strain suffered by both the patient and the immediate family also needs input from support counsellors.

***Survival During and After Exenteration***  
Operative mortality rates associated with the exenteration procedure are reported

to be between 6.3-20 %, <sup>26-29</sup> but in modern specialised units 4-5 % is more common.

As discussed previously, recurrent cervical cancer has a poor survival rate: 15% at 1 year reducing to 5% at 5 years with non-surgical treatment. However, the exenteration procedure can salvage a significant number of patients: 5-year survival rates range from 20-50%.<sup>26-29</sup> Several factors have been shown to influence survival following exenteration (see table 8).

Some clinicians studying the effect on outcome of detecting recurrence early in the course of disease showed improved survival rates,<sup>26,35</sup> while others have seen



***Recurrent cervical cancer has a poor overall prognosis***

## Palliative Exenteration

This treatment may be selected for two differing groups of patients. One group consists of patients with metastases or disease that is considered resectable, with the aim of surgery being to bring about an increase in survival with a slight chance of cure. In the second group, surgery is performed for the relief of symptoms – i.e. when the patient is young, fit, and QOL is impaired by symptoms of urinary or bowel fistulae. There is limited published material concerning exenteration procedures for symptom relief.

Stanhope and Symmonds<sup>36</sup> reported the outcome of surgery following RT on a subgroup of patients with extensive disease considered incurable (lymph node disease, pelvic wall involvement, etc.). Patients with pelvic nodal disease had a median survival of 19 months, with over a quarter surviving  $\geq 5$  years. Four of the seven patients with pelvic wall or pubic bone involvement lived  $> 3$  years. However, those with macroscopic residual disease following surgery died  $< 8$  months after the procedure. These results compare favourably with survival figures of fewer than 10% in cases of residual disease post-RT.<sup>18,26</sup>

Therefore a variety of factors have to be considered: tumour extent; performance status; perceived benefit with respect to operative morbidity; and the extent of surgery required. This evaluation should be undertaken by an experienced gynaecological oncology team.

no effect.<sup>33</sup> In general, clinicians suspect that detecting a recurrence early affects the natural course of the disease — hence the many patients attending regular follow-up clinics. However, better evidence is needed to support this concept. Frequent radiological investigations are not justified in the asymptomatic, and neither is the use of vault smears in those with previous RT.

### Pelvic Sidewall Recurrence

Earlier in this article, pelvic sidewall recurrence was considered a contraindication to radical surgery, a viewpoint which has recently been challenged.<sup>37</sup> This group of patients traditionally have a poor survival outcome, with recurrence usually occurring after previous treatment including RT and chemotherapy.<sup>2,38-41</sup>

### Surgical Innovation

LEEPRT, a new surgical procedure for sidewall recurrence, has been reported by Hockel,<sup>37</sup> who has classified sidewall recurrence according to location: ischiopubic (anterior); acetabular (midpelvic); sac-

Table 8. Factors shown to influence survival following exenteration

Prognostic factor	Survival (%)		Reference
	Present	Absent	
Age > 35 years	43.9	68.1	30
Margins involved:			
-anterior exenteration	0	63	26
-posterior exenteration	10	49	
Tumour volume > 5 cm	34.6	83.3	31
Lateral wall involved	28.2	77.2	30
Bladder invasion	29-36.5	54.4-78	26,30,32
Hydronephrosis	15.3	69.2	30
Rectal invasion	25.7	50.6	30,32
Lymph nodes involved	26	58	30
<i>Indeterminate factors</i>			
Detection of recurrence:			
- > 5 years	No difference		33
- > 1 year	Improved survival		26
Histology (adenocarcinoma vs squamous)	No difference		34
	22	73	18

ral (posterior); and peri-iliac (superior) and infra-iliac (inferior) with respect to the external iliac blood vessels.<sup>45</sup> LEEPRT has been designed for infra-iliac pelvic sidewall recurrence with an *en bloc* procedure removing parietal endopelvic fascia and pelvic wall muscles, with or without internal

## Comment on CORT

CORT is a new approach to treatment which has been trialled for pelvic sidewall recurrence. In cases where it is not possible to achieve tumour-free margins during debulking surgery, CORT allows better local control by using RT directly into the tumour area, minimising exposure to previously irradiated structures. CORT treatment has been shown to improve local control and survival.<sup>42,43</sup>

In a recent study of 32 women with pelvic recurrence (84% having had extensive RT), 14 central recurrences were treated with exenteration alone while the remaining 18 with pelvic sidewall recurrence (confirmed by histology) underwent CORT.<sup>44</sup> At the 2-year follow-up stage, the number of recurrences was not significantly different between the two groups, with 7/14 in the central group treated with surgery alone and 11/18 in the group treated with CORT. Factors that affected the prognosis included: tumour size; age; and the disease-free interval, but not the relapse location. After multivariate cox analysis, however, only size influenced survival.

At present the CORT approach remains experimental pending the accumulation of further research data.



iliac vessels. If the margins are involved on frozen section then, the surgical procedure is combined with CORT.

This technique was offered to 18 patients with pelvic sidewall recurrence up to 5 cm in diameter, but without evidence of distant metastases.<sup>37</sup> Pelvic reconstruction entailed urinary diversion procedures (conduit or a continent pouch), pelvic floor surgery with the TRAMP procedure,<sup>46,47</sup> vaginal wall reconstruction, and colorectal anastomosis or an end-to-end colostomy. Six of the patients had tumour-free margins and the remaining 12 had microscopic tumour extension or lymphovascular spread at, or close to, the margins. All had tumour-free biopsy of the remaining tumour bed area.

During follow-up (median observation time 19 months), 10/18 were alive with no evidence of disease, two were alive with disease, and six had died of progressing cancer. The 3-year survival rate in this study was 40%, and the 3-year disease-free survival rate was 33%. However, this surgery is associated with a long operation time (9-15 hours) and Hockel's study was limited in its design (e.g. small patient numbers, short follow-up period, not a randomised controlled trial). Also, issues of QOL were not examined in this study. Nonetheless, it remains an interesting concept which warrants further research attention.

## Conclusions

- Surgery for recurrent cervical cancer is an option, as the disease is usually slow-growing and spreads beyond the pelvis late in the natural history, some rare histological subtypes being the exception.
- Pelvic exenterative surgery is associated with three important phases: adequate pre-operative patient investigation and counselling; a thorough exploratory

## QOL

Few studies comment on this aspect of care, yet a recent publication quoted a 62% morbidity rate with total pelvic exenteration,<sup>48</sup> which is in keeping with rates of 40-80% in other series.<sup>49,50</sup> World Health Organisation (WHO) toxicity criteria grade III or IV have been found in as many as 46% of patients, with 40% requiring further surgery.<sup>48</sup> Another study reported a 29% re-operation rate.<sup>51</sup> This data, together with the experience of the gynaecological oncology team, must be presented to the patient as part of the pre-operative decision-making process.

laparotomy; and a surgical procedure tailored to the intraoperative findings.

- Exenterative surgery offered to a carefully-selected patient population can achieve cure rates of 30-50%, with a 5-10% operative mortality.
- New techniques are being investigated to deal with the traditionally inoperable pelvic sidewall recurrence.

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**QOL issues should be discussed during decision-making**

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# Contraceptive Knowledge and Use: A Survey of New Delhi Women

**Suneeta Mittal** (Professor)  
**P. N. Anandalakshmy** (Additional Professor)  
**M. Lakhatia** (Research Officer)

*Department of Obstetrics and Gynaecology\*, Department of Statistics and Demography\*\*, All India Institute of Medical Sciences (AIIMS), New Delhi, India.*

## Introduction

The demand for effective contraception is rapidly rising in developing countries. However, contraceptive coverage still continues to be poor in India. Lack of awareness and knowledge regarding EC is one important reason why more than 11 million induced abortions are performed in India each year.

The present survey was carried out to sample the knowledge, attitude, practice and perceptions of various contraceptive methods in a group of women of reproductive age, with special emphasis on awareness regarding EC.

## Patients and Procedures

The survey was undertaken over a 2-year period (1996-1998) in the Department of

## Editor's Comment

*This medium-sized survey of contraceptive practices among mainly rural or semi-urban women in the North of India highlights a lack of awareness of EC and, consequently, the need to impart greater information on this subject. This being the case, the present opportunity is taken to discuss in more detail EC and its role.*

## Summary

- Two thousand women of reproductive age were interviewed regarding their contraceptive behaviour.
- Of the married women participating in the survey, very few used any form of contraception for the first 2 years of marriage, or immediately postpartum.
- However, the majority (99%) agreed that spacing of children was essential; 55% believed that the ideal time interval between children was 3-5 years.
- Only 6% of women taking part were aware of emergency contraception (EC).
- Patient education is the key to overcoming many of the hindrances to EC.

Obstetrics and Gynaecology outpatients clinics of AIIMS. During this time, a total of 2000 women of reproductive age were interviewed by a qualified doctor using a well-structured questionnaire. Data requested is summarised in table 1. The respondents were specifically questioned about their awareness of EC and asked whether they could have avoided an unwanted pregnancy or abortion if they had had prior knowledge of EC.

The median age of the women at the time of interview was approximately 28 years. Eighty six percent were married (mean age at marriage 26.42 years). Five percent (n = 100) were married below 19 years of age, and 15.4% (n = 304) were married above 30 years of age. Parity ranged from 0 to 6 living children.

The majority of the interviewed



**Contraceptive use  
remains low in  
India**

Correspondence to:  
Dr Suneeta Mittal  
Dept. of Obstetrics &  
Gynaecology,  
AIIMS  
New Delhi-110029  
India  
Email:  
[SuneetaMittal@aol.com](mailto:SuneetaMittal@aol.com)

women were Hindus (87%); Muslims and Christians were in a minority (10% and 3%, respectively). Most of the women were housewives with only 24% employed. A sizeable group of women belonged to the lower-middle strata of society with low level of schooling and had a rural or semi-urban background.

## Results

### **Contraceptive Awareness**

More than 80% of the women surveyed named at least one modern method of contraception spontaneously without prompting. Moreover, awareness of modern methods of contraception exceeded that of traditional methods (e.g. the Rhythm method).

Survey findings indicated almost 82% of the women had heard of more than one contraceptive method (see table 1). The best known methods were oral contraceptives (OCs) and condoms, followed by intrauterine devices (IUCDs) and sterilisation. The use of the rhythm method, periodic abstinence, or injectable contraception as contraceptive methods was appreciated by a smaller number (< 40%). It should be noted, however, that positive recall indicated an awareness of the method only, and was not necessarily associated with an understanding of the correct use of that contraceptive approach.

Although a small proportion of women (approximately 6%) knew about EC, none were aware of the correct timing of its use.

### **Contraceptive Use**

Methods of contraception ever used by those surveyed included, in order of frequency, condoms, OCs, the rhythm method, sterilisation, and IUCDs (see table 2). None of the women reported ever using EC.

The most popular contraceptive among recently married women was the condom (66.6%). Only 2% of subjects used a contraceptive during their first sexual encounter within marriage. Further, only one in five married women had used condoms in the first 2 years to delay childbearing.

### **Duration of Use**

Fifty-four percent of contraceptive users continued with contraception for < 2 years, while 5% used  $\geq 1$  method for > 5 years. Ten percent were occasional users of contraceptives.

### **Postpartum Contraception**

Nearly 42% of women had resumed sexual activity within the postpartum period (i.e.  $\leq 42$  days after delivery), but only 2.7% were using contraception during this period. Among those who had resumed sexual activity, 9.3% started contraception  $\leq 3$  months after delivery and another 12.3% started within 6 months (see figure 1). Ten percent had not resumed sexual activity at 1-year postpartum, while 59% had not commenced contraceptive use.

### **Desired Fertility**

Desired fertility and actual fertility did not tally in this survey. Nearly 64% reported a wish for two children, while approximately 21% preferred to have three children. Only

Table 1. Information obtained at interview

- Age
- Age at marriage
- Education
- Occupation
- Religion
- Number of living children
- Contraceptive practice after marriage
- Current use of contraceptive with duration of use
- Resumption of sexual activity after delivery
- Use of contraception after delivery
- Desired fertility
- Sex preference
- Perceived ideal interval between births
- Awareness of emergency contraception

**Condoms were the most commonly used contraceptive**

Table 2. Awareness and use of family planning methods

Method of contraception	Awareness [no. (%)]	Ever used [no. (%)]
<i>Traditional</i>		
Rhythm method	762 (38.1)	346 (17.3)
<i>Modern</i>		
Condoms	1630 (81.5)	1332 (66.6)
IUCD	1384 (69.8)	64 (3.2)
OCs	1634 (81.7)	402 (20.1)
Sterilisation	1240 (62.0)	186 (9.3)
Injectables	660 (33.1)	-
EC	118 (5.9)	-

14.4% of women wished to have one child. One percent wanted  $\geq$  four children.

**Family Planning**

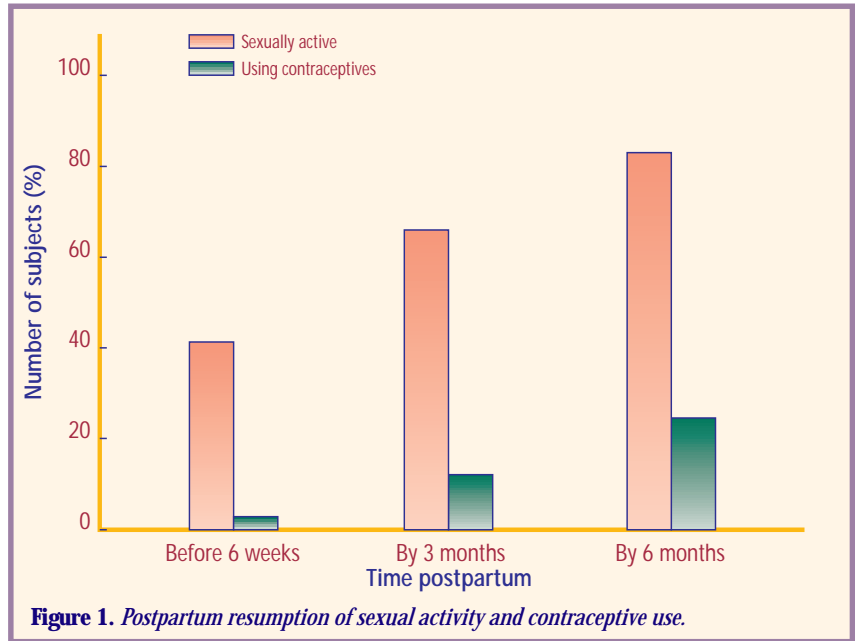
Although almost all women (99%) felt that spacing of children was essential for the child’s health, the impact of frequent childbearing on their own health was not perceived as an issue. The ideal interbirth interval was judged to be 3-5 years (by 55% of women), < 3 years (18%), and > 5 years (27%).

**Discussion**

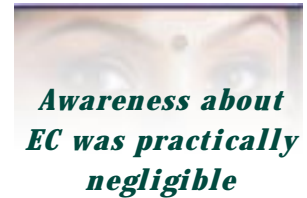
This survey revealed that even subjects who were aware of at least one form of contraceptive method did not practice it regularly, giving the potential for a high number of unplanned and/or unwanted pregnancies. Common reasons apparent for non-use of contraception include lack of awareness about methods to suit the individual and the fear of side effects. Only 2% of women used contraception during their first sexual encounter on entering matrimony, suggesting possibly the societal endorsement of a ‘cloak of coyness’ in women.

The survey also indicated that short-duration contraception (i.e. condom use) is more popular than prolonged use of contraceptives (e.g. OCs, IUCDs). Nonetheless, awareness about EC was practically negligible among the surveyed women.

Surveys of EC awareness have been carried out in some Western countries, but there is a lack of similar studies in developing countries to date. A survey conducted in Finland<sup>1</sup> showed that women under 25 years were more aware of EC (10%) than their older counterparts (4%). However, none of the women surveyed used EC as their sole contraceptive method. Overall, the findings indicated ap-



propriate use of EC in this population studied, but suggested that further information about this mode of contraception was still needed.



A postal survey of a random sample of 2000 Scottish women aged 18-47 years revealed that 94% were aware of EC – and knew how to obtain it – but only 39% knew about the correct timing of use.<sup>2</sup> As above, the authors concluded that greater dissemination of information about EC was desirable.

**Gender Preference**

Almost half (51.7%) of the women interviewed did not indicate any gender preference, so long as they had the desired number of children. Gender preferences are reported in table 3. It is interesting to note that none of the subjects wanted to have more than two daughters; only 2% wanted to have one daughter only.

Preference	%
None	51.7
Preferred boys only	18.3
- one boy	12.4
- two boys	5.5
- three boys	0.4
One boy and one girl	27
Two boys and two girls	1
One girl only	2

## Explaining EC<sup>6</sup>

Currently, EC can be provided in one of three ways:

- Combined oestrogen and progestin pills ['emergency contraceptive pills' (ECPs); Yuzpe method).
- Progestin-only ECPs.
- Insertion of a copper IUCD.

### Yuzpe Method

The Yuzpe method is the current standard for EC, but remains underutilised. First described in 1974, this regimen consists of ethinyl oestradiol (100 mcg) and levonorgesterol (0.5 mcg) given in two doses, 12 hours apart. The dedicated product *Preven* is now available in the West.

It is important to take the first dose as soon as possible after having unprotected intercourse — the effectiveness declines significantly with increasing delay before initiating treatment (see below) — and that the second dose follows in 12 hours to sustain serum levels. In most cases (98%), menses is to be expected within 21 days. However, it may be early or delayed, depending on when in the cycle the ECPs were taken.

The Yuzpe method reduces the risk of pregnancy by approximately 75% (range 55-94%). If started within 12 hours of unprotected intercourse, the failure rate with this method is 0.5%, increasing to 4% after a 72-hour wait. Nausea and vomiting are the most common side effects with the Yuzpe method, but can be avoided by taking antiemetics, ideally 1 hour before the ECPs. If vomiting occurs within the first hour, the patient should repeat the dose. Other side effects may include headaches and breast tenderness.

No studies have reported evidence-based criteria contraindicating the use of the Yuzpe regimen, although some studies have excluded those with contraindications to taking OCs. To date there are no reports of major cardiovascular or neurologic complications, for example venous thromboembolism. While the oestrogen/progestin dosage in the Yuzpe regimen is greater than that used with OCs, the duration is very short and does not seem to have the same risk profile.

A recent international trial of 2000 women suggests:<sup>7</sup>

- The Yuzpe regimen may have some effectiveness up to 5 days.
- Norethindrone may be used instead of levonorgesterol.
- A single — as opposed to the usual double — dose of the regimen may be sufficient to prevent pregnancy (with less nausea and vomiting).

### Progestin-only ECPs

Recently approved by the United States Food and Drug Administration (FDA), Plan B<sup>®</sup> is the first progestin-only pill and contains two levonorgesterol tablets (0.75 mg) taken 12 hours apart, preferably within 72 hours of unprotected intercourse.

In a recent World Health Organisation study, the progestin-only method reduced the risk of pregnancy by 85%. This increase in effectiveness over the Yuzpe Method may be secondary to decreased nausea and vomiting, making it easier to take the second dose. Contraindications to the progestin-only method are: known or suspected pregnancy; hypersensitivity to one of the components of the pill; and unexplained vaginal bleeding.

### Copper IUCD

The copper T380A IUCD reduces the risk of pregnancy by 99%. When inserted up to 7 days after unprotected intercourse or 5 days post-ovulation, it has a failure rate < 1%. Once inserted, the IUCD has the additional advantage of providing a continuing (10-year) contraceptive method.

## ECPs are ...

- A safe option when an ongoing method fails or when unprotected intercourse occurs.
- Not, however, designed to be used as a routine form of contraception (e.g. often less effective; offer no protection against sexually-transmitted diseases).
- Not to be confused with anti-abortion medications. Rather, their mechanism of action seems to be inhibition of ovulation.
- Cost-effective when used as the emergency arises, or provided beforehand as a preventive measure.
- Obtainable 'over-the-counter' in many countries in the West. These dedicated products, which can be self-administered correctly at the appropriate time without adverse effects, have helped increase the availability of EC to the general population.

Also in Scotland, Graham *et al.*<sup>3</sup> surveyed teenaged girls and boys regarding their knowledge about EC. The findings showed that a large percentage (93%) had heard of EC, 76.8% knew how to obtain it, and 31.4% of sexually-active girls had used it previously. Although use of EC is not uncommon amongst teenagers in the United Kingdom,<sup>4</sup> those who become pregnant commonly express ignorance about the EC option.

In contrast, a survey from the United States has indicated that those teenagers who took part may have a more limited knowledge about EC. Only 36% of respondents indicated that they knew 'something could be done' after unprotected intercourse, and only 1% had ever used EC.<sup>5</sup>

Comparing this overseas experience with the results of the present New Delhi survey, and, taking into account the increasing numbers of Indian adolescents who are sexually-active, there is an urgent need to increase the local population's knowledge about EC. It is essential for doctors to actively discuss EC with their patients at the same time they are planning their ongoing contraceptive needs.<sup>6</sup>

## Conclusion

Information on contraceptive methods, including EC, is crucial to the reproductive health of Indian women and to the socioeconomic development of the country as a whole. Effective contraception has the potential to reduce the number of unsafe abortions and to considerably reduce the overall medical and social costs of unintended pregnancies.<sup>8</sup>

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**Indian women have an urgent need for contraceptive information**

# Postpartum Pulmonary Embolism

Rajiv Bhardwaj (Assistant Professor)

Department of Cardiology, I.G. Medical College, Shimla, India

## Introduction

Annually, PE and DVT afflict millions of individuals worldwide, with women more frequently diagnosed than men. In fact, PE is the most common cause of death associated with childbirth in the United States.<sup>1</sup>

## Case Report

Mrs N., a 39-year-old woman, had had a stillbirth at 26 weeks' gestation – 15 days prior to this presentation. When seen in Cardiology Outpatients, she had reported a history of dyspnoea beginning 6 days previously, which progressed to New York Heart Association Class III.

There was no history of orthopnoea or paroxysmal nocturnal dyspnoea, chest pain, cough, or haemoptysis. Swelling or pain over the calf muscles and bleeding diathesis was also absent and there was no significant past history of thromboembolic disease. Mrs N. had had two full-term

normal vaginal deliveries 18 years and 6 years previously.

On examination, blood pressure (BP) was 130/96 mm Hg, radial pulse was 130/minute (and regular), and respiratory rate was 24/minute. There was no evidence of pallor, cyanosis, or jaundice. Mrs N.'s right jugular venous pressure (JVP) was not raised, but the wave pattern showed prominent Y collapse.

Cardiovascular examination revealed the apex beat to be in the 5<sup>th</sup> intercostal space in the midclavicular line and there was Grade II parasternal heave. On auscultation, the first heart sound (S1) was loud and the second heart sound (S2) showed normal splitting with a loud pulmonary component. There was evidence of a right ventricular (RV) third heart sound (S3) and tricuspid regurgitation (TR).

Electrocardiogram (ECG) findings showed right-axis deviation, an S-wave in lead I, and a Q-wave and inverted T-wave in lead III (S1, Q3, T3). There was also T-wave inversion in leads V2 and 3, and S-

## Summary

- Women have a higher risk of pulmonary embolism (PE) in comparison to men.
- Thrombolytic therapy is more effective than heparin in producing rapid lysis of emboli, but is less cost-effective.
- Heparin is more effective as a preventive measure against recurrent PE than as a treatment for an acute event.
- Echocardiography is a useful technique for identifying right ventricular overload following PE.

## Editor's Comment

*Here, a case presenting postpartum with many of the classical findings of severe PE on examination and investigation is described. The author also highlights the efficacy of thrombolytic therapy in the management of PE and deep vein thrombosis (DVT).*

*Correspondence to:  
Dr Rajiv Bhardwaj  
I. G. Medical College  
Shimla-171001  
India*

wave persistence in leads V5 and 6. The S1, Q3, T3 pattern is a classical one associated with significant PE (see right), but is usually not seen.<sup>2</sup>

Chest X-ray revealed a cardiothoracic (CT) ratio of 56% and focal oligemia in the right lower lung zone. A complete blood count elicited the following results: haemoglobin (Hb) = 11.5 gm/dL; total lymphocyte count (TLC) = 7100 mm<sup>3</sup>; and erythrocyte sedimentation rate (ESR) = 15 mm in the first hour. Blood glucose was 90 mg%, urea 30 mg%, and serum creatinine 0.8 mg%.

Echocardiography showed dilation of the RV and right atrium (RA). There was moderate TR and RV hypokinesia (see table 1).

Pulmonary artery angiography (PA) – the gold standard diagnostic technique for PE – was completed and showed a large filling defect in the right PA and decreased filling of the left lower lobe (see table 2 and figure 1).

The patient was consequently given thrombolytic therapy with streptokinase 250,000 units intravenously (IV) over 30 minutes, and then infusion of 100,000 units/hour for 24 hours. Mrs N.'s symptoms improved markedly after thrombolytic therapy. Repeat angiography 3 days later showed no filling defect (table 2 and figure 2) and normal perfusion. Repeat echocardiography showed normal RV functions (table 1).

**Discussion**

There is an increased risk of thromboembolic disease during pregnancy, with possible contributing factors including:

- Venous compression by the gravid uterus.

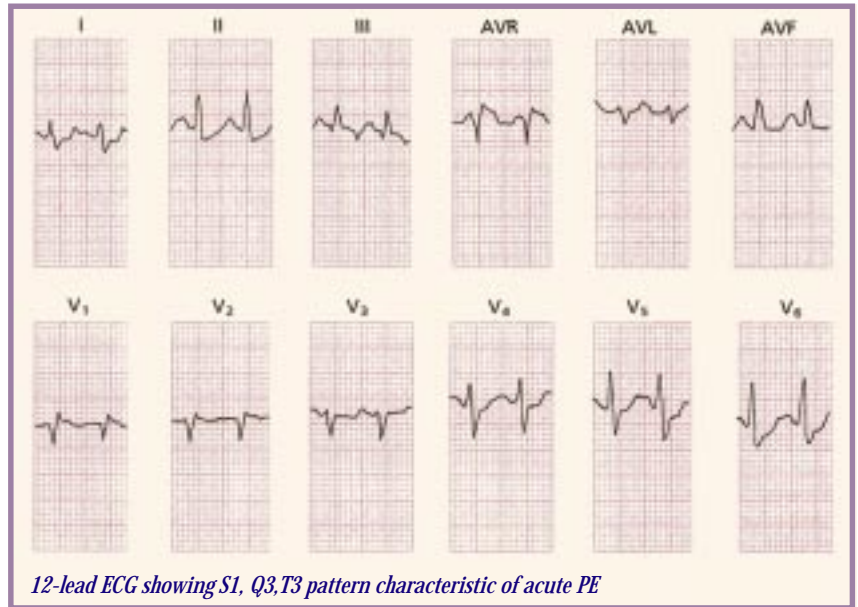


Table 1. Echocardiographic findings

Measurement	Pre-thrombolysis	Post-thrombolysis
RV cavity (mm)	23	18
RV contractions	hypokinetic	normal
RVEDV (mL)	55	31
LVESV (mL)	47	7
LVEF (%)	11	77
TR	Moderate	Nil
TR velocity (m/ses)	4.4	-
TR gradient (mm Hg)	77	Nil
TR jet area (cm <sup>2</sup> )	4.47	-
RA area (cm <sup>2</sup> )	22.9	4.5

*Abbreviations:* RVEDV = RV end diastolic volume; LVESV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction.

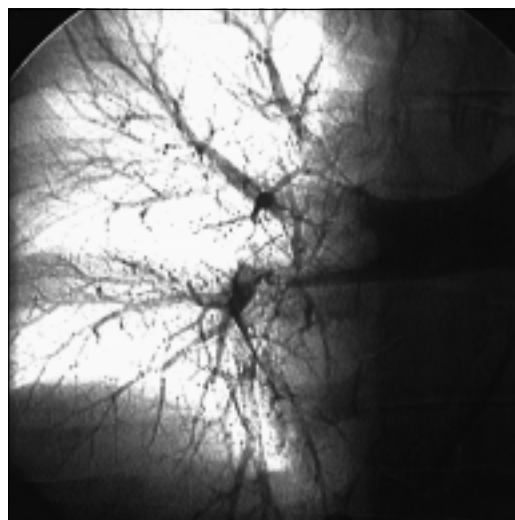


Figure 1. Pulmonary angiogram showing large filling defect in right PA.

**Risk of thromboembolism increases in pregnancy**



**Figure 2.** Pulmonary angiogram shows resolution of filling defect following thrombolytic therapy.

- Decreased vasomotor tone due to increased prostaglandins.
- Hypercoagulability due to increased levels of coagulation factors I, II, VIII, IX, and X.
- Decreased plasma fibrinolytic activity.

This particular patient demonstrated successful clinical as well as angiographic improvement with thrombolytic therapy given approximately 1 week after the presumed onset of PE. There is a wide window of opportunity for treatment of PE with thrombolysis: equivalent efficacy has been demonstrated in patients receiving thrombolytic therapy 6-14 days after the onset of signs or symptoms compared with those treated within 5 days of onset of PE.<sup>3</sup> Patients can therefore be considered for thrombolytic therapy despite a 2-week history of PE, if indicated.

Treatment of PE with heparin constitutes prevention of recurrent PE rather than primary therapy. Thrombolytic therapy is more effective than heparin in producing rapid lysis of thromboemboli. However, it is also more expensive than heparin, is associated with a higher risk of bleeding, and is not required for most patients with PE because they do well on

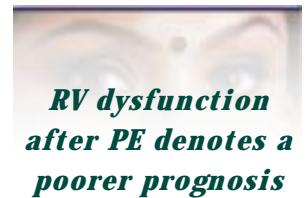
**Table 2.** Angiographic findings

Measurement	Pre-thrombolysis	Post-thrombolysis
PASP (mm Hg)	62	31
RV	Dilated	Normal size
TR	Grade III: - Large filling defect in right PA - Decreased filling of lower lobe	- No filling defect - Normal filling

*Abbreviation:* PASP = PA systolic pressure.

anticoagulant therapy only. Thrombolytic therapy has life-saving potential for patients with massive PE who have syncope, hypotension, severe hypoxaemia, or RV dysfunction. It should also be considered for patients with sub-massive embolism who have underlying cardiac or respiratory disease.

Echocardiography is a rapid, practical, and sensitive technique for identification of RV overload following PE. Kasper *et al.*<sup>4</sup> reported that the frequency of RV dilation exceeded 90% when PE was accompanied by PA hypertension; RV free wall asynergy was present in 81% of patients with PE. Patients with RV dysfunction after PE have a worse prognosis and may be at increased risk for recurrent PE and death.



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# Constipation and Vomiting in Pregnancy

Vidya S. Kakhandki (Doctor)

Bagalkot, Karnataka

## Introduction

Constipation is a normal physiological change occurring in pregnancy, presumably as a result of altered progesterone and oestrogen levels which decrease intestinal transit. Nausea and vomiting are prominent symptoms in patients with disordered gastrointestinal motility.

## Patients and Procedures

This study was done over a 1-year period. The sample consisted of 30 pregnant patients with excessive vomiting during the first trimester. None of these women had vomiting unrelated to pregnancy, e.g. on account of acute gastroenteritis, acute pyelonephritis, acute intestinal obstruction, twisted ovarian cyst, uraemia, cerebral tumours, etc. Likewise, none of the patients responded to routine treatment with antiemetics, intravenous fluids, or vitamin B12 injections. All, however, had a history of constipation and irregular bowel habit.

Patients were given a soap-water enema before being discharged for follow-up along with advice to take stool softeners, as well as plenty of fluids and fibre, and green leafy vegetables and fruits.

## Results

The results were very encouraging in all patients. Immediately after receiving the soap-water enema, each one reported objective and subjective improvements in

This descriptive study typifies the constant efforts of obstetricians and gynaecologists who practice in remote, resource-poor villages in India. Despite a lack of infrastructure and modern research facilities, findings can highlight potential patient benefits as here, derived from adhering to simple clinical measures.

constipation (i.e. stool frequency *and* consistency). Their vomiting disappeared and some patients even experienced an enhanced appetite.

Five patients were lost to follow-up. However, the remaining 25 were all totally relieved of their constipation/vomiting complaint once they had had the enema *and* strictly adhered to the medical advice. For example, 5 patients who did not properly comply with the medical advice remained symptomatic and therefore repeated the treatment (enema + advice) – this time with strict adherence. All were subsequently relieved of their symptoms (table 1).

## Conclusions

This study suggests that soap-water enema together with dietary modifications can, in the absence of drug intake, be useful in eradicating the nagging problem of constipation in pregnancy. This treatment is very simple, economical, and safe, since systemic therapy is not involved.

Table 1. Results: total symptom relief of constipation/vomiting

First visit	Second visit	Total
20 <sup>a</sup> /25	5/5 <sup>b</sup>	25/25
<sup>a</sup> All patients who had strictly adhered to dietary advice. <sup>b</sup> All patients who, at the time of the first follow-up visit, had not strictly adhered to dietary advice, but who repeated the treatment.		

Correspondence to:  
 Dr Vidya S. Kakhandki  
 Kakhandki Nursing Home  
 Ilkal-587125  
 Dist. Bagalkot  
 Karnataka  
 India  
 Phone: 08351 40414

# Acute Respiratory Failure in Pregnancy

**M.K. Daga** (*Associate Professor*)  
**K.K.Sawhani** (*Senior Resident*)

*Department of Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi, India*

## Introduction

ARF in pregnancy continues to be one of the predominant causes of maternal morbidity and mortality, accounting for more than 30% of maternal deaths.<sup>1</sup> Causes of ARF in pregnancy include aetiologies shared by non-pregnant women such as ARDS, gastric aspiration, venous air embolism, asthma, thromboembolism, and heart disease. In addition to these conditions — the management of which is made more difficult by the complex physiological alterations in the respiratory system (see below) — there are further causes of ARF unique to pregnancy, namely amniotic fluid embolism (AFE) and tocolytic-induced pulmonary oedema.<sup>2</sup>

## Physiological Changes

In the great majority of patients, the pulmonary system copes adequately with the added demands of pregnancy, including

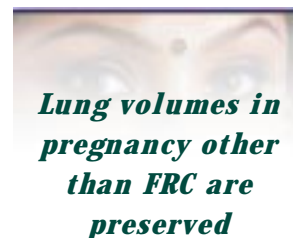
## Key Points

- Acute respiratory failure (ARF) is an important cause of maternal and foetal morbidity and mortality.
- Knowledge of normal maternal-foetal physiology and determinants of foetal oxygen delivery (i.e. uterine blood flow, placental transfer, foetal circulation) can help sustain normal foetal development, usually without compromising maternal care.
- Treatment of ARF in pregnancy is largely supportive, including mechanical ventilation, haemodynamic support, nutrition, and prophylaxis against thromboembolism.
- Pregnant patients with asthma need to be followed-up particularly closely.
- Optimal management of the maternal-foetal pair requires the cooperation of an obstetrician well versed in cardiopulmonary physiology and physicians skilled in intensive care medication.

the 30-50% increase in maternal blood volume and (in late pregnancy) cardiac output.

## Pulmonary Respiration

In the third trimester, increased blood volume causes engorgement of the pulmonary vessels leading to reductions in the expiratory reserve volume (ERV) and residual volume (RV). The overall result is a fall in the functional residual capacity (FRC). A raised diaphragm due to upward pressure by the gravid uterus also acts to decrease residual air in the lungs at this time.<sup>3</sup> Other lung volumes, however, are preserved (see figure 1 on page 39).



***Lung volumes in pregnancy other than FRC are preserved***

## Editor's Comment

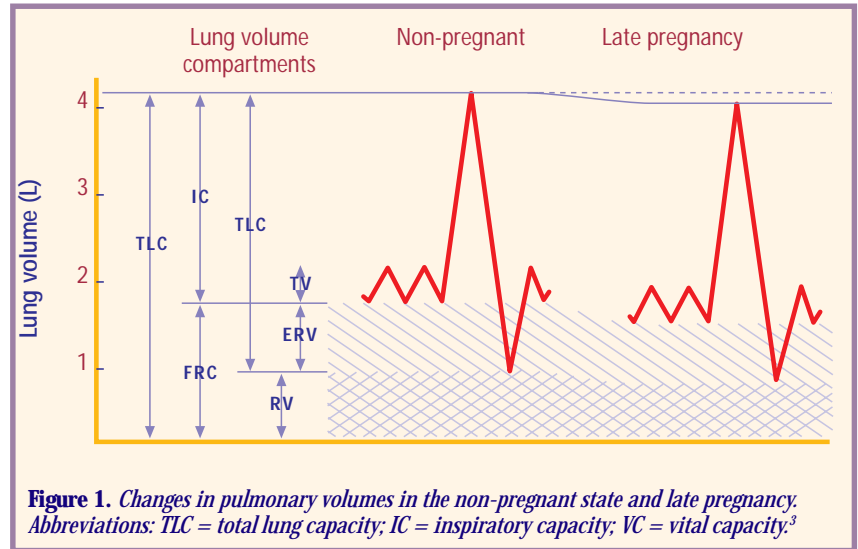
*This overview discusses the features and management of some of the respiratory-related conditions that can complicate pregnancy.*

The major adaption in pregnancy is an increase in tidal volume (TV) which is due to the effects of progesterone - centrally on the respiratory centres in the brain and peripherally on the bronchial musculature.

*Correspondence to:  
 Dr M.K. Daga  
 Department of Medicine,  
 Maulana Azad Medical College  
 and Associated Lok Nayak  
 Hospital,  
 New Delhi,  
 India*

Table 1. Causes of acute respiratory failure in pregnancy<sup>2</sup>

Hypoxic	Hypercapnic hypoxic
• ARDS	• Asthma
• Aspiration pneumonia - intentional - iatrogenic	• Overdose
• Pulmonary emboli	• Myasthenia gravis
• AFE	• Gullian-Barre syndrome
• Venous air embolus	
• Atelectasis	
• Pneumonia	
• Cardiogenic pulmonary oedema	
• Pneumothorax	



This change is in fact apparent early, with a 40% increase in the minute volume at rest seen in the first trimester. Minute ventilation (VE) at term has been seen to increase by almost 50%.<sup>4</sup> This increment in VE reflects the increase in TV rather than an increase in respiratory rate (which is not significantly changed).<sup>5,6</sup>

### Tissue Respiration

The decrease in residual air in the lungs in later pregnancy causes a fall in carbon dioxide tension ( $\text{PaCO}_2$ ) from 30-40 mm Hg to 30-32 mm Hg, which in turn helps the foetus to dispose of  $\text{CO}_2$  across the placenta. There is a corresponding increase in oxygen tension ( $\text{PaO}_2$ ) to around 85-92 mm Hg, again beneficial for the foetus.<sup>3</sup> At term,  $\text{O}_2$  consumption has increased by 20% and basal metabolic rate by 14%.<sup>4</sup>

### Symptoms

Dyspnoea (breathlessness) is a common symptom, occurring in as many as 60-70% of woman, particularly during mid pregnancy.<sup>4</sup> It may be due to a heightened 'stretch reflex' due to capillary engorgement. Dyspnoea appears related to the hyperventilation of pregnancy, although the two conditions have a different time-frame: the maximum incidence of onset

of breathlessness is between 28-31 weeks' gestation,<sup>7</sup> whereas ventilation increases from before 4 weeks. While other contributing factors have been postulated, the currently accepted explanation for hyperventilation of pregnancy is still the effect of progesterone.<sup>6</sup>

### ARF

ARF can be separated into two distinct groups based on the cause of decompensation (see table 1). In the remainder of this review, some of these underlying causes of ARF are described and discussed.

### ARDS

ARDS can be described as a final common pathway of pulmonary injury which has a myriad of different causes (see table 2). The most common predisposing diseases for ARDS complicating pregnancy are sepsis, pneumonia, gastric aspiration (Mendelson Syndrome; see below), and AFE. In addition to the latter, uniquely obstetric causes of ARDS include pre-eclampsia and tocolytic therapy.

Briefly, the pathogenesis of ARDS results from immune system activation in the lung in response to a severe systemic event

**Pre-eclampsia and tocolytic therapy may precipitate ARDS**

Table 2. Predisposing conditions for ARDS

- Gastric aspiration
- Drug-induced
- Venous fluid embolism
- Septic abortion
- AFE
- Sepsis
- Pneumonia
- Fat embolism
- Blood transfusion
- Eclampsia
- Seizures
- Abruptio placentae
- Trauma
- Dead foetus syndrome
- Overdose
- Retained products of conception

or injury. Inflammatory mediators damage pulmonary epithelial and endothelial tissues, producing an increase in vascular permeability and atelectasis. The characteristic clinical consequences of this are diminished pulmonary compliance and respiratory shunt-mediated hypoxaemia. Diagnostic criteria for ARDS are acute, non-cardiogenic lung injury, with a ratio of  $\text{PaO}_2/\text{FiO}_2$  \* oxygen  $< 200$ . The initial pulmonary injury in ARDS may be further worsened by therapeutic hyperoxia and barotrauma.<sup>8</sup> [\*Fi = fraction of inspired oxygen.]

ARDS, although rarely encountered in association with pregnancy, is nonetheless highly lethal. In one series of 16 pregnant patients with ARDS treated between 1986 and 1992, the reported mortality rate was 44%.<sup>9</sup>

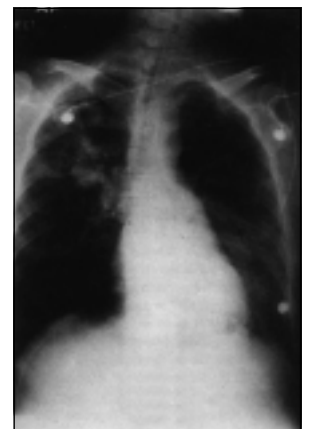
The generalised goals of ARDS treatment are to limit lung injury and to provide overall support until the underlying disorder(s) are corrected or have resolved. Crucial management issues include:<sup>10</sup>

- Support of maternal oxygenation and cardiac output.
- Myriad interactions between the pulmonary process and its treatment, with regard to maternal-foetal physiology.
- Decision making regarding delivery.

According to Van Hook,<sup>8</sup> management of ARDS during pregnancy is simultaneously similar and different to that in non-pregnant patients. However, pregnant patients with ARDS often have potentially reversible disease processes and may, therefore, benefit from aggressive use of advanced techniques and measures. This author advises to generally maintain relatively physiological  $\text{PaCO}_2$  levels during mechanical ventilation and a  $\text{PaO}_2$  of 60 mm Hg. The decision to mechanically ventilate a pregnant patient should ideally be made in such a way as to (if possible!) allow the elective intubation of the patient. Careful observation for impending respiratory failure should be part of the care for any non-intubated pregnant patient with ARDS. Limiting peak-plateau airway pressure to  $< 35$ -40 mm Hg during mechanical ventilation may reduce barotrauma.<sup>8</sup>

Fluid and volume homeostasis in the pregnant patient with ARDS is in effect a three-way compromise involving lung fluid, maternal and foetal (organ) perfusion, and oxygen delivery. Van Hook<sup>8</sup> advocates relative fluid restriction, provided that foetal tolerance is evident, metabolic acidosis is not present, renal and other organ perfusion is maintained, vasopressors are not required, and haemodynamically influential modes of mechanical ventilation are not required. If these conditions cannot be met with relative fluid restriction, empirical volume administration and/or invasive monitoring is usually required. Because of the additional nutritional requirements of pregnancy, indirect calorimetry may be advisable for the long-term monitoring of the enterally- or parenterally-fed pregnant patient.<sup>8</sup>

A review of the literature by Catanzarite and Willms<sup>10</sup> suggests that for the pregnant patient requiring antepartum



Characteristic chest x-ray (CXR) changes as ARDS develops: day 1 (top), day 2 (upper middle), day 3 (lower middle), and day 4 (bottom)

intubation for ARDS, except at a very early gestational age or when pyelonephritis or varicella pneumonia is the cause of respiratory compromise, delivery will likely be required for maternal and/or foetal indications, and an early decision for delivery may be beneficial. Postpartum management is similar to that for the non-pregnant state.

### Gastric Aspiration

In 1946, Mendelson<sup>11</sup> described a series of obstetric patients who aspirated gastric contents into the lung. In the preceding 13-year period from 1932-1945, he observed that 66 pregnant patients from a series of 44,016 had an aspiration event, an incidence of 0.15%. Table 3 lists factors predisposing to aspiration during labour and delivery.

Table 3. Factors predisposing to gastric aspiration during labour and delivery<sup>2</sup>

- Delayed gastric emptying
- Gravid uterus
- Recent food or drink
- Relaxed oesophageal sphincter
- Frequent examination
- Supine position
- Analgesia
- Anaesthesia

The severity of the aspiration event directly correlates with the amount aspirated, the pH of the aspirate, and its particulate content. Management focuses on the prevention of this event by using regional anaesthesia, not giving patients anything by mouth, employing histamine (H<sub>2</sub>) blockers, and ensuring cricoid pressure if endotracheal intubation is deemed necessary.

### Amniotic Fluid Embolism

First described in 1941 by Steiner and Lushbaugh,<sup>12</sup> AFE is a pulmonary condition uniquely associated with pregnancy. Characteristically, the patient experiences sudden collapse with dyspnoea, cyanosis, and hypotension. AFE is a rare condition (ap-

proximately 1 in 80,000 pregnancies), but again, as in the case of ARDS, one which is highly lethal: the mortality rate is 80-90%, and accounts for 4-10% of all maternal deaths.<sup>13,14</sup>

The pathophysiology of AFE is poorly understood. Historically, it has been thought to induce cardiovascular collapse by mechanical obstruction of the pulmonary circulation. Briefly, amniotic fluid enters the maternal circulation where, on account of its high thromboplastic activity,<sup>15</sup> it causes disseminated intravascular coagulation (DIC), resulting in pulmonary insufficiency and a haemorrhagic diathesis. Foetal squames, lanugo hairs, meconium, fat, mucin, and bile also embolise to the maternal pulmonary circulation.<sup>13</sup> However, a review of the largest case series to date has concluded that the physiologic and haematologic manifestations of AFE bear a greater resemblance to septic and anaphylactic shock than to any embolic phenomenon.<sup>16</sup>

AFE can occur at any time during pregnancy<sup>17</sup> and has been reported up to 48 hours postpartum.<sup>18</sup> Predisposing factors remain uncertain, but among those that have been put forward are advanced maternal age, uterine rupture, low uterine segment laceration, high parity, meconium-stained amniotic fluid, caesarean section, and as a complication of amino-infusion for either a therapeutic instillation<sup>19</sup> or to induce abortion.<sup>20</sup>

There is no diagnostic test for AFE; the finding of foetal elements in the maternal circulation is non-specific. In an anaesthetised patient, differentiation from inhalation is important. Bronchospasm is common in inhalation, but very rare in AFE. DIC is an early presenting feature in AFE, but occurs late after inhalation.



There is no specific therapy for AFE and treatment remains supportive:<sup>21</sup> immediate oxygenation, restoration of normal blood pressure and circulating blood volume, and correction of coagulopathy. Fresh, frozen plasma is given if the fibrinogen level is low.

## Asthma

Asthma is the most common pulmonary complaint complicating pregnancy, occurring in up to 4% of pregnancies.<sup>22</sup> A recent literature review of the interrelationships between asthma and pregnancy by Schatz<sup>23</sup> concluded that pregnancy can affect the course of asthma and asthma can affect pregnancy outcomes.

Asthma course may improve (in about one-third of pregnant patients), worsen (one-third), or remain unchanged (one-third). Severe asthma is more likely than mild asthma to worsen during pregnancy. Although the course in an individual woman is largely unpredictable, it tends to be consistent from one pregnancy to the next.<sup>24</sup> In cases where there is a decrease in the frequency and severity of asthma attacks,<sup>25</sup> this may be brought about by factors such as an increase in circulating free cortisol, a decrease in bronchomotor tone and airway resistance, and an increase in serum concentration of cyclic adenosine monophosphate (cAMP).

Available data, although certainly not totally consistent, suggest that asthma is associated with increased frequencies of adverse pregnancy outcomes. For example, infants born to hospitalised asthmatic mothers have lower birthweights.<sup>26</sup> However, the reductions are small and probably of little significance. There are also reports that the risk of prematurity is either slightly increased<sup>26</sup> or unchanged<sup>27,28</sup> in patients with asthma. In his review, Schatz<sup>23</sup> stresses that the distinction must be made between

asthma control and asthma severity and points out that patients treated by asthma specialists appear less likely to manifest complications such as low birthweight and prematurity. Indirectly, at least, this supports the hypothesis that better-controlled disease is associated with improved perinatal outcomes.<sup>23,29</sup>

Management of asthma during pregnancy differs little from management in the non-pregnant state,<sup>30</sup> in each case the primary aim is to achieve a stable asymptomatic state using whatever medications are necessary to achieve the best possible pulmonary function (see table 4). Inhaled  $\beta_2$ -adrenergic receptor agonists and corticosteroids provide the cornerstone of pharmacotherapy,<sup>22</sup> while xanthine bronchodilators (e.g. theophylline) and anticholinergics are third-line choices (see box). Medications used to control asthma during pregnancy can contribute to the poor outcome, although this risk appears to be much less than that of adverse outcomes related to severe uncontrolled asthma.<sup>23</sup>

### **Antenatal Management**

Because foetal distress can occur even in the absence of maternal hypoxia, foetal monitoring is obligatory during management of an acute exacerbation of asthma once foetal viability is reached. For gravidas with moderate or severe asthma, serial sonography for foetal growth and third trimester antepartum foetal assessment are indicated.

Self-monitoring of peak expiratory flow-rate (PEFR) is an invaluable part of asthma management, especially in patients who have a poor perception of the severity of their condition. The gravida should establish her personal best PEFR and therapeutic adjustments be based on this.<sup>22</sup>

Table 4. Asthma in pregnancy: therapeutic goals

- Maintain normal pulmonary function
- Control symptoms
- Prevent exacerbations
- Avoid adverse effects of medication
- Delivery of a healthy baby



**Increased foetal monitoring is indicated in moderate-severe asthma**

## About Available Anti-asthma Agents<sup>23</sup>

### $\beta$ 2-Adrenergic Bronchodilators

$\beta$ 2-Adrenergic agonists...

- Produce the greatest bronchodilation in patients with bronchial asthma.
- Can be administered by inhalation, oral, or parenteral route.
- Are preferred for the relief of acute symptoms and for the prevention of exercise-induced symptoms.
- Are safe in pregnancy (especially inhaled albuterol, metaproterenol, terbutaline).

Asthmatic patients treated with  $\beta$ 2-adrenergic bronchodilators, whether inhaled or taken orally, do not have any delay in the onset of labour, nor do they have prolonged labours.

### Corticosteroids

Corticosteroids ...

- Are the most effective anti-inflammatory agents available.
- Can be administered by inhalation, oral, or parenteral route.

Currently, it is recommended that inhaled corticosteroid therapy should be added when inhaled  $\beta$ 2-adrenergic bronchodilators are required more than once-a-day.

Advocating the use of corticosteroids early in the treatment process recognises that airway inflammation is a component of disease, even in patients with mild asthma.

Inhaled beclomethasone achieves very low blood concentrations and is therefore safe for the foetus: Schatz et al. found no independent associations between beclomethasone use during pregnancy and adverse pregnancy outcomes. Inhaled disodium cromoglycate (cromolyn) is also safe for the foetus.

Oral corticosteroids, on the other hand, should not be prescribed unnecessarily during pregnancy. Their use in the first trimester has been associated with risk of oral clefts, while other studies suggest — but do not conclusively prove — an association with an increased risk of pre-eclampsia.

### Theophylline

Theophylline appears to be safe for pregnancy.<sup>31</sup> It does not seem to add any benefit for routine treatment of acute exacerbations of asthma in patients receiving optimal therapy with inhaled  $\beta$ 2-adrenergic bronchodilators and corticosteroids, but may be justified in patients with severe acute symptoms who prove unresponsive to these first-line therapies.

An increased incidence of congenital malformations has not been reported with theophylline, but data regarding other complications (e.g. eclampsia) has been conflicting.

### Anticholinergics

Inhaled atropium and ipratropium bromide achieve very low blood concentrations and are therefore safe for the foetus. These compounds may be useful in patients refractory to  $\beta$ 2-adrenergic bronchodilators.

### **Peripartum Management**

Asthma medications should be continued peripartum. As their hypothalamo-pituitary-adrenal axis may be suppressed, pregnant asthmatics requiring corticosteroid therapy should receive parenteral hydrocortisone during labour and for 24 hours postpartum.

Oxytocin is preferred over the various prostaglandin preparations for induction of labour and over ergometrine for the management of the third stage of labour. It is also the drug of choice for postpartum haemorrhage. If a general anaesthetic is necessary during the first and second stages of labour, pretreatment with atropine and glycopyrrolate may provide a bronchodilatory effect.<sup>22</sup>

### **Tocolytic-associated Pulmonary Oedema**

Use of beta-sympathomimetic agents in pregnancy has been associated with an incidence of acute pulmonary oedema of 0-4.4%, especially with accompanying maternal infection.<sup>38</sup> However, the underlying pathophysiology of this pulmonary oedema has not been defined.

Treatment involves withdrawal of the causative agent and supportive care. Typically, resolution takes place within 24 hours without the use of diuretics, and respiratory failure necessitating mechanical ventilation is rare.

### **PE**

[*Editor's note: Issue 3.1 of **Obstetrics & Gynaecology Communications** will feature a detailed discussion of the incidence and management of pulmonary embolism (PE) in pregnancy.*]

PE is a significant cause of maternal mortality; in some studies it is cited as the

## **Non-asthma Obstructive and Restrictive Pulmonary Diseases**

Obstructive pulmonary diseases aside from asthma are uncommon in pregnancy. There is no information about emphysema and pregnancy except for the case report of a patient with alpha 1-antitrypsin deficiency.<sup>32</sup> This patient delivered a normal infant after an uneventful labour at 38 weeks.

Teirstein<sup>33</sup> has suggested that uncomplicated bronchiectasis should not be considered as an indication for therapeutic abortion.

Patients with cystic fibrosis who become pregnant should be counselled that there is a 1 in 20 to 1 in 44 chance that the child will have the condition, if the father's status is unknown.

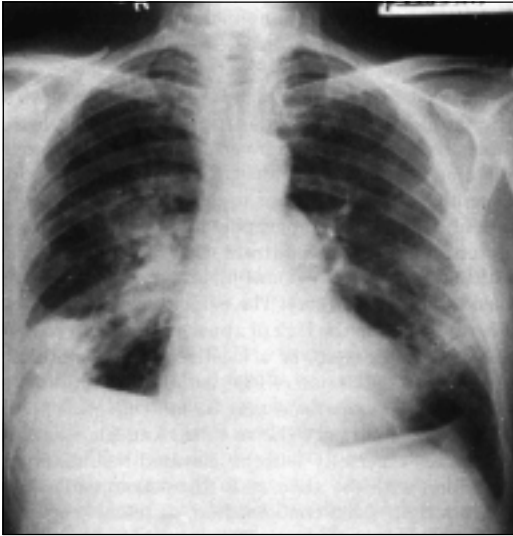
Table 5 lists factors indicative of a poor prognosis in sarcoidosis and pregnancy.<sup>34</sup> Although pregnancy should be discouraged during a period of active disease progression, studies suggest that pregnancy in itself does not aggravate sarcoidosis, and may even improve the condition somewhat.<sup>35-37</sup> One possible explanation for this fact is the increased concentration of circulating cortisol during pregnancy. Patients should be advised not to take vitamin D to which they may be very sensitive.



*CXR of acute, diffuse sarcoidosis affecting both lungs, with alveolar and interstitial infiltration and gross hilar and mediastinal involvement*

**Table 5. Poor prognostic factors in sarcoidosis**

- Parenchymal lesions on CXR
- Advanced roentologic staging
- Advanced maternal age
- Low inflammatory activity
- Requirement for drugs other than corticosteroids
- Presence of extrapulmonary sarcoidosis



*CXR showing recent PE in the right lower lobe. Characteristic tenting of adjacent hemidiaphragm can also be seen*

second most common cause of maternal deaths.<sup>42</sup> Symptoms of PE are often vague and may include dizziness, syncope, tachypnoea, dyspnoea, tachycardia, and anxiety. Suspicion, or the awareness of increased risk, is essential in these cases. An appreciation of the risks to the foetus associated with certain diagnostic studies is critical, but the focus remains on maternal well-being.

Treatment includes IV heparin to achieve an activated partial thromboplastin time (APTT) 1.5 times the upper level of laboratory control values. Management of patients exhibiting respiratory failure is supportive (mechanical ventilation) while this diagnosis is aggressively explored.

### **Pulmonary TB**

Before the advent of anti-TB therapy, tuberculosis (TB) was the cause of many maternal deaths, particularly in the puerperium. [*Editor's note: the management of TB in pregnancy has been reviewed in this journal previously.*<sup>43</sup>]

In terms of diagnosis, a high index of suspicion is needed, especially if the

## **Pneumonia and Pyelonephritis**

Pneumonia is an uncommon complication of pregnancy. Treatment includes antibiotics and antipyretic therapy. Approximately 10% of all reported cases of varicella pneumonia have been in pregnant women. Maternal mortality has been approximately 45% among pregnant cases in comparison with 15-20% mortality among non-pregnant patients.<sup>39,40</sup> Therefore, all pregnant patients who have close exposure to varicella zoster virus and demonstrable antibody should receive zoster immune globulin. Those who develop varicella should receive acyclovir 10-30 mg/kg/day in three divided doses for 5 days.

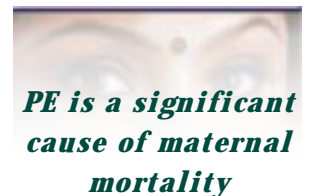
Pyelonephritis in pregnancy carries a significant and perhaps underestimated morbidity rate: ARDS, for example, can occur as a complication of acute pyelonephritis.

More aggressive treatment of patients with pneumonia or pyelonephritis during pregnancy is warranted.<sup>41</sup>

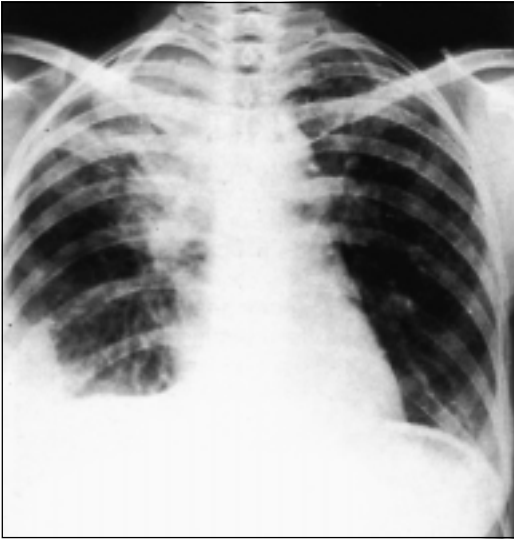
mother has had TB in the past, or is in a high-risk group for the disease. Response to the tuberculin plasma protein derivative (TTPD) skin test is unaffected by pregnancy; it is thus the most appropriate method for screening for TB in pregnancy. Any TTPD test result should be interpreted in the light of known risk factors. In particular, women with both human immunodeficiency virus (HIV) and TB infections may show no reaction to the test, so all pregnant women at risk of (or with known) HIV infection, should be thoroughly examined and screened for TB. Although routine CXR is not recommended in pregnancy, it should be performed (with appropriate shielding) in those pregnant women with:<sup>44</sup>

- Positive TTPD test (recent converter).
- Symptoms suggestive of TB (especially if other risk factors are present).
- A history of recent migration from a high-risk area.

Treatment of the pregnant patient with TB is essentially the same as for the non-



*PE is a significant cause of maternal mortality*



*CXRs from a 4-month pregnant woman with miliary TB showing diseased right upper lung and right pleural effusion (left) and after isoniazid-based treatment (right)*

pregnant patient. However, streptomycin should be avoided and ethionamide should not be used because of reported foetal complications. Rifampicin, isoniazid, ethambutol, pyrazinamide can all be used safely.<sup>45</sup>

### Primary Pulmonary Hypertension (PPH)

Primary pulmonary hypertension (PPH) is a pulmonary vascular disease characterised by an elevation in mean pulmonary artery pressure and pulmonary vascular resistance. It is an uncommon entity, but one which becomes lethal when associated with pregnancy.<sup>46</sup> In one series of 27 patients described by Weiss et al.,<sup>47</sup> maternal mortality due to PPH was reported to be 30%, with neonatal survival at about 90%.

In Weiss's series, dyspnoea at rest and, less frequently, a hoarse voice, hemoptysis, syncope, cyanosis, or toxæmia of pregnancy indicated hospital admission during pregnancy. Importantly, treatment was individually-tailored to each patient and consisted of bed rest and oxygen supplementation, digoxin (occasionally), diuretic agents, and vasodilators.<sup>47</sup>

Eleven parturients delivered at term, 10 between 32-36 weeks, and six 31 weeks. The major postpartum complications were worsening of dyspnoea, cyanosis, hemoptysis, pulmonary hypertensive crisis (in one patient after use of oxytocin), and systemic hypotension. Eight women died of therapy-resistant heart failure, all shortly after delivery; the timing of these maternal deaths thus emphasises the need for intensive medical therapy and care during the highly vulnerable postpartum period. Foetal mortality rate was 11%.<sup>47</sup>

### Conclusions

- Complex physiologic changes occurring during pregnancy influence maternal respiratory function and gas exchange.
- The risks of ARF from various causes are increased during pregnancy.
- ARDS, aspiration, venous air embolism, asthma, thromboembolism, and heart disease have aetiologies shared by non-pregnant women. However, their management is complicated by the mechanical and biochemical changes occurring during pregnancy.
- AFE and tocolytic-induced pulmonary oedema are unique to pregnancy and



***Consider the foetal toxicity of anti-TB medications***

must be added to the list of causes of ARE

- Diagnostic and supportive care is difficult and must be directed with the mother and foetus in mind. This dictates a thorough understanding of maternal physiology, and the safety of drug use during pregnancy.

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# Endometriosis 2000 7<sup>th</sup> Biennial World Congress

London, United Kingdom, 14-17 May 2000

## Relationship of Endometriosis to Infertility



**D. Healey**  
Monash Medical Centre,  
Melbourne, Australia

The evidence for endometriosis as a cause of infertility remains unproven according to Dr Healey. A literature search on the aetiology of endometriosis and associated infertility carried out by epidemiologists at the Centre for Clinical Effectiveness, Monash Medical Centre, found 463 abstracts on infertility and endometriosis (table 1). However, of 42 pertinent articles, only six were eligible for critical appraisal: two randomised controlled trials (RCTs)

The 7<sup>th</sup> Biennial World Congress on Endometriosis was held at the Queen Elizabeth II Conference Centre, London, United Kingdom, from 14-17 May, 2000. Attracting endometriosis experts from around the globe, the meeting entitled 'Evidence-based Medicine (EBM): Endometriosis and Infertility' contained a lively debate on the controversial issue of infertility associated with endometriosis, followed by discussion of the potential role of various therapies. Contributing editor Mary Smith reports.



Trafalgar Square, London

and four cohort or case-control studies.<sup>1-6</sup>

One reason for the lack of controlled trials is that gynaecologists tend to report case series or single case studies, an approach to publication that has recently given way to EBM. Epidemiologists from the Centre for Clinical Effectiveness at Monash Medical Centre require more substantial data to prove that endometriosis causes infertility, explained Dr Healey.

These researchers suggest that, in general, gynaecologists need to clearly identify the following points for research:

- Patient groups for comparison.
- Consistent measures of exposure.
- Consistent and objective measures of outcome.
- Temporal relationships and dose-response effects.

*Endometriosis as a cause of infertility remains unproven*

Table 1. Monash Medical Centre search strategy

Search criteria	Inclusion criteria
Patients – wishing for pregnancy	Primary studies of pregnancy rates
Exposure – minimal or mild endometriosis	Women with endometriosis
Comparison – no endometriosis	Women without endometriosis
Outcome – pregnancy	Pregnancy rates according to stage of endometriosis

# Role of Medical Therapy



**J.L.H. Evers**  
*Academisch Ziekenhuis  
 Maastricht, Maastricht,  
 The Netherlands*

In order to address the problem of ‘endometriosis-associated infertility’, Dr Evers referred to Taylor and Collins analysis of 22 studies of women with unexplained subfertility (n = 2026).<sup>7</sup> These researchers noted that 33% of the women (n = 669) went on to achieve spontaneous pregnancy. In 1996, Adamson found a crude pregnancy rate of 34% in 1063 patients with endometriosis.<sup>8</sup> However, eight RCTs of surgery or medical therapy for endometriosis show a 17-47 % spontaneous pregnancy rate for the women in the untreated control groups (table 2).<sup>1,9-14</sup> Similar pregnancy rates for women with endometriosis and untreated controls suggests that endometriosis does not, in fact, cause infertility.

Regarding the role of medical therapy for endometriosis, Dr Evers suggested that treatment tends to be palliative rather than curative, as shown by a study of second-look laparoscopy 2 months after treatment and resumption of menses (figure 1).<sup>15</sup> While endometriosis implants are reduced in size and number during treatment, implantation resumes when treatment stops.

A common misconception is that if the endometriosis can be cured, then the accompanying infertility will also be cured. However, this theory is dependent on a causal link between endometriosis and infertility, which has not yet been established – the pregnancy rates for patients

Table 2. Spontaneous pregnancy rates among women with endometriosis (untreated controls)

Trial	Control patients	Number of pregnancies	Pregnancy rate (%)
Thomas <sup>9</sup>	17	4	24
Bayer <sup>10</sup>	38	17	47
Telimaa <sup>11</sup>	14	6	43
Fedele <sup>12</sup>	36	17	47
Overton <sup>13</sup>	18	7	39
Marcoux <sup>1</sup>	169	29	17
GISE <sup>14</sup>	45	13	29

*Abbreviation: GISE = Gruppo Italiano per lo Studio dell’Endometriosi.*

Table 3. Spontaneous pregnancy rates among patients and controls in RCTs of medical therapy for endometriosis

Trial	Pregnancy rates		OR
	Patients (%)	Controls (%)	
Thomas <sup>9</sup>	25	24	1.1
Bayer <sup>10</sup>	35	47	0.6
Telimaa <sup>11</sup>	33	43	0.7
Telimaa <sup>11</sup>	41	43	0.9
Fedele <sup>12</sup>	49	47	1.1
Overton <sup>13</sup>	47	39	1.4

and controls in the six medical studies listed in table 2 are similar with odds ratios (ORs) for treatment at approximately 1 (table 3).<sup>9-13</sup> The Cochrane analysis found an OR ratio of 0.9 [95% confidence interval (CI) 0.6–1.4], indicating that there is no treatment effect.<sup>16</sup>

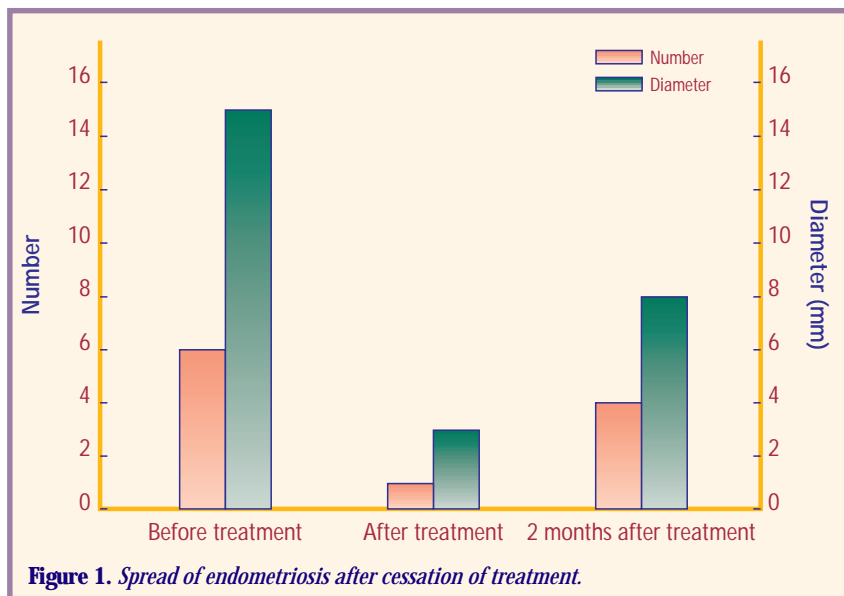


Figure 1. Spread of endometriosis after cessation of treatment.

## In Conclusion

Dr Evers suggested that the proposed link between endometriosis and infertility may be due to an epiphenomenon, that is a phenomenon that occurs with — and seems to result from — another. The evidence is lacking for a link between minimal or mild endometriosis and infertility. With no problem to solve, there is no requirement for a solution in the form of medical therapy.

## Role of Surgical Therapy



**I. Cooke**  
University of Sheffield,  
Jessop Hospital for  
Women, United Kingdom

The highest quality evidence is that obtained from meta-analysis of RCTs, explained Dr Cooke. While RCTs *are* available, most of the evidence falls into the lower level categories for EBM; there are insufficient numbers of *prospective* RCTs in gynaecological surgery. However, Dr Cooke drew on evidence from trials published during the past 5 years to discuss the role of surgery in endometriosis.

Adamson *et al.*<sup>17</sup> and Hughes *et al.*<sup>18</sup> agree that laparoscopy results in less blood loss and a shorter recovery period than laparotomy. However, not all women with endometriosis can be treated by laparoscopy.

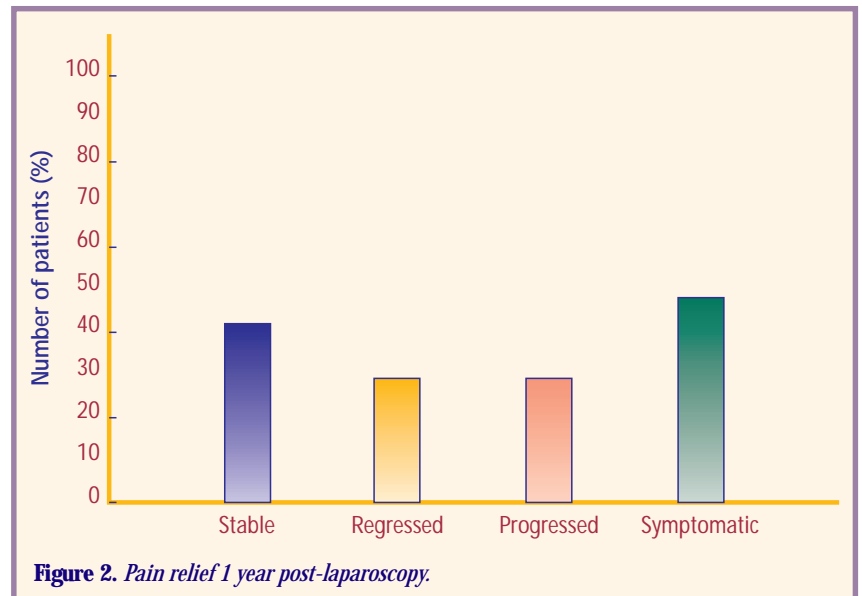
Marcoux *et al.*<sup>1</sup> found that ablation performed via laparoscopy at the time of diagnosis resulted in a significantly higher pregnancy rate than for women not treated at diagnosis (30.7 vs 17.7%,  $p < 0.006$ ). However, Dr Cooke pointed out that this

study was flawed in its selection criteria. In addition, the status of laparoscopy as a routine investigation for women presenting with infertility remains unresolved.

Vercellini *et al.*<sup>19</sup> indicated that medical therapy without surgical debulking gave no fertility benefit, although pain was reduced. These authors felt that there was no satisfactory evidence to support continuation of adjuvant medical therapy after conservative surgery. Four other RCTs found that there was no fertility effect from this approach, but pain control was improved.<sup>20-23</sup> Dr Cooke concluded that adjuvant medical therapy with surgery “*has no obvious role at the present time.*”

A review of surgery and adjuvant barriers found that while interceed (an absorbable adhesion barrier) has a role in therapy, there was nevertheless adhesion reformation.<sup>24-26</sup> Franklin *et al.*<sup>27</sup> found a reduction in ovarian adhesions with interceed, although early second-look laparoscopy is recommended and pain and pregnancy outcomes need to be established and fully described.

While it is easy to dismiss the role of adjuvant medical treatment, questions remain unanswered. Donnez *et al.*<sup>28</sup> gave a gonadotrophin-releasing hormone ana-



logue for 3 months in conjunction with laparoscopic ovarian cystotomy to 814 women with endometrial cysts. This study resulted in a pregnancy rate of 51% at 1 year and a low recurrence rate of 8% at 2 years.

Recent comparisons of techniques in ovarian surgery found that pregnancy occurred earlier following fenestration and coagulation (after 1.4 years) in comparison to laparoscopic cystectomy (2.2 years) or open microsurgery (2.4 years).<sup>29</sup> However, by 3 years, the rates were comparable. Beretta *et al.*<sup>30</sup> felt that cystectomy was a better procedure as it was associated with less dysmenorrhoea, dyspareunia, pelvic pain, and a longer time to recurrence with higher pregnancy rates seen in the 64 women evaluated. However, the possibility of ovarian compromise and live birth rates following these techniques need to be considered.

Surgery for control of pain from endometriosis has been addressed. Uterine nerve ablation showed no significant pain relief after 6 months, although Candiani *et al.*<sup>31</sup> and Tjaden<sup>32</sup> found that presacral neurectomy may help midline pain (see also reference<sup>33</sup>).

Laparoscopic treatment of pain associated with endometriosis has been shown to be beneficial for 63% of treated patients versus 23% of controls.<sup>34</sup> However, the poorest outcomes were found in the earlier stages of the disease, with better effect for women with more severe disease. At 1 year, 90% of responders maintained pain relief and second-look laparoscopy confirmed disease status (figure 2).

### In Conclusion

Since surgery for lower-grade peritoneal endometriosis is commonly performed for large numbers of patients, it *is* possible to perform randomised trials. However, few surgical techniques are appropriate for

randomised study and (therefore) it is unlikely that complex surgery will ever be fully evaluated.

Future studies need to address symptom relief, fertility outcome, and recurrence. An important consideration for high quality data is improved technical training in the newer techniques for complex surgery.

## IVF and Endometriosis



**J-L. Pouly**  
Centre Hospitalier  
Universitaire, Clermont-  
Ferrand, France

A review of the literature between 1990-1999 found limited data on the role of *in vitro* fertilisation (IVF) in endometriosis-associated infertility and the evidence was conflicting.

Kodama *et al.*<sup>35</sup> found a non-significant difference between IVF treatment and no treatment after laparoscopy, with a cumulative pregnancy rate at 3 years of 62% and 43%, respectively. In a limited group of 32 patients, there was a significant difference between IVF treatment and no treatment (59% vs 29%). In addition, Pagidas *et al.*<sup>36</sup> found a significant difference between IVF treatment and no treatment after failure of laparoscopic surgery (69.9% vs 24.4%). However, neither of these studies were randomised.

Dr Pouly described his prospective cohort study of 242 women, which resulted in 81 deliveries (33.5%) following laparoscopy and 80 (33.1%) following IVF treatment. Soliman *et al.*<sup>37</sup> performed the only prospective randomised study to date, which found no difference in crude and



cumulative delivery rates between IVF treatment and surgery.

Dr Pouly maintained that the evidence for IVF in endometriosis is inconclusive and suggested that the ideal control group for this type of study is fertile women undergoing IVF, which is impossible to arrange.

Reviewing the evidence by stage of IVF, Dr Pouly found that four studies of ovarian hyperstimulation suggested that women with endometriosis-associated infertility had fewer oocytes than controls,<sup>38, 41</sup> while seven maintained that there was no difference.<sup>42-48</sup> Dr Pouly's own study found that women with endometriosis had more oocytes than women with tubal infertility, although healthy controls (treated for male infertility) had the highest number of oocytes (table 4).

Endometriosis	Tubal infertility	Male infertility
10.58	9.98	11.33

Regarding fertilisation and cleavage, seven publications found a lower fertilisation rate in women with endometriosis<sup>38,39,41,47,49-51</sup> and five found a similar rate.<sup>42,44-46,48</sup> There are also controversial data on the relationship between American Fertility Society stage and fertilisation rate, although most authors agree that even if the fertilisation rate decreases, the transfer rate is not affected. Dr Pouly's own study showed a significant difference in the fertilisation rate between women with endometriosis and other women undergoing IVF, although there was no difference in the transfer rate (figure 3).

Implantation is more complex; four trials found a decreased implantation rate,<sup>39,42,43,52</sup> six found a similar implantation rate,<sup>38,41,44-46,49</sup> and four found an *increased* implantation rate.<sup>37,47,48,53</sup> Dr Pouly's own

Table 5. Implantation and pregnancy rates for all causes of infertility

	Endometriosis	Tubal infertility	Male infertility	Unexplained infertility
Implantation rate (mean)	2.54	2.68	2.48	2.59
Pregnancy rate (%)	35.4	33.6	32.1	36.3

study found a similar rate for transfer and pregnancy between the groups (table 5).

Most authors did not find any difference in pregnancy outcome, although Yanushpolsky<sup>54</sup> found more miscarriages in women with endometrioma. Most authors found a similar delivery rate, although a decreased rate was shown in four studies,<sup>39,43,42,52</sup> and an increased rate in two.<sup>37,48</sup> Dr Pouly's own study found a similar delivery rate for all causes of infertility, except male infertility. The baby rate per transfer of embryo was similar for all causes.

There is no difference in biological data (stimulation duration, oestradiol, blastocyst/embryo transferred, blastocyst/embryo obtained) between women with endometriosis and those without endometriosis. However, some authors have clearly demonstrated that the quality of the oocytes is reduced in women with endometriosis, with fewer blastomeres in the embryo, abnormal granulosa cell secretion, fewer blastocysts at day 5, and more

*The evidence for IVF in endometriosis is equivocal*

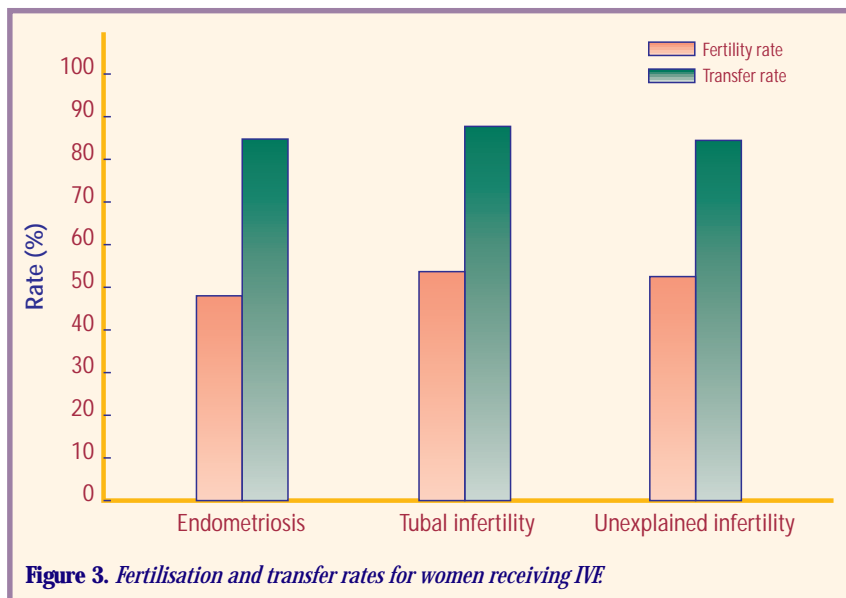


Figure 3. Fertilisation and transfer rates for women receiving IVF

apoptotic granulosa cells.<sup>50,52,55</sup> Yet, Dr Pouly felt that these abnormalities were small and did not influence the final results of IVF for endometriosis.

## In Conclusion

IVF provides similar results for infertility associated with endometriosis as for tubal or unexplained infertility. The crude delivery rate after 3-5 attempts is approximately 50-60 %; endometriosis status does not affect the results. While IVF is the lead-choice therapy for endometriosis associated with tubal infertility, laparoscopic surgery remains the first-line therapy for endometriosis, followed by IVF if necessary.

A future area for study may involve surgery followed by ovarian hyperstimulation plus intrauterine insemination *before* resorting to IVF. Progress in EBM is likely to come from comparison of these more complex protocols.

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# Endosonography in Obstetrics and Gynaecology

Editor: Gautam Allahbadia

It may be time to consider routine use of endovaginal ultrasonography, as this diagnostic tool picks up many abnormalities the bimanual exam misses. In her study of 633 premenopausal women, Dr M. Lynee Reuss of Bellvue Women's Hospital in Niskayuna, New York, reported that bimanual exams missed 36% of fibroids and 70% of abnormalities in the corresponding adnexa that were later detected by ultrasound.<sup>1</sup> Ultrasound was also useful in distinguishing uterine from adnexal masses, she noted.

The development of high frequency probes is literally producing a diagnostic revolution in gynaecology. Those who think this is an overstatement have either not used the technique or have not invested the time to become proficient enough with the technique to appreciate its real potential.

***Endosonography in Obstetrics and Gynaecology***, a wonderfully edited volume by Dr. Gautam Allahbadia, is truly a composite text for gynaecologists who are not familiar with the techniques of endovaginal ultrasound and for radiologists who are not very familiar with gynaecologic diseases. Essentially, this book has been written for sonographers by (foremost) sonographers, and readers are assured of accurate, current, and proven information.

Not only does the book focus on technique, but also on anatomy, physiology, and pathology. In addition, practical clinical areas such as color flow Doppler and ultrasound-guided invasive techniques, the ap-

plication of endosonography to male infertility and urogynaecology, and the diagnosis of congenital anomalies, are summarised. Along with basic chapters on historical aspects and safety of ultrasound and pregnancy, the use of this technique in varied indications such as vaginosonographic pelvimetry and vaginosonographically-guided chorionic villus sampling has been incorporated. A comprehensive section on transperineal ultrasound is also included.

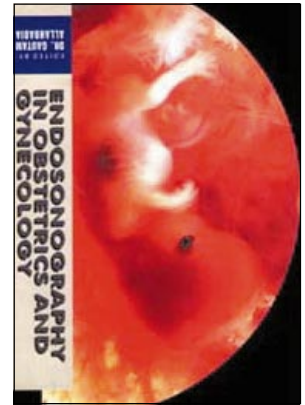
More than 200 colour pictures are included. Normal and abnormal ultrasound findings are illustrated, and clinical correlations for imaging data are provided. Chapters on 3-D ultrasound and newer imaging modalities such as computed tomography and magnetic resonance imaging keep readers informed on the latest advances.

With this book, the authors/editor have succeeded in covering the 'leading edge' application of endosonography in obstetrics and gynaecology, and have presented a timely and authoritative overview of all the new developments in the field. As such, ***Endosonography in Obstetrics and Gynaecology*** will serve as a very important reference source, both for students in the field as well as practising clinicians and ultrasound technologists.

Dr OA Shawki

## Reference

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## About the Reviewer...

Dr Osama Ahmed Shawki is Associate Professor of Obstetrics and Gynaecology at Cairo Faculty of Medicine, Kasr El Einy Hospital. He is an elect active member of the American Society for Reproductive Medicine (ASRM).

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**Email:** [shmoon@plaza.snu.ac.kr](mailto:shmoon@plaza.snu.ac.kr) or [cjhaines@cuhk.edu.hk](mailto:cjhaines@cuhk.edu.hk)

## JULY 2001

**10-13**

**Title:** 29<sup>th</sup> British Congress of Obstetrics and Gynaecology

**Venue:** Birmingham, England, UK

**Contact:** Royal College of Obstetricians and Gynaecologists, Congress House, 65 West Drive, Cheam, Sutton, Surrey, SM2 7NB, England, UK

**Phone:** + 44 208 661 0877

**Fax:** + 44 208 661 9036

**Email:** [info@conforg.com](mailto:info@conforg.com)

## SEPTEMBER 2001

**6-9**

**Title:** 2<sup>nd</sup> Congress on Controversies in Obstetrics, Gynaecology, and Infertility

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**Phone:** + 972 3 5140014

**Fax:** + 972 3 5140077

**Email:** [controversies@kenes.com](mailto:controversies@kenes.com)

**23-26**

**Title:** 1<sup>st</sup> Congress of the World Society for Breast Health

**Venue:** Istanbul, Turkey

**Contact:** C&S Public Relations, Istanbul, Turkey

**Phone:** + 90 212 232 7015

**Fax:** + 90 212 230 2123

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**20-25**

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**Contact:** Angelia Pitman, Administrative Secretary, Pamela McDonald, 1209 Montgomery Highway, Birmingham, Alabama 35216-2809, USA

**Phone:** + 1 205 978 5000

**Fax:** + 1 205 978 5005

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# The Endometriosis Association

**Mary Smith**  
London, United Kingdom

*Mary Smith is a Contributing Editor for Obstetrics and Gynaecology Communications*

## Introduction

Endometriosis is characterised by the growth and proliferation of endometrial tissue at sites outside the uterus, e.g. the ovary, bladder, intestine, or pelvic peritoneum.<sup>1</sup> Since definitive diagnosis can only be made by direct visualisation of the peritoneal cavity, the prevalence of endometriosis remains unknown. However, studies estimate that the prevalence is 10% among women of reproductive age. While the aetiology of endometriosis is unclear, it is thought that immune mechanisms may contribute to the disease process. Amongst other symptoms, endometriosis causes pain, fatigue, diarrhoea, and other intestinal symptoms, and dyspareunia (table 1).<sup>2</sup> In addition, endometriosis can result in significant impairment of quality of life.<sup>3</sup>

## Endometriosis Association

The Endometriosis Association is an international organisation of women with endometriosis, doctors, researchers, and other professionals associated with the disease whose ultimate goal is to find the cause of — and a cure for — endometriosis. Established in 1980, this non-profit organisation provides support and information for women with endometriosis, educates the public and the medical community about the disease, and promotes and conducts research related to endometriosis.

Table 1. Symptoms of endometriosis according to incidence (Endometriosis Association Study<sup>a</sup>)

Symptom	%
Dysmenorrhoea and/or pain throughout the menstrual cycle	95
Fatigue, exhaustion, low energy	87
Abdominal bloating	84
Diarrhoea, painful bowel movements, and other intestinal upsets with menses	65
Heavy or irregular bleeding	64
Dyspareunia	64
Nausea with menses	63
Dizziness, headaches with menses, or pain	43
Low resistance to infection	41
Infertility	32
Low-grade fever	1

<sup>a</sup>N = 4000 patients.

During the past two decades, the Endometriosis Association has grown from its roots in the United States to become an international organisation, with a network of members and groups in 66 countries. Information about endometriosis is available in 28 languages, including Hindi.

## Endometriosis Association Study

The Endometriosis Association is committed to funding research into the disease and its effect on women. As part of the research programme, the Endometriosis Association performed a survey of 4000 women with endometriosis.<sup>2</sup> The results of the 1998 Endometriosis Association Study found some startling data about the disease (table 2), which were presented at the 6<sup>th</sup> World Congress on Endometriosis.

Pain remains the number one symptom for women with endometriosis, and is often particularly severe for those whose pelvic symptoms start with menstruation. Interestingly, the number of girls experi-

Table 2. Endometriosis Association Study: key findings (1998)

- Endometriosis appears to be starting at a younger age than for previous generations
- Women whose symptoms start at a young age (< 20 years) may experience more severe symptoms
- Pain remains the most important symptom for women with endometriosis, closely followed by fatigue and diarrhoea
- The average time to diagnosis is 9.28 years
- The earlier the onset of symptoms, the longer the time to diagnosis

encing symptoms of endometriosis at the onset of menstruation has increased from 15% in the early 1980s to 38% in the most recent survey.

Of the many treatments available, the survey found that:

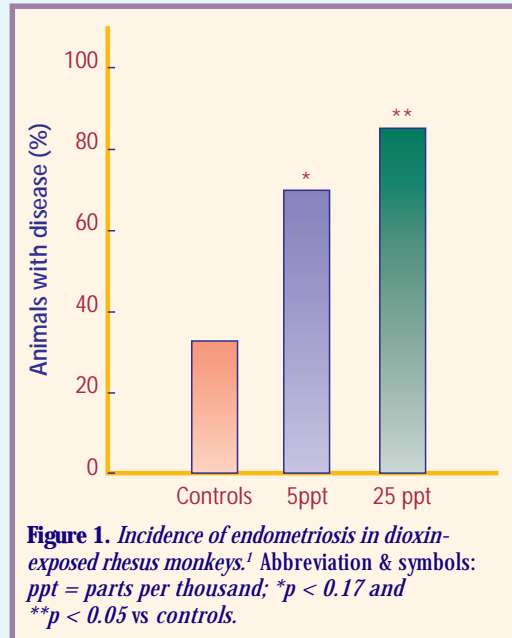
- Medical therapy helped 56-57% of women.
- Laparoscopy for removal of endometriosis was at least partly helpful for 66% of women.
- Hysterectomy was successful for 41%.

Complementary approaches achieved positive results, with the most successful being treatment for candidiasis (65% of women reported symptom relief). Other helpful approaches included exercise, dietary changes and supplements, and acupuncture.

The data registry of women with endometriosis produced by the survey is maintained by the Endometriosis Association.

### The Role of Dioxins

Research from the United States suggests that the age of menarche is younger for today's adolescents than for previous generations.<sup>4</sup> There is speculation that hormonally active chemicals that mimic female hormones (particularly dioxins) may be responsible for the earlier onset of puberty.<sup>2</sup> Dioxins tend to concentrate in the food chain, particularly fish and animal products. Exposure may also occur from contaminated air and water, and dioxins



are commonly found in breast milk. Since the genes targeted by dioxins influence hormone metabolism and growth factors, reproduction and immune functions may be adversely affected.

A study supported by the Endometriosis Association was undertaken to investigate the long-term reproductive effects of exposure to dioxin in rhesus monkeys.<sup>1</sup> The results showed that the incidence of endometriosis was significantly greater in the exposed monkeys than in control monkeys ( $p < 0.05$ ) and the severity of endometriosis was directly correlated with the dose of dioxin administered (figure 1). These researchers indicated that female reproductive abnormalities in monkeys could be associated with dioxin exposure. The Endometriosis Association continues to provide funding for this important research into the association between dioxin exposure and the development of endometriosis.

### Research Support

The Endometriosis Association has established a special research programme at Dartmouth Medical School in the United States and has additionally provided funds

for research in various parts of the world. In 1999, the Endometriosis Association joined forces with the Vanderbilt University School of Medicine to create a dedicated research facility to address the cause of endometriosis. Funding provided by the Endometriosis Association will be matched by funding from the Vanderbilt University School of Medicine to provide a research facility and fund a multidisciplinary research team. In addition, a grant from the National Institutes of Health in the United States has been secured.

Other research projects include:

- A study of dioxin-exposed women in Italy.
- Assistance with a genetic study at Oxford University, England.

- Investigation of a non-invasive diagnostic technique pioneered in the United States.
- Provision of grants and tissue samples for researchers studying dioxin and other toxins related to endometriosis.

### References

1. Rier SE, Martin DC, Bowman RE, *et al*. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin. *Fundam Appl Toxicol* 1993;21:433-441.
2. Ballweg ML. New EA research shows disease is starting younger, is more severe. *Endometriosis Association Newsletter* 1999;19:6-10.
3. Garry R, Clayton R, Hawe J. The effect of endometriosis and its radical laparoscopic excision on quality of life indicators. *B J Obstet Gynaecol* 2000;107:44-54.
4. Herman-Giddens M. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric office settings network. *J Pediatr* 1997;99:505-512.



*'Black lesions': puckered black lesions have been described as 'classical' and 'typical'. These areas of endometriosis are the easiest to see and the most common to document by biopsy or excision of the dark area*

## An Interview With ...

*In a discussion with Lone Hummelshøj, International Representative Endometriosis Association, London, UK, Obstetrics and Gynaecology Communications discovered more about the important work of the Endometriosis Association.*

### **Q: What is the Endometriosis Association?**

**Ms Hummelshøj:** The Endometriosis Association is a non-profit organisation, intended to help women with the disease, educate people about the disease, and facilitate research. In general, the association is run by women with endometriosis, as it is essential that support and empathy comes from someone who has personal experience of the disease. However, we do not consider ourselves to be a traditional patient organisation because we work closely with the medical profession to raise awareness of the disease and campaign for better treatment. Physicians are able to direct women with endometriosis to the relevant support

groups where they may obtain further information about their illness and general support and counselling if required.

The Association should not be exclusive, and encompasses all people involved with this disease. This is primarily the women, their physicians, and endometriosis specialists, along with counsellors, nutritionists, and complementary therapists who help with symptom relief.

There are currently five separate endometriosis groups in the world, which started up within a few years of each other, not knowing that other groups existed. These groups work together for a common goal, but remain independent of each other. The Endometriosis Association helps new groups to establish themselves by training personnel and providing materials and support, and has thus grown into its international status.

Funding comes primarily from membership and private donations, with additional funds coming from the sale of literature and occasional donations from the pharmaceutical industry.



*'White-scarring': white scarred areas are easier to see when the intraluminal areas of the glands contain debris from bleeding. These areas are brown or black*

**Q: Which professional bodies are you associated with?**

**Ms Hummelshøj:** The World Endometriosis Society has selected the Endometriosis Association as their preferred patient organisation to work with and the Vanderbilt University School of Medicine in the United States has approached the Endometriosis Association with a proposal for a combined research programme. Our funds have been matched by funding from the medical school, with an additional grant from the National Institutes of Health in the United States.

The Endometriosis Association's 'Millennium Campaign for the Cure' aims to raise \$US 2.6 million for research and educational programmes throughout the world. Part of this money will go to the Endometriosis Association's research programme at the Vanderbilt University School of Medicine. One of our educational goals is to improve front-line physicians' recognition of the symptoms of endometriosis and to appreciate the need for specialist referral.

**Q: Does the Endometriosis Association know why endometriosis is starting at a younger age and has become more severe?**

**Ms Hummelshøj:** One theory is based on the link with environmental toxins, in particular dioxin. Research has shown that disease severity is correlated with the level of dioxin exposure. Importantly, the Endometriosis Association discovered the link between the disease and environmental toxins and funded the groundbreaking research performed by Dr Sherry Rier and colleagues.<sup>1</sup> Interestingly, Japan has one of the highest recorded prevalence rates for endometriosis in the world and also has the highest recorded levels of dioxin.

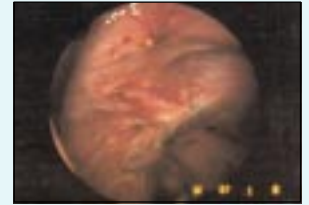
**Q: There appears to be controversy surrounding the cause and effects of endometriosis. What is the Association's view of this?**

**Ms Hummelshøj:** It is true that there is no correlation between disease extent and symptom severity. Some women may have visually minimal disease but are completely debilitated, while others may have extensive disease and no symptoms. The reasons for this are unknown. Importantly, not every woman with pelvic pain has endometriosis and investigations may be required to rule out other causes. The link between endometriosis and subfertility remains unproven, but to take a positive view, many women with endometriosis *do* become mothers. More research is required to understand any potential link.

Research from Iceland, presented in poster form at the Endometriosis 2000 7<sup>th</sup> Biennial World Congress in London, England, found a clear pattern of disease in women from 18 families, with the women either getting the disease at menarche (mean age at onset 14 years) or having late-onset disease (mean age at onset 28 years). This result clearly defines two types of endometriosis. Interestingly, when a mother and her daughter had endometriosis they both had the same type, suggesting an inherited or environmental link.

**Q: Can you explain the link between endometriosis and cancer?**

**Ms Hummelshøj:** When the second batch of data from the 1998 Endometriosis Association Study were analysed, we discovered there was an increased risk for certain cancers in women with endometriosis, notably breast and ovarian cancer, melanoma, and non-Hodgkin's lymphoma. This may suggest that the immune system is compro-



*'Red polyps': when white scarred areas are associated with red polyps, the latter are most commonly endometriosis*



*'Teen polyps': Teenagers commonly have small red or pink polyps and white blebs as isolated findings. In this 19-year-old, the largest lesion was 400 µm in diameter and is the small red polyp near the centre of the slide. The white light reflections on the left of the slide are 200 µm epithelial lesions*

mised in some way. Genetic studies may shed more light on this phenomenon, particularly if mothers and daughters with same-type endometriosis also develop similar cancers.

**Q: Does the Endometriosis Association have a branch in India?**

**Ms Hummelshøj:** We have met with many Indian doctors who are interested in helping with educational campaigns in the country. One doctor is intending to start up a branch in Calcutta, which we will help to establish.

We hope to become more active in developing countries in order to assess the scale of the disease and its impact on women in these areas. We are now investigating the possibility of working in China and a study tour is currently underway in the country. We are keen to help and if women's groups, doctors, or politicians are able to help, we will work closely with them to establish local or national networks.

## Endometriosis Association – India Network

If you would like to help women with endometriosis, please contact the Endometriosis Association with your ideas, questions, or purely for support. Doctors, women's health groups, women with endometriosis, and any other interested party are very welcome to contact the Endometriosis Association for free brochures in Hindi to distribute to health centres, hospitals, and pharmacies, or for their own use. The representatives are:

### India

Dr Siya S. Sharma  
Assistant Professor and Consultant  
Obstetrician and Gynaecologist  
Sita Bari, Near Airport  
Jaipur-302011, Rajasthan, India  
**Tel:** + 91 141 552 364/550 823  
**Fax:** + 91 141 550 886  
**Email:** [drsiya@yahoo.com](mailto:drsiya@yahoo.com)

### Or

Department of Obstetrics and  
Gynaecology  
Kasturba Medical College  
Manipal-576119, India  
**Tel:** + 91 8252 71201 Ext: 2211  
**Fax:** + 91 8252 70061/ 70062  
**Tel:** +91 8252 73463 (Res)  
**Email:** [drsiya@yahoo.com](mailto:drsiya@yahoo.com)

### International

Lone Hummelshøj  
International Representative  
89, Southgate Road  
London N1 3JS, United Kingdom  
**Email:** [loneh@attglobal.net](mailto:loneh@attglobal.net)

Why not visit the website of the Endometriosis Association at:  
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1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *JAMA* 1993;269:2282-6.

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