AOGD BULLETIN

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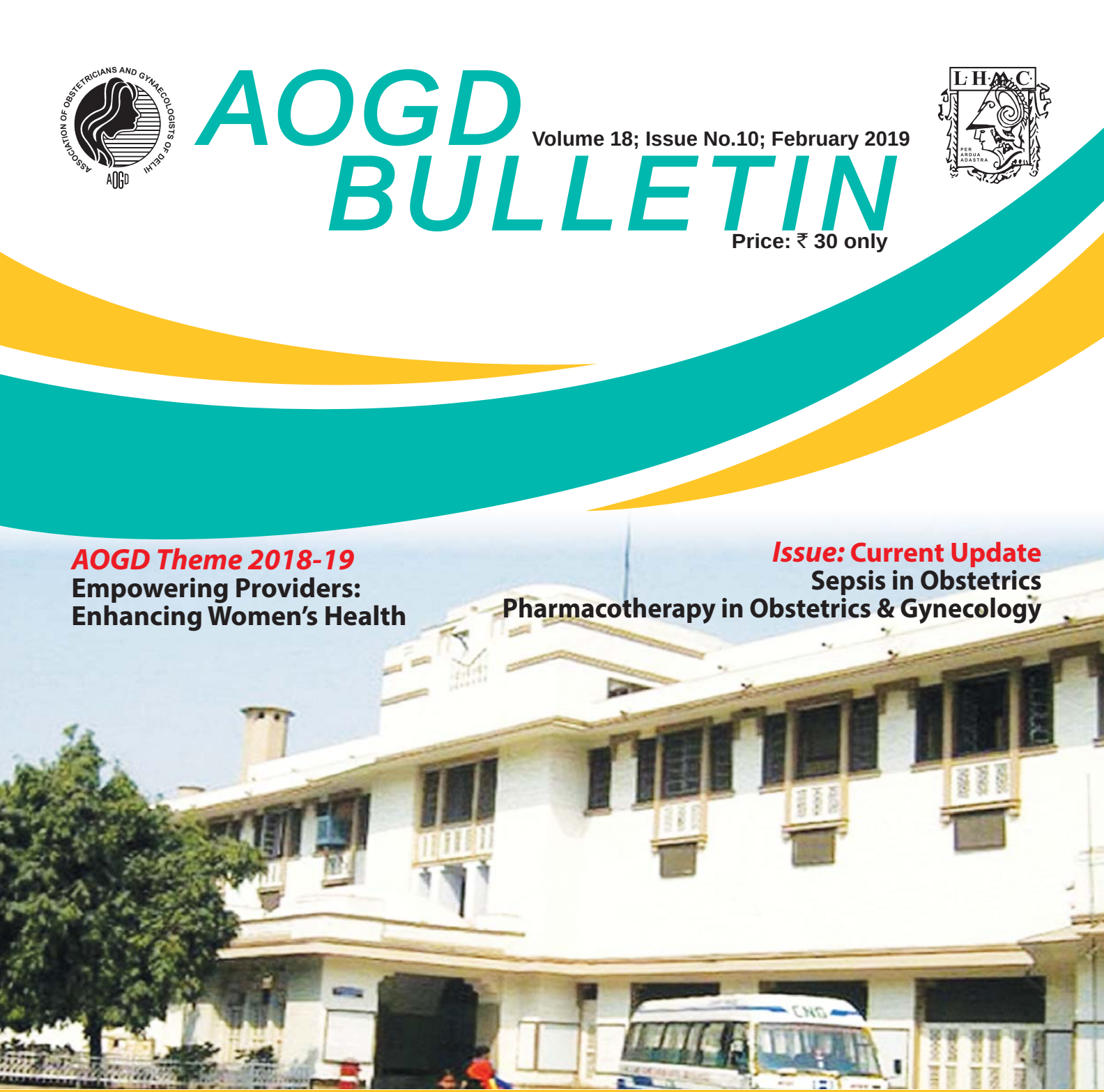
AOGD Theme 2018-19

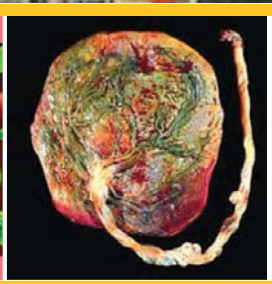
Empowering Providers: Enhancing Women's Health

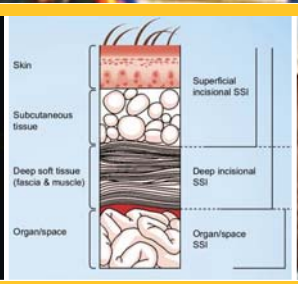
***Issue:* Current Update**

Sepsis in Obstetrics

Pharmacotherapy in Obstetrics & Gynecology







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President's Message

Dear AOGD Members,

Basant Panchami greetings to one and all.

There was a significant representation from Delhi at the 62nd All India Congress of Obstetrics Gynaecology held at Bengaluru from 8th-12th January 2019. AOGD was honoured with the "FOGSI Champion's Trophy". Heartiest congratulations to all the AOGD members who were inducted as Fellow of Indian College of Obstetrics & Gynaecology.

Sepsis is a major contributor to maternal mortality. With the emergence of drug resistance to higher antibiotics need for rational use of antibiotics has become imperative. We must strictly adhere to the guidelines for appropriate use of prophylactic antibiotics in various obstetric indications to prevent any further escalation in drug resistance. Prevention of infection through proper hand hygiene & aseptic techniques cannot be overemphasized. Diagnosis of early sepsis and its prompt management will help to avert adverse outcome.

"Pharmacotherapy in Obstetrics and Gynaecology" including antihypertensive in pregnancy, tocolytics and drug therapy in hyperemesis gravidarum and endometriosis is also discussed in this issue.

Three interesting cases were discussed at a clinical meeting held in RML Hospital on 25/1/19 namely: Hyperparathyroidism in pregnancy, atypical presentation of Dengue fever in pregnancy and psuedo meigs syndrome. Attendees must have benefited from the deliberations.

It is the duty of each and every AOGD member to work towards the achievement of mental, physical and social well-being of every women around us. Our commitment to the theme of AOGD, **"Empowering providers, Enhancing women's health"** is total. We envisage to carry forward the legacy of AOGD in scaling newer heights in women's health through our outreach activities, community service and educational programs.

Dr Abha Singh
President AOGD (2018-19)

Secretary's Message

Greetings from the AOGD Secretariat, LHMC.

Greetings for Basant Panchami. We all pray that goddess of wisdom and learning will always bestow her blessings on all of us. January and early part of February were action packed with AICOG at Bangalore and North Zone Yuva FOGSI at Noida. It was a star performance by AOGD at AICOG. AOGD members won number of prestigious awards (details already there in the previous bulletin).

There were orations, panel discussions and talks, free paper presentations done by the AOGD members. A record number of members received FICOG. North zone Yuva FOGSI also saw active participation from AOGD members.

There are number of activities lined up. Wellness of Woman a FOGSI and Brahmkumari's initiative is planned from 15th-17th Feb at Manesar. The next module of Infertility for postgraduates will be there soon. International day of women on 8th March will be celebrated at LHMC. We will update you through SMS and on the website.

Another meticulously compiled issue of AOGD Bulletin is with you addressing maternal sepsis and pharmacotherapeutics.

All the latest guidelines in the management have been put forth for various management strategies.

Herewith there is a request to all the members. Please attend the monthly clinical meeting in large numbers. The cases presented and discussion is worth attending. It is scheduled on last Friday of every month. This information is for the new members. Details of the venue are in this bulletin.

See you all at GTB Hospital for the next clinical meeting on first March 2019.

Dr Kiran Aggarwal
Secretary AOGD (2018-19)

Please note the change of the date

Monthly Clinical Meeting

Monthly Clinical Meet will be held at University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi on **Friday, 1st March, 2019 from 04:00pm to 05:00pm**.

Editorial Team's Message

Dr Ratna Biswas
Editor

Dr Pikee Saxena

Dr Sharda Patra

Dr Swati Agrawal

Co-Editors

Hello Friends !

The February Issue of the AOGD Bulletin has two very important theme topics: Sepsis in Obstetrics & Pharmacotherapy in Obstetrics & Gynecology.

The opening topic in this issue is "Prevention of Surgical Site Infection" in the Standard of care section. It focuses on identification of high risk factors for sepsis and principles for prevention of surgical site infection. Emphasis is on prophylactic single dose antibiotics in uncomplicated cesarean delivery or episiotomy. Indiscriminate use of antibiotics has led to the emergence of drug resistance to even high order antibiotics. With the advent of drug resistance to carbapenems, the alarm bells are ringing and damage control measures such as the antibiotic stewardship programs need to be implemented in earnest.

Recent Advances delves with the "Paradigm shift in Diagnosis of Maternal Sepsis". Early diagnosis of sepsis is pivotal to prevent morbidity and mortality. "One hour bundle" is a key component of surviving sepsis campaign which consists of sending appropriate investigations like cultures and serum lactate levels, fluid resuscitation, vasopressors and initiation of broad spectrum antibiotics within an hour.

Controversy surrounds the diagnosis and management of subclinical chorioamnionitis. Biomarkers and histopathology are the benchmark for diagnosis of subclinical chorioamnionitis. Decision for starting antibiotics and termination of pregnancy in subclinical infection is complex since without confirmatory diagnosis of infection delivery of a preterm infant may be unjustified. On the other hand prolongation of pregnancy will add on to the infectious morbidity. Hence search is on for reliable diagnostic modalities. Extensive research on proteomic technology for the diagnosis of subclinical infection is ongoing but it has not been approved for clinical practice yet.

Case approach to puerperal peritonitis has comprehensively covered the different presentations of peritonitis in the puerperium. Localized pelvic peritonitis may be managed conservatively but abdominal peritonitis with purulent aspirate needs prompt exploration and lavage. Whether to do hysterectomy or conserve uterus would depend on the state of the uterus. But, at times, an apparently normal looking uterus externally may have micro-abscesses in the myometrium and endometritis within. If, the patient is in septic shock, then the source of infection has to be removed which might necessitate hysterectomy.

Our motivational article is on "Freedom from Hatred". Control of negative emotions including hatred is beneficial for one's inner peace and mental well being and this can be attained by practice and meditation.

Pharmacotherapy section deals with antihypertensives, tocolytics and anti-emetic drugs in pregnancy and drugs for endometriosis.

The maze of knowledge-crossword, pictorial quiz, journal scan and proceedings of the clinical meeting are the icing on the cake. So do not leave any page unturned. Every page has some important information to offer.

Once again we are immensely grateful to our authors for their invaluable contribution.

Hope you all enjoy reading this edition too!!

Editorial Team

STANDARD OF CARE

Prevention of Surgical Site Infections in Obstetric Surgeries


Dr Krishna Agarwal

Sneha Mishra[1], Krishna Agarwal[2]

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Introduction

Infections in obstetrics account for second most common cause of maternal mortality (11%) next to post-partum hemorrhage (34%)[1]. It is also one of the most important factors responsible for the increased treatment cost and prolonged hospital stay. Hence, it is important to know about the factors responsible for infections and to undertake optimal precautions during surgery so as to minimize surgical site infections (SSI).

Factors responsible for SSI

A number of factors are responsible for development of surgical site infections[2]. They can broadly be classified into 4 major categories (table 1).

Table 1: Factors are responsible for development of surgical site infections

Patient related factors	Poor nutrition Prior surgery Diabetes Obesity Smoking Steroid use
Pre-operative factors	Glycemic control Skin cleaning / washing Hair removal
Intra-operative factors	Prophylactic antibiotics Abdominal / vaginal preparation Supplemental oxygen Temperature Hydration Suture Wound closure
Post-operative factors	Glycemic control Supplemental O2 Blood transfusionn Wound dressing

Centers for Disease Control and Prevention (CDC) define SSI as infections of the incision or organ or space that occurs after the surgery[3].

The most common obstetric major surgery is cesarean section and the reported LSCS rate in India is 17.2%[4]. Incidence of SSI after LSCS ranges from 3%-15% which is responsible for three fold increase in duration of hospital stay and readmission[5].

The most common obstetric minor surgical procedure is episiotomy. Incidence of episiotomy wound infection 0.1% increasing up to 2% in third and fourth degree perineal tears.[6]

Table 2: Centers for Disease Control and Prevention (CDC)National Health-care Safety Network Criteria for Surgical Site Infection

Superficialincisional surgical site infection	• Occurs within 30 days • Involves only skin and subcutaneous tissue of the incision • And at least one of the following a. Purulent drainage with or without laboratory confirmation b. Organisms isolated from an aseptically obtained sample c. At least one of following: pain or tenderness, localized swelling, redness, or heat
Deep incisional surgical site infection	• Occurs within 30 days • involves deep soft tissue (e.g. fascia, muscle) of the incision • And at least one of the following a. Purulent drainage from the deep incision b. Deep incision spontaneously dehisces or is deliberately opened c. Patient has at least one of the following: fever (>38°C), localized pain or tenderness
Organ/space surgical site infection	• Occurs within 30 days • Infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs and spaces) other than the incision which was opened or manipulated during an operation • and at least one of the following: a. Purulent drainage from a drain that is placed through a stab wound into the organ/space b. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space during re-operation, or by histopathology or radiologic examination

Certain principles could be adopted during pregnancy and at the time of surgery which would help in prevention of SSI.

Principles for prevention of SSI

Preoperative period

Optimization of health during antenatal period which includes taking care of risk factors such as malnutrition, hypertension, uncontrolled diabetes, obesity, smoking etc. Assessment and timely treatment for infections like urinary tract infections, respiratory tract infections, skin infections, dental infections etc.[7]

Patient preparation prior to surgery is an important step but it is often neglected. Bathing prior to surgery using

a plain or antimicrobial soap is advisable as it decreases the skin microbial colony counts. In most cases hair removal is not necessary. If required hair clippers should be used. Shaving should not be done as it leave micro abrasions on skin which become potential sites of bacterial entry.[8] Patient should be wearing a clean gown and head cover when entering the OT.

Intra-operative period

Operating room preparation

Every person entering the OT brings additional flora and increases the risk of contamination. Hence, only the people directly involved in surgery should remain inside OT. The opening and closing of doors should also be kept to minimum. Operating room should be disinfected ideally everyday. Surgical instruments and linen used during surgery should be autoclaved.

Surgeon and staff preparation

Everyone entering inside operation theater (OT) should change the dress and foot wears. The OT dress and slippers should be provided at the entrance of the OT and should be worn ONLY inside the OT. Surgical cap should be worn so as to cover hair on head and face. The Face mask should be worn to cover the mouth and the nose.

Surgical hand preparation is an important step. Scrubbing with soap (preferably an antimicrobial soap) and water or alcohol- based- hand- rub (ABHR) is recommended[7]. The commonly used soaps for surgical hand scrubbing contain chlorhexidine or povidone-iodine. Their application reduces the microbial colony count by 70-80% and with repeated applications the colony count reduces up to 99%. Alcohol-based-hand-rubs have been shown to be superior than scrubbing with soap and water. Studies have found that formulations containing 50-95% of alcohol combined with quaternary ammonium compounds (chlorhexidine) are more effective than other agents in reducing microbial colony counts. Isopropanol plus chlorhexidine 0.5% may be the product of choice, since chlorhexidine provides a residual antibacterial effect. The duration of scrub recommended is 5 minutes but can be variable according to manufacturer's guidelines.[9]

All members of surgical team should wear double gloves and change gloves whenever perforation of the glove is observed.

Patient's preparation

Prophylactic antibiotics – A single dose of 1st generation cephalosporin (cefazolin 1gram intravenously) is recommended to be given 30-60 minutes prior to skin incision. A repeat dose is recommended if surgery lasts for >3hours or blood loss is > 1.5 liters.[10]

Abdominal preparation- Antiseptic solutions containing chlorhexidine gluconate (savlon) followed by povidone iodine (betadine) are recommended for patient's skin preparation prior to surgery. Alcohol based solutions are preferred over aqueous solutions but the best approach for surgical site preparation still remains unclear.[7]

Supplemental oxygen – In patients receiving general anesthesia with endotracheal intubation, adequate oxygenation facilitates wound healing. A FiO2 of 30-35% is maintained throughout the surgery and postoperatively oxygen should be given by mask.[11]

Goal directed fluid therapy should be used to prevent hypovolemia and SSIs.

Glycemic control: blood sugar level should be maintained below 200mg% throughout procedure. Intravenous insulin along 20% dextrose solution is used for maintenance of recommended blood sugar levels.[12]

Use of warming devices to maintain normothermia (>36 degree Celsius) facilitates wound healing.[7]

Irrigation of incisional wound with aqueous solution of povidone iodine (0.35%) solution is recommended to prevent SSIs.[13]

Postoperative prevention of SSI

Post operative antibiotics are not recommended for prevention of SSI. Ideally, prophylactic antibiotics should be discontinued after skin closure.

Use of IV cannulas and catheters should be limited to decrease post operative infections.

Glycemic control: blood glucose levels should be maintained below 200mg%. Capillary sugar monitoring should be performed every 4 hourly and Injection plain insulin should be given according to sliding scale.

Be vigilant for signs and symptoms of wound sepsis in post operative period. Look for fever, malaise, pain, redness, and increased local temperature of incision site, swelling and any discharge from surgical site.

Following these simple principles of surgical asepsis, it is possible to largely prevent the surgical site infections and the morbidity and costs associated with it.

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Calendar of Monthly Clinical Meetings 2018-19

Months	Name of the Institute
February, 2019	UCMS & GTB Hospital
March, 2019	LHMC
April, 2019	Apollo Hospital

RECENT ADVANCES

Paradigm Shift in Diagnosis of Maternal Sepsis


Dr Jyoti Bhaskar

Jyoti Bhaskar[1], Meenakshi Sharma[2]

[1]Senior Consultant Obstetrician & Gynaecologist, IVF Specialist, Max Superspeciality Hospital, Vaishali

[2]Senior Obstetrician and Gynaecologist, Yashoda Hospital, Kaushambi

Introduction

According to the World Health Organization (WHO), maternal mortality worldwide has decreased by around 44 per cent between 1990 and 2015. Despite the falling rate, the WHO admits that maternal mortality remains "unacceptably high", with some 830 women dying from pregnancy or childbirth-related complications worldwide every day.[1]

The third leading cause of maternal death globally is maternal sepsis, representing about 11% of all maternal deaths with greatest burden being in Southern Asia and Sub saharan Africa. Severe sepsis with acute organ dysfunction has a mortality rate of 20 to 40%, which increases to 60% if septic shock develops. In an Indian study conducted in Safdarjung hospital in Delhi the prevalence was found to be 16.5/10000 live births with a very high mortality rate of 78 %.[2]

Sepsis is a preventable cause with a high mortality rate. Yet, it has received less attention and research than other leading causes of maternal mortality.

Definition of Maternal Sepsis

The Global Maternal Sepsis Study (GLOSS) carried out in 2018 recognised that the effective prevention, early identification and management of maternal sepsis are essential factors in reducing the impact of the disease on maternal mortality.

However, a key problem in moving forward to achieve this is the lack of a standard criteria to identify women with maternal sepsis.

Although the recently published Third International Consensus on Sepsis in 2016[3] published a standard definition and a set of identification criteria to help identify adults with sepsis, it specifically excluded pregnant women.

To address this, the WHO has now issued a new definition of maternal sepsis, which is as follows:[4]

"A life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period."

The new definition of maternal sepsis reflects the thinking embedded in the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3). Previously defined as an infection with a Systemic Inflammatory Response Syndrome (SIRS), the SEPSIS-3 consensus shifts the focus of the definition of sepsis from inflammatory response to life-threatening organ dysfunction.

Further, SEPSIS -3[3] laid down clear criteria to define Organ dysfunction and Septic shock.

Organ Dysfunction can be identified as an acute change in total SOFA score of 2 points consequent to the infection.

- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- A SOFA score 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.

Septic shock: Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Patients with septic shock can be identified with a clinical construct of sepsis

1. with persisting hypotension requiring vasopressors to maintain MAP 65 mm Hg
2. and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

With these criteria, hospital mortality is in excess of 40%.

Identification criteria for maternal sepsis cases should be based on the presence of suspected or confirmed infection plus signs of mild to moderate organ dysfunction (e.g. tachycardia, low blood pressure, tachypnoea, altered mental status, reduced urinary output).

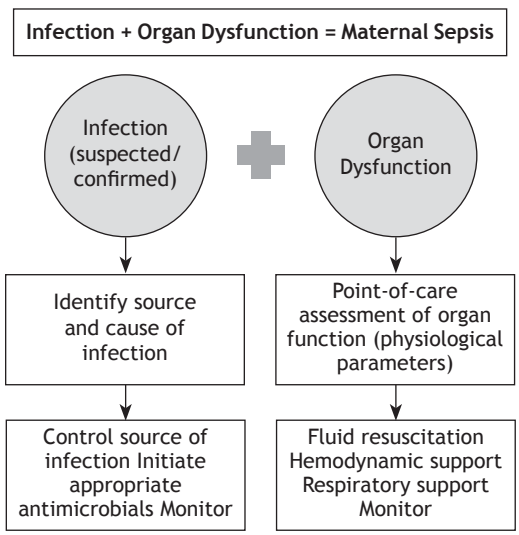


Figure 1: Approach for implementation of the new WHO definition of maternal sepsis

Think Sepsis

The 'think sepsis' term was coined and recommended by the MBRRACE - UK in Maternal Mortality report of 2014.[5] All healthcare professional should 'Think Sepsis' at an early stage when presented with an unwell pregnant or recently pregnant woman, take all appropriate observations and act on them.

The key actions for diagnosis and management of sepsis are:

- Timely recognition
- Rapid administration of intravenous antibiotics
- Quick involvement of experts - senior review is essential

Timely recognition of Sepsis

The signs and symptoms of sepsis in pregnant women may be less distinctive than in the nonpregnant population and are not necessarily present in all cases; therefore, a high index of suspicion is necessary. Detailed history to identify the risk factors and cause of sepsis should be taken.[6]

Risk Factors for Sepsis in Obstetrics[6] are:

- Obesity
- Impaired glucose tolerance / diabetes
- Impaired immunity/ immunosuppressant medication
- Anaemia
- Vaginal discharge /History of pelvic infection
- History of group B streptococcal infection
- Amniocentesis and other invasive procedures
- Cervical cerclage
- Prolonged spontaneous rupture of membranes
- GAS infection in close contacts / family members

Clinical features suggestive of Sepsis are:.[6,7]

Clinical symptoms suggestive of sepsi	Clinical signs indicative of sepsis
• Fever or rigors • Diarrhoea or vomiting - may indicate exotoxin production (early toxic shock) • Rash (generalised streptococcal maculopapular rash or purpura fulminans) • Abdominal /pelvic pain and tenderness • Offensive vaginal discharge (smelly suggests anaerobes; serosanguinous suggests streptococcal infection) • Productive cough • Urinary symptoms **Puerperium** • Breast engorgement / redness • Wound infection – spreading cellulitis or discharge • Delay in uterine involution, heavy lochia	**General variables:** Fever (>38°C), Hypothermia (core temperature <36°C) Tachycardia (>100 beats per minute) Tachypnoea (>20 breaths per minute) Impaired mental state Significant oedema or positive fluid balance (>20 ml/kg over 24 hours) Hyperglycaemia in the absence of diabetes (plasma glucose >7.7 mmol/l) **Haemodynamic variables:** Arterial hypotension (systolic blood pressure <90 mmHg; mean arterial pressure <70 mmHg or systolic blood pressure decrease >40 mmHg)

'Red flag' signs and symptoms (see below) should prompt urgent referral for hospital assessment and, if the woman appears seriously unwell, by emergency ambulance:[7]

RED FLAGS -- For immediate referral in Primary Care/ Community

- Pyrexia more than 38°C
- Sustained tachycardia more than 90 beats/minute
- Breathlessness (respiratory rate more than 20 breaths/minute; a serious symptom)
- Abdominal or chest pain
- Uterine or renal angle pain and tenderness
- Diarrhoea and/or vomiting
- Woman is generally unwell or seems unduly anxious or distressed.

Early presentation of sepsis (less than 12 hours post-birth) is more likely to be caused by streptococcal infection, particularly GAS, and severe continuous pain suggests necrotising fasciitis.

Genital tract sepsis may present with constant severe abdominal pain and tenderness unrelieved by usual analgesia, and this should prompt urgent medical review.

Etiology of sepsis in obstetrics

It is important to know the etiology of sepsis in obstetrics as this helps in directing the investigations to find and subsequently treat the source of infection.

Common causes of Sepsis in Obstetrics
• Urinary tract infection/pyelonephritis
• Chorioamnionitis/ Endometritis/ Genital tract Sepsis
• Pneumonia
• GI perforation/rupture
• Retained Products of Conception
• Mastitis
• Surgical Site Infections

The Most common organisms identified in Maternal Sepsis are **Group A Beta Haemolytic Streptococcus and E. Coli.** Chorioamnionitis is due to mixed infections with both Gram-positive and Gram-negative organisms. Puerperal infection is caused by variety of microorganisms like Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, GAS, also known as Streptococcus pyogenes, methicillin-resistant S. aureus (MRSA), Clostridium septicum and Morganella morganii. Invasive puerperal infections caused by GAS and MRSA are increasing worldwide and have high morbidity and mortality.[7]

Appropriate investigations[6]:

Appropriate investigations should be done as early as possible prior to administration of antibiotics.

1. **Blood cultures are the key investigation and should be obtained prior to antibiotic administration; however, antibiotic treatment should be started without waiting for microbiology results.**
   - Appropriate blood cultures include at least two sets (aerobic and anaerobic)
   - Blood cultures and other samples as guided by clinical suspicion of the focus of infection (e.g. throat swabs, mid-stream urine, high vaginal swab, or cerebrospinal fluid)

- If the methicillin-resistant Staphylococcus aureus (MRSA) status is unknown, a pre-moistened nose swab may be sent for rapid MRSA screening where such testing is available
- Any woman with symptoms of tonsillitis/pharyngitis should have a **throat swab** sent for culture

2. **Serum lactate should be measured within one hour of the suspicion of severe sepsis:**
   - If initial lactate is elevated (> 2 mmol/L), it should be remeasured within 2–4h to guide resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue perfusion.
   - While serum lactate is not a direct measure of tissue perfusion, it can serve as a surrogate, as increases may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess beta-adrenergic stimulation, or other causes associated with worse outcomes.
   - Randomized controlled trials have demonstrated a significant reduction in mortality with lactate guided resuscitation.
3. **Any relevant imaging studies should be performed promptly in an attempt to confirm the source of infection**
   - Prompt imaging may identify the source of the infection, allowing early definitive treatment, and should not be deferred on the grounds of pregnancy.
4. **Other Relevant Blood investigations:** CBC, CRP, Procalcitonin, LFT, KFT, Coagulation Profile

Operationalization of Clinical Criteria Identifying Patients with Sepsis and Septic Shock

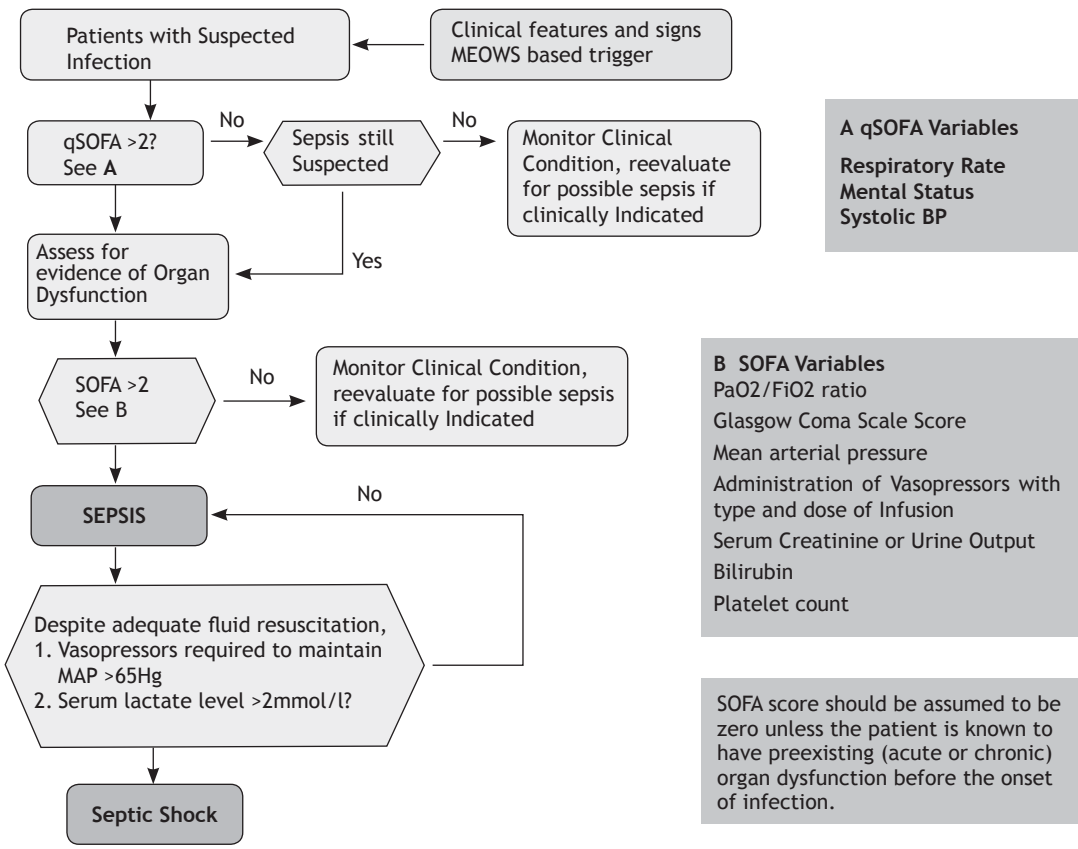
Scoring systems

The Scoring systems to identify infected patients at risk for morbidity and mortality from sepsis and to predict likelihood of intensive care (ICU) admission have been widely used in emergency departments, medical and surgical units, and ICUs.

All sepsis scoring tools utilize varying combinations of vital signs, clinical evaluation, and laboratory parameters to predict morbidity and mortality and identify patients who require interventions. As a result, maternal morbidity may be overestimated given the physiologic changes in pregnancy, which artificially increase scores. Therefore, applicability of these scoring systems and early recognition of sepsis in pregnant women has been complicated by normal physiologic adaptations to pregnancy. For example, decreases in blood pressure and increases in heart rate and white blood cell count are just a few of the changes that can be difficult to distinguish from pathologic changes in a patient at risk for sepsis.

Scoring systems such as the Modified Early Obstetric Warning Score (MEOWS) and quick Sequential (sepsis-related) Organ Failure Assessment score (qSOFA) are

(The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)).[3]



intended for patients with suspected sepsis for prediction of ICU admission while the SOFA score is intended for prediction of mortality in ICU-admitted patients

MEOWS Chart:

Physiological changes in pregnancy with increased cardiovascular reserve can mask signs of severe maternal illness and deceptively normal pregnant woman can collapse suddenly and early warning signs of impending maternal collapse go unrecognised.[9,10] MEOWS is an Early Warning Score (EWS) that is modified for use in pregnant and postpartum women that will help in the early recognition, treatment and referral of women who have, or are developing, a critical illness.[8] Early recognition of critical illness, prompt involvement of senior clinical staff and authentic multi-disciplinary team working remain the key factors in providing high quality care to sick pregnant and postpartum women.

The Modified Early Obstetric Warning Score MEOWS is a way of formalizing measurement of vital parameters (respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate and conscious level) and also include parameters specifically relevant to pregnant and postnatal women (diastolic blood pressure, severity of pain, antenatal discharge and/or postnatal lochia and proteinuria). The values of the observations are then allocated a score which has a critical threshold, above which medical review and intervention is required (MEOWS Escalation Algorithm). Early detection will trigger subsequent prompt intervention that will either reverse further physiological decline or facilitate timely referral to appropriate personnel. MEOWS Scoring system is an efficient tool that should be introduced and used for all obstetric women, including those being cared for outside the obstetric setting to facilitate prompt detection and early treatment in maternal sepsis.[9,10]

The Process for use of MEOWS

- Every time a set of observations is performed on antenatal or postnatal women, MEOWS should be calculated and recorded in the hand-held records or on the observation chart as applicable.
- All women presenting to Triage/MAU who are having

Addressograph

Kettering General Hospital NHS Foundation Trust NHS

Modified Early Obstetric Warning System Chart

This form should be used for the recording of physiological observations and MEOWS Score. All actions/ communications in relation to a deteriorating obstetric patient must be documented in the maternal notes.

Carry out Observations Page 2 → Score (See below) → Follow Appropriate Pathway (page 7)

Green Pathway
Amber Pathway
Red Pathway

ALWAYS CONSIDER SEPSIS (PAGE 6)

Physiological Parameter	3	2	1	0	1	2	3
Respiratory Rate	<12			12 - 20		21 - 25	>25
Oxygen Saturations	<92	92 - 95		>95			
Any supplemental Oxygen		Yes		No			
Temperature	<36			36.1 - 37.2		37.3 - 37.7	>37.7
Systolic BP	<90			90 - 140	141 - 150	151 - 160	>160
Diastolic BP				60 - 90	91 - 100	101 - 110	>110
Heart Rate	<50	50 - 60		61 - 100	101 - 110	111 - 120	>120
Level of Consciousness				A			V, P or U
Pain (excluding labour)				Normal			Abnormal
Discharge / Lochia				Normal			Abnormal
Proteinurea						+	++ >

Exclusion to 4hrly observations. Patient considered fit for discharge and for 12 hourly observation unless condition changes.				Exclusion to 4hrly observations CANCELLED			
Date	Time	Signature	Name (PRINT)	Date	Time	Signature	Name (PRINT)

baseline observations carried out should have a MEOWS calculated and documented.

- Women in active labour do not require regular MEOWS scoring.
- All obstetric in patients must have a full set of observations and a MEOWS calculated at every transfer to a new area. The MEOWS chart used in one area should be transferred with the patient to the next area in order to help identify changes in trends of observations.
- Any woman who triggers a MEOWS of ≥ 4, or 3 in any one parameter should have their oxygen saturations recorded with each full set of observations.

Management of patients in response to MEOWS

The Escalation algorithm sets out the action which need to be taken in response to individual MEOWS. This should be followed to ensure that appropriate clinicians are called and appropriate management and care is undertaken. All actions taken must be clearly documented in the handheld records along with a plan of care. Reduced or altered conscious level is not an early warning sign; it is a red flag which indicates established illness.[5]

MEOWS should not be considered as a substitute for clinical evaluation and assessment while assessing an unwell woman in community or hospital. In the latest MBRRACE report of 2017, they have recommended that when assessing an unwell woman, consider her clinical condition in addition to MEOWS score.

qSOFA SCORE

This new measure, termed *qSOFA* (for quick SOFA), provides simple bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes.[3]

Although qSOFA is less robust than a SOFA score of 2 or greater in the ICU, it does not require laboratory tests and can be assessed quickly and repeatedly.

The task force suggests that qSOFA criteria be used to prompt clinicians

1. To further investigate for organ dysfunction,
2. To initiate or escalate therapy as appropriate,
3. And to consider referral to critical care or increase the frequency of monitoring, if such actions have not already been undertaken.
4. To consider possible infection in patients not previously recognized as infected.

qSOFA (Quick SOFA) Criteria	Score
• Respiratory Rate: ≥ 22 breaths/min	1
• Altered Mentation: GCS ≤ 15	1
• Systolic BP : ≤ **100** mmHg	1

Interpretation

- A "positive" qSOFA Score (≥2) suggests high risk of poor outcome in patients with suspected infection. These patients should be more thoroughly assessed for evidence of organ dysfunction.
- A positive qSOFA Score by itself should not trigger

Deteriorating Obstetric Patient Escalation Algorithm

Green Pathway

Total MEOWS = 0

Continue routine 4 hourly observations

Repeat observation if patient condition changes

Total MEOWS = 1-4

Inform midwife/nurse in charge who must assess the patient immediately.

Midwife/nurse to decide if increased frequency of monitoring and/ or escalation of clinical care are required.

If concerned about patient contact SHO

If symptoms of pre edampsia (headache, visual disturbance, abdominal pain) lower threshold for escalation.

**** CONSIDER SEPSIS ****
(SEE PAGE 6)

Document all actions

Amber Pathway

Total MEOWS = 5-6

or

If Any individual parameter = 3

Continue routine 4 hourly observations

Inform midwife/nurse in charge (consider critical care outreach)

Midwife/nurse to immediately review the patient

Contact middle grade doctor obstetric (ST/Reg/Trust Grade) and consider early consultant involvement

Inform obstetric anaesthetist

Care to be provided in appropriately monitored environment

Increase the frequency of observations to 1 hourly

If symptoms of pre-eclampsia (headache, visual disturbance abdominal pain) lower threshold for escalation

**** CONSIDER SEPSIS ****
(SEE PAGE 6)

Document all actions

Red Pathway

MEOWS ≥ 7

or

Acutely concerned regarding sudden deterioration

Contact middle grade doctor obstetric (ST/Reg/Trust Grade) and obstetric anaesthetist immediately

Consider 2222 for obstetric emergency team

Inform midwife/nurse in charge

Commence continuous monitoring of vital signs

Consider immediate referral to ICU or HDU obstetric

Consider critical care outreach team (bleep 654)

**** CONSIDER SEPSIS ****
(SEE PAGE 6)

Document all actions

sepsis-directed interventions like initiation of broad-spectrum antibiotics; rather, it should prompt clinicians to further investigate for presence of organ dysfunction or to increase frequency of monitoring.

- The Sepsis-3 task force recommends that a positive qSOFA Score should prompt the calculation of a SOFA score to confirm the diagnosis of sepsis. This remains controversial, as qSOFA has been shown to be more predictive than SOFA outside of the ICU setting.

SOFA Score

The Sequential Organ Failure Assessment (SOFA) score is a scoring system that assesses the performance of several organ systems in the body (neurologic, blood, liver, kidney, and blood pressure/hemodynamics) and assigns a score based on the data obtained in each category.[3] The higher the SOFA score, the higher the likely mortality.

It is recommended to use a change in baseline of the total SOFA score of 2 points or more to represent organ dysfunction. The baseline SOFA score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection.

- The SOFA score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient.
- It is validated for use in patients admitted to the ICU and is performed on admission and every 2 hours thereafter
- It is intended for prediction of mortality in ICU-admitted patients. Patients with a SOFA score of 2 or more had an overall mortality risk of approximately 10% in a general hospital population with presumed infection.[3]

The Golden Hour of Sepsis

Where sepsis is suspected a sepsis care bundle should be applied in a structured and systematic way with urgency.

The Golden Hour of Sepsis stresses the relationship between timely initiation of administration of antibiotic and outcome: each hour of delay reduces the survival by 7.6%.

Although this principle is not validated for pregnancy or puerperium due to lack of studies, it is even more important in these women.

One Hour Bundle[11]

The surviving sepsis campaign bundle 2018 has combined the 3 hour and 6 hour bundle into the "hour-1 bundle" with explicit intention of beginning resuscitation and management immediately. It reflects the clinical reality at the bedside of these seriously ill patients with sepsis and septic shock—that clinicians begin treatment immediately, especially in patients with hypotension, rather than waiting or extending resuscitation measures over a longer period. More than 1 hour may be required for resuscitation to be completed, but initiation of resuscitation and treatment, such as obtaining blood for measuring lactate and blood cultures, administration of fluids and antibiotics, and in the case of life-threatening hypotension, initiation of vasopressor therapy, are all begun immediately.

Hour 1 Surviving Sepsis Campaign Bundle[11]

- Measure lactate level, remeasure if lactate > 2 mmol/l
- Obtain Blood cultures prior to start of Antibiotics
- Administer Broad spectrum antibiotics
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate >4 mmol/l
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mmHg

'Time Zero' or time of 'Presentation' is defined as the time of triage in emergency department or if presenting from another care venue from the earlier chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

This new sepsis "hour-1 bundle," based on the 2016 guidelines, should be introduced to emergency department, floor, and ICU staff as the next iteration of ever-improving tools in the care of patients with sepsis and septic shock as we all work to lessen the global burden of sepsis.

SOFA Score

Organ System Measurement	SOFA Score				
	0	1	2	3	4
Respiration PaO^2/FiO^2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4	3.5-4.9 (300-440) or <50 mL/day	>5.0 (>440) or <200 mL/day

*Source: Vincent et al., 1996.
**Adrenegic agents administered for at elas 1 hour (doses given are in mcg/kg/min).

Conclusion

Maternal sepsis is a preventable cause of maternal mortality and in recent years recommendations of international bodies like WHO, Surviving Sepsis, RCOG, UKOSS have made paradigm shift in the diagnosis and management protocols of Sepsis. Though maternal sepsis has not been directly included in many of these, efforts are on to identify criteria for diagnosis and management of maternal sepsis.

Key Points

- Each hospital or health facility should have their own structured protocols for diagnosis and management of maternal sepsis
- Consideration should be given to 'DECLARING SEPSIS'[9], analogous to activation of the major obstetric haemorrhage protocol, to ensure the relevant members of the multidisciplinary team are informed, aware and act.
- Women should be advised, within 24 hours of giving birth, of the symptoms and signs of conditions, including sepsis, that may threaten their lives and require them to access emergency treatment.
- Critical care should be provided early by adopting one-hour bundle to ensure prompt administration of appropriate antibiotics and supportive therapy. Timely recognition of maternal sepsis and fast administration of intravenous antibiotics is critical to prevent mortality. Delay caused by bed pressures in a critical care unit is not a reason to postpone critical care.

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CONTROVERSY

Diagnosis and Management of Subclinical Chorioamnionitis


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Introduction

Chorioamnionitis is a dreaded complication of pregnancy associated with significant maternal, fetal and neonatal adverse outcomes. It can present in both clinical and subclinical forms, complicating 40–70% preterm births with premature membrane rupture or spontaneous labor[1] and 1–13% term births[2]. Clinical chorioamnionitis can be diagnosed on the basis of maternal symptoms such as fever, abdominal pain, abnormal vaginal discharge and leucocytosis, but early diagnosis and appropriate management of subclinical chorioamnionitis, which occurs more frequently is the main challenge in today's obstetric practice.

Definition and classification: Subclinical chorioamnionitis, is defined as inflammation of the chorion and amnion without any clinical features of chorioamnionitis such as high fever, maternal or fetal tachycardia, elevated white blood cell (WBC) count, uterine tenderness, and foul smelling amniotic fluid. Subclinical chorioamnionitis can be subdivided into histologic chorioamnionitis (HCA), intra-amniotic infection (IAI) and intra-amniotic inflammation. (Figure 1)

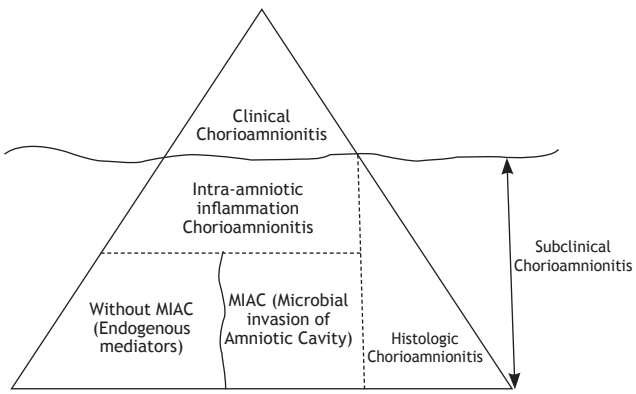

Figure 1: Schematic diagram illustrating types of Chorioamnionitis: Clinical Chorioamnionitis, Subclinical Chorioamnionitis (Intra-amniotic inflammation, Intra-amniotic infection & Histologic Chorioamnionitis).

Intra-amniotic infection and inflammation

Intra-amniotic infection (IAI) is defined as elevated concentration of inflammatory markers, such as Interleukin 6 (IL-6), and Matrix metalloproteinase -8 (MMP-8) in amniotic fluid in the presence of microbial invasion of the amniotic cavity (MIAC). The microbial colonization per se, is not considered consistent with infection; an inflammatory component is necessary. IAI is intra-amniotic inflammation in presence of microbial invasion of amniotic cavity. Intra-amniotic inflammation in the absence of MIAC results from activation of endogenous mediators which evoke a host response and lead to progression of an inflammatory process.

Histologic Chorioamnionitis

Histological chorioamnionitis (HCA) refers to inflammatory changes, i.e. neutrophil infiltration, mainly polymorphonuclear leukocytes, in the chorionic plate, the chorioamniotic membranes, and the umbilical cord. The HCA can be subdivided according to inflammatory changes in the villus tree (villitis), vessels (vasculitis), or umbilical cord (funisitis). Funisitis is considered a more severe stage of HCA, since it reflects the spread of inflammation to the umbilical cord, and is the fetal counterpart to the maternal infection.

HCA covers two subtypes of chorioamnionitis: with MIAC (infectious) and without MIAC (sterile). Manifestation of the infection depends on the virulence of microbes in the chorioamniotic space: subsequent clinical chorioamnionitis follows infection by highly virulent microbes, whereas subclinical HCA usually occurs in the presence of low virulence microbes. The prevalence of HCA is related to gestational age and duration of labour. Lower the gestational age higher the prevalence and longer the duration of labour there is increased frequency of HCA. This is being reported in 20–30% of deliveries following labour compared to clinical chorioamnionitis.[3]

The diagnosis of HCA is based on placental histopathologic examination after delivery. There exist several staging systems for assessment of HCA severity. The most popular definition and staging of acute HCA and funisitis according to the Amniotic Fluid Infection Nosology Committee are:[4]

- Stage 1 (acute subchorionitis / acute chorionitis): presence of neutrophils in the subchorionic zone or in the extraplacental membranes chorionic trophoblast layer.
- Stage 2 (acute chorioamnionitis): more than a few neutrophils accumulated in the chorionic plate and connective tissues or in the amniotic membrane.
- Stage 3 (necrotizing chorioamnionitis): robust neutrophilic infiltration with visible degenerating neutrophils, thickened amniotic basement membrane,

and focal epithelial necrosis of the amniotic membranes.

Pathogenesis: Chorioamnionitis is usually polymicrobial in origin, involving aerobic and anaerobic bacteria from the vaginal flora. Most common organisms are Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis and less commonly Group B streptococcus, Escherichia coli. It predominantly occurs by ascending infection from the lower genital tract to the amniotic cavity. During pregnancy, immune function is relatively low; thus, various pathogens from the vulva and cervix invade the uterus, which commonly results in subclinical chorioamnionitis. This may lead to inflammatory cell exudation, leukocyte infiltration edema, fibrous tissue proliferation and reduced elasticity/increased brittleness of fetal membrane, ultimately leading to premature rupture of membranes (PROM). Following the PROM, the environment of the uterus and vagina is altered in response, promoting bacterial proliferation and exacerbating the subclinical chorioamnionitis. Chorioamnionitis may rarely occur after invasive procedures (eg. amniocentesis or chorionic villus sampling) or by a hematogenous route secondary to maternal systemic infection (eg. Listeria monocytogenes) (Figure 2).

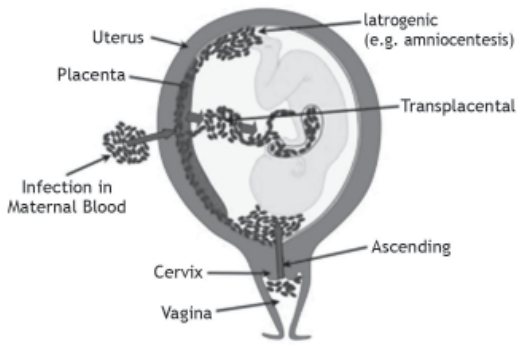

Figure 2: Routes of infection

Risk factors: Preterm premature rupture of membranes (PPROM) and the latency time between membrane rupture and delivery are major risk factors for chorioamnionitis. Other risk factors are prolonged labour, nulliparity, internal monitoring of labour, multiple vaginal examinations, meconium-stained amniotic fluid, smoking, alcohol or drug abuse, immune-compromised states, epidural anesthesia, colonization with group B streptococcus, bacterial vaginosis and sexually transmitted genital infections.

Maternal complications - Increased risk of preterm delivery, dysfunctional labour requiring intervention, postpartum uterine atony with hemorrhage, endometritis, peritonitis, sepsis, adult respiratory distress syndrome and, rarely death may occur.

Fetal complications –Most dreaded complication is Fetal Inflammatory Response Syndrome (FIRS), which is associated with short-term and long-term neonatal morbidity and mortality even after adjustment for gestational age. FIRS is determined as elevation of circulating cytokines (IL-6) in the fetal circulation capable of causing damage to multiple fetal organs including chronic lung disease, periventricular leukomalacia, cerebral palsy and threatening onset of preterm delivery. The fetal response is more severe in preterm pregnancies with intact membranes than in those with PPROM. Histologic indicators of FIRS include funisitis and vasculitis in the chorion, and funisitis by itself, is associated with adverse neonatal outcomes. Neonatal complications such as pneumonia, meningitis, sepsis, and death may also occur. (Figure 3)

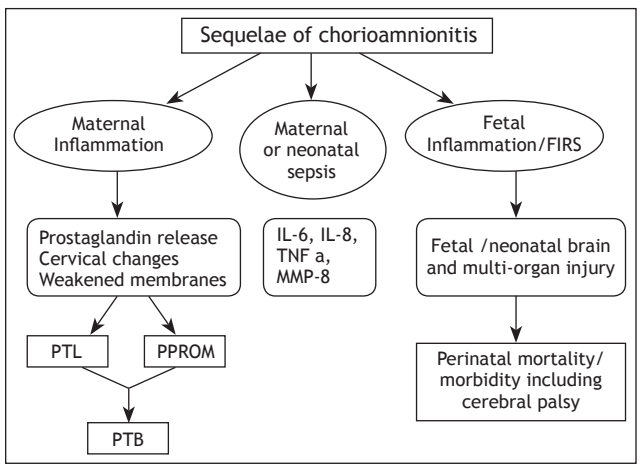

Figure 3: Sequelae of chorioamnionitis

Presumptive Diagnosis: Due to the imprecise nature of the defining criteria and varying clinical manifestations, there is no unanimity in the approach towards diagnostic work-up, or obstetric and neonatal management of chorioamnionitis. To address these issues, the National Institute of Child Health and Human Development (NICHD), Society for Maternal Fetal Medicine, American College of Obstetricians and Gynecologists, and American Academy of Pediatrics invited a group of maternal and neonatal experts to a workshop. Workshop panel noted that clinicians often use the term "chorioamnionitis" even when the only sign is a maternal fever. The panel of experts agreed that maternal fever alone should not lead to a diagnosis of infection (or chorioamnionitis) and to antimicrobial therapy. A new terminology was recommended that differentiates the mere presence of fever from infection or inflammation or both. The panel proposed to discontinue use of the term "chorioamnionitis" and instead use "Intrauterine Inflammation or Infection or both" or "Triple I" (Table 1).[5]

Subclinical chorioamnionitis is 2-3 times more common than clinical chorioamnionitis. It is now believed that subclinical chorioamnionitis is a cause of preterm premature rupture of membranes (PPROM) and/or preterm labor (PTL) and, is an important contributor of neonatal morbidity and mortality. Evidence has also emerged that supports a link between subclinical chorioamnionitis and cerebral palsy in children born either prematurely or at term.[6] Antepartum diagnosis of subclinical chorioamnionitis would therefore, help providers determine whether the benefits of prolonging

Table 1: Triple I diagnostic criteria

Isolated maternal fever ("documented fever")	Suspected Triple I	Confirmed Triple I
1. Maternal oral temperature 39.0˚C or greater (102.2˚F) on any one occasion is documented fever. 2. If the oral temperature is between 38.0˚C (100.4˚F) and 39.0˚C (102.2˚F), repeat the measurement in 30 minutes; if the repeat value remains at least 38.0˚C (100.4˚F), it is documented fever	Fever without a clear source plus any of the following: 1. baseline fetal tachycardia (greater than 160 beats per min for 10 min or longer, excluding accelerations, decelerations, and periods of marked variability) 2. maternal white blood cell count greater than 15,000 per mm3 in the absence of corticosteroids 3. definite purulent fluid from the cervical os	All of the above plus: 1. amniocentesis-proven infection through a positive Gram stain 2. low glucose or positive amniotic fluid culture 3. placental pathology revealing diagnostic features of infection

pregnancy outweigh the risks in the woman with PTL or PPROM at less than 34 weeks estimated gestational age.

Laboratory Diagnosis: Diagnosing subclinical chorioamnionitis is a challenge since there are no clinical signs and symptoms and no definite diagnostic criteria. There are certain laboratory tests which have been studied for diagnosing subclinical chorioamnionitis.

1. **Leucocytosis:** Maternal leucocytosis (defined as WBC >15,000/mm3) often supports the diagnosis of chorioamnionitis. However, isolated leucocytosis in the absence of other signs or symptoms is of limited value since it may be induced by several other conditions including labor and steroid use. Therefore, routine monitoring of CBC in high-risk women (e.g., with preterm premature membrane rupture) in the absence of clinical signs of chorioamnionitis is not useful.[7]
2. **C Reactive Protein (CRP):** Some studies have suggested that levels of CRP in blood is elevated during amniotic infection. However, the CRP threshold used varied among these studies and there are several other causes of increased CRP that must be excluded, which makes CRP less than ideal for a conclusive diagnosis of subclinical chorioamnionitis.[7]
3. **Blood culture:** The evidence supporting the use of blood cultures for the diagnosis of chorioamnionitis is also limited. Routine use of maternal blood cultures rarely provides information that justifies a change in clinical management when patients are treated in accordance with a specific antibiotic protocol.[8]
4. **High vaginal swab:** There is no good-quality evidence to show the benefit of use of high vaginal swabs in the diagnosis and management of chorioamnionitis. RCOG recommends that in the management of PPROM, weekly high vaginal swabs need not be performed.[9]
5. **Amniotic fluid culture:** Although amniocentesis with culture of the amniotic fluid is ideal for isolating bacteria and is the reference standard for the purpose of diagnosis, this test is associated with a delay of at least 48 hr for cultures. Berger etal[10] conducted a study on use of amniocentesis, placental swabs and neonatal skin swabs in the subsequent management of chorioamnionitis following delivery. A strong association between positive amniotic cavity culture results and clinical early onset neonatal sepsis was found; however, there is insufficient evidence to justify the routine use of amniocentesis for diagnosis.
6. **Amniotic fluid glucose:** The glucose concentration of amniotic fluid is another potentially useful rapid test for detection of microbial invasion of amniotic cavity(MIAC). Studies have shown an inverse association between amniotic fluid glucose and the rate of MIAC. A low vaginal 'pool' amniotic fluid glucose measurement (<5 mg/dL) has been shown to be a predictive but not sensitive marker for infection in women with PPROM.[11]
7. **Amniotic fluid Gram stain:** is a rapid and cheap method for identifying MIAC. Its basis is to stain bacteria according to their cell structure. The presence of any bacteria and leukocytes (at least six leukocytes per high-power field) is suspicious for infection as the amniotic fluid is sterile in uncomplicated pregnancies with intact membranes. For a positive culture, Gram stain has a sensitivity of 60% and specificity of 99%.[12]
8. **Biomarkers:** Amniotic fluid assessment of several potential biomarkers for diagnosis of subclinical chorioamnionitis have been identified, including IL-6, IL-8, matrix metalloproteinase-8 (MMP-8), ferritin and placental alkaline phosphatase. However, effectiveness of these biomarkers has not been confirmed in clinical trials. A recent Cochrane review found that the quality of evidence regarding their utility is poor.[13] Some studies have suggested that levels of these proteins particularly interleukins are also increased in other complications of pregnancy, such as pre-eclampsia thus questioning their diagnostic accuracy.[14]

Protein markers including neutrophil defensin-1, defensin-2, calgranulin-A and calgranulin-C, have been associated with inflammation in the amniotic fluid and placenta. These have been correlated with stages of histological chorioamnionitis.

Extensive research has revolved around the use of proteomic technology to identify these protein biomarkers that may be used in the accurate diagnosis of subclinical chorioamnionitis and prediction of maternal and neonatal outcomes. SELDI-TOF-MS (Surface-enhanced laser desorption / ionization time-of-flight mass 67 spectrometry) also known as protein fingerprinting uses a protein microarray and mass

spectrometry to measure proteomic profiles.[15]The use of SELDI-TOF-MS based on magnetic beads is a novel technique for the early diagnosis of subclinical chorioamnionitis. Currently, proteomics is a research technique, and is not used in clinical practice; however, future development of this technology and other diagnostic tests may prove to be important in diagnosing subclinical chorioamnionitis.

To overcome the need for amniocentesis, many investigators have searched for markers in biological fluids that can be sampled noninvasively (urine) or through minimally invasive approaches (maternal blood, cervicovaginal secretions, vaginal amniotic fluid, or vaginal washings fluid). However, in clinical practice confirmed intraamniotic infection in laboring women at term will most commonly be made after delivery, based on placental histopathology. Therefore, until better and less invasive intrapartum diagnostic tools become available, any practical distinction between suspected and confirmed intraamniotic infection will remain meaningful only in research settings and not in routine clinical practice.

Management: Mainstay of management for chorioamnionitis is intrapartum antibiotic treatment and delivery. Intrapartum antibiotic treatment decreases the rate of neonatal bacteremia, pneumonia, sepsis, maternal febrile morbidity and length of hospital stay. Therefore, in absence of any clearly documented overriding risks, administration of intrapartum antibiotics is recommended whenever intraamniotic infection is suspected.

Antibiotic therapy should be broad-spectrum (effective against a wide range of both Gram-positive and Gram-negative organisms) and cover both aerobes and anaerobes. A combination of a ß-lactam (e.g., penicillins, cephalosporins, carbapenems or monobactams) and an aminoglycoside (e.g., gentamicin) is commonly recommended. Ampicillin plus gentamicin is an efficacious regimen and has become the standard treatment. If a cesarean delivery is performed, the addition of anaerobic coverage after delivery may be considered (clindamycin or metronidazole) to decrease the risk of endometritis.

Common antibiotics recommended for treatment of suspected intraamniotic infection as per ACOG recommendation are shown in Table 2.[16]

Table 2: Recommended antibiotic regimen for chorioamnionitis (ACOG)

Primary regimen	
Recommended antibiotics	Dosage
• Ampicillin and • Gentamycin	2 gm IV every 6 hrs 2 mg/kg IV load followed by 1.5 mg/kg every 8 hrs or 5 mg/kg IV every 24 hrs
Recommended antibiotics (mild penicillin allergy)	Dosage
• Cefazolin and • Gentamycin	2 gm IV every 8 hrs 2 mg/kg IV load followed by 1.5 mg/kg every 8 hrs or 5 mg/kg IV every 24 hrs
Recommended antibiotics (severe penicillin allergy)	Dosage
• Clindamycin or • Vancomycin and • Gentamycin	900 mg IV every 8 hrs 1 gm IV every 12 hrs 2 mg/kg IV load followed by 1.5 mg/kg every 8 hrs or 5 mg/kg IV every 24 hrs
Alternative regimen	
• Ampicillin-sulbactum • Piperacillin-tazobactum • Cefotetan • Cefoxitin • Ertapenem	3 gm IV every 6 hrs 3.375 gm IV every 6 hrs or 4.5 gm IV every 8 hrs 2 gm IV every 12 hrs 2 gm IV every 8 hrs 1 gm IV every 24 hrs
Post cesarean delivery: One additional dose of chosen antibiotic is indicated. Add clindamycin 900 mg IV or metronidazole 500 mg IV for at least one additional dose. **Post vaginal delivery: No additional doses required, but if given, clindamycin not indicated**	

Delivery: Chorioamnionitis is not an indication for immediate delivery, and route of delivery in most cases should be based on obstetric indications. If appropriate antibiotic therapy has been initiated and labour is progressing, cesarean section to shorten labour has not shown to significantly improve either maternal or neonatal outcomes. Proper labor progression should be ensured, given the association between intraamniotic infection and dysfunctional labour progression. In case of protracted labour, augmentation should be done in absence of contraindications.

Regardless of institutional protocol, when a case of chorioamnionitis is diagnosed or suspected, communication with the neonatal care team is essential to optimize neonatal evaluation and management. Post-delivery, umbilical cord gases should be obtained and the placenta should be sent for histopathology if possible.

Postpartum antibiotic treatment: Continuation of antimicrobial agents postpartum should not be automatic, but rather based on risk factors for postpartum endometritis. Women who deliver vaginally are less likely to have postpartum endometritis and therefore do not require postpartum antibiotics. In women undergoing cesarean delivery, one dose of antibiotics postpartum is sufficient. However, presence of bacteremia or persistent fever in postpartum period may be used to guide for continuation and duration of antibiotic therapy.

Role of antenatal corticosteroids: Administration of corticosteroids in the setting of chorioamnionitis is a controversial issue. In 2015 WHO has given a conditional recommendation based on low quality evidence that antenatal corticosteroid therapy is not recommended in women with chorioamnionitis who are likely to deliver preterm. However, based on findings of a large systematic review, WHO also states that antenatal corticosteroid use in women with histological chorioamnionitis was

associated with a significant reduction in neonatal deaths, RDS and intraventricular haemorrhage (IVH) but similar benefit was not found in cases of clinical chorioamnionitis.[17]

Conclusion: Chorioamnionitis is a well-known risk factor for spontaneous preterm delivery and can even affect the term deliveries. With improvement in prenatal care, the clinical presentations of chorioamnionitis are becoming less frequent. On the other hand, subclinical chorioamnionitis has become more common. Thus, recognition of intrapartum intraamniotic infection and implementation of the treatment are essential for effectively minimizing maternal and neonatal morbidity and mortality. Without a confirmatory diagnosis of infection, overuse of antibiotics or inadequate antibiotic coverage is common in clinical practice. Further research and development of guidelines for prompt diagnosis and management of subclinical chorioamnionitis is the need of the hour.

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CASE APPROACH

Puerperal Peritonitis

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Dr Kiran Aggarwal

Severe postpartum sepsis though becoming less is yet not uncommon. WHO estimates 15% of 500000 maternal deaths due to puerperal sepsis annually. 11% of maternal deaths were due to puerperal sepsis as per special survey of death 2001-2003 (National Health Portal of India)

Operative interference is one of the most important causes of puerperal sepsis. Caesarean sections cause 10to 20 fold increase in severe sepsis postpartum as compared to vaginal delivery[1]. Severe sepsis with acute organ dysfunction has a mortality rate of 20–40%, rising to around 60% if septicaemic shock develops.[2]

Causes:

Preterm premature rupture of membranes with prolonged latency period for delivery, caesarean sections, prolonged labor, multiple pelvic examinations during labor, vaginal procedures like gel administration, invasive fetal monitoring etc. predispose to puerperal sepsis.

Maternal conditions like Diabetes mellitus, immunosuppression, transplant recipients, autoimmune disorders & HIV infection have a higher risk of puerperal sepsis.

The major pathogens causing sepsis in the puerperium are[3]: • GAS, also known as Streptococcus pyogenes • Escherichia coli • Staphylococcus aureus • Streptococcus pneumoniae • Meticillin-resistant Staphylococcus. aureus (MRSA), Clostridium septicum and Morganella morganii

Another very important presentation in our country is flaring of Tuberculosis postpartum which present as tubercular peritonitis.

'Red flag'signs and symptoms as mentioned below should call for urgent assessment[4]:

• Pyrexia more than 38°C • sustained tachycardia more than 90 beats/minute • breathlessness (respiratory rate more than 20 breaths/minute; a serious symptom) • abdominal or chest pain • diarrhoea and/or vomiting • uterine or renal angle pain and tenderness • woman is generally unwell or seems unduly anxious or distressed.

Common manifestation of severe sepsis[5]

Loss of consciousness, delirium, and disorientation may indicate impending circulatory shock. Prostration indicates a serious condition.. Unusual temperature elevations, leukocytosis >2500/mmm3, leukopenia <1000mm3, hemoconcentration >45%, low hematocrits <10%, or poor urinary output, cardiac failure indicate severe infection.

Unusual signs: may need a surgical exploration[5]

Septic shock, adult respiratory distress syndrome, disseminated intravascular coagulation, pulmonary emboli, hemolysis, sudden anasarca, or cardiac failure indicating severe sepsis may be needing surgical exploration

Careful physical examination will usually reveal signs of peritonitis with an ileus and rebound tenderness in both upper and lower quadrants of the abdomen. It is important during the physical examination to exclude other sources of fever, particularly from wound, intravenous line, or lung infection

Here we present four case scenarios from our own patients and represent different types of situations causing postpartum peritonitis and their management approaches.

CASE 1.

Para 4 with all live issues was delivered by a trained birth attendant at Primary Health Center 6 days back. The delivery was uneventful but she had difficulty in removal of placenta. For past three days patient had fever with chills, pain lower abdomen, foul smelling discharge per vaginum,. She was constipated but passing flatus with decreased urine output.

On examination she was febrile 39 degree Celsius, pulse 128/minute, blood pressure 100/70 mm of Hg, dehydrated, pale, clinically a haemoglobin of 6gm%, tachypneic with a respiratory rate of 36/min, oxygen saturation 95%, cardiovascular system normal and chest was clear. Per abdomen extreme tenderness was present in lower abdomen upper abdomen soft, Bowel sounds present. Uterus 18 wks size, tender.

Pelvic examination revealed 18 wks size uterus with os one finger dilated draining foul discharge with no products, fornices tender no mass, pouch of douglas free no fullness. On catheterisation only few cc of high colored urine drained.

Patient was propped up, oxygen was given, fluid was started, blood and urine culture and also a high vaginal swab was sent.

Investigations revealed a Hb of 6gm%, TLC 29ooo/mm3 with shift to left with 92% poly morhps, platelets 4.5lakhs/mm3, with deranged kidney function tests. Ultrasound revealed normal upper abdomen with subinvoluting uterus with minimal fluid in the uterine cavity. No retained products of conception were seen.

A diagnosis of puerperal sepsis with pelvic peritonitis with renal failure was made. Patient was managed

conservatively. She was started on broad spectrum antibiotics. (Piperacillin and tazobactum with clindamycin), Renal failure was managed conservatively with consultation with medicine department.

Case 2

24 year old para 1live1 delivered two days back by a caesarean section in a rural setup for apparently non progress of labor with duration of labor for 48 hours was brought to the hospital with delirium, fever, severe pallo , BP 80/50, saturation 94%, pain and distension of abdomen, inability to pass flatus and no urine output.

On examination she was sluggishly responding to commands, pulse 132/min, fever 103 degree Celsius, Respiratory rate 40/min, chest had Bilateral crepts, abdomen distended with guarding and rigidity all over with absent bowel sounds, uterus not clearly palpable. Per speculum examination revealed dirty purulent discharge, uterus 18wks tender not clearly defined, tenderness and fullness in all the fornices.

Immediately resuscitation was started. Oxygen was given, fluid resuscitation, immediate cultures and serum lactate was done. Broad spectrum intravenous antibiotics were started. Blood was arranged. After stabilising a bedside ultrasound was done followed by an ascitic tap. Purulent fluid was aspirated. Patient was prepared for laparotomy.

On laparatomy 3 liters of frank pus was drained. Unhealthy necrotic uterus with congested tubes with pus exuding from the fimbriae was seen. The stitches in the lower segment had also partially given way and pus was exuding from it. Ovaries were normal. Omentum and other peritoneum were oedematous and congested. Gut was explored. After counselling the relatives Total abdominal hysterectomy was done. With supportive hemodynamic treatment, antibiotics and ICU care patient completely recovered.

Case 3

A 29 year old women presented on14th day of puerperium after normal vaginal delivery with high grade fever and generalised abdominal pain. She had frequent spikes of fever since last 3 days. Patient had tachycardia, tachypnoea and mild abdominal distension with guarding and rigidity in left iliac fossa, no definite lump was palpable. On pelvic examination, per speculum examination was normal, there was no foul-smelling discharge although left fornix fullness and marked tenderness was noted. Blood investigation showed neutrophilic leucocytosis and USG was suggestive of collection in left iliac fossa.

In view of her poor general condition and clinical features suggesting puerperal sepsis decision for laparotomy was taken under antibiotic coverage. Intraoperatively there was extensive pelvic abscess confined to left and posterior to the uterus contained by peritoneal, omental and bowel adhesion. Uterus was postpartum bulky but normal looking, right tube and ovary was also normal. Left sided tubo-ovarian mass along with omental and bowel adhesion was present. Left sided tube and parametrium were grossly edematous almost engulfing the ovary. The abscess appeared to be arising from left tubo-ovarian mass with gross appearance of tube suggestive of acute salpingitis.One litre of pus was drained, left salpingectomy was done conserving uterus, right tube and both the ovaries. Abscess wall was removed as far as possible. After peritoneal lavage, abdomen was closed. Patient was put on broad-spectrum antibiotics. she recovered well in postoperative period.

Thus, the proposed mechanism in this case could be Pre-existing tubo-ovarian abscess during pregnancy followed by disturbed or ruptured abscess in postpartum period leading to puerperal peritonitis.

CASE 4

Para2 presented to casualty with pain abdomen, fever off and distension of abdomen and cessation of passage of flatus for 4 days. She had aborted 7 days back a 24 wks pregnancy in a private hospital. She had history of bleeding after the delivery and an evacuation was done.

All routine investigations including XRAY chest, ECG was done. Ascitic tap showed a straw colored fluid. Her symptoms worsened and she was prepared for an exploratory laparatomy., 2 litres of pus was drained. caseous nodule were seen on omentum and pelvic peritoneum. biopsy was taken. Uterus and tubes were congested but normal. Mesenteric lymph node were also enlarged.pus was washed off and a drain was put.. Patient responded to ATT though had a wound dehiscence later on.

Tubercular flare up postpartum or postabortal may occur and should be kept as an important differential when managing such cases.

Management Concerns

Puerperal peritonitis indicates severe maternal sepsis. It presents with systemic inflammatory response syndrome with infection. It may also be associated with organ dysfunction, hypoperfusion of tissues due to hypotension.

Management should be done by a multidisciplinary team headed by a senior obstetrician and comprisisng of infectious disease specialist, surgeons, intensivist and microbiologist.

The appropriate components of treatment of puerperal peritonitis and intraabdominal sepsis are:

- Volume resuscitation, correction of electrolyte and coagulation abnormalities, and empiric broad-spectrum parenteral antibiotic coverage.
- Intensive care with hemodynamic, pulmonary, and renal support
- Early control of the source of infection.

Appropriate specimens should be sent for urgent examination. Antimicrobials should be started within 1

hour of recognition of severe sepsis. This is the golden hour of management.

A precise clinical acumen is essential to judge when to continue conservative therapy with antibiotics and supportive therapy and when to intervene surgically. A serious infection must be rapidly and accurately diagnosed. Many serious potentially life-threatening postpartum infections do not respond solely to antibiotic therapy, and surgical intervention becomes necessary.

Tasks to be performed within the first 6 hours of the identification of severe sepsis; (modified from the Surviving Sepsis Campaign Resuscitation Bundles)[2]

- Obtain blood cultures prior to antibiotic administration
- Administer broad-spectrum antibiotic within 1 hour of recognition of severe sepsis
- Measure serum lactate
- In the event of hypotension and/or a serum lactate greater than 4 mmol/l: Deliver an initial minimum 20 ml/kg of crystalloid or an equivalent
- Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure above 65 mmHg.
- In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or serum lactate greater than 4 mmol/l, achieve a central venous pressure of ≥ 8 mmHg
- Achieve a central venous oxygen saturation ≥ 70% or mixed venous oxygen saturation ≥ 65%

Antiobiotics

A combination of either piperacillin/tazobactam or a carbapenem plus clindamycin provides one of the broadest ranges of treatment for severe sepsis. MRSA may be resistant to clindamycin, hence if the woman is highly likely to be MRSA-positive, a glycopeptide such as vancomycin or teicoplanin may be added until sensitivity is known. Breastfeeding limits the use of some antimicrobials, hence the advice of a consultant microbiologist should be sought at an early stage.[3]

Nonsteroidal anti inflammatory drugs should not be given in sepsis as they inhibit the fighting capacity of polymorhps against sepsis like streptococcus.

Adnexal Pathology

The presentation of post-partum tubo-ovarian abscess with a relatively healthy uterus is a rare clinical scenario under puerperal peritonitis. Pelvic abscess is unusual during pregnancy. Appendicitis and, rarely, abscess from salpingitis[6] constitute the most likely sources of an intra-abdominal abscess during pregnancy.

In non-pregnant state ascending infection is the most important mode of transmission leading to formation of tubo-ovarian mass and abscess, while in pregnancy there are mechanisms to prevent ascending infection which act as barriers. These include presence of cervical mucus plug, intact fetal membranes and the decidua covering the openings of the fallopian tubes.

Ovarian abscess can also complicate the pregnancy or puerperal period leading to peritonitis. It may occur due to secondary infection in a dermoid cyst, serous cystadenoma or simple ovarian cyst. Ovarian abscess is also a known complication of transvaginal oocyteretrieval or transcervical embryo transfer, occurring inapproximately 0.2-2.2 % of cases[7].

These abscesses are often asymptomatic because infection remains contained within the abscess wall and remains separated from the vasculature and adjacent organs. During pregnancy, the uterus usually constitutes part of the abscess wall. After delivery with decreasing size of uterus, the uterine portion of the abscess wall is disturbed and pus leaks into the peritoneal cavity. Infection can then spread, causing frank peritonitis and sepsis. A ruptured abscess may be difficult to recognize, particularly if the leak is slow and there are no sudden peritoneal findings.

Hysterectomy usually is not indicated when the abscess is well contained and uterine myometrium appears healthy.

Conclusion

Virtually all postpartum septic shock develops from a source of infection that is amenable to surgical drainage or removal. It is mandatory to look for a surgically treatable infection when signs of severe infection occur. The surgeon must not relinquish this responsibility when the patient with shock is transferred to an intensive care specialist. Surgery should be performed as soon as possible after restoration of adequate circulation. Endotracheal intubation with minimal balanced general anesthesia is preferable to regional anesthesia

Exploratory laparotomy can be lifesaving for patients with unchecked bacteremia and uncontrolled intra-abdominal sepsis. Laparotomy should be particularly considered when no apparent source of infection is evident. Obviously infected or necrotic structures need to be removed, whereas normal organs and tissue should be conserved. Removal or drainage of an abscess can be undertaken without removal of the uterus or fallopian tubes, if these organs are not extensively infected.

The extensively infected uterus is usually pale, yellow, or obviously necrotic, often with extensive thrombosis of ovarian and adnexal vessels. When these findings are present and patients have increasingly severe and life-threatening disseminated coagulopathy or respiratory distress, hysterectomy can be lifesaving. The uterus usually contains areas of frank necrosis or micro-abscesses in the myometrium. Life-threatening coagulopathy or respiratory distress from sepsis slowly resolves with removal of infected tissue.

Surgery that becomes necessary despite a deteriorating circulatory function is hazardous but occasionally

lifesaving if a defined focus of infection exists. Expertise of the obstetrician and precise clinical judgement go a long way in managing this severe maternal morbidity.

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AOGD Sub Committee Nomination (2019-2021)

Nominations are invited for the post of chairperson of the following sub-committees for the year 2019-2021

1. Urogynecology committee
2. Endoscopy Committee
3. Adolescent Committee
4. Safe Motherhood Committee
5. Fetal Medicine and Genetics -committee
6. Oncology Committee
7. Endometriosis Committee
8. Reproductive Endocrinology Committee

Eligibility Criteria

1. Person should be a member of AOGD and have at least 10 years standing in the profession with at least 5 years duration of holding senior position in the respective institutions.
2. Chairperson of a subcommittee has to be a member of any subcommittee earlier for at least 1 year.
3. No repeat nomination will be considered after one term of two years.
4. In case of two people applying for the same post, the decision of the executive will be final.
5. In case of any deviation, the decision would be taken by executive committee.
6. Two posts cannot be held by any member at one particular time.

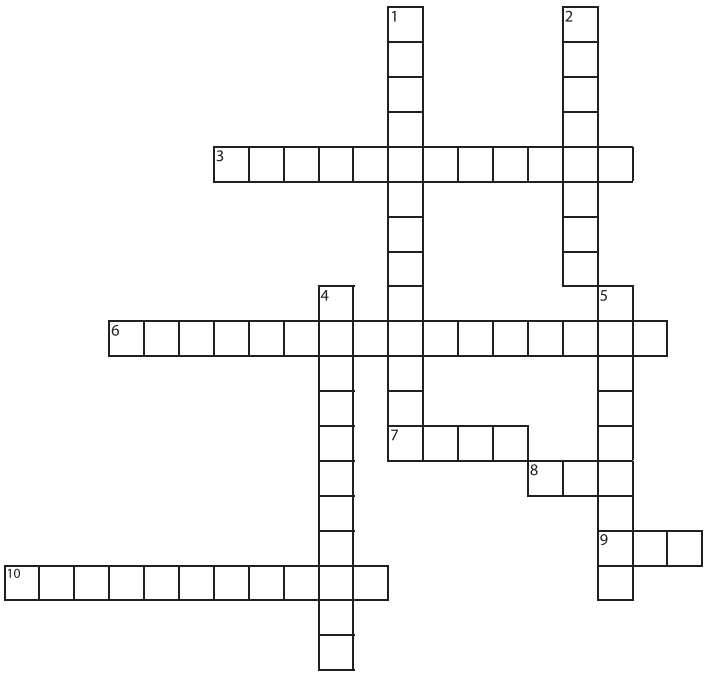
The nominations on plain paper should reach: AOGD Secretariat: Gyne Office, Ground Floor, New Building, Lady Hardinge Medical College, by 20th March, 2019 along with the bio-data stating the eligibility

CROSSWORD

The Maze of Knowledge

Swati Agrawal
Associate Professor, Department of Obs & Gynae, LHMC & SSK Hospital, New Delhi


Dr Swati Agrawal



Down

1. Complication of puerperal sepsis
2. New tocolytic commercially available in India
4. New treatment modality for medical management of endometriosis
5. Designer progesterone

Across

3. Drug used for the management of polyhydramnios
6. Complication of PTPROM
7. Pathogen responsible for surgical site infection
8. Treatment for uncontrolled hypertension in woman with pulmonary edema
9. A model to identify risk of morbidity for sepsis in pregnancy
10. An asymptomatic infection which may be responsible for LMW & preterm babies

PICTORIAL QUIZ

A Picture is Worth a Thousand Words

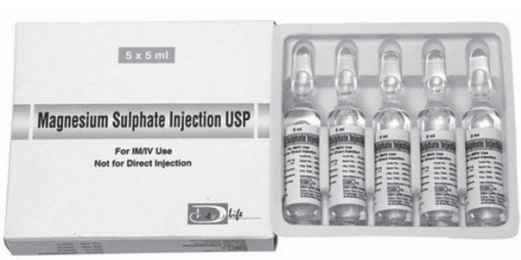


Figure 1:

Q1. What are the indications for the use of the above drug?

Q2. What is the additional advantage when it is used in preterm pregnancies?

Figure 2:

Q1. What is the qSOFA score?

Q2. Which criteria are included in this score?

WhatsApp your answers to 9953938995.
The names of first three correct entries will be mentioned in our next issue.

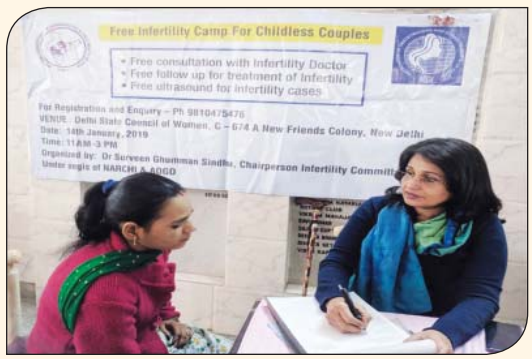
Refer page 36 for previous answer key.

Events Held

- Glimpses of AICOG held between 8th - 12th January, 2019 at Bangalore.

- Glimpses of AICOG held between 8th - 12th January, 2019 at Bangalore.

- Infertility Camp on 14th January, 2019 at Delhi State Council of Women, New Friends Colony under aegis of AOGD, Infertility Committee and NARCHI.



- Public Awareness program on "PCOS and Menstrual Hygiene" on 15th January, 2019 at Miranda House, Delhi University under aegis of Adolescent Committee AOGD.

- Public Awareness program on "PCOS and Menstrual Hygiene" on 15th January, 2019 at Miranda House, Delhi University under aegis of Adolescent Committee AOGD.

- Monthly Clinical Meeting on 25th January, 2019 at Dr Ram Manohar Lohia Hospital.

- North Zone Yuva FOGSI 2019 on 1st - 3rd February, 2019 at Radisson Blu, NOIDA

Dr Richa Sharma received 'FOGSI - Leaders of Tomorrow' Award

Dr Swati Aggarwal delivered Dr Kamini Rao Oration

- CME on Endoscopy (Live Endoscopy Workshop) under the aegis AOGD on 7th February, 2019 at Maulana Azad Medical College, New Delhi

- Cervical & Breast Cancer Screening Camp under aegis of AOGD at Gynae OPD, LHMC on 11th February, 2019.

DISTRESS TO DE-STRESS

Freedom from Hatred

Mohit D Gupta
Professor of Cardiology, GB Pant Institute of Postgraduate Medical Education and Research, New Delhi
Author is Associated with Brahma Kumaris World Spiritual University


Dr Mohit D Gupta

"I have decided to stick to love ... Hate is too great a burden to bear - Martin Luther King Jr"

Not just in one day, but often in an hour, or even a minute, we can have a flood of emotions that have the power to take control of our mood and govern our life. These emotions can be positive or negative. Unfortunately, we are living in a world where negative emotions have taken a lead and are spreading fast, leading to disharmony, restlessness, dissatisfaction, annoyance, anger and so on. This has infiltrated into our belief system in such a way that we often feel it is normal to harbor such emotions.

One of the worst emotions that have taken toll over peace is rage. Rage has many offspring (children), such as hate, anger, intolerance, insistence, irritation, obsession, sarcasm (taunt), envy, the abuse of authority, impatience, the lack of forgiveness. Today, when we see the world become more and more divided, it's easy to get pulled into the vortex of hatred that threatens to consume us all—no matter where you stand on issues. One of the most beautiful art is to manage your emotions and take the situation confidently and assertively. If we are able to do so, we can establish ourselves on a more positive footing.

Let us understand the genesis, manifestations and simple remedies of hate.

Just remember last time when I felt hate for someone. If we analyze the reasons, they will fall in the following categories:

1. Our Wish to Control Others

A big mistake we make in our lives is living with the belief that we have the power to control others. We think we can govern their thoughts, there actions, the way they live, the way they perform. How is it possible? How commonly we have thoughts that we don't want? How often we speak words that should not have been spoken? Do we regret doing something in our life ever? The answer is yes. So, if we don't have the ability to govern ourselves, then what power do we have to govern lives of others?

This leads to anger, irritation and hatred, that gets reflected in our behavior.

2. When Our Expectations are not Fulfilled

Just pause; think and reflect: Is it possible for us to fulfill every expectation of others? Or is it possible for anyone to fulfill all our expectations? It is not. Let us understand this with an example: often I am performing my duties and my work perfectly; but people behave in an undesirable way that hurts me. I never expected this from them and I create anger and hate for them. This leads to unrest in my life and I lose my peace.

Interestingly, when we go through these emotions, we feel that the other person is responsible for my situation. It is often difficult for us to realize that our anger and hate is created by no one but ourselves. Although it seems that the behavior of the other person is responsible for our emotional state, the truth is that the hate is our reaction. Every response created by us is a conscious choice but we forget because it seems that the hate comes out of our inside in a natural way. In reality, we are allowing ourselves to be driven by our auto pilot, where our subconscious habits, which are based on our beliefs and our perception, influence and control our conscious thoughts and actions. That is the sign of mental and emotional weakness; in that state, we lose our power to think with clarity and take precise decisions.

Can hate be justified? Can it improve things? Can hate be healthy in any circumstance?

The answer is no.

Hate affects your physical, mental, social and spiritual health; it poisons our heart, kills our inner peace and destroys love and happiness. The person often stays isolated and aloof, thinking negative continuously because mind is filled with that rage. Hate destroys your concentration and kills the capacity to act with dignity and excellence. When we say that people have let us down and they have wounded us and broken our heart, we then try to answer this wound with revenge. We want to make them pay for it and in this way we will do justice. In fact, this hate keeps us tied to the person that we hate. Instead of accepting them, forgiving them and letting go of them, we tie ourselves to them more, nourishing and increasing the pain and the conflict.

What can we do to free ourselves from hate?

1. **Understanding that hate is a form of emotional illness:** We can only get rid of something that we strongly understand is not healthy. Hate is like a messenger and the stress that we create continues to grow. Finally, it turns into such a habit that, even if we try to relax and destress, we feel uncomfortable.
2. **Accept that we are responsible for our own rage:** Every feeling experienced by me is a conscious

choice that I create. No one can make me angry or depressed. Only I allow those feeling to enter my energy field and become a part of my aura. Let us choose only powerful and positive energies to become a part of my aura.

3. **The other is free to act as they like, we can't change them, but we can improve our response:** Once I understand that the only person who can listen to me and act according to me is myself, then I can take control over my emotions. I choose them wisely in such a way that I am happy and peaceful in all situations.
4. **Be prepared to observe, challenge and change the beliefs and perceptions that we base ourselves on and that create our emotional pain:** Coming out of our comfort zones created by ourselves is what is needed. As I have learned to live with the belief that anger is natural and normal reaction, now I choose to transform it into a new and original belief that love and acceptance is natural. I train my mind to behave with love and peace in every situation. I accept people and there responses understanding that they are free to choose the way they live.
5. **Create emotional stability:** To be emotionally stable, I need to be immune and flexible. Just as doctors take proper precautions while examining patients, similarly I choose to increase immunity of my mind so that pain radiated by people doesn't become part of my energy. Also, flexibility is key to health. Similarly, I make my mind flexible to accept situations and behavior of people.
6. **Practice Meditation:** Creating thoughts that heal ourselves and others is the best way to be. We have a deeper understanding that the present behavior of any person is because of the external influences that one allows to enter our mind. In meditation, we see the original nature of every soul as a pure, elevated, loving and powerful.. We create and radiate such thoughts and forgive everyone including ourselves. This takes away guilt and brings peace in our life.

Wishing you a life full of love and Joy!

Forthcoming Events

- Wellness of Women "Ek Kadam Cancer Se Bachao ki Ore" organized by FOGSI & Brahma Kumaris Initiative on 15th -17th February, 2019 at Om Shanti Retreat, Manesar
- Global Conference on Reproductive Health with Focus on "Occupational, Environmental & Lifestyle Factors" to be held on 22nd – 24th February, 2019 at JNU Convention Centre, New Delhi. Contact: Dr J B Sharma 9868138205
- Next Monthly Clinical Meeting on 1st March, 2019 (4:00 pm - 5:00 pm) at LT- 1, College Building, UCMS & GTB Hospital, New Delhi
- International Women's Day, Women's health on 8th March, 2019 Organized by AOGD at Lady Hardinge Medical College, New Delhi

BEST PRACTICES

Prescribing Antihypertensives

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Dr Bindiya Gupta

Introduction

Hypertensive disorders in pregnancy are one of the leading cause of maternal & fetal morbidity and mortality. Hypertension is the most common medical problem encountered during pregnancy, complicating up to 10% of pregnancies.[1]Preeclampsia occurs in 3-6% of all pregnancies and the incidence is 1.5 to 2 times higher in primigravidas.[2] Population-based data indicate that approximately 1% of pregnancies are complicated by chronic hypertension and 5-6% by gestational hypertension (without proteinuria).[3]

Classification of Hypertension in Pregnancy

The American college of Obstetricians and Gynecologists (ACOG) classified hypertension in pregnancy as chronic hypertension (diagnosed before pregnancy or before 20 weeks' gestation), preeclampsia-eclampsia (gestational hypertension with either proteinuria or an end-organ manifestation consistent with preeclampsia; eclampsia as presence of convulsions with hypertension), preeclampsia superimposed upon chronic hypertension & gestational hypertension (diagnosed at equal to or greater than 20 weeks).[1] Acute-onset, severe hypertension (equal to or greater than 160/110 mm Hg) that is accurately measured using standard techniques and is persistent for 15 minutes or longer is considered a hypertensive emergency.[4]The International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018 have further added sub categories like white coat hypertension, masked hypertension and transient gestational hypertension.[5] The latter is defined as elevated BP documented, usually in the office/clinic setting, but follow-up BP measurements are normal, often in day assessment units or at home. It is of importance as transient gestational hypertension is associated with a 40% risk of developing true gestational hypertension or preeclampsia at some point in that pregnancy, mandating close follow-up.[5]

Management of Acute Severe Hypertension

Acute severe hypertension in pregnancy is a medical emergency requiring treatment to lower blood pressures within 30 minutes of confirmation to reduce risk of maternal stroke. The goal should be to lower BP to non-severe levels (ie, <160/110 mm Hg) over hours without reducing it by more than 25% initially, with gradual lowering over hours thereafter. There is a risk of underperfusion to the fetus in case there is a sudden drop in blood pressure as the fetoplacental unit, does not autoregulate blood flow; appropriate fetal heart rate (FHR) monitoring should be instituted by the obstetrician. The intravascular volume depletion of preeclampsia can precipitate hypotension after the administration of short-acting antihypertensive agents.[6]

First line drugs used for rapid lowering of blood pressure are **intravenous (IV) labetalol, oral immediate release nifedipine and IV hydrazaline, (Figure-1).**[4] **Labetalol is treatment of choice for control of acute hypertension** as it is more effective and has low incidence of side effects. Labetatol should be avoided in women with asthma, heart disease, or congestive heart failure. Hydralazine is contraindicated in coronary artery disease, mitral valve disease. Hydralazine is associated with more feto-maternal complications like maternal hypotension, increased number of caesarean sections, placental abruption ,maternal oliguria fetal bradycardia and low Apgar scores at one minute.[7] The nifedipine preparations that are appropriate for the treatment of severe hypertension are the capsule and the intermediate-acting (PA) tablet, where available; the former should not be bitten or punctured. The 10 mg tablet may be associated with less maternal hypotension as compared with the 10 mg capsule when it is bitten/punctured.[8]

When urgent treatment is needed before the establishment of IV access, the oral nifedipine algorithm can be initiated, or a 200-mg dose of labetalol can be administered orally. The latter can be repeated in 30 minutes if appropriate improvement is not observed.[4]

In rare instances where BP is not controlled by all these drugs sodium nitroprusside (0.25µg/kg/min to max dose 5µg/kg/min) can be used. Sodium nitroprusside should be reserved for extreme emergencies and used for the shortest amount of time possible because of concerns about cyanide and thiocyanate toxicity in the mother and fetus or newborn, and increased intracranial pressure with potential worsening of cerebral edema in the mother. Other drugs used infrequently, often for refractory hypertension during critical care, include clonidine and captopril, nitroglycerin infusion and mini-bolus diazoxide.[9]

Magnesium sulfate is not recommended as an antihypertensive agent, but magnesium sulfate remains the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia. It blocks neuromuscular transmission causing decrease acetyl choline release from nerve endings and decrease motor end plate sensitivity to acetylcholine. It is contraindicated in Myasthenia gravis and impaired renal

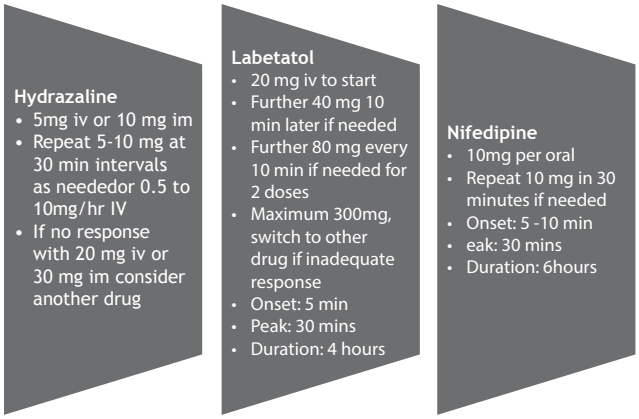

Figure1: First line drugs for management of acute severe hypertension

function. For treatment of eclampsia : 4 g intravenous (over 5 min), then 1 g/h intravenous; if patient is already receiving $MgSO_4$, give additional 2–4 g intravenous (over 5 min) and increase infusion to 2 g/h intravenous.[5] The Pritchard regime includes a loading dose: 4 gm iv (20ml of 20% solution), 5gm (50%) im in each buttock followed by maintenance dose: 5gm (50%) deep im on alternate buttock every 4 hours. The parameters that need to monitored include respiratory rate, knee jerk and urine output. Common side effects are flushing, headache, muscle weakness, pulmonary edema and cardiac arrhythmias.

Antihypertensive Therapy for Non-severe Hypertension (BP of 140-159/90 -109 mm Hg)

The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension. The effect on other clinically important outcomes remains unclear.[10]Treatment of maternal hypertension benefits the mother, and although treatment might affect fetal growth, it does not increase illness or death of the infant.

Threshold for Treatment

The CHIPS trial was a large definitive trial that provided evidence that non-severe hypertension in pregnancy (chronic hypertension and preeclampsia) should be treated with antihypertensive therapy. [11] They classified BP control as "Tight" BP control (target diastolic BP of 85 mm Hg) (vs "less tight" control, target diastolic BP of 100 mm Hg). Results showed that "Tight" (vs "less tight") control resulted in similar rates of the adverse perinatal outcomes and birth weight <10th percentile. However, "tight" (vs "less tight") control resulted in fewer adverse maternal outcomes of severe maternal hypertension (40.6% vs. 27.5%), platelet count $<100\times10^9$/L, and symptomatic elevated liver enzymes; there was no difference in serious maternal (end-organ) complications. Post hoc analyses determined that severe hypertension, independent of any associated preeclampsia, was a risk factor for complications for the mother and the baby and, in the "less tight" control arm specifically, severe hypertension was associated with more serious maternal complications.[11]

SOGC Guidelines[12]

Antihypertensive treatment in hypertension without co- morbidities (Renal disease/ gestational diabetes)

Treatment is offered when systolic BP is 150-160 mm Hg or more, diastolic BP > 100-105 mmHg. Antihypertensive drug therapy may be used to keep systolic blood pressure at 130 to 155 mmHg and diastolic blood pressure at 90–105 mmHg. (grade I-B).

For Non-Severe Hypertension (BP of 140-159/90–109 mmHg) With Comorbid Conditions

Women with preexisting end- organ damage from chronic hypertension should have a lower threshold for starting antihypertensive medication (ie, >139/89). Antihypertensive drug therapy should be used to keep systolic blood pressure at < 140 mmHg and diastolic blood pressure at <90 mmHg.

Drug therapy

Guidance for choice of the antihypertensive drug, including effects on fetal heart rate or neurodevelopment, is sparse. Methyl dopa and labetalol are both safe in pregnancy, while angiotensin converting enzyme inhibitors and angiotensin –II receptor blockers are contraindicated in pregnancy due to fetotoxicity. Atenolol and Prazosin are not recommended prior to delivery as atenolol may reduce fetal growth while prazosin can cause stillbirth.[12] Thiazide diuretics can be considered for hypertensive women, but their use is limited to specific circumstances, such as medullary sponge kidney, despite concerns that they may inhibit the normal plasma volume expansion of pregnancy. Thiazide use after the first trimester did not adversely affect maternal or perinatal outcomes or prevent preeclampsia in RCTs.

According to NICE guidelines[13] in *chronic hypertension, if* blood pressure is well controlled on an agent pre-pregnancy, except angiotensin-converting enzyme inhibitors & angiotensin II receptor blockers, the same drug can be continued. Most antihypertensive agents do not increase the risk of major malformations above the baseline risk of 1% to 5%. Methyldopa is recommended as first line therapy. NICE guidelines recommend treatment with aim to keep lower than 150/100 mm Hg but diastolic BP should not be below 80 mm Hg. **In preeclampsia, first** line of treatment is labetalol & alternative therapies are methyldopa and nifedipine.[13]

Individual variation in pre-eclampsia haemodynamics, assessed by cardiac output or peripheral vascular resistance, might interact with effects of

Table 1: Antihypertensive Therapy for Nonsevere Hypertension (BP of 140-159/90-109 mm Hg)[12-14]

Agents	Mechanism of action	Dosage	Contraindications	Adverse effects	FDA category
Methyldopa	Stimulate central inhibitory α-adrenergic receptors	250-500 mg po BD or QID (max 2000 mg)	Acute hepatitis, cirhossis	Sedation, lethargy, fluid retention, positive coomb's test, hemolytic anemia. flu like illness	Category B
Labetalol	Selective α-1 & nonselective beta blocking agent	100-400 mg po BD-TDS (max dose 1200 mg/day)	-Asthma -Heart block -Congestive heart failure	Fatigue, weakness, orthostatic hypotension, Fetal growth restriction, neonatal hypogycemia	Category C
Nifedipine	Calcium channel blocker	20-60 mg/dose po once daily, max 120 mg/day (sustained release preparation is preffered)	Myocardial infarction	Hypotension, headache, tachycardia, coronary steal phenomenon, inhibition of labor	Category C

antihypertensive drugs, but whether individualised therapy improves outcomes is unknown.[14]

According to a recent Cochrane meta-analysis 2018, beta blockers and calcium channel blockers together in the meta-analysis appear to be more effective than methyldopa in avoiding an episode of severe hypertension (RR 0.70; 95% CI 0.56 to 0.88; 11 trials, 638 women). There was also an increase in this risk when other antihypertensive drugs were compared with calcium channel blockers (RR 1.86; 95% CI 1.09 to 3.15; 5 trials, 223 women), but no evidence of a difference when methyldopa and calcium channel blockers together were compared with beta blockers (RR1.18, 95% CI 0.95 to 1.48; 10 trials, 692 women). They concluded that if antihypertensive drugs are used, beta blockers and calcium channel blockers appear to be more effective than the alternatives for preventing severe hypertension.[10]

The drugs, mechanism of action, indications, contraindications, dosage are summarized in Table-1.[12-14]

Post Partum Drug Therapy

Drugs safe in management in post partum period include labetalol, nifedipin, enalapril, captopril, atenolol and metoprolol . hydralazine, labetalol, and nifedipine have been used for severe hypertension; all are appropriate during breastfeeding.[15] Nifedipine may be more effective postnatally when administered with furosemide.[16] Antihypertensive treatment where there is insufficient evidence on the safety in babies receiving breast milk include ARBs, amlodipine, ACE inhibitors other than enalapril and captopril. Only 2 antihypertensive agents are not recommended for use during breastfeeding: sodium nitroprusside, because toxic metabolites (thiocyanate and cyanide) may cross into breast milk; and oral clonidine, because of high serum drug levels in breastfed infants.

Drugs to Prevent Preeclampsia

Aspirin

NICE guidelines advise woman to take aspirin 75 mg/day from 12 weeks until birth if at least two moderate risk factors or at least one high risk factor for preeclampsia exists.[13] They state that this is an unlicensed indication and that informed consent should be taken. There is support for the use of low-dose aspirin before 16 weeks with investigators suggesting the possibility that because normally the transformation of uterine spiral arteries by trophoblasts is completed by 16–20 weeks and this is abnormal in preeclampsia; early use of aspirin may be beneficial.[17]

Metformin[17]

A metaanalysis has shown that that compared to insulin, metformin reduced the risk of hypertension in women with gestational diabetes

- Antioxidants, calcium supplementation & fish oil are also used to prevent preeclampsia but no definite evidence is available.

Novel agents

Angiogenesis, aminopeptidases, heme oxygenase 1, Marinobufagenin, G protein-coupled receptor (GPCR) targets, Inhibitors of the enzyme poly ADP ribose polymerase (PARP), Gasotransmitters are few potential therapeutic targets under investigation.

To conclude, there is a need for adoption of standardized, evidence-based clinical guidelines for managing patients with preeclampsia. Individuals and institutions should have mechanisms in place to initiate the prompt administration of medication when patient presents with a hypertensive emergency. Guidelines on the management of hypertension needs to balance the potential benefits of these drugs in pregnancy for the mother against the potential harms to the fetus.

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Congratulations !!

Dr Anita Rajhoria and Dr Anuradha Singh for correctly answering the quiz and crossword of January issue

* * * * *

Answer: January Issue

Crossword

Down: 2. UAE, 3. Hysterectomy, 4. LNG-IUS, 5. MTP, 7. Inversion, 9. COC

Across: 1. Chattisgarh, 6. Mifepristone, 8. AKI, 10. Oxytocin

Pictorial Quiz

Figure 1: Ans 1. HIFU or MRgFUS

Ans 2. Limitations: Less effective in patients with extensive cutaneous scars, presence of concomitant severe adenomyosis, or multiple fibroids counting more than five in numbers or over 10 cm in size.

Figure 2: Ans 1. Placenta acreta

Ans 2. 11%

RECENT ADVANCES IN

Tocolysis

Beenu Kushwah Singh[1], Neha Khatik[2]

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Dr Beenu Kushwah Singh

Every year, an estimated 15 million babies are born preterm (before 37 completed weeks) and this number is rising. Complication related to preterm birth are the leading cause of death among children under 5 years of age accounting for approximately 1 million deaths in 2015[1]. Out of total preterm births worldwide, more than 60% occur in Africa and South Asia[2]. India stands first amongst the list of top 10 countries having highest number of preterm babies. Use of antenatal steroids remains a critical component for management of preterm labor, also being a very simple and cost effective measure it remains the most commonly utilized intervention. But for antenatal corticosteroids to obtain optimum levels in the fetus, a period of at least 48 hours from administration to delivery is desirable. In addition delaying delivery can provide time for transfer of the pregnant lady to a facility with a well equipped neonatal intervention care unit which is significant in countries like India where resources are limited. To serve this purpose tocolytic drugs are used. They are a group of pharmacological agents which inhibit uterine contractions. They are essentially given along with corticosteroids, as an initial intervention for treatment of preterm labor in order to delay delivery for next 48 to 72 hours, in order to achieve both the above mentioned goals.

Selection of patient: As most of the tocolytic agents are associated with certain maternal complications, tocolysis is initiated when the overall benefits of delaying delivery outweighs the risks[3]. Practice bulletin of the American College of Obstetricians and Gynecologists opined[3] that, "Interventions to reduce the likelihood of delivery should be reserved for women with preterm labor at a gestational age at which a delay in delivery will provide benefit to the newborn. Because tocolytic therapy is generally effective for up to 48 hours, only women with fetuses that would benefit from a 48 hour delay in delivery should receive tocolytic treatment". Women in the early phases of acute preterm labor, when cervical dilation has not reached above 3 centimeters, are optimum candidates for tocolytic therapy[4]. There are some general contraindications to use of tocolytics, either due to medical factors present in mother or due to certain obstetrics factors. Contraindications listed in Box-1 should be ruled out before initiating tocolysis.

Lower and upper gestational age limits for initiating tocolysis: The minimum gestational age at which inhibition of preterm labor should be done, is controversial, and should be individualized based on the particular clinical scenario. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend not administering tocolysis before 24 weeks of gestation, but consider its use at 23 weeks based on individual circumstances[5]. Upper gestational age limit for initiating tocolysis is generally taken as 34 completed weeks. ACOG and SMFM both recommend that 34 weeks of gestation defines the threshold at which perinatal morbidity and mortality are too low to justify the potential maternal and fetal complications and costs associated with inhibition of preterm labor and short-term delay of delivery[3,6].

Box-1: Factors contraindicating tocolysis

- Intrauterine fetal demise, Lethal fetal anomaly, Nonreassuring fetal status
- Cervical dilation ≥4 centimeters
- Preeclampsia with severe features or eclampsia
- Maternal hemorrhage with hemodynamic instability
- Intraamniotic infection
- Medical contraindications to the particular group of tocolytic drug like heart disease, allergy to drug etc.

Currently available tocolytic agents: Six main classes of tocolytics, which are being used worldwide, are: Beta$_2$-adrenergic agonists, Magnesium sulfate, Calcium channel blockers (CCB), Cyclooxygenase inhibitors (COX)/Prostaglandin Synthetase inhibitor (PGSIs), Vasopressin/Oxytocin receptor antagonists (VOT) and Nitric oxide donors. Out of these CCB, COX inhibitors/PGSIs and Vasopressin/Oxytocin receptor antagonists (VOT) are the preferred recent choices[7,8,9] over Magnesium sulfate, Nitric oxide donors & Beta-2 agonists, because of adverse effects associated with later three groups of tocolytics[9,10]. Table-1 discusses these three groups of tocolytic agents, mechanism of action, dosage and maternal & fetal adverse effects along with contraindications of using these drugs. The choice of tocolytic should be based on maternal condition, potential adverse effects, gestational age, and cost.[11] Once treatment is initiated, the patient's response to tocolysis, including adverse effects, should be continuously monitored.[12]

Role of Atosiban as an effective & safe tocolytic agent (APOSTEL III Trial): In the UK and Western Europe, Nifedipine and Atosiban already are generally first-line choices[9]. In India also Nifedipine is being used as a first line tocolytic for almost a decade now but Atosiban is a new entrant and has been only recently been licensed as a tocolytic agent. Atosiban is still not licensed for use in the USA and Australia because of certain controversy over its associated fetal complications[18,30], especially when administered before 28 weeks of

gestation. Likewise a recent Cochrane review published in 2014[31], does not recommend Atosiban as tocolytic of choice. Nevertheless, results of APOSTEL III trial[32] (The Assessment of Perinatal Outcome after Specific Tocolysis in Early Labor) was published in 2016. This was a trial of Nifedipine versus Atosiban for the treatment of threatened preterm labor. The trial was a nationwide multicenter, randomized controlled study. Primary outcome was a composite measure of severe neonatal mortality and morbidity. Secondary outcomes were time to delivery, gestational age at delivery, days on ventilatory support, admission to NICU, length of stay in NICU, total days in hospital until 3 months corrected age, convulsions, apnea, asphyxia, proven meningitis, pneumothorax, and maternal side effects. An economic evaluation of the treatment was also performed. The primary and secondary outcome rates were comparable between the groups, and the authors concluded that, in women in threatened preterm labor, Nifedipine and Atosiban had similar adverse rates of perinatal outcome, but there was a non-significant but possibly clinically relevant increase in neonatal mortality in the Nifedipine group that questioned its safety and required further analysis. After the results were published there has been an obvious increase in use of Atosiban as a first line tocolytic agent worldwide, although its high cost in countries like India, may remain a limiting factor to use it widely.

Retosiban, a specific, high-affinity OT receptor antagonist, is now been developed and used for the inhibition of uterine contractions in spontaneous preterm labor. In a phase II, randomized, double-blind, placebo-controlled proof-of-concept study to confirm the efficacy and safety of intravenous Retosiban in women experiencing preterm labor between 30 and 35 completed weeks gestation, the maternal, fetal, and neonatal adverse events were comparable between the Retosiban and placebo groups[33].

Combination use of Nifedipine as tocolytic & Magnesium sulfate for neuroprotection in preterm labor: Use of Magnesium Sulfate as a neuroprotective agent in preterm labor, especially in cases of threatened preterm delivery before 32 weeks of gestation, has become a standard of care now and combining Magnesium sulphate with Nifedipine has always been described as a dangerous regime because of theoretical risk of the this combination causing more cardiovascular complications and life threatening neuromuscular blockade to the mother[34]. It is for this reason that ACOG had to comment on it in its practical bulletin in year 2012[35] "Hospitals that elect to use magnesium sulfate for fetal neuroprotection should develop uniform and specific guidelines for their departments regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials." **Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland And Health Service Executive also stated on use of Antenatal magnesium sulphate for fetal neuroprotection[36] (Revised 2015)** "Use of calcium channel blockers: The potential interaction between calcium channel blockers, such as Nifedipine, and magnesium sulphate leading to hypotension and neuromuscular blockade mandates more intensive monitoring of maternal haemodynamic status."The NICE guidelines on preterm labor and birth[37] (Nov 2015) gives no information about safety of using magnesium sulphate for neuroprotection in women being given Nifedipine as a tocolytic. A recent Cochrane review[38] of combination of tocolytic agents for inhibiting preterm labor (Vogel) which aimed to assess the effects on maternal, fetal and neonatal outcomes (including adverse drug reactions) found no trials of regimens including Nifedipine.

Tocolytic maintenance therapy for preterm labor after first-line tocolysis*:* As per recent WHO recommendations[39] (based on recently available evidences[40]), there were no significant differences in the rates of preterm birth before 37 weeks of gestation for women receiving oral Betamimetics, Magnesium sulfate, Nifedipine or Atosiban as maintenance therapy when compared with placebo or no treatment. Compared with placebo or no treatment, none of the maintenance therapies led to a significant reduction in the rates of birth before 28 weeks or 32 weeks of gestation. There was no significant difference in mean gestational age at birth (weeks) for women receiving tocolytic maintenance therapy compared with placebo or no treatment. As far as neonatal complications are concerned, there was no statistically significant difference in perinatal mortality between groups receiving maintenance tocolytic therapy and placebo or no treatment. Therefore maintenance therapy for inhibition of preterm labor is not indicated as per recent recommendations.

Conclusion: Recent evidences support the use of short-term tocolytic drugs to prolong pregnancy for at least 48 hours to allow for administration of antenatal steroids and also allow for transport of the mother to a tertiary care facility, it additionally provides time for administration of magnesium sulfate to reduce the risk of cerebral palsy in a preterm neonate. Although till date Nifedipine has been the drug of choice for the purpose of Tocolysis worldwide, recent addition of Atosiban, which is a considerably safer drug, may become a widely accepted practice soon. However, its high cost and need of parenteral administration may be a limiting factor for its acceptability across the practitioners. It has been a common practice to use maintenance tocolysis, but without any robust evidence and seeing the adverse effects & potential complications caused to mother and baby both, this practice should be abandoned. With the introduction of use of Magnesium sulfate for neuroprotection for a preterm fetus, combination Tocolysis, which was not favored earlier, may soon become a standard practice but definitely requires strict maternal monitoring, preferably in an intensive care unit while administering combination Tocolysis.

Group of Tocolytic	Mechanism of action	Dosage	Adverse effects	Contraindications
Calcium channel blockers	1. Block the influx of calcium ions through the cell membrane 2. Decreases intracellular free calcium 3. Inhibits calcium-dependent myosin light-chain kinase (MLCK) phosphorylation, leading to myometrial relaxation 4. Commonly used calcium channel blockers - nifedipine	• Loading dose -30mg • Maintenance -10 to 20 mg every four to six hours for 48 hours [4](ACOG)	• Nausea, flushing, headache, dizziness, and palpitations due to peripheral vasodilatation • Compensatory rise in cardiac output (reflex increase in heart rate and increased stroke volume)[13] due to decreased vascular resistance	• Known hypersensitivity • Hypotension, • Preload-dependent cardiac lesions • left ventricular dysfunction or congestive heart failure[14,15]
Vasopressin/ Oxytocin receptor antagonists	1. Atosiban is a selective oxytocin-vasopressin receptor antagonist. 2. Oxytocin stimulates contractions by conversion of phosphatidylinositol to inositol triphosphate, which binds to a protein in the sarcoplasmic reticulum causing release of calcium into the cytoplasm. 3. Oxytocin receptor antagonists compete with oxytocin for binding to oxytocin receptors in the myometrium and decidua, thus preventing the increase in intracellular free calcium [16]. 4. It also inhibit oxytocin-induced production of prostaglandin F2alpha, but not prostaglandin E2[17].	• Atosiban is administered intravenously beginning with a bolus of 6.75 mg • Maintenance - 300 mcg/ min infusion for three hours, and then 100 mcg/ min for up to 45 hours[18]. Initial and terminal half-lives are 13 and 102 minutes, respectively.	• Hypersensitivity and injection site reactions. • Adverse maternal cardiovascular effects have not been reported • The overall frequency of side effects in women given Atosiban is significantly less than that reported for any other drug used for inhibition of preterm labor[19,20] • Use of Atosiban was associated with a significantly lower risk of maternal side effects requiring cessation of treatment than beta-agonists	• There are no absolute contraindications to use of Atosiban[21].
COX inhibitors/ Prostaglandin-Synthetase inhibitor (PGSIs)	1. Nonspecific inhibitors reduce prostaglandin production by inhibition of both COX 1 and 2 Specific inhibitors inhibition of COX 2, which is primarily responsible for PG synthesis in myometrium 2. Indomethacin, a nonspecific COX inhibitor, is the most commonly used tocolytic of this class as there is a limited information available on the use of COX-2 inhibitors for treatment of preterm labor in humans Indicated only when CCB or Oxytocin receptor antagonists cannot be administered due to availability concerns	• The dose of indomethacin is 50 to 100 mg loading dose (may be given orally or per rectum), followed by 25 mg orally every four to six hours. Caution: • If indomethacin is continued for >48 hours or after 32 weeks, USG & doppler evaluation for liquor and narrowing of the fetal ductus arteriosus is warranted at least weekly[24,25]	• Nausea, esophageal reflux, gastritis, and emesis • Platelet dysfunction • Oligohydramnios • Constriction of the ductus arteriosus ,premature narrowing or closure of the ductus arteriosus, pulmonary hypertension and tricuspid regurgitation in the fetus.[26] • Neonatal complications: bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, periventricular leukomalacia, and intraventricular hemorrhage although these associations are controversial.[27,28,29]	• Platelet dysfunction or bleeding diathesis • Hepatic dysfunction • Gastrointestinal ulcerative disease • Renal dysfunction • Asthma • Hypersensitivity to aspirin

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CONTROVERSY

Drug Therapy in Endometriosis

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Introduction

Endometriosis is a widely spread disease with poorly understood etiology. It is presence of functional endometrial gland outside uterine cavity. The incidence is 10 % in women of reproductive age group. Endometriosis usually presents with infertility, chronic pelvic pain, dyspareunia.

There are various theories to explain endometriosis. Retrograde menstruation is the theory most attributable to endometriosis. Most common site of involvement in endometriosis is ovary, cul-de-sac, fallopian tube but may involve distant organs as well.

Diagnosis is usually confirmed with visual inspection as early stage disease cannot be diagnosed by imaging modalities. Staging of disease is based on extent of involvement and adhesions but it does not correlate well with the symptoms. Patient may be symptomatic without extensive lesions. Histopathological examination confirms the diagnosis, but negative histology does not exclude it.

Endometriosis is an oestrogen dependent entity, hence use of hypoestrogenic drugs or drugs antagonising estrogenic action are used. Medical management used for 6 months helps in reducing pain and improving quality of life of patient. Suppression of ovarian function is not useful in improving fertility outcome in women with endometriosis. There is still a search of an ideal medical therapy which helps in reducing symptoms with minimal side effects.

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs is usually first line drug in management of pain and dysmenorrhea in endometriosis. NSAIDs inhibit the cycloxygenase enzyme (COX) which is responsible for production of inflammatory mediators causing pain. Both non-specific and specific COX inhibitors are used. There was initial evidence of high efficacy of selective cycloxygenase 2 inhibitor because of higher concentration of COX 2 enzyme in endometriotic implants however, rofecoxib has been withdrawn from the market due to its cardiovascular side effects.

NSAIDs has gastrointestinal side effects. Despite being used as a first line in treatment of endometriosis there is no conclusive evidence of NSAIDs in reducing pain associated with endometriosis.[1]

Combined Oral Contraceptive Pills (COCs)

Continuous use of estrogen and progesterone combined pills help in decidualization of endometriotic implants and are therefore increasingly used in medical management of endometriosis. Continuous use of COCs for 6 months has been seen to be effective in reducing pain associated with endometriosis[2]. Easy availability and easy administration have increased its use in endometriosis. There is a long term risk of thrombosis associated with COC usage.

Progestins

Progestins in management of endometriosis has been used as a treatment for the painful symptoms of endometriosis. The precise mechanism by which it reduces painful symptoms is not known but possible mechanisms have been suggested. It may help by ovarian suppression which decreases active bleeding from ectopic endometrial implants[3], decidualization and atrophy of both eutopic and ectopic endometrial implants[4,5], modulation of immune responses preventing proliferation of endometriotic stromal cells[6]. Side effects associated with use of progestins include weight gain, mood changes, bloating, fatigue, depression, breakthrough bleeding and adverse effect on lipid profile. Various progestins have been studied for use in endometriosis.

Norethisterone acetate (NA) in a dose of 2.5 mg daily continuously over 6 months is found to be effective in pain relief. This association was found in two studies comparing NA with placebo and NA with dinogest. It has been found to be effective in symptomatic rectovaginal and colorectal endometriosis. It is beneficial over other progestins in reducing uterine blood flow and lack of harmful effects on lipoprotein profile. Medroxyprogesterone acetate (MPA) in a dose of 15-50 mg continuously for 3 months has been found to be effective over placebo in reliving painful symptoms. the major disadvantage of using MPA is breakthrough bleeding. Cyproterone acetate is antiandrogenic drug with weak progestational activity. It has been found to relieve endometriosis associated pain when used in a dose of 12.5 mg continuously for 6 months. The disadvantage is its association with depression, decreased libido, hot flushes, vaginal dryness.

Dienogest used in dose of 2 mg/day continuously has a good tolerability and efficacy in treatment of endometriosis when used for 6 months.

Depot medroxy progesterone acetate (DMPA) used as 150 mg intramuscular every 3 months has an incidence of inducing amenorrhea and in reducing pain and improving quality of life. However, it is associated with a disadvantage of delayed resumption of ovulation

in women desiring future pregnancy, breakthrough bleeding and bone demineralization.

Implanon (etonorgestrol containing implant) has been shown to have good efficacy upto 12 months in treatment of pain in endometriosis. It is useful in women desiring long term contraception.

Levonorgestrel intrauterine device (LNG-IUD) has been shown to reduce pain efficaciously. It is especially used in rectovaginal endometriosis and in reducing risk of recurrence of dysmenorrhea after conservative surgery. It has a better compliance because of one time insertion with fewer hypoestrogenic side effects. Disadvantage like other progestins is irregular bleeding.

Progestins preparation has been found to effectively reduce pain in endometriosis. It is preferable over combined hormonal pills to avoid metabolic effects of oestrogen.

Gonadotropin Releasing Hormone Antagonists (GnRH antagonists)

Usage of GnRH antagonist has been seen to cause regression of endometriotic implants and improvement in symptoms[7]. As opposed to GnRH agonist they do not cause the initial flare and have a lower degree of hypoestrogenism.

Selective Progesterone Receptor Modulator (SPRMs)

These drugs have variable effects both agonist and antagonist. Ulipristal acetate, a SPRM inhibits endometrial growth and has been used in treatment of endometriosis. They do not have any hypoestrogenic side effects. But the recently studied side effect on liver profile have limited its use.

Danazol

It is an androgen agent which inhibits LH surge and inhibits ovarian steroidogenesis. Its use has been seen to be associated with pain control in endometriosis[8]. Its androgenic side effects i.e. acne, hirsutism, deepening of voice has limited its use in endometriosis.

Aromatase inhibitors

Aromatase enzyme regulates the last and rate limiting step in estrogen synthesis. Aromatase enzyme is found in higher concentration in women with endometriosis. Even after surgical and medical managements, it has been observed that patients still continue to have pain. Continued local oestrogen production may in part be responsible for resistance to medical therapy. Women who have failed surgical and medical management with other drugs may benefit from aromatase inhbitors. It has been studied that 6 months treatment with aromatase inhibitors may relief pain in resistant cases of endometriosis.[9]

Anastrazole taken in combination with other drugs used in medical management of endometriosis has been seen to have more promising result especially in reducing pelvic pain. Anastrazole used in combination with oral contraceptive pills[9] and with norethisterone acetate[10] has been found to reduce pelvic pain more efficaciously than using either of the drugs alone. The side effects of anastrazole are relatively few. It is associated with headache, nausea and diarrhoea. Proloned use carries a risk of hypoestrogenic symptoms like hot flushes and osteoporosis.

Future Research

A role of statins and pentoxifylline requires further research. Statins have been used in lowering cholesterol level in the body. Apart from decreasing cholesterol levels it also has anti- inflammatory, antiangiogenic, antioxidant properties which makes statins a potential agent for further research for use in endometriosis.

Pentoxifylline is a tumour necrosis factor alpha inhibitor, works as an immunomodulator and has been seen to improve visual analog pain scores in 2 to 3 months[11], however it may not improve the fertility outcome in women with endometriosis.

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CASE APPROACH

Hyperemesis Gravidarum

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Introduction

Nausea and vomiting in pregnancy (NVP) are common symptoms affecting up to 80% of pregnant women but these are mostly self limiting and resolve by 16-20 weeks' of gestation. Hyperemesis gravidarum (HG) can be defined as intractable vomiting associated with more than 5% of pre-pregnancy weight loss, dehydration, electrolyte disturbances, or need for hospital admission. This affects 0.3-3.6% of all pregnancies[1].

There is a high risk of recurrence of HG in subsequent pregnancies. Up to 20 percent of those hospitalized in a previous pregnancy for hyperemesis will again require hospitalization[1]. There could be an ethnic or familial predilection[1,2].

The etiopathogenesis of HG is multifactorial. It has a relation to high or rapidly rising serum levels of pregnancy-related hormones. Putative culprits include human chorionic gonadotropin (hCG), estrogens, progesterone, leptin, placental growth hormone, prolactin, thyroxine, and adrenocortical hormones.[3]

Diagnosis

The patient with HG is usually exhausted, requires hospitalisation, close monitoring and parenteral therapy. Diagnosis is not difficult with full-blown symptoms, but a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index may be beneficial to assess the severity and therefore guide the management[1]. Ultrasound of the pelvis may reveal the presence of multiple or molar pregnancies-, both of which may lead to HG.

Features in the history, examination and investigations to monitor severity and other causes (RCOG)

History

- Previous history of NVP/HG
- Quantify severity using PUQE score: nausea, vomiting, hyper-salivation, spitting, loss of weight, inability to tolerate food and fluids, effect on quality of life
- History to exclude other causes: – Abdominal pain
  - Urinary symptoms
  - Infection
  - Drug history

Examination

- Vitals monitoring
- Oxygen saturation
- Signs of dehydration
- Body Weight
- Abdominal examination
- Signs of hypokalemia (muscle weakness), hypocalcemia (Chvostek's or Trousseau's sign) or thyrotoxicosis
- Other examination as guided by history

Investigations:

- Complete blood count
- Urea and electrolytes, Calcium, Phosphate
- Blood glucose monitoring: – exclude diabetic ketoacidosis if diabetic
- Midstream Urine Analysis (to rule out infections) and Urine dipstick: – quantify ketonuria
- Ultrasound scan: – confirm viable intrauterine pregnancy – exclude multiple pregnancy and trophoblastic disease
- In refractory cases or if there is history of previous admissions, check:
  - TFT: hypothyroid/hyperthyroid
  - LFTs: exclude other liver disease such as hepatitis or gallstones, monitor malnutrition
  - calcium and phosphate
  - amylase: exclude pancreatitis
  - ABG: exclude metabolic disturbances to monitor severity

(ABG arterial blood gas; LFTs liver function tests; TFTs thyroid function tests).

Modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index[1]

Total score is sum of replies to each of the three questions. PUQE-24 score: Mild ≤ 6; Moderate = 7-12; Severe = 13-15.

Motherisk PUQE-24 scoring system					
In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
In the last 24 hours have you vomited or thrown up?	7 or more times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	I did not throw up (1)
In the last 24 hours how many times have you had retching or dey heaves without bringing anything up?	No time (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)

PUQE-24 score: Mild ≤ 6; Moderate = 7-12; Severe = 13-15

How many hours have you slept out of 24 hours? _____ Why _____

On a scale of 0 to 10, how would you rate your wellbeing? _____

0 (worst possible) → 10 (the best you felt before pregnancy)

Management

Women with mild NVP should be managed at home with antiemetics. Ambulatory day care management should be used for suitable patients when home/primary care measures have failed and where the PUQE score is less than 13.

American College of Obstetricians and Gynecologists (2015) recommends hospitalization if vomiting persists after rehydration and failed outpatient management.

Criteria for Hospitalisation:

- continued nausea and vomiting not controlled on oral antiemetics OR
- continued nausea and vomiting associated with ketonuria and/or weight loss (greater than 5% of body weight) OR
- confirmed or suspected comorbidity (such as urinary tract infection and inability to tolerate oral antibiotics).

Management of the patient may be divided into:

- Diet
- Fluid therapy
- Antiemetics
- Vitamins
- Complementary therapies and Non-pharmacological measures.
- Psychological support

Weight of the patient, and electrolytes and ketonuria should be checked every day. Return of appetite is a good signal to begin oral intake and as soon as the patient tolerates food orally, parenteral treatment may be stopped.

Diet

Modification of the amount and size of meals consumed throughout the day may help relieve symptoms. Having smaller amounts of food and fluids more often can help prevent mild cases of nausea and vomiting from worsening. The meals should contain more carbohydrate than fat and acid.[1]Protein-rich meals also decrease symptoms. Drinks that contain electrolytes and other supplements are advised. If certain foods or food preparations trigger nausea, they should be avoided.

Fluid Therapy

Following hospitalisation, the first attempt should be towards correction of fluid loss and electrolyte imbalance.

Rehydration therapy (RCOG 2016)

- There is no evidence to determine which fluid regimen is most appropriate but as most women admitted to hospital with HG are hyponatraemic, hypochloraemic, hypokalaemic and ketotic, normal saline with potassium chloride (depending on serum potassium levels) is the most appropriate intravenous hydration.
- Dextrose infusions are not appropriate[4] unless the serum sodium levels are normal and thiamine (100mg thiamine) has been administered).
- Dextrose solution can precipitate Wernicke's encephalopathy in thiamine-deficient states.

Antiemetics

A Cochrane review[5] and other systematic reviews and meta-analyses[1] have reported on the safety and efficacy of many antiemetics for use in NVP and HG, with no increased risk of teratogenesis or other adverse pregnancy outcomes. Combinations of different drugs should be used in women who do not respond to a single antiemetic. For women with persistent or severe HG, the parenteral or rectal route may be necessary and more effective than an oral regimen.

Classification of drugs used for antiemetic therapy

First line	**Antihistamines**	Doxylamine[a]
		Cyclizine[b]
		Promethazine[c]
		Dimenhydrinate[c]
	Antipsychotics (Phenothiazines)	Prochlorperazine[c], Chlorpromazine[c]
Second line	**Dopamine Antagonists**	Metoclopramide[b], Domperidone[b]
	Serotonin Antagonists	Ondansetron[b]
Third line	**Corticosteroids**	Hydrocortisone[c], Prednisolone[c]

[a] Food and Drug Administration Category A; [b] Food and Drug Administration Category B;

[c] Food and Drug Administration Category C

1. Antihistamines: These are usually the first-line drugs for treatment[6,7].

   Doxylamine: It is a first generation antihistamine. Food and Drug Administration (2013) approved a combination of doxylamine10 mg and pyridoxine 10 mg. It has been proven safe and effective[8,9]. The usual dose is two tablets orally at bedtime. Additional doses, one in the morning and mid afternoon may be added whenever required for complete relief (max upto four times daily).

   Promethazine: Another first generation antihistamine. Common side effects include confusion and sleepiness and sedation

   Dose:12.5–25 mg 6–8 hourly Orally, IM or IV

   In a recent study, promethazine and metoclopramide were found to have similar therapeutic effects and the latter was tolerated better by the patients[10].

2. Antipsychotics: Prochlorperazine and Chlorpromazine, both are dopamine (D_2) receptor antagonist that belongs to the Phenothiazines class of antipsychotic agents. This D_2 blockade results in antipsychotic, antiemetic and other beneficial effects.

   Dose: 5-10 mg 6 hourly orally, IM or IV; 25 mg per rectally.

3. Metoclopramide: This is a Dopamine Receptor Antagonists. It is safe and effective, but because of

the risk of extrapyramidal effects it should be used as second-line therapy. Drug-induced extrapyramidal symptoms and oculogyric crises can occur with the use of phenothiazines and metoclopramide. If this occurs, there should be prompt cessation of the medications. Dose: 5-10 mg 8 hourly orally, IV or IM (maximum 5 days' duration).

4. Ondansetron: Serotonin antagonists are most effective for controlling chemotherapy-induced nausea and vomiting[11]. Their use in pregnancy is limited, but these drugs appear to be safe[8]. It was slightly more effective than a combination of doxylamine and pyridoxine in a randomized trial[12]. Its side effects include potential maternal effects from prolonged QT-interval and serotonin syndrome[9]. Dose: 4-8 mg 6-8 hourly PO; 8 mg over 15 minutes 12 hourly IV.
5. Corticosteroids: ACOG (2015) does not routinely recommends steroids for the management of HG because of their teratogenic effects.

   Steroids deserve attention as a last attempt to control the symptoms and to prevent deterioration and not be used until conventional treatment with intravenous fluid replacement and other antiemetics are ineffective. The suggested dose is intravenous hydrocortisone 100 mg twice daily, and once clinical improvement occurs convert to oral prednisolone 40–50 mg daily, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached.
6. Diazepam : It is not recommended for the management of HG. Its use may be reserved for intractable cases as it is a class D drug

Vitamins

1. Pyridoxine: It has been widely used against nausea and HG in combination with doxylamine. Pyridoxine alone is not recommended for NVP and HG (RCOG). A Cochrane review[5] concluded that there is a lack of consistent evidence that pyridoxine is an effective therapy for NVP.
2. Thiamine: It should be routinely supplemented in patients with protracted vomiting especially to prevent Wernicke's encephalopathy[13]. With this encephalopathy, an abnormal electroencephalogram (EEG) may be seen, and usually there are findings on MR imaging[14]. At least three maternal deaths have been described, and long-term sequelae include blindness, convulsions, and coma[15]. Pregnant women require a total of 1.5 mg/day. If this cannot be taken orally, 100 mg of thiamine may be diluted in 1000 mL of normal saline and infused at the maintenance rate desired for adequate hydration of patient.

Complementary therapies and other Non-Pharmacological measures

1. Ginger: It may be used in mild to moderate NVP. The effectiveness of ginger is because of its aromatic, carminative, and absorbent effects. It acts on the GI tract to increase motility, and its absorbent property may decrease stimuli to the chemoreceptor zone in the medulla that sends stimuli to the emetic center of the brain stem. Ginger also blocks the GI responses and consequent nausea feedback. In a study by Vutyavanich et al. the improvement in the nausea and vomiting of patients receiving ginger was significantly greater than that of the placebo group[16].

   No increased risk of major malformations has been reported with use of ginger[1]; however, one review[1] highlighted potential maternal adverse effects, including an anticoagulant effect, stomach irritation and a potential interaction with beta blockers and benzodiazepines.
2. Acustimulations – acupressure and acupuncture: In addition to standard treatment, acupuncture to PC6 (Pericardium 6 point), which is the point 5 cm proximal to the wrist crease on the palmar side of the forearm between the tendons of palmaris longus and flexor carpi radialis, could quicken the resolution of hyperemesis[17]. Acupressure may improve NVP. These are safe in pregnancy[1].

Psychological support: It is an important issue and should not be omitted[1]. If associated psychiatric and social factors contribute to the illness, the woman usually improves remarkably while hospitalized[1].

Role of Thromboprophylaxis

- Increased risk of Venous thromboembolism (VTE) due to dehydration and immobilization in hospitalized pts.
- Low Molecular Weight Heparin should be given if the risk factor score for VTE is 3 or more.

Women admitted with HG should be offered thromboprophylaxis with low-molecular-weight heparin (LMWH) unless there are specific contraindications such as active bleeding. It can be discontinued upon discharge.

Role of Enteral (Nasogastric feeding) and Total Parenteral Nutrition

In the small percentage of women who continue to have recalcitrant vomiting, consideration is given for enteral nutrition. Stokke et al. (2015)[1] described successful use of nasojejunal feeding for up to 41 days in 107 such women. A randomized trial failed to show any advantages from early enteral feeding.[20]

Only a very few women will require parenteral nutrition[1]. In a study of 599 women, by Peled et al. (2014)[21] reported that 20% required central venous access to be established for nutrition. TPN shifted the patients from a catabolic state to an anabolic state and improved their nutritional status. This method, however, does have associated risks.

Differential Diagnosis

With persistent vomiting after hospitalization, appropriate steps should be taken to exclude possible

underlying diseases as a cause of hyperemesis. Other potential causes include gastroenteritis, cholecystitis, pancreatitis, hepatitis, peptic ulcer, and pyelonephritis. In addition, severe pre- eclampsia and fatty liver are more likely after mid pregnancy.

Complications of Hyperemesis Gravidarum

Maternal:

- Weight loss and dehydration
- Electrolyte abnormalities
  - Hyponatremia (leading to headache, lethargy, seizures) OR overzealous correction of hyponatremia which can lead to central pontine myelinolysis
  - Hypokalemia (skeletal muscle weakness and cardiac arrhythmias)
- Acute kidney injury
- Vitamin Deficiencies

Vitamin B1 deficiency- Wernicke's encephalopathy

Vitamin K deficiency- Hypoprothrombinemia

- Vitamin B12 & B6 deficiency-Anemia and peripheral neuropathies
- Diaphragmatic rupture
- Esophageal rupture—Boerhaave syndrome (Oesophageal gastroduodenoscopy is safe in pregnancy[1] and indicated if there is haematemesis or severe epigastric pain).
- Mallory-Weiss tears
- Post Traumatic stress disorder and depression [18]

Fetal Complications: Fetal Growth Restriction and prematurity[18,19]

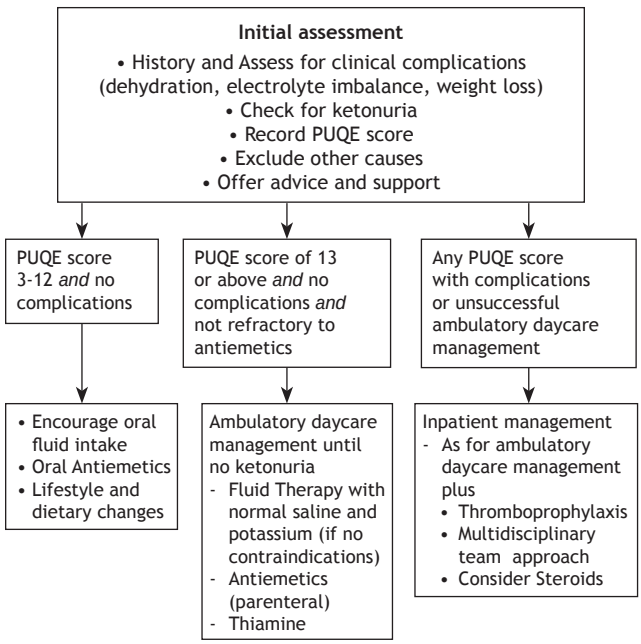
Discharge and follow-up: Women with severe NVP or HG who have continued symptoms into the late second or the third trimester should be offered serial scans to monitor fetal growth. With treatment, most women will respond well and may be sent home with antiemetic therapy. The readmission rate is 25-35 percent in most prospective studies, symptoms may relapse in these women, and some go on to develop posttraumatic stress syndrome[22]. For some women, hyperemesis can be an indication for elective termination[1].

Summary: Nausea and vomiting in pregnancy are common, but they are mostly self limiting. Women need reassurance and support. In a subset of women, symptoms can be severe and hyperemesis gravidarum can develop. It is usually seen in 1/200 pregnancies, but previous hyperemesis gravidarum increases risk rate to 15%. Most of the patients with hyperemesis gravidarum require hospitalisation: Fluid therapy, correction of electrolyte imbalance, antiemetic agents and vitamins are the usual treatment modalities. Early treatment may be necessary to avoid maternal metabolic disturbances which may affect the fetus. Finally, Hyperemesis gravidarum has remained and will keep on remaining as a challenging problem, but this tough time of early gestation may be overcome by careful medical and psychological support.

Key Points:

- Antihistamines (H1 receptor antagonists) and phenothiazines are first line antiemetics.
- Metoclopramide and Ondansetron are second line therapies.
- Normal saline with KCL should be ideal IV fluid for hydration.
- Thiamine supplementation should be given to all women admitted with prolonged vomiting.
- Ginger found to significantly improve symptoms of hyperemesis.
- Women with HG who are admitted to hospital should receive thromboprophylaxis with LMWH unless contraindicated.
- Helicobacter pylori infection should be considered when the patient does not respond to usual treatments; early pregnancy is not a contraindication for endoscopic diagnosis.
- With severe hyperemesis, more invasive measures have been shown to improve symptoms.

Treatment algorithm for NVP and HG (RCOG Green-top Guideline No. 69)



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Journal Scan

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Expert Opin Pharmacother. 2017 Sep;18(13):1391-1397. doi: 10.1080/14656566.2017.1359258. Epub 2017 Jul 28

Efficacy of Elagolix in the Treatment of Endometriosis

Alexandra Perricos &René Wenzl

Introduction

Much research has gone into developing medications that can be used to alleviate endometriosis-associated symptoms. In addition to already established medications, a new GnRH antagonist, elagolix, is in development. The novelty of this drug compared to other GnRH antagonists, is its nonpeptide structure, allowing it to be administered orally.

Areas Covered

We analyzed several Phase I, II and III clinical trials that have evaluated the safety and efficacy of this new medication.

Expert Opinion

Since many medications have been put on the market and have gained popularity for the treatment of endometriosis-associated symptoms, the demonstration of equality or superiority of effect, tolerability, as well as patient compliance should be assessed when introducing a new drug. While elagolix may have an advantage over established GnRH agonists, in that it does not lead to a 'flare-up' effect, it too, takes a toll on bone mineral density. Nevertheless, studies have shown that this new oral GnRH antagonist is well tolerated, and the side effects have been described as 'mild or moderate'. However, in order to examine whether elagolix can compete with or even surpass established gold-standard medical treatments in this field, further studies that directly compare elagolix to said treatments, might be necessary.

Editor's Comments

GnRH antagonist have not been extensively used in endometriosis. It has the distinct advantage over GnRH agonist i.e. no flare up effects. Oral route of administration of this drug will increase compliance to its use.

Gynecol Obstet Fertil Senol. 2018 Mar; 46(3):267-272. doi: 10.1016/j.gofs.2018.02.028. Epub 2018 Mar 3.

Medical Treatment for the Management of Painful Endometriosis without Infertility: CNGOF-HAS endometriosis guidelines

Sauvan M, Chabbert-Buffet N, Canis M, Collinet P, Fritel X, Geoffron S, Legendre G, Wattier JM, Fernandez H.

Objective

To provide clinical practice guidelines for the management of painful endometriosis in women without infertility.

Methods

Systematic review of the literature literature since 2006, level of evidence rating, external proofreading and grading of the recommendation grade by an expert group according to HAS methodology.

Results

Combined hormonal contraceptives (COP) and the levonorgestrel-releasing intra-uterin system (LNG-IUS) are recommended as first-line hormonal therapies for the treatment of painful endometriosis (grade B). Second-line therapy relies on oral desogestrel microprogestative, etonogestrel-releasing implant, GnRH analogs (GnRHa) and dienogest (grade C). It is recommended to use add-back therapy containing estrogen in association with GnRHa (grade B). After endometriosis surgery, hormonal treatment relying on COP or LNG-IUS is recommended to prevent pain recurrence (grade B). COP is recommended to reduce the risk of endometrioma recurrence after surgery (grade B) but the prescription of GnRHa is not recommended (grade C). Continuous COP is recommended in case of dysmenorrhea (grade B). GnRHa is not recommended as first line endometriosist reatment for adolescent girl because of the risk of bone demineralization (grade B). The management of endometriosis-induced chronic pain requires an interdisciplinary evaluation. Physical therapies improving the quality of life such as yoga, relaxation or osteopathy can be proposed (expert agreement). Promising medical alternatives are currently under preclinical and clinical evaluation.

Editor's Comment

When fertility is not an issue, the first line of medical management for pain in endometriosis is combined hormonal contraceptive pill or LNG-IUD. Progestogens have been used in different formulations like oral, injectable, lintrauterine system or implants, however LNG-IUS is preferred method since it is a long acting device which is locally active and has less metabolic side effects.

Lancet. 2016 May 21;387(10033):2117-2124.doi: 10.1016/S0140-6736(16)00548-1. Epub 2016 Mar 2.

Nifedipine Versus Atosiban for Threatened Preterm Birth (APOSTEL III): A multicentre, randomised controlled trial

Van Vliet EOG, Nijman TAJ, Schuit E, Heida KY, Opmeer BC, Kok M, Gyselaers W, Porath MM, Woiski M, Bax CJ, Bloemenkamp KWM, Scheepers HCJ, Jacquemyn Y, Beek EV, Duvekot JJ, Franssen MTM, Papatsonis DN, Kok JH, Van der Post JAM, Franx A, Mol BW, Oudijk MA

Background

In women with threatened preterm birth, delay of delivery by 48 h allows antenatal corticosteroids to improve neonatal outcomes. For this reason, tocolytics are often administered for 48 h; however, there is no consensus about which drug results in the best maternal and neonatal outcomes. In the APOSTEL III trial we aimed to compare the effectiveness and safety of the calcium-channel blocker nifedipine and the oxytocin inhibitor atosiban in women with threatened preterm birth.

Methods

We did this multicentre, randomised controlled trial in ten tertiary and nine teaching hospitals in the Netherlands and Belgium. Women with threatened preterm birth (gestational age 25-34 weeks) were randomly assigned (1:1) to either oral nifedipine or intravenous atosiban for 48 h. An independent data manager used a web-based computerised programme to randomly assign women in permuted block sizes of four, with groups stratified by centre. Clinicians, outcome assessors, and women were not masked to treatment group. The primary outcome was a composite of adverse perinatal outcomes, which included perinatal mortality, bronchopulmonary dysplasia, sepsis, intraventricular haemorrhage, periventricular leukomalacia, and necrotising enterocolitis. Analysis was done in all women and babies with follow-up data. The study is registered at the Dutch Clinical Trial Registry, number NTR2947.

Findings

Between July 6, 2011, and July 7, 2014, we randomly assigned 254 women to nifedipine and 256 to atosiban. Primary outcome data were available for 248 women and 297 babies in the nifedipine group and 255 women and 294 babies in the atosiban group. The primary outcome occurred in 42 babies (14%) in the nifedipine group and in 45 (15%) in the atosiban group (relative risk [RR] 0·91, 95% CI 0·61-1·37). 16 (5%) babies died in the nifedipine group and seven (2%) died in the atosiban group (RR 2·20, 95% CI 0·91-5·33); all deaths were deemed unlikely to be related to the study drug. Maternal adverse events did not differ between groups.

Interpretation

In women with threatened preterm birth, 48 h of tocolysis with nifedipine or atosiban results in similar perinatal outcomes. Future clinical research should focus on large placebo-controlled trials, powered for perinatal outcomes.

Emerg Med J. 2018 Jun;35(6):345-349. doi: 10.1136/emermed-2017-207120. Epub 2018 Feb 21.

qSOFA, SIRS and NEWS for Predicting in Hospital Mortality and ICU Admission in Emergency Admissions Treated as Sepsis

Robert Goulden, Marie-Claire Hoyle, Jessie Monis, Darran Railton, Victoria Riley, Paul Martin, Reynaldo Martina, Emmanuel Nsutebu

Background

The third international consensus definition for sepsis recommended use of a new prognostic tool, the quick Sequential Organ Failure Assessment (qSOFA), based on its ability to predict in hospital mortality and prolonged intensive care unit (ICU) stay in patients with suspected infection. While several studies have compared the prognostic accuracy of qSOFA to the Systemic Inflammatory Response Syndrome (SIRS) criteria in suspected sepsis, few have compared qSOFA and SIRS to the widely used National Early Warning Score (NEWS).

Methods

This was a retrospective cohort study carried out in a UK tertiary centre. The study population comprised emergency admissions in whom sepsis was suspected and treated. The accuracy for predicting inhospital mortality and ICU admission was calculated and compared for qSOFA, SIRS and NEWS.

Scoring systems

SIRS criteria are defined as a heart rate >90 beats per minute, a respiratory rate >20 breaths per minute, a temperature <36°C or >38°C and a white blood cell count <4000/mm^3 or >12 000/mm^3. A positive score is defined as ≥2 out of 4.13 qSOFA criteria are a systolic blood pressure ≤100 mm Hg, a respiratory rate ≥ 22 breaths per minute and a Glasgow Coma Scale score<15. A positive score is defined as ≥2 out of 3.4 The NEWS score ranges from 0 to 20 and is based on respiratory rate, oxygen saturations, use of supplemental oxygen, temperature, systolic blood pressure, pulse rate and level of consciousness. A positive score is defined as ≥5 out of 20, the threshold suggested as representing a 'red score' indicative of significant physiological derangement.7

Results

Among 1818 patients, 53 were admitted to ICU (3%)

and 265 died in hospital (15%). For predicting inhospital mortality, the area under the receiver operating characteristics curve for NEWS (0.65, 95% CI 0.61 to 0.68) was similar to qSOFA (0.62, 95% CI 0.59 to 0.66) (test for difference, P=0.18) and superior to SIRS (P<0.001), which was not predictive. The sensitivity of NEWS≥5 (74%, 95% CI 68% to 79%) was similar to SIRS≥2 (80%, 95% CI 74% to 84%) and higher than qSOFA≥2 (37%, 95% CI 31% to 43%). The specificity of NEWS≥5 (43%, 95% CI 41% to 46%) was higher than SIRS≥2 (21%, 95% CI 19% to 23%) and lower than qSOFA≥2 (79%, 95% CI 77% to 81%). The negative predictive value was 88% (86%–90%) for qSOFA, 86% (82%–89%) for SIRS and 91% (88%–93%) for NEWS. Results were similar for the secondary outcome of ICU admission.

Conclusion

NEWS has equivalent or superior value for most test characteristics relative to SIRS and qSOFA, calling into question the rationale of adopting qSOFA in institutions where NEWS is already in use.

Key messages

What is already known on this subject

- Multiple studies have demonstrated that the quick Sequential Organ Failure Assessment (qSOFA) score has higher specificity but lower sensitivity than the Systemic Inflammatory Response Syndrome (SIRS) criteria for predicting adverse outcomes in sepsis.
- Only one previous study has compared these scores to the National Early Warning Score (NEWS).

What this study adds

- In this retrospective cohort of patients in whom sepsis was suspected and treated, NEWS had similar or superior values across most measures of prognostic accuracy compared with qSOFA or SIRS.
- This study calls into question the value of qSOFA in institutions where NEWS is already in use.

Editor's comment

SIRS, qSOFA and NEWS are used to identify women with sepsis at risk of poor outcome so that the resuscitative and management measures are intensified in women who are more critically ill. However, this study has been done in non pregnant population and hence there are limitations to its use as a predictive tool in pregnant woman. The vital parametres like PR, BP, RR are physiologically altered in pregnancy which may cause error in interpretation. NEWS appear to be have a better predictive value since it has included more parameters including O2 saturation. Clearly a multidisciplinary focused team with good clinical skills and frequent review of the patient's condition and management tailored to fit the condition will improve the outcome.

Clinical Proceedings of AOGD Clinical Meeting held at Dr Ram Manohar Lohia Hospital and PGIMER, New Delhi on 25th January, 2019

Management of Pseudohypoparathyroidism in Pregnancy

Mrinalini, Indu Chawla, Renuka Mallik, Anjum Ara

Pseudohypoparathyroidism is very rare and during pregnancy poses multiple challenges related to its monitoring and management. A primigravida (30yrs) diagnosed with pseudohypoparathyroidism at 22yrs of age presented to RML Obs/Gynae OPD at 5+5 wks of POG. She was managed by serial monitoring of serum calcium, phosphate and vitamin D with dose modification of Calcium and Vitamin D supplementation. Daily Calcium requirement increased from 1gm daily to 3.5gm daily. During her course of pregnancy, she developed Gestational hypothyroidism, GDM, IHCP and Gestational hypertension which was controlled and managed successfully. She had an elective caesarean section at 37+3wks POG for transverse lie. She had good maternal and perinatal outcome. Patient was discharged with advice to continue monitoring of S.Calcium, Phosphate, Vitamin D life long.

A Rare Case Presentation of Pseudo Meig Syndrome

Namita Chopra, P Singh, Sushma, Kamna Datta, Geetanjali

Adnexal masses represent a wide spectrum of gynecological disorders. Though we cannot undermine the value of clinical examination, the exact nature & extent of the disease can be made by imaging techniques & biochemical markers. A 40 years old female P_3 L_3, A_1, married for 21 years presented to OPD with pain abdomen for 6 months, shortness of breath, and abdominal distension for 4 months. Patient looked cachexic. On chest examination, there was decreased air entry on right side. Abdomen was grossly distended. Fluid thrill was present. On Per vaginum examination- size of uterus could not be made out due to tense ascites, bilateral fornices were full, no nodularity in POD. Ultrasound reported gross ascites & well defined heterogeneously hyperechoic solid cystic lesion in left adnexa 5.7x6.5x7 cm with internal vascularity on colour doppler. Right adnexa & uterus were normal. CA 125 levels were 2400 IU/ML. MRI revealed 6x 5.6 cm thick walled cystic lesion with mixed intensity with internal septation in left adnexa with multiple small para aortic lymph nodes & omental caking. Ascitic fluid was transudative & pleural fluid was exudative. Both were negative for TB PCR and malignant cells. CT PET revealed metabolically active solid cystic left ovarian mass with mild FDG uptake. Patient was planned for staging laparotomy with possibility of ovarian malignancy. Seven litres ascitic fluid was drained. There was 7x8 cm solid mass with small mucoid areas (with greenish jelly like substance) arising from left ovary, mobile with intact capsule, no adhesions, no vascularity. TAH with BSO with infracolic omentectomy was done. Histopathology revealed acini filled with colloid and lined by cuboidal epithelium with eosinophilic cytoplasm with surrounding normal ovarian parenchyma. TTF (Thyroid transcription factor) was positive with findings suggestive of STRUMA OVARII. Follow up scans at 3 weeks showed complete resolution of fluid accumulation. The final diagnosis was Pseudo Meig Syndrome with Struma ovarii. Only 10-11 cases have been reported till now. Such benign effusions resolve spontaneously after resection of tumor, as in present case. TFT is normal in majority. Only 8% of cases develop hyperthyroidism. Raised CA 125 has been associated with Pseudo Meigs in 5% of the cases, as in the present case. It was a confounding factor in the diagnosis with utility only in follow up. Definitive diagnosis of Struma ovarii relies on histopathology and immunohistochemistry. Management is unilateral salpingo-oophorectomy for young patients & total hysterectomy with bilateral salpingoophorectomy in elderly patients.

The aggressive clinical course & radiological indicators pointing towards malignancy eventually surfaced as Pseudo Meig Syndrome, a benign condition. It should be considered a differential while evaluating adnexal mass with third space fluid collection.

Atypical Manifestation of Dengue Fever Complicating Pregnancy- Dengue encephalopathy

Priyanka Bhadana, Alka Goel, Veena Ganju Malla, Poonam Yadav, Preeti Sania

Dengue viral infections represent a significant burden of disease and is increasingly being recognized in pregnancy. Disease spectrum is varied and may include wide range of neurological features, noted in 0·5–21%. Among the neurologic manifestations, acute encephalopathy is the most frequent manifestation, and although previously

thought to be non-encephalitic, increasing evidence of dengue viral neurotropism has been suggested. We report a rare case of dengue encephalopathy in pregnancy.

Patient, a booked case, 34 years old G4P1L1A2 with 36weeks 6 days period of gestation with previous LSCS done for obstructed labour and GDM controlled on diet, presented with history of high grade fever (103°F) of two days duration with myalgia, chills and sore throat. She developed irritability, somnolence, aggressive behaviour and altered sensorium a day after fever subsided. Patient was afebrile, confused, poorly responsive to commands(GSC=9) with no signs of meningism. Cranial nerves were intact. Pyramidal and extrapyramidal signs were absent. Dilated fundoscopy did not reveal any papilledema. Respiratory, cardiovascular and obstetric examination were unremarkable and NST was reactive. Profound thrombocytopenia and mild derangement of liver function tests with positive NS1 antigen and serology for Dengue with EEG changes was noted. A diagnosis of suspected Dengue encephalopathy with live term pregnancy was made in consultation with physician. In the absence of any definitive evidence based management protocol for this rare presentation, and in view of a grave prognosis for mother and non improvement of neurological symptoms over next 48 hours, decision to terminate pregnancy was taken in consultation with neurologist, senior physician and relatives. Emergency LSCS was done under GA after 6 platelet transfusion and 4 FFP. Patient delivered a 3kg baby girl with apgar score-7,9. Patient shifted to ICU for intensive monitoring. She had resolution of neurological symptoms by postoperative day 3 and was discharged on day 10 along with baby with no residual symptoms. Baby had grade 1 HIE. NS1 and dengue serology of baby on day 1 and 10 was negative. USG cranium on day 10-normal.

Dengue encephalopathy is an uncommon condition with no definitive evidence based treatment modality available at present. Further evidence based multidisciplinary studies are needed for diagnosis and management protocols with regard to this rare entity in pregnancy to prevent adverse feto-maternal outcome.

Association of Obstetricians & Gynaecologists of Delhi

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RCOG UK Franchise MRCOG Final Preparation: Part III Written Course

Sunday 17th – Monday 18th March 2019 (Total 2 Days)

Limited to 56 candidates only (First Come First Serve basis)

Overview

This Part 3 Clinical Skills Course will give delegates a unique opportunity to practice and rehearse the clinical tasks set down in the new MRCOG Part 3 oral examination. There will be two different circuits, each with 14 active stations where you will receive individual feedback after each of the tasks from the examiners, some of which will use local role players and lay examiners.

There will also be workshop-based sessions incorporating communication skills with patients and colleagues, issues of patient safety, applied clinical knowledge and information gathering using different task materials to increase the delegate's exposure to more questions.

Videos of different tasks types will be presented and discussed.

After the examination, we plan to send the delegates a feedback survey to help maintain and improve the quality of this course for the future.

Before attending the course be: Read your 14 core curriculum, StratOG, Green-top guidelines, Scientific Impact Papers, Consent Advice, Good Practice, TOG, & BJOG. Read Ed Neale's book on Part 3- "Part 3 MRCOG, Your Essential Revision Guide" Lisa Joels & Edmund Neale"

MRCOG Part 3 examination will be conducted in Delhi 29-30 April 2019

Who should attend?

- Candidates who have passed the MRCOG Part 2 written examination and plan to sit the next MRCOG Part 3 Examination

Learning objectives

- To describe the structure and format of the MRCOG Part 3 examination
- To reproduce the components parts of the blueprint matrix of the MRCOG Part 3
- To relate the five clinical skills domains to clinical situations from the 14 modules of the MRCOG Part 3 Syllabus at an ST5 level of competence
- To identify personal strengths and weaknesses in the clinical skills domains exposed during the course, identify good and unsatisfactory performances
- To reflect on how to improve individual performances prior to the examination

Course Fee: Rs 45,000

Venue - Sant Parmanand Hospital
18 Sham Nath Marg, Civil Lines, Delhi- 110054

UK Conveners of International Part 2 Revision Course -
UK Course Organizer & Convener - Dr Sanjeev Sharma/ Dr Jyotsna Acharya

India Conveners and Contacts for details - Dr Nirmala Agarwal (n.menoky@gmail.com / 9811888732)
Dr Arbinder Dang (arbidang@gmail.com 9871356917)

For Accommodation, Hotel Bookings, Travel Enquiry Contact Miss Carolina Fernandez Cox & Kings +919711992043/ Carolina.fernandes@cox&kings.com

Certificate of attendance for this course will be provided by the RCOG UK

Registration Guidelines (Online registration available on website)

- Registration form to be downloaded from website **www.aiccrcognzindia.com**
- Bank Transfer or Demand Draft must be made in favour of "RCOG NZ 2012 Plus" payable at New Delhi. (Cheques not accepted).
- There will be no refunds on cancelation.
- Registration request along with Demand Draft to be posted to the Secretariat mailing address as given below:-

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