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SOCIETY OF OBSTETRIC MEDICINE OF AUSTRALIA AND NEW ZEALAND

The SOMANZ

Position Statement for the Investigation and Management of Sepsis In Pregnancy

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These are the recommendations of a hospital based multidisciplinary working party convened by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ). They reflect the current medical literature and the clinical experience of members of the working party. This Position Statement replaces the SOMANZ Guidelines for the Investigation and Management of Sepsis in Pregnancy published in 2017.1

Throughout this document we refer to the pregnant person primarily as mother or woman and use the pronouns she/her but acknowledge that not all those who are pregnant identify as mother or woman and may use other pronouns.

When we use the term pregnancy we are referring to all forms of gestation whether they are viable or not.

Short Title: SOMANZ Sepsis Position Statement

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1) Evidence was sought from MEDLINE, EMBASE and PUBMED searches and based on an extensive review of this literature, a fully referenced position statement was written. The quality of evidence was evaluated and the recommendations made according to NHMRC principles. However, a formal NHMRC process to grade the evidence was not undertaken. Where the group assessed there was insufficient evidence, the expert opinion of the position statement group was sought, and agreement reached by majority opinion, with this distinction included in this paper.

2) The authors form a hospital-based multi-disciplinary team

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Summary of Recommendations and Audit Points for Implementation

This clinical position statement addresses the issue of sepsis in pregnancy (we refer to all forms of pregnancy including miscarriage, ectopic and termination of pregnancy) and the peri-partum period. It contains recommendations to guide clinical practice and improve patient outcomes. We have identified several key outcomes that can be audited allowing individual centres to assess their performance in implementation of this position statement.

Assessment of sepsis

Numerous measures can be used to screen for sepsis. In addition, assessment for end organ dysfunction should be undertaken. Consideration needs to be given to the altered physiology of pregnancy.

- Screen for sepsis using standardized maternal observation charts where possible or standard observation charts where not possible.
- Consider sepsis in any pregnant or postpartum patient with abnormal vital signs (fever, increased respiratory rate, hypoxia, hypotension, tachycardia, altered consciousness and/ or risk factors for sepsis, see table 2 Chapter 2 for normal pregnancy ranges per trimester
- Assess for any evidence of end organ dysfunction by reviewing for signs such as oliguria or by using obstetrically modified sequential organ failure assessment (omSOFA) score (increase >2)
- Septic shock is a complication of sepsis and is diagnosed when, despite adequate fluid resuscitation, there is hypotension and a requirement for vasopressors. It is associated with an elevated serum lactate and has increased mortality.

Audit point: What is the Incidence of sepsis as a proportion of all births?

Fever in pregnancy

- Anti-pyretics have a beneficial effect in reducing adverse pregnancy outcomes for patients experiencing fever in pregnancy, non-steroidal anti-inflammatory drugs should be used with caution.
- Up to 1:4 women will experience fever with epidural anaesthesia in labour, the mechanism is usually pro-inflammatory not infective, however investigations should proceed if the fever does not settle with simple analgesia.

Audit point: What proportion of pregnant patients presenting with fever are administered anti-pyretics?

Aetiology of sepsis

The etiology of sepsis can be bacterial, viral or non-infective conditions mimicking sepsis.

- Maternal death from sepsis is most commonly caused by Group A streptococcal (GAS) infection.
- *E. Coli* is the commonest cause of maternal bacterial infection.
- Always consider that non-bacterial or non-infective conditions may mimic sepsis.

Audit point:
What is the prevalence of the different microorganisms causing sepsis?
What proportion of cases of sepsis are caused by GAS?

Investigations in sepsis

The type of investigations undertaken to establish the cause of sepsis are important. However, what is more important is that they occur in a timely manner.

- Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement of antimicrobial therapy; however, this should NOT delay administration of antibiotics or antivirals.
- Imaging should not be withheld because the patient is pregnant or breastfeeding.
- Be aware of pregnancy-appropriate normal ranges for investigations and observations.

Audit point:
What proportion of patients with suspected sepsis have blood cultures taken?
What proportion of patients have a microorganism identified from microbiological cultures or viral testing?

Timely Treatment: The golden hour

- All patients with suspected sepsis require prompt treatment, ideally within the first hour of presentation.
- Commence fluid resuscitation immediately to stabilize the mother.
- Administer empiric antibiotic therapy immediately and preferably within one hour.
- Do not wait for investigation results to commence treatment
- Do not wait for transfer to another setting to commence treatment
- Where the source of sepsis is identified, refine appropriate antibiotics.
- Consider the impact of the antibiotics on pregnancy and breastfeeding.

Audit point:

What proportion of patients were administered intravenous fluids within the first hour of the suspicion of sepsis?
What proportion of patients with sepsis were administered empiric antibiotics within the first hour?
What proportion of patients were administered anti-viral medication?

Fetal surveillance

It is important to consider the wellbeing of the fetus whilst treating the patient with sepsis.

- Consider the most appropriate method of monitoring fetal wellbeing during maternal sepsis. e.g. cardiotocography, Doppler heart rate monitoring, ultrasound
- If preterm viable delivery is required, corticosteroids should be considered for fetal indications. Sepsis is not a contra-indication to antenatal corticosteroids for the purpose of fetal lung maturation.
- The onset of chorioamnionitis may be non-specific or insidious, but rapid deterioration is common. Chorioamnionitis requires urgent delivery on both maternal and fetal grounds.
- Preterm delivery may be required for either maternal or fetal indications.

Audit point:

What proportion of fetuses of a suitable gestation (greater than 24 weeks) were assessed with electronic fetal monitoring whilst treating patients with sepsis? (Local practices will determine the lower limit of the gestation at which electronic fetal monitoring should be instigated)
What proportion of women received antenatal corticosteroids prior to preterm birth?

Emergency Department

- *Many pregnant and postpartum patients will present with deceptively benign symptoms such as diarrhea or sore throat as is the case with Group A Streptococcus (GAS).*
- Resuscitation commences in the emergency department, antibiotics and anti-virals should not be withheld because of pregnancy
- Imaging should not be withheld because of pregnancy.

Audit point:

What proportion of pregnant and postpartum patients with suspected sepsis presented to ED?
What proportion were recognized as potentially septic?

Anaesthetic care

- Neuraxial blocks in patients with untreated sepsis may be undertaken only after careful assessment, taking into consideration the increased risk of complications in the short and long term.
- Pregnant women with sepsis may experience increased hemodynamic instability during anaesthesia.
- Anaesthesia during pregnancy in a woman with sepsis does not increase mortality but may be associated with other adverse obstetric events.

Audit point:

What proportion of pregnant patients with sepsis undergo anaesthetic consultation?
What proportion of pregnant patients with sepsis, receive neuraxial blockade?
What proportion of septic pregnant patients develop complications from neuraxial blockade, in particular hemodynamic and neurological complications?

Intensive care issues

In a primary care setting, arrange urgent transfer to hospital. Empirical treatment with antibiotics can be started in primary care.

In a hospital setting, intensive care support may be required for patients with severe sepsis.

- Liaise early with intensive care if the patient has cardiorespiratory compromise (including tachypnea/hypoxia), evidence of end organ dysfunction or hypoperfusion.
- There is a paucity of data regarding the resuscitation of pregnant women in the intensive care unit. The preferred fluid is an isotonic crystalloid.
- Admit to ICU when:
    - Despite adequate fluid resuscitation there is ongoing haemodynamic instability with evidence of systemic hypoperfusion (e.g. an elevated lactate)
    - Organ supports such as ventilation or circulatory support are being considered.

Audit point:
What proportion of pregnant/postpartum patients with sepsis require intensive care admission?
What proportion of patients with evidence of end-organ dysfunction secondary to sepsis are referred to intensive care?

Midwifery/nursing care

- Generate a multi-disciplinary, woman-centered care plan.
- Define the scope of practice for midwives caring for septic patients.
- Facilitate and support breastfeeding where possible.
- Liaise with a woman's General Practitioner – including providing a comprehensive clinical transfer of care on discharge

Abbreviations

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ALT	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
ARDS	Adult Respiratory Distress Syndrome
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
AUC	Area under the curve (statistical)
BD	Twice daily
BMI	Body mass index
°C	Degrees Celsius
C/S	Caesarean section
CI	Confidence interval
CMV	Cytomegalovirus
COVID 19	Coronavirus Disease 2019 caused by SARS CoV 2
CNS	Central nervous system
CRP	C-reactive protein
CT	Computerised tomography
CTG	Cardiotocography
CXR	Chest X-ray
DD	Developmental delay
DILI	Drug induced liver injury
DVT	Deep vein thrombosis
eCART	Electronic cardiac arrest triage
ECMO	Extra-corporeal membrane oxygenation
ED	Emergency department
EFM	Electronic fetal monitoring
EGDT	Early goal-directed therapy
EGFR	Estimated glomerular filtration rate
ESBL	Extended spectrum beta lactamase producers
eTG	Electronic therapeutic guidelines
Fi02	Fraction of inspired oxygen
GAS	Group A streptococcus
GBS	Group B Streptococcus
GCS	Glasgow coma score
GGT	Gamma-glutamyl transferase
GRADE	Grading of recommendations assessment, development and evaluation
Hb	Haemoglobin
HCW	Health care worker
HIV	Human immunodeficiency virus
HR	Heart rate
HSV	Herpes simplex virus

Abbreviations

ICU	Intensive care unit
INR	International Normalised Ratio
IV	Intravenous
kg	Kilogram
L	Litre
LMWH	Low molecular weight heparin
MAP	Mean arterial pressure
MCS	Microscopy, culture and sensitivity
mg	Milligrams
mL	Millilitres
mmHg	millimetres of mercury
mmol/L	Millimoles per litre
MRSA	Methicillin resistant Staphylococcus aureus
NHMRC	National Health and Medical Research Council
NSAID	Non-steroidal anti-inflammatory drug
NSW	New South Wales
OR	Odds ratio
Pa02	Partial pressure of oxygen
PCR	Polymerase chain reaction
PCT	Procalcitonin
PPROM	Preterm premature rupture of membranes
omSOFA	Obstetrically modified Sequential Organ Failure assessment score
qSOFA	quick Sequential Organ Failure Assessment score
RAT	Rapid antigen test
RR	Respiratory rate
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment score
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
TB	Tuberculosis
Th1	T helper 1
TIN	Tubulo-interstitial nephritis
™	Trademark
TNFα	Tumour necrosis factor alpha
UH	Unfractionated heparin
UK	United Kingdom
U/L	Units per litre
µmol/L	Micromoles per litre
VZV	Varicella Zoster virus
WCC	White cell count
WHO	World Health Organisation

1. Introduction

SOMANZ published its first sepsis in pregnancy and the postpartum period guideline in 2017. This second edition position statement updates clinical practice with a review of the subsequent literature. In particular the definition and screening tools for the diagnosis of sepsis have changed during the intervening period. This position statement has abandoned the use of the qSOFA score to diagnose sepsis due to its poor performance in clinical practice[2, 3]. However, we do suggest its use to assess end organ dysfunction as it predicts the need for intensive care.

Despite an overall decline in maternal mortality in Australia, the maternal mortality rate from sepsis has remained stable at 0.6 per 100,000 in 2003-2005 to 0.6 per 100,000 in 2011 to 2020. In the period 2008-2012, sepsis accounted for 11.4% of all maternal deaths in Australia, more recent data indicates that the maternal mortality rate from sepsis in the decade of 2011-2020 was 10.3%, this is unlikely to reflect deaths from Covid 19 during the global pandemic declared by the WHO in March 2020[4]. Group A beta hemolytic streptococcal (GAS) infection remains the most deadly and aggressive pathogen resulting in up to 50% of maternal deaths from sepsis in Europe.[5] Sepsis continues to be one of the major causes of maternal mortality among Aboriginal and Torres Strait Islander women. Over the time period 2006 – 2018 in New Zealand infection accounted for 8.8% of direct maternal deaths[6].

Rapid recognition, early antimicrobials and involvement of senior staff remain essential factors to improving outcomes. Undifferentiated symptoms followed by sudden collapse characterise many deaths from sepsis in all reporting countries [7]. In Australia, the Clinical Excellence Commission developed the "Sepsis Kills" program to reduce poor outcomes from sepsis by improving recognition and management[8]. The majority of institutions have pre-existing pathway for management of sepsis, we recommend that specific maternal pathways still need to be created and implemented by individual institutions.

Sepsis can arise at any time during the antepartum (including with intact membranes), intrapartum and postpartum periods and is often associated with a delay in diagnosis. A number of factors contribute to this including the normal physiological changes of pregnancy that may mask early signs of sepsis [9,10]. Management plans need to consider the altered immunological response in the parturient [11]. Early recognition and timely treatment by any healthcare workers essential in the clinical management of sepsis in the obstetric patient.

The parturient also has a unique 'organ perfusion monitor' namely the fetus. Maternal sepsis with or without hemodynamic instability may present with fetal distress as the uteroplacental circulation is not auto-regulated [12]. Thus any maternal cardiovascular insufficiency may also result in compromised fetal perfusion.

2. Definition of Sepsis in Pregnancy

KEY POINTS

- **Consider sepsis in any pregnant woman presenting with abnormal vital signs**
- **Sepsis may be present with or without fever**
- **Sepsis may present without an obvious source of infection.**
- **Septic shock is a complication of sepsis and is diagnosed when, despite adequate fluid resuscitation, there is hypotension and a requirement for vasopressors. It is associated with an elevated serum lactate and has increased mortality. Assess for evidence of end organ dysfunction using omSOFA (increase ≥2) See Appendix 1**

The definition of sepsis has evolved over time and this is in part due to it being a syndrome rather than a specific illness. Despite significant advances, the pathophysiology of sepsis remains incomplete with no current gold standard diagnostic investigation existing.

Sepsis is broadly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[13]. It is this dysregulated response and subsequent organ dysfunction that differentiates sepsis from infection. Sepsis can occur at any time during pregnancy or in the early postpartum period. The clinical signs may be insidious until they become overwhelming. Therefore early detection of sepsis is essential to allow for appropriate multidisciplinary management to ensure the best outcomes for the mother and her baby. Septic patients can progress to develop septic shock.

Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities substantially increase mortality[13].

2.1 Recognition of the patient with sepsis

Considering sepsis as a differential diagnosis and recognising the patient has sepsis is paramount and is the first step in appropriate assessment and management. The clinical steps involved in the assessment and management of sepsis in pregnancy have been summarised in a flow chart (Appendix 2).

Sepsis must be considered in a pregnant woman presenting with any one of the following signs; fever, increased respiratory rate, hypoxia, hypotension, tachycardia or altered mentation. Pregnancy-specific vital sign reference ranges are provided in the table below[14]. Diarrhoea can also be a presenting symptom of sepsis in pregnancy, particularly for Group A Streptococcus. Any women presenting with symptoms of gastroenteritis and abnormal vital signs should be considered as having sepsis.

The previous version of this guideline recommended using omSOFA as a screening tool for sepsis. However, multiple studies have shown that qSOFA has poor sensitivity for morbidity from sepsis in the non-obstetric population[2, 3] and it is now recommended against as a single screening tool in international sepsis guidelines[15]. To date only one study has evaluated qSOFA in the obstetric population. This found that qSOFA had a sensitivity of 0.38 and specificity of 0.7 for severe maternal morbidity secondary to sepsis[16]. For this reason, this guideline no longer recommends qSOFA has a screening tool for sepsis in pregnancy.

Sepsis must be considered in a pregnant woman presenting with any one of the following signs; fever, increased respiratory rate, hypoxia, hypotension, tachycardia or altered mentation. Pregnancy-specific vital sign reference ranges are based on a range of historical data and statistical methods. The most comprehensive, prospective data was obtained by Green et al and is summarized in Table 2.1 below.

Table 2.1: Normal upper limits for HR, RR, BP in pregnancy Median/Mean [3rd,97th centile]

Median [3rd-97th centile]	12 weeks	19 weeks	34 weeks	40 weeks
Systolic BP	114 [95-138]	113 [95-136]	-	121 [102-144]
Diastolic BP	70 [56-87]	69 [55-86]	-	78 [62-95]
Heart rate	82 [63-105]	-	91 [68-115]	-
Temperature	36.7 [35.6-37.5]		36.6 [35.4-37.5]	

New Zealand have a national maternity observation chart, however in Australia there is no agreement across states and territories as to the normal range of maternal observations in pregnancy (Table 2.2).

Table 2.2: Maternity Specific Observation Charts Across New Zealand and Australian States and Territories, normal ranges

State or Territory	Heart Rate (beats/minute)	Blood pressure (mmHg)	Temperature (°C)	Respiratory Rate (breaths/minute)	Oxygen saturation (%)
Australian Capital Territory	50-99	90-139/50-89	36.0-37.4	9-20	=>95
New Zealand	60-99	100-139/40-88	36.0-37.9	10-20	=>95
NSW	50-119	90-139/50-89	36.0-37.4	10-25	=>95
Northern Territory	No specific territorial chart identified				
Queensland	50-99	100-139/60-89	36.0-37.4	13-20	=>95
South Australia	60-109	90-150/60-89	36.1-37.5	13-25	=>97
Tasmania	No specific state chart identified				
Victoria	50-109	90-139/not specified	36.0-37.4	10-19	=>95
Western Australia	No specific state chart identified.				

2.2 Definition of sepsis in pregnancy – using a modified SOFA score

Sepsis is broadly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[13]. In clinical practice any new sign or organ dysfunction should trigger deep concern, investigation and management. A scoring system that identifies patients with organ dysfunction due to an abnormal host response to infection can be valuable. Many scoring systems have been developed with most used in research rather than clinical management. In the non-pregnant population, the SOFA (Sequential (sepsis related) Organ Failure Assessment) score has been shown to reliably identify patients with a suspected infection who have a greater morbidity and mortality[17] (Table 2.3) and hence forms the basis of the current international consensus definition for sepsis. The elements involved in assessing organ dysfunction for the SOFA score are: coagulation, platelet count, liver function (bilirubin), cardiovascular system (mean arterial pressure (MAP) or presence and dose of inotropes and or vasopressors), neurological system (Glasgow Coma Scale: GCS), renal function (creatinine and urine output) and respiration (partial pressure of arterial oxygen(PaO_2)/ fraction of inspired oxygen(FIO_2))[18, 19]. Each parameter is scored from 0 to 4 –employing the worst available result for the day of assessment. Fever does not form part of the SOFA scoring system as it has been felt to not be indicative of a dysregulated response to sepsis. However, a fever in a pregnant woman **should** prompt the clinician to undertake a thorough investigation for infection and assessment for sepsis. In the pregnant woman, the parameters of the SOFA must be adjusted to account for the physiological alterations of pregnancy.

If sepsis is suspected, then assessment for end-organ dysfunction should be undertaken. This has been defined as an acute change in the total SOFA score of ≥2 points consequent to the infection[20]. The baseline SOFA score is generally assumed to be zero where there is no pre-existing organ dysfunction. In the general population a SOFA of ≥2 is associated with an overall mortality of 10%, however this data is yet to be fully validated in the obstetric population. The SOFA score has been found to be significantly higher in pregnant women who have died compared to those who have survived in an intensive care setting[21], however the SOFA score has not undergone appropriate validation in pregnant and postpartum populations. Most studies that exist have been small, retrospective and undertaken in resource challenged environments which may limit their applicability generally. A meta-analysis from 2018 reviewed five studies and found that the pooled AUC for predicting maternal mortality from sepsis was 0.92 (0.81, 0.97) indicating good discriminative ability[22]. A more recent prospective study in a low resource setting found that a SOFA score of >=6 had a sensitivity of 84.4% and specificity of 61.3% for predicting critical care admission for pregnant women with sepsis[23].

We recommend several modifications when applying the SOFA score to pregnancy to assess end organ dysfunction(obstetrically modified SOFA- omSOFA) as indicated:

- To demonstrate evidence of end organ dysfunction a score of ≥2 needs to be attained. Therefore, scores of 3 or 4 in each category have been removed for the purposes of simplification.
- During pregnancy, serum creatinine levels are significantly reduced with the normal range being 35-80µmol/L[24]. Accurate assessment of renal function may be performed using 24 hour urinary creatinine or inulin clearance[25], however these are impractical in the acute setting. For practical purposes, the serum creatinine cut off for the scores of 0, 1 or 2 have been adjusted to <90µmol/L, 90-120µmol/L or greater than 120µmol/L respectively[26]. Estimated glomerular filtration rate (eGFR) is not currently a component of the current definition for organ dysfunction.
- As the GCS is not routinely assessed on maternity wards, the central nervous system category has been changed to reflect the maternal observation chart. Alert will be scored 0, rousable by voice as 1 and rousable only by pain as 2. Any score other than 0 or alert will trigger a GCS to be performed.
- Healthy pregnant women may have a mean arterial pressure less than 70mmHg. Thus their vital signs should be interpreted in the context of the woman's premorbid blood pressure.

Table 2.3: Obstetrically modified SOFA score (omSOFA)

System Parameter	Score		
	0	1	2
Respiration PaO_2/FIO_2	≥400	300 - <400	<300
Coagulation Platelets,x10^6/L	≥150	100-150	<100
Liver Bilirubin (µmol/L)	≤20	20-32	>32
Cardiovascular Mean Arterial Pressure(mm Hg)	MAP≥70	MAP<70	Vasopressors required
Central Nervous System	Alert/Oriented	Rousable by voice	Rousable by pain
Renal Creatinine (µmol/L)	≤90	90-120	>120

2.3 Septic shock

If sepsis progresses, septic shock may develop, in which underlying circulatory and cellular metabolic abnormalities are profound enough to substantially increase mortality compared to sepsis alone[20]. The clinical criteria validated to identify these in non-pregnant patients include:

- Hypotension requiring vasopressor therapy to maintain a **MAP 65mmHg** or greater (despite adequate fluid resuscitation) and
- Serum lactate **greater than 2mmol/L** after adequate fluid resuscitation[17]

No alterations have been made to these definitions for pregnancy.

All women who are being assessed for sepsis should be monitored on the appropriate maternity early warning observation chart[27]. Physiologically, a woman's gravid state means that the cut-offs for clinically significant changes vary significantly compared to non-pregnant patients.

2.4 Postpartum

The postpartum period is defined as birth till 6 weeks after the time of birth. After birth, changes in maternal physiology gradually return to pre-pregnancy levels. Systolic blood pressure increases after delivery, reaching a peak at 5 days postpartum with the average reading being 121mmHg and 3rd – 97th centiles being 102-143mmHg[28]. Blood pressure readings return to pre-pregnancy levels by day 14 postpartum. Heart rate returns to normal after one week postpartum and all other parameters including oxygen saturations, temperature, respiratory rate and GCS are unchanged postpartum[28].

Given that maternal physiology has mostly returned to normal 1 week postpartum, we recommend the definition of postpartum sepsis be the same as for non-pregnant patients after the first week postpartum.

3. Fever in Pregnancy

KEY POINTS

- **Anti-pyretics may have a beneficial effect in reducing adverse fetal/child outcomes for patients experiencing fever in pregnancy.**
- **Anti-pyretics such as paracetamol may be beneficial in reducing adverse pregnancy outcomes**
- **Avoid using Non-Steroidal Anti-inflammatories (NSAIDs)**

3.1 Thermoregulation and mechanisms of fever

The human body temperature is carefully regulated to be maintained between 36.5°C and 37.5°C to protect the delicate balance of cellular mechanisms regulating homeostasis. Thermo-regulation is governed by the hypothalamus and interfered with by pyrogenic cytokines, most commonly produced during infection[29].

Pyrogenic cytokines such as interleukin 1 and 6 and tumour necrosis factor alpha (TNFα) act on the hypothalamus and increase maternal body temperature[30]. This interrupts protein synthesis and enzyme production, creating an alteration in cellular processes such as proliferation, migration and apoptosis[31]. This becomes particularly relevant in pregnancy during embryogenesis, when survival is achieved at the expense of normal development via the heat shock response. The febrile response activates the innate immune system and improves the body's response to infection. Various negative feedback systems exist to ensure the hyperthermic response is controlled. Fever increases the body's metabolic rate by up to six-fold thus speeding up the process of eliminating the body of pathogens [32]. Fever in itself, (within a certain temperature range), can therefore be considered a valuable part of the human response to infection. A fever above 40°C however can have direct effects upon key cellular processes, hence the dangers of malignant hyperthermia [31].

The phenomena of heat shock response is a survival response so the organism may survive thermal stress, however this may occur at the expense of cellular damage. Heat shock proteins are produced to enhance cellular resistance to the thermal stress: chaperone proteins adhere to hydrophobic sites on newly synthesised proteins to prevent the formation of functionless aggregates and therefore cell death [33].

This response can occur at any gestation in the pregnancy, however, there are differing potential effects based on the gestation at which the heat shock response occurs (in particular neural tube defects). Later in pregnancy, the effect of heat shock response may be more teratogenic to certain organs or circulations, particularly the fetal brain. Various reports have documented an association between mothers who have suffered from a fever, usually from a suspected viral illness and an increased incidence of cerebral palsy [34-36]. It is unclear however, whether the virus itself or the fever is associated with the brain injury.

3.2 Hyperthermia as a teratogen

3.2.1. During embryogenesis

When the heat shock response is initiated at crucial points during embryogenesis, it can take precedence over other cellular activities such as protein synthesis and cell proliferation which can harm the developing fetus. Animal studies have demonstrated vulnerable periods during organogenesis when fever can be teratogenic: in particular around 4 to 5 weeks of gestation appears critical[31]. An animal embryo must be exposed to a certain level of heat for a certain duration to cause teratogenesis. In rats and guinea pigs this appears to be at least 2 – 2.5°C above normal maternal temperature. The lower the elevation in temperature; the longer is the interval of exposure necessary to cause teratogenesis[31, 33].

The most recorded teratogenic effects of fever from animal studies are neural tube defects, microphthalmia, microcephaly and neurogenic contractures. There is a weaker association with oral cleft and congenital heart disease[33]. Studying fever in human pregnancy is methodologically very difficult and largely reliant upon retrospective case-control or population studies. In a comprehensive systematic review and meta-analysis of fever in human pregnancy and the health impacts on the offspring, Dreier and colleagues[37] reported an increase in the rate of pregnancies affected by a neural tube defect in mothers who experienced fever in the first trimester or peri-conceptually (pooled odds ratio of 2.9 (95% Confidence Interval [CI] 2.22-3.79)) Oral clefts were also more common in mothers with early fever (OR 1.94, 95% CI 1.35-2.79) and congenital heart defects were weakly associated with early maternal fever (OR 1.54, 95% CI 1.37-1.74). More recently these authors examined fever in pregnancy and the risk of congenital malformations from the Danish National Birth Cohort, the largest study to date. In this large cohort of 100,418 pregnant women and their offspring recruited between 1996 and 2002, eight thousand three hundred and twenty-one (8321) women experienced fever during the first trimester, this formed 10.8% of the cohort. Of the cohort 2876 infants were diagnosed with congenital anomalies - 3.7% reflecting other population studies. Fever during the first trimester did not affect the risk of overall fetal congenital malformation (OR 0.99, 95% CI 0.88-1.12), neither was there any significant increase in the grouped sub analyses of oro-facial, uro-genital or nervous system anomalies[38].

Human studies appear to vary from animal studies in the absence of a dose-response relationship. In animals where a temperature elevation of greater than 2°C was documented there was a greater risk of teratogenic outcome[33]. In human studies, reliance on self-reported temperature may lead to inaccurate results[37].

3.2.2 Later in pregnancy: fever and fetal death, preterm labour, fetal growth restriction

In the systematic review by Dreier and colleagues [37] no effect of maternal fever was seen on the risk of miscarriage, stillbirth or preterm labour. This may be because recruitment to studies may be too late for women experiencing spontaneous miscarriage early in pregnancy. Whilst there appears to be no direct link between fever and the incidence of preterm labour, it is well documented that infection – particularly asymptomatic infection of the urinary tract is linked with an increased risk of miscarriage and preterm labour[39] .

3.2.3 Long term neuro-developmental outcome: cerebral palsy, autism

There is a lack of quality studies to document the long term developmental outcomes of fever in pregnancy. The CHARGE (Childhood Autism Risks from Genetics and Environment) study[40] recognizes that no single factor accounts for all autism cases, nor is there on event or exposure that can be responsible for the rapid increase in diagnoses over the last few decades. In the CHARGE study, mothers of children diagnosed with autism spectrum disorder (ASD) or developmental delay (DD) were asked retrospectively, 2 – 5 years after their pregnancy, whether or not they had suffered from flu or a fever in pregnancy. Neither ASD nor DD were associated with self-reported influenza in pregnancy. However, both ASD and DD were associated with the report of fever during pregnancy, OR 2.12 (95% CI 1.17-3.84) and OR 2.50 (95% CI 1.20 – 5.20) respectively. Further, the offspring of mothers who took anti-pyretic medications had a lower risk of ASD, OR 1.30 (0.59-2.84) compared with those who did not OR 2.55 (1.30-4.99).

A meta-analysis of this retrospective data and other cohort and prospective data collection studies does suggest an association between first and second trimester fever and autism spectrum disorder diagnoses. A positive association between fetal exposure to fever and subsequent ASDs was found. For first and second trimesters exposure, the odds ratio was 1.49 (95% CI; 116-1995) and 1.48 (95% CI; 1.22-1.80) respectively. When all nine studies were collapsed, the odds ratio was 1.238 (95% CI; 1.048- 1.462). Prenatal exposure to maternal fever was found to be associated with fetal neurotoxicity during critical windows of CNS development and increased risk for ASD. However, more research is required to establish a direct association.

3.3 Epidural Related Maternal Fever (ERMF)

Epidural related maternal fever is common, occurring in 15 - 25% of labouring women who receive an epidural[41]. The phenomena is exclusive to labouring women and not demonstrated in non-labouring women or women receiving epidural anaesthesia for elective Caesarean section[42]. The mechanism is thought to be pro-inflammatory, not infective: a consequence of local anaesthetic causing increased cytokine release in the labouring woman.

Epidural hyperthermia is not necessarily a benign condition, it should be treated with anti-pyretics e.g. Paracetamol (APAP) and intra-venous fluid, however if the fever does not respond to these measures the usual investigations for possible sepsis should proceed[43].

3.4 Anti-pyretic use: is it beneficial to pregnancy outcome?

Dreier's systematic review[37] included 10 studies of the use of anti-pyretics and pregnancy outcome. Most studies reported a positive effect of the use of anti-pyretics in women suffering from fever during pregnancy, with an attenuation of the risk of neural tube defect, oral cleft and congenital heart disease. Aspirin and Paracetamol are commonly taken through pregnancy and this systematic review seems to indicate that their use, across several populations is safe in pregnancy.

Results from the Norwegian Mother and Child Cohort study following more than 114,000 children at 8 years of age report that children were more likely to receive a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) if their mothers were exposed to fever in the first trimester or pregnancy compared to those children who were unexposed, OR 1.31, 95% confidence interval (CI) = 1.06–1.61). For children exposed twice or more in the first trimester, the OR was 2.64 (CI = 1.36–5.14). Exposure to Paracetamol (APAP) made no difference to the diagnosis of ADHD[44].

In 2021 a statement was issued by a consensus group mainly comprising public health physicians raising concerns over the use of Paracetamol (N-acetyl-para-aminophenol or acetaminophen – APAP) during pregnancy and an increase in the rate of childhood neurodevelopmental disorders and congenital malformations[45]. The scientific validity of the data on which the authors based their conclusions has been heavily criticised[46]. Publicity at the time created a great deal of anguish for pregnant women and their care providers, the American College of Obstetricians and Gynaecologists and the Society for Maternal Fetal Medicine released statements noting that all of the referenced studies were observation and that there is no evidence of causation between prudent use of APAP and disorders of fetal development and stated that patients should not be frightened away from the many benefits of APAP[47, 48]. SOMANZ agrees with this position and recommends the continuing prudent use of APAP for the treatment of fever and/or severe pain in pregnancy.

High-dose aspirin and non-steroidal anti-inflammatory agents should be used with caution during the third trimester due to the risk of premature closure of the fetal ductus arteriosus.[49] Alternative agents should be considered.

4. Aetiology of Sepsis

KEY POINTS

- **The commonest cause of maternal death from sepsis is infection with Group A streptococcus species**
- **E.Coli is the commonest cause of maternal bacterial infection**
- **Always consider that non-bacterial or non-infective conditions may mimic sepsis**

Although most commonly bacterial in aetiology, sepsis can also result from viral and other causes (Table 4.1). Several non-infective conditions can mimic clinical sepsis and should be considered by clinicians.

Table 4.1: Infectious causes of sepsis in pregnancy and postpartum

Infection	Pathogens
Bacterial -common	Group A- beta-haemolytic Streptococcus (GAS) pyogenes Escherichia Coli Group B Streptococcus Klebsiella pneumoniae Staphylococcus aureus Streptococcus pneumonia Proteus mirabilus Anaerobic organisms
Bacterial –less common	Haemophilus influenza Listeria monocytogenes Clostridium species MycobacteriumTuberculosis
Viral	Influenza COVID-19 Varicella zoster virus Herpes Simplex virus Cytomegalovirus

4.1 Common bacterial pathogens

4.1.1 Group A beta-hemolytic streptococcus (Streptococcus pyogenes)

The **most common** organism causing maternal mortality from sepsis is Group A beta-haemolytic streptococcus (GAS)[7]. Although considered rare it is a devastating disease. Pregnant and postpartum women have a 20-fold increase in the incidence of invasive group A streptococcal (GAS) infection compared with non-pregnant women[50]. The reasons for the increased incidence of invasive GAS and GBS disease among postpartum women are not clear[51].

Group A streptococcus is typically found in the community with 5–30% of the population being asymptomatic carriers of the bacteria on the skin or in the throat. It is easily spread by person to person contact or by droplets. Group A streptococcus can also cause serious illness such as rheumatic fever, scarlet fever, bacteraemia, streptococcal shock syndrome and necrotising fasciitis. In pregnancy and the postpartum period GAS sepsis can present with non-specific symptoms such as fever, sore throat or vomiting and diarrhoea[52]. The clinical presentation can be variable and it is essential to be aware of the possibility of GAS infection in pregnant and postpartum women. Clusters of Group A streptococcal infection can occur in maternity services either because of carriage by health care workers or a rise in community acquired infection[53].

Historically it is the classic organism associated with puerperal sepsis and was a common cause of maternal mortality before antiseptic practice was introduced. Consider a woman at potential risk of GAS sepsis if she presents with atypical symptoms such as sore throat, diarrhoea and abdominal pain ante or postnatally.

4.1.2 *Escherichia coli*

E. coli is the most common cause of bacterial infection in pregnancy[54, 55] and is the second most common cause of maternal death due to sepsis[7]. It is the predominant bacteria causing infections in the urinary and genital tracts. In a large series of acute antepartum pyelonephritis *E. coli* was the infectious agent in 70%[56]. *E. coli* sepsis was the cause of 5 maternal deaths in the United Kingdom in the triennium 2006-2008[7]. *E.Coli* is the commonest cause of acute pyelonephritis in pregnancy and systemic sepsis is the commonest maternal complication[57].

4.1.3 Group B streptococcus (*Streptococcus agalactiae*)

Group B Streptococcus (GBS) frequently colonises the lower genital and gastro-intestinal tracts. Whilst GBS colonisation is usually asymptomatic in the mother IV penicillin is given when the risk of neonatal sepsis is increased; women who screen GBS positive in pregnancy, have a history of previous GBS neonatal sepsis, or GBS negative or unknown with rupture of membranes for longer than 18 hours, women in preterm labour or with PPROM who are GBS positive or unknown. Maternal colonisation rates of GBS in pregnancy in Australia vary from 10-30%[58]. An Australian study found a 25% incidence of GBS carriage in women with pre-labour rupture of membranes at term[59]. GBS is a frequent cause of asymptomatic bacteriuria, urinary tract infection, upper genital tract infection, intra-amniotic infection, chorioamnionitis, endometritis and bacteraemia[54, 55]. It is the second most frequent cause of acute antepartum pyelonephritis[56] and may lead to bacteraemia without an obvious focus.

4.1.4 *Klebsiella pneumoniae*

Klebsiella pneumoniae is typically a nosocomial pathogen but can cause pneumonia, bacteraemia and urinary tract infection. Community acquired infections are less common and it is a less common cause of urinary tract sepsis than *E. coli*[54, 56]. Community acquired infections usually occur in cases with underlying chronic disease such as pulmonary disease, diabetes or alcoholism.

4.1.5 *Staphylococcus aureus*

Staphylococcus aureus colonises the skin and mucous membranes. It is a common cause of surgical wound infection and mastitis in the postpartum period[54]. The risk of surgical wound infection may be as high as 26.8% in women with a body mass index (BMI) of >45[60]. Methicillin-resistant *S. aureus* (MRSA) is increasing in prevalence in the Australian community. MRSA now accounts for 17-18% of all *S. aureas* bacteraemia[61].

4.1.6 *Streptococcus pneumoniae*

Streptococcus pneumoniae is a common bacterial cause of community acquired pneumonia and can affect all age groups. Postpartum women have an increased rate of *S. pneumoniae* infection compared to non-pregnant women[50].

4.1.7 *Proteus mirabilis*

Proteus mirabilis is a Gram negative rod shaped bacteria and can also cause urinary tract infections. It is the third commonest cause of acute pyelonephritis after *E coli* and *Klebsiella*[57].

4.1.8 Anaerobic infections

Anaerobic infections are often polymicrobial caused by both anaerobic Gram-negative and Gram-positive organisms. The more common anaerobic organisms causing infections are *Bacteroides* sp., *Prevotella* sp., *Prophyromonas* sp., *Peptostreptococcus* sp. and *Finegoldia* sp. These can occur at any stage of pregnancy but are more common in the postpartum period, especially after caesarean section[54, 55]. They can be the causative agents in pelvic infection, endometritis, wound sepsis and rarely necrotizing fasciitis.

4.2 Less common bacterial pathogens

4.2.1 *Haemophilus influenzae*

H. influenzae is a Gram negative coccobacillus that frequently causes non-invasive upper respiratory tract infections in children and older adults. It is a far less common cause of infection following the introduction of the Hib vaccine. It can colonise the female reproductive tract and cause pelvic inflammatory disease. In pregnancy invasive *H. influenzae* disease presents with bacteraemia, pneumonia and rarely meningitis[62]. Intrauterine H. influenzae infection can occur causing fetal loss and preterm birth. In New Zealand the overall incidence of pregnancy-associated invasive H. influenzae disease was 19.9 cases/100,000 births, which exceeded the reported incidence of pregnancy-associated listeriosis[63].

4.2.2 *Listeria monocytogenes*

Listeria monocytogenes is an intracellular Gram positive bacillus which causes infection following ingestion of contaminated food. It is generally contracted from processed ready to eat meats, unpasteurised cheeses, unpasteurised milk, and seafood[64, 65]. It is very rare in Australia, with an overall incidence of 0.3 per 100,000 of the population. Maternal-fetal infections declined from 2002 to 2003 and the age specific rate of infection in the 20-39 age group is only 0.1 per 100,000 [65]. Studies have suggested 20% of cases involve neonatal infection[64].

Although rare it is 13-20 times more common in pregnancy than in the non-pregnant population and infections are more likely to occur in the third trimester (66%) than in the first trimester (3%)[66].

The presentation of listeriosis in pregnancy is often non-specific with fever, flu-like symptoms, headache, vomiting and diarrhoea. The placenta can become infected and can provide a reservoir for re-infection. It is associated with spontaneous miscarriage, stillbirth and preterm birth[64]. While maternal illness may be mild, neonatal illness is often severe and can be fatal. Disease in the neonate can be early onset, associated with chorioamnionitis and preterm birth, or late onset occurring between five days and two weeks postpartum, typically in term neonates[64]. Diagnosis of neonatal listeriosis is important as antibiotic therapy can improve outcomes.

4.2.3 Tuberculosis

Worldwide, tuberculosis is one of the leading non obstetric causes of maternal mortality and is the third cause of death for women aged 15-44[65, 67, 68]. Tuberculosis can be more difficult to diagnose in pregnancy because symptoms such as fatigue, shortness of breath, sweats and tiredness are similar to physiological symptoms of pregnancy. Furthermore, pregnancy suppresses the T-helper 1 (Th1) pro-inflammatory response which can mask symptoms while increasing susceptibility to new infection and reactivation of tuberculosis[69]. Although congenital tuberculosis appears rare, tuberculosis can be transmitted to the infant in patients with miliary TB through hematogenous spread, aspiration of amniotic fluid during delivery, or in those with pulmonary TB via respiratory droplets postpartum[69].

In Australia the incidence rate of tuberculosis notifications is 5.8 per 100,000 population, and is highest in the overseas-born population which makes up 86% to 89% of cases. The rates in the Australian-born Indigenous population are 4.6 per 100,000 compared to only 0.9 per 100,000 in the Australian-born non-Indigenous population . Only 2% of cases in Australia have multidrug resistant TB and these usually occur in overseas born individuals[70]. In New Zealand the incidence rate of tuberculosis notifications is 6.3 per 100,000 population, and similar to Australia. Again it is highest in the overseas-born population which make up 80.5% of the TB notifications in New Zealand. The rate for Maori was 2.9 per 100,000 and for Pacific peoples 5.1 per 100,000[71].

4.3 Viral pathogens

Although sepsis is often considered to be attributable to bacterial infections, viral infections in pregnancy can be associated with severe disease and sepsis. Commonly occurring viruses that can be associated with severe disease and sepsis include SARS-CoV-2, influenza, varicella, herpes simplex.

4.3.1 Coronavirus Disease 2019 (COVID-19) from Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 (Covid 19) infection during pregnancy can range from asymptomatic to severe disease, sepsis, septic shock and death[72]. It was recognised early in the pandemic, that pregnant women, similarly to other viral pathogens such as influenza, were at increased risk of severe sequelae related to infection compared to non-pregnant women of reproductive age. These sequelae included increased rates of maternal (1.2% (95%CI 1-1.4 and neonatal mortality (3%; 95% confidence interval, 2–4), hospitalisation(60.5% vs. 17.0%, $P<0.001$), mechanical ventilation, extracorporeal membrane oxygenation (ECMO), intensive care admission (4.6% (95CI 3.4-6.2))[73, 74]. Infection during pregnancy has also been associated with increased risk for developing pregnancy complications including preterm birth and stillbirth[75-77]. The risk of serious disease and sequelae is reduced by vaccination and may also be impacted by the circulating variant[78]. For example, severe sequelae were reported more commonly with the delta variant compared to Omicron, although other factors such as background vaccination rates and immunity from previous infection may confound this finding[79].

4.3.2 Influenza

Pregnant women are more at risk of developing respiratory complications of influenza, with increased rates of hospital admission and increased mortality compared to the non-pregnant population[80]. Both seasonal and pandemic influenza are associated with increased morbidity and mortality in pregnancy[81]. In non-pandemic years, hospital admission rates for pregnant women with influenza have been estimated as similar to the rate of admission for the elderly (65-69 years), with 1 in 1000 healthy pregnant women hospitalized in a Canadian retrospective cohort study[82]. In Australian data from 2019, the Influenza Complications Alert Network, a sentinel hospital-based surveillance program reported 1.7% of hospital admissions were pregnant women. In that cohort, pregnancy was not associated with an increased rate of ICU admission[83].

4.3.2 Varicella

Varicella-zoster virus (VZV) is a highly contagious member of the herpesvirus family, and causes both varicella (chickenpox) and herpes zoster (shingles). Varicella is usually a self-limiting condition that involves the development of a rash approximately 14-16 days post exposure. The rash is initially erythematous macules evolving to produce vesicles which then crust over the subsequent 46-48 hours. The rash is usually accompanied by fever, malaise, anorexia and headache. Varicella can be associated with severe complications, for example encephalitis, cerebellar ataxia and pneumonia/pneumonitis.

Historically the incidence of varicella was estimated at 1-5/10,000 pregnancies, with maternal pneumonia reported to complicate approximately 20%[84] with a mortality rate of approximately 40%. A large cohort study examining 7.7 million pregnancy admissions in the USA from 2003-2010 reported a varicella incidence of 1.21/10000, with an incidence of pneumonia of 2.5% and no maternal deaths[85]. In those women with pneumonia, 13% had ARDS/acute respiratory failure, 13% required ventilation and 4.4% had severe sepsis.

Infant complications related to maternal disease will depend on gestational age of exposure. Multiple obstetric and infectious disease guidelines address the health and management of the fetus and newborn exposed to varicella[86-88].

4.3.3 Herpes simplex virus

Several guidelines outline the management of genital herpes in pregnancy, which is outside the scope of this document[89-91]. While a small proportion (<2% estimated) of pregnant women will seroconvert to Herpes simplex virus (HSV), severe disseminated maternal infection is rare (there are less than 40 cases reported in the literature[92-94]). Outside pregnancy disseminated HSV is more likely in those immunosuppressed. However the cases in pregnancy do not detail risk factors

for immunosuppression. Features of disseminated HSV may include encephalitis, thrombocytopenia, leucopenia and coagulopathy [95]. Additionally, liver dysfunction has been a common presenting feature of these cases and HSV should be considered in the differential diagnosis of women with severe liver dysfunction in pregnancy[96]. A review of reported HSV hepatitis cases found 23% were in pregnant women, mortality was 88% if untreated and 51% in acyclovir treated patients[97]. Maternal mortality from herpes hepatitis from 2000 onward has been reported at approximately 9%[93].

4.4 Non-infectious conditions that can mimic sepsis.

In the pregnant or postpartum woman, a number of conditions may resemble aspects of the sepsis syndrome and should be considered in the differential diagnosis. These are listed in Table 4.2.

Table 4.2: Non- infectious conditions that can mimic sepsis in pregnancy.

Condition	Common Maternal Clinical Features
Acute pulmonary embolism	Hypotension, tachypnoea, tachycardia, low grade fever
Amniotic fluid embolism	Hypotension, tachycardia, haemorrhage
Acute pancreatitis	Fever, nausea, vomiting, abdominal pain
Acute Fatty Liver of Pregnancy	Fatigue, nausea, vomiting, abdominal pain, jaundice, impaired level of consciousness
Adverse drug reactions, drug fever	Hypotension, relative bradycardia, fever, rash, angio-oedema
Acute liver failure-drug related, viral	Jaundice, nausea, vomiting, abdominal pain impaired level of consciousness
Acute adrenal insufficiency	Weakness, fatigue, nausea, anorexia, weight loss, hypotension, fever
Acute pituitary insufficiency	Failure to lactate, hypotension, relative bradycardia, polyuria, polydipsia
Autoimmune conditions	Low grade fever, rash (e.g. malar rash), arthritis, dry eyes or mouth, mouth ulcers, diagnostic serology
Concealed haemorrhage including ectopic pregnancy	Hypotension, tachycardia, low grade fever
Disseminated Malignancy	Low grade fever, weight loss
Pelvic Thrombosis	Pelvic pain, fever,
Transfusion reactions	High fever, rigors, dysrhythmia, tachypnoea, hypotension, rash, bleeding, haematuria

5. Investigations in Sepsis

KEY POINTS

- **Blood cultures and appropriate microbiological specimens should be obtained ideally prior to commencement; however this should NOT delay administration of antimicrobials.**
- **Imaging should not be withheld just because the patient is pregnant or breastfeeding**
- **Reference pregnancy-appropriate normal ranges for investigations and observations**

Sepsis in the obstetric patient may be difficult to diagnose as symptoms and signs may be multiple, varied and nonspecific. Normal pregnancy physiological changes may mask the recognition of sepsis and as such it is important to consider sepsis, investigate early and commence treatment as decreasing time to treatment improves outcome[15,98]. Maternity units should ensure observations are recorded on maternity specific charts on all obstetric and up to a week postpartum patients. Their utilization has been shown to promote earlier detection and therefore treatment of the women developing a critical illness[99]. The most recent Surviving Sepsis Campaign recommends in the setting of unconfirmed infection, continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected[15].

Once infection is suspected, treatment should be commenced and the likely source and severity of sepsis elucidated via history, examination and further investigations. Investigations are directed at determining the aetiology of sepsis and allow risk stratification of the patient and organisation of care in the most appropriate area. Sepsis during pregnancy will require maternal investigations as detailed below and fetal wellbeing assessment with cardiotocograph and / or ultrasound. Appropriate routine blood cultures should be obtained before commencing antimicrobial therapy in suspected sepsis or septic shock if this is not associated with delay in the start of antimicrobials[15]. Table 5.1(see page 22) lists the first line investigations to be undertaken in sepsis, possible changes in sepsis and normal pregnancy reference ranges if different from the non pregnant state. Table 5.2 lists additional investigations which can be undertaken depending on initial investigation results and the likely source of infection.

- The priorities for initial investigation in maternal sepsis are: full blood count with differential and film, serum lactate, blood cultures and cultures of other relevant sources[15].
- Two sets of peripheral blood cultures should be taken sequentially from different sites (not the same cannula) immediately and if possible before administration of antibiotics. Their collection should not delay antibiotic treatment.
- Cultures should also be taken from all vascular catheter lines (catheter blood cultures) and any other potential sources of infection as determining the etiology of the infection will allow targeting of antimicrobial therapy. Other sites to consider are the urinary, genital, respiratory tract, surgical wounds (including previous vascular access sites) and if applicable, breast milk.
- Arterial or venous blood gases should be undertaken to determine the presence of hypoxia, hypercapnea, metabolic state and lactate level. If arterial lactate levels are unobtainable a venous level can be collected. Elevated lactate levels are an indication of tissue hypoperfusion with values greater than 2 mmol/L being associated with increased mortality in pregnancy[100]. The sampling site of the blood does not affect the lactate results (eg. arterial, venous or capillary)[101].

Table 5.1: First line investigations recommended for suspected sepsis - **over page >**

Table 5.1: First line investigations recommended for suspected sepsis

*prioritised investigations

Investigation[15, 52, 98, 102]	Results in non-obstetric sepsis[15, 98]	Obstetric reference range (if relevant)[24]
Blood cultures* - **At least 2 sets from separate sites, prior to antibiotic commencement as long as there is no delay in antibiotic administration.** - **Obtain samples from 2 different sites** - **Cultures should also be obtained from IV access devices**	May be positive for organism – around 50% if collected before antibiotic administration	
Other Cultures * - **Obtain cultures of additional sites as clinically indicated and as soon as possible** **E.g. urine MCS and urine antigen testing** **wound swab - episiotomy, caesarean** **vaginal swabs** **placental swabs** **amniotic fluid** **sputum MCS** **naso-pharyngeal aspirate/swab** **Nasal/Salivary RAT or PCR for Covid 19** **cerebrospinal fluid** **stool culture**	May be positive for organism	
Arterial/venous blood gases –detect acidosis, hypoxaemia, lactate as below		PaO_2 : 1st trimester: 93-100 mmHg 2nd trimester: 90-98mmHg 3rd trimester: 92-107mmHg $PaCO_2$: 25-33mmHg, Arterial pH: 7.4-7.47 HCO3 16-22mmol/L
Lactate* - **elevated levels in sepsis relate to tissue hypoperfusion and are associated with an increased sepsis mortality risk** - **may be normal in early sepsis, elevated in septic shock**	≥ 2mmol/L associated with increased mortality	0.6-1.8 mmol/L
Full blood count and film *	WCC >12 X10 9/L or <4 x10^9 /L Normal WCC count with > 10 % immature forms Thrombocytopenia is a severe sign of sepsis (Platelet count <100x10^9/L indicates organ dysfunction)	WCC 6-17 X 10^9/L WCC in hours post-delivery between 9-15 X 10^9 (steroids also increase WCC) Platelets – 150-420 x10^9/L may fall below 150 in 8% of pregnancies
Coagulation studies, including APTT and INR	May be abnormal in sepsis with INR >1.5 , APTT > 60 secs and fibrinogen < 2.0 indicating disseminated intravascular coagulopathy and end organ dysfunction	No change
Creatinine urea and electrolytes – **Measure at baseline and until the patient improves** – **Elevated creatinine is a sign of severe sepsis** – **Abnormal electrolytes and elevated urea may be seen in sepsis**	Sepsis is severe if [103]: Creatinine >120µmol/L (presuming premorbid baseline renal function was normal)	Creatinine Varies with Gestation (reference ranges) : 1st trimester 35-62µmol/L 2nd trimester 35-71µmol/L 3rd trimester 35-80µmol/L
Liver function tests – **Baseline test** – **May be elevated if sepsis source is from hepatic or perihepatic infections** – **May be elevated due to septic shock affecting hepatic blood flow and metabolism**	Plasma total bilirubin >70µmol/L indicates organ dysfunction	AST 3-33 U/L ALT 2-33 U/L Alkaline Phosphatase 17-229 U/L GGT 2-26 U/L Total Bilirubin 1.7-19 µmol/L
CXR	May show evidence of infection such as consolidation or pleural effusion	Diaphragm elevation may be distorted by fundus, cardiac axis rotated in pregnancy
Fetal Assessment – CTG and /or fetal wellbeing ultrasound		A non-reassuring CTG/fetal ultrasound suggests inadequate uteroplacental perfusion and may reflect maternal organ hypoperfusion

Table 5.2: Subsequent investigations to be considered in women with suspected sepsis

Investigation to Consider	Comments
Lumbar puncture	If meningitis or central nervous system infection is suspected
Echocardiogram	Useful in known or suspected Intravenous drug users or women with known cardiac anomalies to detect endocarditis. All women with blood cultures positive for staphylococcal bacteraemia should have an echocardiogram. Also useful in determining cardiac function
Imaging modalities – Pelvic ultrasound – Abdominal ultrasound – CT abdomen or chest	May define infective source or collection and allow drainage. Consider if localising symptoms or signs present or ongoing sepsis with unknown source
C reactive protein (CRP) Nonspecific investigation but can aid in monitoring treatment efficacy	Obstetric specific normal ranges CRP : 0.4-20.3mg/L
Viral Infections suggested from history, examination and other blood tests Hepatitis A, B, C, EBV, CMV ,HIV ,Herpes, Varicella Zoster serology, **Covid 19, Influenza**	Nasal swab
Clostridioides Difficile – If patient has recently had antibiotics and develops diarrhoea	Send stool sample for microscopy, culture and sensitivity as well as for Clostridioides difficile toxin
Other atypical infections suggested from history e.g. Listeria monocytogenes- pregnant women are more susceptible.	Investigate with blood cultures (best for Listeria) and urine or stool cultures for other infections
Procalcitonin – Can consider the use of procalcitonin and clinical evaluation to assist with decision making regarding timing for commencement and discontinuation of antibiotics in adults with sepsis[15]	Recent studies have demonstrated procalcitonin levels are similar in pregnant and non-pregnant populations and may be a valuable adjunct to assist with sepsis management in pregnancy. Upper reference limit 0.05ng/mL[104] Further studies are required to guide usage

Clinically indicated radiological imaging investigations should **not** be withheld in pregnancy due to concerns regrding fetal radiation or maternal breast tissue exposure. It is necessary to balance the risks of the procedure with the maternal benefits in assisting with diagnosis and management. Almost all maternal diagnostic imaging procedures involve fetal radiation dosage <50 mGy and below this threshold there are no associated increases in miscarriage or stillbirth, genetic damage, teratogenicity, growth impairment, mental retardation, or sterility.[105]

Procalcitonin (PCT) is the inactive propeptide of calcitonin, which is released by C cells of the thyroid gland, hepatocytes and peripheral monocytes. Recent meta-analysis has demonstrated an AUC value of 0.84 for PCT with modest sensitivity and specificity (0.80 (95% confidence interval 0.75 to 0.84) and 0.75 (95% confidence interval 0.67 to 0.81)). The clinical value of PCT to assist with improved clinical outcomes in sepsis is still in investigative stages and further research may assist in guiding its use in the future[106]. The 2022 Surviving Sepsis Campaign recommends against the use of PCT to decide when to start antimicrobials, as compared to clinical evaluation alone for adults with suspected sepsis or septic shock; and in the presence of adequate source control where optimal duration of therapy is unclear, recommends for the use of PCT AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone. Both recommendations are weak with low quality of evidence[15].

Serum C-reactive protein (CRP) is an acute-phase protein that shows increased expression in the presence of infection, injury and inflammation. CRP levels are slightly higher in pregnancy than in the non-pregnant state and increase in labour and delivery. A systematic review has demonstrated that CRP and other biomarkers are consistently elevated in confirmed maternal infection however paucity of prospective data on biomarkers limits their clinical applicability.[107]

6. Timely Treatment: The Golden Hour

KEY POINTS

- **Commence resuscitation immediately to stabilize the mother.**
- **Administer empiric therapy immediately and preferably within one hour**
- **Commence thromboprophylaxis**
- **Where a source of sepsis is localized, refine antibiotic prescribing to appropriate antibiotics**
- **Consider the impact of the antibiotics on pregnancy and breastfeeding**

The treatment of women with suspected sepsis is multifaceted. Treatment should be commenced as soon as practical - ideally within the first hour ('golden hour') of sepsis being suspected. The treatment should include antimicrobials (antibiotics or antivirals as appropriate) as well as supportive therapies such as anti-pyretics and intravenous fluids. Recommendations have been made on the currently available relevant obstetric literature where available.

6.1 Fluid resuscitation

In most circumstances the initial treatment of hypotension in sepsis is fluid administration. Fluid resuscitation is vital to restore circulating volume, improve blood pressure, fetal circulation and tissue perfusion. The preferred fluid for resuscitation is usually a crystalloid (normal saline). The use of albumin, in an intensive care setting in a heterogeneous group of non-pregnant patients requiring intravascular fluid resuscitation, showed no overall improvement in mortality compared to normal saline for fluid resuscitation[108, 109]. Blood may be used as a means of fluid replacement if there is evidence of symptomatic blood loss or severe anaemia (Hb </=70g/L).

In the general ward setting, fluid resuscitation to a maximum of 20mls/kg, up to 2 litres, is appropriate. Prior to further fluid administration, consider escalation to either intensive care or high dependency unit if the mean arterial pressure and other indices do not improve, where vasopressors may be required[110] (refer to 'Intensive Care Issues' below).

As part of the Surviving Sepsis Campaign[111] a number of 'care bundles' were introduced, focusing on early fluid resuscitation, prompt administration of antibiotics after appropriate cultures, targeting of physiological parameters such as a mean arterial pressure of >65mmHg and the monitoring of serum lactate levels[111] It is worth noting that pregnant patients were excluded from these studies. These interventions focused on the first 6 hours of sepsis care, which typically would occur in an emergency department. This early goal-directed therapy (EGDT) has been re-evaluated in three subsequent harmonised international randomised controlled trials[112-114] including one primarily conducted in Australia and New Zealand[112]. None of these trials found any benefit of EGDT over usual care.

6.2 Treatment in the Early Stage for bacterial sepsis

When bacterial sepsis in pregnancy or postpartum is suspected, treatment with antibiotics as early as possible (and preferably within the first hour) is important for maternal survival; mortality can increase by 8% for each hour antibiotic administration is delayed[115]. Australia and New Zealand antibiotic stewardships recommends that antibiotic treatment needs to be appropriate for the suspected infection, whilst minimising the risk of adverse effects and reducing the emergence of antibiotic resistance[116, 117].

A consultant obstetrician and a physician experienced in the management of sepsis in pregnancy should be involved in the care of a pregnant or postpartum patient once sepsis is being considered, however, investigation and treatment should not be delayed while waiting for expert consultation. Once a source of sepsis is identified, source control is a priority and assessment and potential delivery of the fetus may be required.

Where women have significant medical co-morbidities such as diabetes or are immunosuppressed by immunomodulators including biopharmaceuticals for solid organ transplant, malignancy or autoimmune disease; chronic infection including HIV; a physician should be involved in decision making as soon as possible; however, this should not delay antibiotic treatment.

6.2.1 Treatment of sepsis of unknown source

Table 6.1 outlines recommendations regarding empiric antibiotic treatment in the 'golden hour'. Traditionally, empiric antibiotic recommendations for pregnancy and postpartum have aimed to cover primarily obstetric sources of sepsis, however, consideration also needs to be given to non-reproductive tract sources which make up a substantial proportion of maternity sepsis.

This position statement has based empirical antibiotic recommendations for obstetric patients with sepsis of unknown source, on national antibiotic guidelines for adults in general, whilst taking into account pharmacological considerations of pregnancy and lactation. We support and recommend adherence to therapeutic prescribing guidelines – whether at local, state or national levels. We have included antibiotic recommendations in this position statement since we are aware of the difficulties health care providers across Australia and New Zealand may have in accessing guidelines in real time.

Antibiotic resistance patterns and local practices will vary so it is important to seek local specialist advice as soon as possible. Aminoglycoside therapy for gram negative sepsis cover varies according to clinical jurisdictions. Reference should be made to local prescribing guidelines. Therapy should be refined as a definitive source and organism is identified. The Australia-wide electronic Antibiotic therapeutic guidelines are available behind a paywall at the following URL: https://tgldcdp.tg.org.au/guideLine?guidelinePage=Antibiotic&frompage=etgcomplete

Table 6.1: Recommendations for initial treatment of antimicrobial treatment of sepsis with unknown source

	Australian[118] and New Zealand[119, 120] Antibiotic Regimens	**Alternative for penicillin hypersensitivity†:**
Community-acquired sepsis (source not apparent)	Aus : **amoxicillin/ampicillin** 2g IV 6-hourly PLUS aminoglycoside e.g. gentamicin 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly NZ: **cefuroxime** 750mg IV 6-hourly PLUS **aminoglycoside e.g. gentamicin** 5mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly If at risk of MSRA sepsis (based on previous swabs/cultures and local epidemiology): ADD **vancomycin** 25-30mg/kg (loading dose) IV * At risk of Group A Streptococcal (GAS) sepsis ADD: **clindamycin** 600mg IV 8-hourly,	Severe: **clindamycin** 600mg IV 8-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* (NZ: seek expert advice due to increasing Group B strep resistance to clindamycin and macrolides [121]) Mild – moderate†: **cefazolin** 2g IV 6-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly
Hospital-acquired sepsis (source not apparent)	Aus: **piperacillin** 4 g + **tazobactam** 0.5g IV 8-hourly AND consider **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* (if local epidemiology suggests Gram negative aminoglycoside susceptibility) NZ: **cefuroxime** 1.5g IV 8-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly At risk of MSRA sepsis¥ (based on previous swabs/cultures and local epidemiology or if line sepsis) ADD **vancomycin** 25-30mg/kg (loading dose) IV* At risk of multidrug-resistant Gram-negative organisms use as a SINGLE AGENT: **meropenem** 1g IV 8-houly At risk of Group A Streptococcal (GAS) sepsis, ADD: **clindamycin** 600mg IV 8-hourly PLUS consider normal immunoglobulin 1-2g/kg IV, for up to 2 doses during the first 72 hours	Severe: **ciprofloxacin** 400mg IV 8-hourly PLUS **vancomycin** 25-30mg/kg IV*
Consider influenza	**Oseltamivir** 75mg BD or **Zanamivir** 2 inhalations (each 5mg) twice daily for 5 days	
Consider SARS-CoV-2 (COVID-19)	Recommend checking your local guideline.	

† Immediate hypersensitivity (anaphylaxis) or severe delayed hypersensitivity; drug induced liver injury or acute interstitial nephritis = severe. Mild/moderate = delayed hypersensitivity.

* Whilst gentamicin has been the example given as an aminoglycoside to use, where possible please use the aminoglycoside advised by your local health service. Use local protocols for aminoglycoside dosing and monitoring.[122].

¥ MRSA risk: recent international travel to areas with a high prevalence of MDR organisms; prolonged hospitalization and previous colonization.

6.2.2 Initial treatment of sepsis of known source

a. Bacterial

Table 6.2 outlines antibiotic recommendation where a specific source of infection is identified. The final decision regarding duration of treatment should take into account the source and type of infection, clinical response and local microbiologist or infectious disease specialist advice.

Table 6.2 : Recommendations for antibiotic treatment for localised sources of sepsis

Clinical diagnosis	Australian[118] and New Zealand[119, 120] Antibiotic Regimens	Alternative for penicillin hypersensitivity
Female Genital Tract source antenatal and postnatal including: **Chorioamnionitis** **Endometritis (postpartum)** **Septic abortion** **Sepsis post miscarriage** **Puerperal sepsis**	Aus: **amoxicillin/ampicillin** 2g IV 6-hourly PLUS a**minoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * PLUS **metronidazole** 500mg IV 12-hourly NZ : as for Aus or **cefuroxime** 1.5g IV 8-hourly PLUS **metronidazole** 500mg IV 12-hourly	Severe: **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **azithromycin** 500mg IV daily PLUS **clindamycin** 600mg IV 8-hourly NZ seek expert advice due to increasing Group B strep resistance to clindamycin and macrolides[121] Mild – moderate: **ceftriaxone** 2g IV daily OR **cefotaxime** 2g IV 8-hourly PLUS **azithromycin** 500mg IV daily PLUS **metronidazole** 500mg IV 12-hourly NZ: **cefazolin** 2 g initially, then 1 g 8-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly
Urinary tract	Aus: **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * PLUS **amoxicillin/ampicillin** 2g IV 6-houly (some NZ regions too, e.g. Waikato region) NZ: **cefuroxime** 750mg-1.5g IV 8-hourly OR a**minoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * alone If aminoglycoside e.g. gentamicin use is contraindicated, use as a SINGLE AGENT: **ceftriaxone** 1g IV daily OR **cefotaxime** 1g IV 8-hourly If anti-pseudomonal cover is required, use as a SINGLE AGENT: **ceftazidime** 1g IV 8-hourly OR **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * OR (if Extended spectrum beta-lactamase producers suspected): meropenem 1g IV 8-hourly	Severe: **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * alone Mild – moderate†: cephalosporin e.g. **cefuroxime** 750mg-1.5g IV 8-hourly OR **ceftriaxone** 1g IV daily
Wound infection	Post C-section: **flucloxacillin** 2g IV 6-hourly (4-hourly for severe sepsis requiring ICU, septic shock) Post episiotomy ADD **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV * New Zealand: ADD **metronidazole** 500mg IV 12-hourly Infected post-op abdominal wounds: as for peritonitis MRSA suspected: ADD **vancomycin** 25-30mg/kg (loading dose) IV * cease **flucloxacillin**	Severe: **vancomycin** 25-30mg/kg (loading dose) IV* Mild – moderate: **cefazolin** 2g IV 8-hourly
Mastitis – postpartum/lactating	**Flucloxacillin** 2 g IV 4- to 6-hourly (4-hourly for severe sepsis requiring ICU, septic shock) assumes methicillin sensitivity (MSSA) If MRSA carrier, use: **vancomycin** 25-30mg/kg (loading dose) IV *	Severe: **clindamycin** 600mg IV 8-hourly Mild – moderate: **cefazolin** 2 g IV 6- to 8-hourly

Table 6.2 Continued over >

Table 6.2 : Recommendations for antibiotic treatment for localised sources of sepsis (Continued)

Clinical diagnosis	Australian[118] and New Zealand[119, 120] Antibiotic Regimens	Alternative for penicillin hypersensitivity
Bacterial pneumonia	Australia: **ceftriaxone** 1g IV daily OR **cefotaxime** 1g IV 8-hourly PLUS **azithromycin** 500mg IV daily x 3-5 days (Tropical regions of Australia: refer to Therapeutic Guidelines) New Zealand: **cefuroxime** 1.5g IV 8-hourly PLUS macrolide (**azithromycin** 500mg IV daily or **erythromycin** 1g IV 6-hourly)	Severe: **moxifloxacin** 400mg PO/IV daily) PLUS **azithromycin** 500mg PO daily x 3-5 days
Acute abdomen with suspected perforation OR post-operative abdominal sepsis	**amoxicillin/ampicillin** 2g IV 6-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly	Severe: **clindamycin** 600mg IV 8-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* Mild – moderate: **cefazolin** 2g IV 6-hourly PLUS **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **metronidazole** 500mg IV 12-hourly
Epidural/Spinal abscess	**aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **flucloxacillin** 2g IV 4 to 6-hourly	Severe: **aminoglycoside e.g. gentamicin** 4-7mg/kg (first dose) IV* PLUS **vancomycin** 25-30mg/kg (loading dose) IV * Mild – moderate **aminoglycoside e.g. gentamicin** contraindicated: **ceftriaxone** 4 g IV daily OR **ceftriaxone** 2g IV 12-hourly OR **cefotaxime** 2g IV 6-hourly

* Use local protocols for aminoglycosides and vancomycin dosing and monitoring[122]

b. Viral:

(i) Influenza

Neuraminidase inhibitors (oseltamivir, zanamivir)

Neuraminidase inhibitors are recommended for the treatment of influenza[123]. Neuraminidase has a role in the promotion of release of viruses from infected cells, and the inhibition of neuraminidase results in aggregation of the viral particles at the host cell surface, and a reduction in the amount of virus released to infect other cells.

Oseltamivir (Tamiflu) is the agent of choice in pregnancy as it has more obstetric safety data than zanamivir (Relenza)[124]. There is a low rate of transplacental transfer, estimated at between 1-14% of maternal concentrations in ex vivo perfusion studies[125]. In the setting of H1N1 pandemic influenza in pregnancy, early antiviral therapy (initiation < 2 days) was associated with an 84% reduction in admissions to intensive care[126]. Further, only 7% of pregnant women who died from H1N1 received treatment with a neuraminidase inhibitor within two days compared with 41% of those who survived[127]. Advice for prevention and treatment is listed in Table 6.3. A recent pharmacokinetic study demonstrated that blood levels are 30% lower in the pregnant compared with non-pregnant adult. Therefore in severe illness consider using higher doses: population pharmacokinetics indicate the dose may need to be increased to 100mg twice daily[128].

Table 6.3: Prevention and treatment of influenza.

Post-exposure prophylaxis and treatment	• Oseltamivir (Tamiflu™) • Prophylactic dose: 75mg orally, taken daily for 7-10 days after exposure. • Treatment dose: 75mg capsule orally twice daily for 5 days. In a woman with symptoms consistent with influenza infection, oseltamivir should be started as soon as possible, preferably within 48 hours.

Influenza vaccine:

The World Health Organisation and the Global Influenza Initiative recommend women are vaccinated for influenza at *any* stage during pregnancy using an inactivated influenza vaccine[129]. The inactivated vaccine is safe in pregnancy;[129] while injection site reactions have occurred, there is no increased risk of maternal or fetal adverse outcomes[129]. In Australian data, a prospective cohort study of 1086 pregnant women and 314 non pregnant female health care workers given the trivalent influenza vaccine in 2014 reported no serious vaccine related adverse events, and no increase in reporting of adverse events in the pregnant women compared to the non-pregnant women[130].

Pregnant women have a similar immune response to the inactivated influenza vaccine as non-pregnant women[131]. Vaccination rates in Australia have improved over time with general acceptance by health care professionals and pregnant women of the safety profile. Maternal uptake of the influenza vaccine was 29.6% in 2010 and 81.8% in 2020[132, 133].

The inactivated influenza vaccine has been shown in randomised trials to reduce the rates of maternal febrile respiratory illness by approximately 35%, laboratory confirmed influenza by 50% and in large registry studies the monovalent H1N1 vaccine or seasonal influenza vaccine reduced clinical diagnoses of influenza by 44-70%[134]. Administration of the inactivated influenza vaccine during pregnancy also confers protection to the infant, reducing laboratory confirmed influenza by up to 60% with a 40-45% reduction in hospitalizations[134].

(ii) SARS-CoV-2 (COVID-19)

Treatment

As the pandemic has evolved, the information and guidance around medical therapy for women with SARS-CoV-2 infection during pregnancy is also changing rapidly. We recommend seeking guidance from local hospital infectious disease team, pharmacy, and referral to the Australian National Clinical Evidence Taskforce living guidance [https://clinicalevidence.net.au/covid-19/] for up to date information and clinical management guidance.

SARS-CoV-2 (COVID-19) vaccination

The WHO recommends that if not already vaccinated, then pregnant women should have SARS-CoV-2 vaccines [WHO/2019-nCoV/FAQ/Pregnancy/Vaccines/2022.1]. Animal studies of use of the vaccines during pregnancy have not shown any adverse effects[135]. Large registry based studies in multiple countries have found no adverse outcomes from maternal vaccination for SARS-Cov-2 during pregnancy[136]. Meta-analysis shows SARS-CoV-2 vaccination during pregnancy reduced risk of COVID-19 infection by 60%, hospitalisation by 53%, and intensive care admission by 82%, stillbirth reduced by 45%, and 33% reduction in preterm birth before 28 weeks gestation. While this might vary with virus subtype, the data for protection for omicron with SARS-CoV-2 vaccine is also reassuring, with vaccine effectiveness for severe complications at 48%, and 76% after a booster dose[78, 137].

(iii) Varicella

Zoster Immunoglobulin should be offered to sero-negative women who do not have two documented doses of varicella vaccine with significant exposures to either acute varicella or herpes zoster (shingles) within 96 hours of exposure[84, 138, 139]. A significant exposure is considered to be: living in the same household as a person with chickenpox or zoster, face to face contact for at least 5 mins or in the same room for at least one hour[86]. In pregnant women with significant exposure who present beyond 96 hours, post-exposure prophylaxis with oral acyclovir should be considered in sero-negative women at high risk of developing severe lung disease (e.g. immunosuppressed women).

Pregnant women with symptoms or signs of pneumonia require appropriate investigation and hospitalisation. Intravenous acyclovir has been recommended for treatment of women with respiratory complications[84, 139] . Use of acyclovir during pregnancy is outside the drug license, however, no adverse effects on a fetus or newborn have been attributed to acyclovir[140]. The pharmacokinetics of acyclovir are not altered by pregnancy[141, 142]. Acyclovir crosses the placenta, with the cord to maternal plasma concentration estimated at 1.3[125]. While based on case reports and case series, maternal and fetal mortality are reduced by the use of acyclovir in the setting of varicella pneumonia[143].

(iv) Herpes simplex virus

Intravenous acyclovir is first line therapy for disseminated disease. Foscarnet has been used in drug resistant infections outside pregnancy. There are only two case reports of Foscarnet use in pregnancy: one in the setting of severe genital HSV with HIV co-infection with no abnormal findings on the newborn examination, and the second in the setting of fulminant herpes hepatitis[93, 144].

6.4 Thromboembolism prophylaxis

Pregnancy and sepsis are independent risk factors for venous thromboembolism[145]. Therefore, prevention of venous thrombosis is critically important. Unfractionated heparin (UH) and low molecular weight heparin (LMWH) have been used extensively in pregnancy and been shown in large clinical trials to be effective in the prevention of thromboembolism[146]. LMWH and UH are both renally excreted and dose adjustment should be considered in women with renal dysfunction[147]. Consideration should be given to weight based dosing (see table 6.4)[148]. Prophylactic dose LMWH should be ceased a minimum of 12 hours and UF heparin at least 6 hours prior to neuraxial analgesia or anaesthesia or surgery[10, 145, 149].

Table 6.4 Weight adjusted thromboprophylaxis dosing for LMWH

Weight	Enoxaparin (mg)	Dalteparin (IU)
<50kg	20mg	2500IU
50-100kg	40mg	5000IU
>100kg	60mg	7500IU

6.5 Potential maternal adverse effects of antibiotics

As with all patients administered antibiotics, there are potential adverse reactions that may occur. These can include allergic reactions, diarrhoea, idiosyncratic drug-induced renal or liver injury.

Allergic or hypersensitivity reactions can occur in several circumstances. These include:

(i) IgE mediated immediate reactions (i.e. anaphylaxis) which may be life-threatening or

(ii) delayed (non-immediate) reactions. The delayed reactions can occur in a variety of forms: mild to moderate (usually rash) or severe (e.g. Stevens-Johnsons syndrome)[118].

Diarrhoea may also occur in which case a stool sample for C. difficile toxin testing should be requested. The mortality of C. difficile colitis is up to 30% in mothers if untreated[150]. Candidal infections and thrush occur at higher rates when receiving antibiotics in pregnancy. Treatment is recommended[151].

Renal impairment and ototoxicity can occur specifically with the use of vancomycin and aminoglycosides (e.g. gentamycin) particularly at supra-therapeutic levels or when these antibiotics are used for extended periods of time. Their therapeutic dosing and monitoring should follow local guidelines.

Idiosyncratic drug-induced renal injury can occur in the form of acute interstitial nephritis (AIN) or tubule-interstitial nephritis (TIN). This is a differential diagnosis for acute kidney injury (AKI) in the setting of treated sepsis, particularly with beta lactam antibiotics. A renal biopsy may sometimes be required for a definitive diagnosis to be made. AIN usually responds to cessation of the offending drug (although this can take some time for recovery to be observed) and recurs with re-exposure[152]. Treatment with corticosteroids may be required and consider consultation with a renal physician.

Idiosyncratic drug induced liver injury (DILI) may be either hepatocellular or cholestatic in nature. This injury is associated with many drugs, especially antibiotics including penicillins and cephalosporins. The reaction is often delayed days to weeks from antibiotic administration, late abnormalities of liver function will need to be investigated to exclude other pregnancy related causes of liver dysfunction. If these are normal, a late drug reaction may be assumed. It is important to diagnose drug-related liver dysfunction to prevent re-administration and further liver damage at another time in the future[153].

6.6 Pharmacological considerations for pregnancy and breastfeeding

Concerns regarding pregnant and breastfeeding women being exposed to antibiotics may be raised. In the case of appropriate sepsis treatment, the risk of maternal and fetal morbidity and mortality is higher than the benefit of non-exposure. Antibiotic therapy should be de-escalated as soon as possible in the interest of maintaining a normal gut microbiota in the infant as well as the mother. Maternal intrapartum antibiotic exposure has been shown to impact the gut microbiota of infants. Disrupted microbiota may be associated with obesity and immune dysfunction later in life. Breastfeeding helps reverse this disruption[154]. Studies[155] are investigating the role of probiotics in pregnancy, although to date there is no conclusive evidence supporting their use.

Most antibiotics cross into breastmilk, however the relative infant dose is usually small. There is the potential for breastfed infants to develop diarrhoea, vomiting, a skin rash, thrush, an allergic response or interference with the infants blood culture results, whilst exposed to maternal antibiotics.

Please see appendix (3) for a list of useful resources and contact information for pharmacy services able to provide patient specific advice on antimicrobials in pregnancy and breastfeeding.

6.7 Infection prevention and control considerations

Infection control measures including contact precautions should be considered and discussed with local infection control colleagues[156]. Women suspected of, or diagnosed with an infectious disease, should be isolated in a single room with ensuite facilities for 24 hours after effective antibiotic treatment has been commenced. Unwell visitors should be instructed to refrain from visiting maternity areas to avoid transmission to pregnant and postpartum women[157].

Some infections are notifiable to the local health department , in particular invasive Group A Streptococcus (GAS)[158]. GAS in close contacts and family members is a risk factor for maternal, particularly postpartum sepsis.

7. Fetal Surveillance and Timing and Mode of Birth

KEY POINTS

- **Maternal sepsis is associated with miscarriage, fetal compromise, fetal death in utero and stillbirth**
- **Consider the most appropriate method of monitoring fetal wellbeing during maternal sepsis according to the gestation. E.g. cardiotocography, ultrasound, Doppler auscultation**
- **If preterm birth is anticipated, antenatal corticosteroids should be considered for fetal indications prior to 35 weeks' gestation and magnesium sulphate should be administered when birth is anticipated prior to 30 weeks' gestation**
- **Chorioamnionitis onset may be non-specific or insidious, but rapid deterioration is possible. Chorioamnionitis requires urgent delivery on both maternal and fetal grounds**
- **Preterm birth may be required for fetal or maternal indications**
- **Perimortem caesarean section (resuscitative hysterotomy) should be considered in cases of maternal cardiorespiratory arrest beyond 20 weeks gestation.**

7.1 Fetal Surveillance

In the setting of sepsis, the goal of fetal surveillance is to assess fetal wellbeing as well as to determine the presence of intrauterine and fetal infection. Non-invasive fetal surveillance relies on the modalities of electronic fetal monitoring (EFM) [159] and ultrasound, while invasive techniques such as amniocentesis are not used in modern obstetric practice in the septic patient.

The decision to undertake fetal surveillance and the mode of fetal surveillance during maternal sepsis will be determined by fetal gestation and the facilities available in the healthcare unit. For example, fetal surveillance at pre-viable gestations or gestations at borderline variability (i.e. prior to 24 weeks) may be limited to ultrasound assessment of fetal viability, whereas assessment at later gestations beyond 26 weeks may include EFM.

In the setting of extra-uterine sepsis (e.g. respiratory or urinary sepsis), fetal wellbeing will largely be determined by maternal status. Electronic fetal monitoring may demonstrate an uncomplicated fetal tachycardia characterised by acceptable short-term variability and absence of decelerations. These findings will often improve with maternal fluid resuscitation and treatment of maternal pyrexia[160].

In contrast, there is a lack of sensitivity and specificity in the EFM findings observed in cases of intrauterine sepsis[161, 162]. Nevertheless, features suggestive of fetal acidosis including reduced or absent variability, baseline tachycardia and/or the presence of persistent late decelerations warrant further assessment and expedited delivery , taking into account the maternal status and ensuring that appropriate maternal resuscitation has been undertaken to allow a safe birth[159, 160].

The role of ultrasound in assessing fetal wellbeing has been investigated predominantly in the setting of women with preterm premature rupture of membranes (PPROM) and as a means of detecting the development of intra-amniotic sepsis. Two studies have investigated the role of the biophysical profile in assessing fetal wellbeing and despite some methodological limitations of these studies; both concluded biophysical profiles are not useful in predicting the development of intra-amniotic infection[163, 164].

7.2 Timing and mode of delivery

The timing of delivery is a complex decision that is guided by:

- The presence of intrauterine sepsis (chorioamnionitis)
- The nature of the maternal sepsis and response to initial resuscitation efforts
- The gestation of the pregnancy
- Fetal status
- Factors such as the care setting, resource and expertise availability, previous obstetric history and if the woman is actively labouring

7.2.1 Intrauterine sepsis (chorioamnionitis)

Intrauterine sepsis should be suspected in the presence of maternal fever (although fever is not essential), and the presence of associated risk factors such as ruptured membranes or recent intrauterine procedures such as amniocentesis[165]. Additional clinical signs include maternal tachycardia, fetal tachycardia, uterine tenderness, offensive vaginal discharge and maternal leucocytosis (white blood cell count > 15,000/ml[166]. It is important to remember that while the onset of chorioamnionitis may be non-specific and insidious, rapid deterioration is possible. Likewise, it is relevant to note that fever may not be a feature in a woman who is developing sepsis and deteriorating rapidly.

In the setting of intrauterine sepsis, delivery should always be considered regardless of the gestation. At pre-viable gestations (less than 23 weeks), where there is little chance of fetal survival, induction of labour is in the maternal interest and reduces the risk of surgical infection compared to operative delivery. At more advanced gestations, the decision regarding mode of delivery must be weighed up carefully, taking factors such as the cervical favourability and hence likelihood of a quick birth, the fetal presentation and chance of neonatal survival, the maternal condition and the suitability of the environment (e.g. Intensive care unit vs birthing suite) into consideration. Commonly, an emergency caesarean section will be required as a means of expediting delivery. Where delivery of a preterm infant is anticipated, this should be undertaken in a facility with access to an appropriate level nursery and neonatal support. The management of neonatal sepsis or suspected neonatal sepsis is beyond the scope of this guideline, however, the importance of communication between the obstetric and neonatal teams is paramount since information regarding identification of causative organisms and details of antibiotic administration and adjunctive treatment (antenatal corticosteroids, magnesium sulphate) may guide the neonatal management.

There is accumulating evidence of the increasing risks of cerebral palsy in association with exposure to intrauterine sepsis, thereby highlighting the need to expedite delivery in fetuses at more advanced gestations with proven or high likelihood of intrauterine sepsis[167, 168]. A meta-analysis identified 12 studies that investigated the association between clinical chorioamnionitis and cerebral palsy and reported a pooled odds ratio of 2.42 (95% confidence interval 1.52-3.84)[169]. However, the studies included in this meta-analysis have a range of limitations including the use of a "clinical diagnosis" of chorioamnionitis, the variable use of microbiological techniques for detection of causative pathogens and the heterogeneity of the included studies.

7.2.2 Extrauterine Sepsis

In cases of extra-uterine sepsis, efforts to treat maternal sepsis and prolong gestation should be considered at gestations remote from term, although it is reasonable to consider delivery in term pregnancies as a means of improving maternal resuscitation and survival. Alterations in maternal physiology in late pregnancy such as the effects of the gravid uterus on the inferior vena cava, (causing supine hypotension) and diaphragm (reduced vital capacity), increased cardiac output and altered capillary permeability, can all contribute to increasing the difficulties associated with resuscitation.

Assessing the response to maternal resuscitation and treatment is a vital component of the assessment and management of sepsis in pregnancy. Delivery should be considered in any case where the maternal response to treatment is felt to be compromised by the pregnancy. For example, women with significant respiratory sepsis or acute respiratory distress syndrome (ARDS) may potentially be difficult to ventilate adequately due in part to the raised intra-abdominal pressure caused by pregnancy at more advanced gestations [160]. The question regarding whether delivery may improve or further compromise resuscitation efforts should always be considered carefully with decisions made by an experienced multidisciplinary team [160]. In one of the largest studies to date regarding the indications for delivery in women with extra-uterine sepsis, the presence of septic shock, multi-organ failure or worsening respiratory status were regarded as the leading indications for delivery [170].

7.3 Premature labour in cases of sepsis

Urinary tract sepsis such as pyelonephritis may in fact trigger labour. While efforts to suppress premature labour by using tocolytic agents (such as nifedipine) in the setting of extra-uterine sepsis should be considered, careful attention to exclude intrauterine sepsis if possible should be taken due to the risks of exacerbating the fetal and maternal condition and contributing to cerebral palsy as previously described. Where labour is suppressed, this should be limited to a defined short period, in clinical practice usually 48 hours, to allow corticosteroids to be administered for fetal lung maturation and transfer if required to an appropriate tertiary facility. Close fetal and maternal surveillance should be undertaken to exclude any evidence of fetal compromise where labour is suppressed.

7.3.1 Antenatal corticosteroids

Corticosteroids should be considered for fetal lung maturation when preterm birth is anticipated prior to 35^{+0} weeks' gestation[171]. Corticosteroids have anti-inflammatory effects and may – at least theoretically – increase the risk of systemic infection. While the majority of randomised trials investigating the role of antenatal corticosteroids in improving neonatal respiratory outcomes excluded women with chorioamnionitis, four trials[172-175] included a proportion of women with chorioamnionitis. In trials that excluded women with chorioamnionitis no significant increase in the rates of puerperal sepsis were reported. The neonatal benefits (decreased respiratory distress and perinatal death) of antenatal corticosteroids for infants born to women with chorioamnionitis are similar to the benefits achieved when corticosteroids are given to women without chorioamnionitis[171]. Similar short-term neonatal benefits were reported in three meta-analyses of non-randomised studies[166, 176, 177]. However, a significant limitation of the majority of studies reporting on antenatal corticosteroid use in the setting of chorioamnionitis is the lack of data regarding maternal outcomes. Unfortunately only 2 of the randomised trials of corticosteroids in the setting of chorioamnionitis reported the rates of puerperal sepsis[174, 175]. Evaluation of the trials that included women with chorioamnionitis suggested a 2.65 fold increase (95% confidence interval 1.18-5.91) in the rates of puerperal sepsis in women who received antenatal corticosteroids. These findings should be interpreted with caution given the limited data and wide confidence intervals. Nevertheless, it is imperative that corticosteroids are considered when maternal status allows, but delivery should not be delayed in women with chorioamnionitis simply to administer corticosteroids. Women with chorioamnionitis who receive antenatal corticosteroids should be observed closely due to the possible increased risk of developing endometritis or puerperal sepsis[171].

7.3.2 Antenatal magnesium sulphate

Magnesium sulphate has been demonstrated to reduce the risk of cerebral palsy when administered prior to preterm birth[178] and is recommended in Australia when birth is anticipated prior to 30 weeks' gestation[179]. Although there continues to be some uncertainty about the optimal timing, duration and dose of magnesium sulphate[178], Australian guidelines recommend administration of a 4g loading dose (administered over 15-20 minutes) followed by an infusion 1g/ hour until birth, timed to be given as close to four hours before birth as possible. The efficacy of magnesium sulphate at gestations between 30 and 34 weeks is less certain[178].

Although no published randomised trials have specifically assessed the benefits of magnesium sulphate in the setting of chorioamnionitis or maternal sepsis, most trials included participants with chorioamnionitis. An individual participant data meta-analysis (IPD-MA) demonstrated no clear differences in the treatment effects on cerebral palsy based on the indication for preterm birth[180]. As there were no episodes of severe maternal morbidity related to treatment amongst the 5,493 women included in this IPD-MA, it would seem there is no maternal disadvantages to using magnesium sulphate for the purpose of fetal neuroprotection in women with sepsis – regardless of the cause) when preterm birth is anticipated.

7.4 Peri-mortem caesarean section (resuscitative hysterotomy)

In the event of maternal cardiorespiratory arrest in cases of severe maternal sepsis, peri-mortem caesarean section should be considered. Multiple case reports and case series have demonstrated an improvement in the ability to resuscitate women following cardiorespiratory arrest due to relief of aorto-caval compression as well as reducing-metabolic requirements [181, 182]. While traditionally regarded as being in the maternal interest, these series have demonstrated improved neonatal survival with early recourse to caesarean section [182]. Even at extreme preterm gestations where neonatal survival is considered to be unlikely, peri-mortem caesarean section is recommended to improve the chances of successful maternal resuscitation, hence the recommendation that it be renamed resuscitative hysterotomy and be performed in the event of maternal arrest if the uterus is palpable at or above the umbilicus (equivalent to 20 weeks gestation), regardless of the presence or absence of fetal cardiac activity[183]. Furthermore, previous recommendations that surgery should commence within 4 minutes of arrest with the aim of achieving delivery within 5 minutes have now been abandoned in favour of a recommendation that surgery commence immediately coinciding with maternal resuscitation efforts, since analysis of case reports and series demonstrates both improved maternal and neonatal outcomes with shorter intervals between commencement of resuscitation and delivery[184].

7.5 Prevention and management of postpartum haemorrhage

Women with sepsis – regardless of the cause – are at increased risk of postpartum haemorrhage due to a combination of factors including sepsis related thrombocytopenia, disseminated intravascular coagulation and uterine atony (particularly in the setting of intrauterine sepsis / chorioamnionitis). Active third stage management and prompt recognition and response to postpartum haemorrhage by clinicians experienced in the management of this obstetric emergency is essential.

8. Maternal Sepsis and the Emergency Physician

The over-riding principal in the management of maternal sepsis is early identification and prompt management of the septic woman with secondary consideration as to whether adjustments can or should be made for pregnancy. Maternal care should not be compromised as this is generally in the best interests of the fetus. Assessment and management should be performed with consideration of pregnancy, not avoided because of pregnancy. Sepsis management after 1 week postpartum is the same as other non-pregnant women with the possible addition of breastfeeding and obstetric sources of sepsis including retained products of conception, mastitis, and wound infection. Please refer to Appendix 2 for a two page summary.

Tachycardia and tachypnoea occur earlier than hypotension. BP decompensation is a late sign and will demand more intensive resuscitative management. Fever and symptoms related to the gastrointestinal, respiratory and urinary tract are common with Group A Streptococcal (Strep pyogenes) sepsis from a pregnancy source.

The fetus and uterus are often silent sources of sepsis. The earliest sign of fetal hypoperfusion may be an abnormal CTG, for example a sustained fetal tachycardia, bradycardia or even stillbirth.

- Inotropes: Noradrenaline as per local administration policy as first line can be given with the temporizing addition of peripheral metaraminol 0.5mg IV aliquots. Avoid femoral lines for administration where possible due to increased infection risk and limitation of access due to the pregnant abdomen. Consider the increased VTE risk and difficulty laying flat with left pelvic tilt. Upper limb long or mid lines may present appropriate compromises where other central access becomes difficult for example. due to positioning/respiratory difficulty lying flat.
- Source control. Seek source at all indwelling lines, urinary, genital and respiratory tract and surgical wounds including previous vascular access sites. Chorioamnionitis should be suspected with abnormal fetal observations, abdominal pain, gastrointestinal symptoms, ruptured membranes or offensive PV discharge. If there is suspicion of chorioamnionitis urgently request obstetric assessment and management and assessment of fetal well being (see Chapter 7)

8.1 Other supportive measures to consider in management of sepsis:

- Uterine displacement (wedge hip, manual displacement or left lateral positioning)
- Antipyretics: Paracetamol 1g PO/IV – avoid ibuprofen and NSAIDS
- VTE prophylaxis with LMWH after renal function, platelets, coagulation and the likelihood for neuraxial anaesthesia or surgery has been determined
- Corticosteroids may be indicated for fetal lung maturation in women at less than 34 weeks of gestation. Sepsis is not a contra-indication to steroids. Most commonly prescribed as Betamethasone 11.4mg IM, two doses 24 hours apart, less commonly Dexamethasone 6mg IM q12h is given

8.2 Involvement of other teams

Obstetric and gynaecology teams should be involved at the earliest opportunity; however review should not delay assessment or management.

Infectious diseases, ICU and obstetric physician advice may be required depending on the cause and severity of sepsis.

ICU should be involved early if:

- vital signs remain outside the normal range despite resuscitation attempts,
- if fluid resuscitation exceeds 2L
- if inotropes are required
- if mentation remains altered past initial resuscitation
- or if monitoring requirements exceed ward capabilities.

Paediatrics/neonatology should be involved if viable delivery is being considered as an option.

For patients presenting in rural or regional centres, consider need for transfer, taking into account likelihood of and likely outcome of delivery (gestational age), likelihood of deterioration (if not transferred, and during transfer), if more time will improve patient stability, and local capacity and capabilities.

8.3 Life-threatening maternal instability/cardio-pulmonary arrest

In the event of an extremely unwell or rapidly deteriorating patient with pregnancy >20 weeks, preparations should be made for the potential need for resuscitative hysterotomy, including identifying the most experienced clinician available who can perform the procedure.

If cardio-pulmonary arrest occurs, in addition to standard resuscitation measures the team should plan to commence resuscitative hysterotomy urgently.

There should not be a delay waiting for an obstetrician or for transfer to the operating theatre. The aim being to deliver the fetus as fast as possible (</=5 mins ideally).

Indication for emergency Caesarean section for fetal distress (based on CTG/fetal U/S) should be guided by the obstetric service.

9. Role of the Anaesthetist in Managing Maternal Sepsis

KEY POINTS

- **Neuraxial blocks in women with untreated sepsis may be undertaken only after careful consideration due to increased risk of complications in the short and long term; but initiation of neuraxial analgesia may reduce the need of general anaesthesia for when operative delivery becomes necessary.**
- **Pregnant women with sepsis experience increased haemodynamic instability during general anesthesia**
- **Anesthesia during pregnancy in a woman with sepsis does not increase mortality but may be associated with other adverse obstetric events.**

The role of the anaesthetist in managing maternal sepsis may include:

- assessment of the patient
- initial resuscitation and stabilisation of the patient
- transfer of the sick patient (to imaging, intensive care unit)
- intra-operative care during delivery
- anaesthesia for surgical management of sepsis

9.1 Initial care and stabilisation

The anaesthetist is often called upon as a member of the multidisciplinary team, and in particular to assist with vascular access, invasive monitoring, initial management and stabilisation of the parturient with sepsis. The principles of managing obstetric patients with sepsis are the same as those for non-pregnant patients.

9.2 Patient transfer

The management of women with sepsis may involve diagnostic imaging, interventional radiology, surgical procedures, and complex treatment such as positive pressure ventilation, inotropic therapy, extra corporeal membrane oxygenation and haemo-filtration in a tertiary intensive care unit. Elements of care will include: safe transport of a compromised patient with reduced physiological reserve; accurate patient assessment and optimisation; co-ordination and effective communication between members of the multi-disciplinary team and utilisation of trained personnel supported by skilled assistance and appropriate equipment. Furthermore, the transport team must be experienced in securing airways, ventilation, resuscitation and other anticipated emergency procedures. In addition, a comprehensive hand over should take place at the receiving facility. The responsibility of intra and inter-hospital transfers often rests with the anaesthetist to provide the standard of care as set out in The Australian and New Zealand College of Anaesthetists professional document, PS52(G) Guideline for Transport of Critically Ill Patients 2015. This guideline states, "the level of care provided during transport must aim to at least equal that at the point of referral and must prepare the patient for admission to the receiving services"[185].

9.3 Intra-operative care

The obstetric patient with sepsis may require anaesthesia for delivery of her fetus or infection control procedures such as removal of the septic focus including drainage of an abscess and debridement of necrotic tissues. The intra-operative management goal is to provide optimal care to a patient with deranged physiology and altered drug handling secondary to the systemic inflammatory response superimposed on pregnancy. For the mother, the aim is to maintain physiological homeostasis: preventing hypotension, hypoxia and hypercapnia, and for the fetus the focus is on optimisation of utero-placental perfusion to avoid fetal asphyxia, minimising unnecessary drug exposure, and the avoidance of preterm labour and fetal loss.

9.4 Delivery

The timing of delivery ultimately rests with the obstetrician, however, co-ordination with resuscitative measures needs to be taken into consideration. Even though neuraxial blockade has generally been the anaesthesia of choice for operative delivery, there are a number of issues for the parturient with sepsis.

9.4.1 Neuraxial anaesthesia

Firstly, underlying sepsis is a risk factor for infectious complications of regional anaesthesia. The greatest concern is infection around the spine and spinal cord, presenting either as meningitis or cord compression secondary to abscess formation with the potential for permanent neurological deficit. Reassuringly, such serious neurological complications are rare in the obstetric

population. It is difficult to accurately quantify the risk of infection following neuraxial analgesia and anaesthesia due to the great variability in the reported incidence in the literature; from an estimated incidence of spinal/epidural abscess after epidural analgesia of 1 in 1,930 to 1.1 infections per 100,000 neuraxial blocks[186]. However, epidural anaesthesia carries a greater risk of infectious complications than spinal techniques [187].

Despite the low risk of central nervous system infection, the decision to proceed with neuraxial blockade in a febrile possibly infected patient must be carefully considered and made on a case by case basis [111, 188, 189]:

1. Expert opinion supports, except in the most extraordinary circumstances, central neuronal block should not be performed in patients with untreated systemic infection.
2. Patients with evidence of systemic infection may safely undergo spinal anaesthesia, provided appropriate antibiotic therapy is initiated before dural puncture and the patient has shown a response to therapy; placement of an indwelling epidural or intrathecal catheter remains controversial.
3. Spinal anaesthesia may be safely performed in patients at risk for bacteremia after dural puncture, given lumbar puncture may form part of the evaluation in patients with pyrexia of unknown origin.

Furthermore, the development of coagulopathy and hemodynamic instability are added contraindications to neuraxial blockade in the septic patient. In the case of hemodynamic instability, hypotension secondary to sympathectomy will be poorly tolerated.

9.4.2 General anaesthesia

The septic obstetric patient often exhibits hemodynamic instability and has a greater (than just pregnancy induced) metabolic oxygen demand. In practice, relevant issues for the administration of general anaesthesia include:

A – Airway
Delayed gastric emptying with increased risk of reflux and aspiration.

Recommendations:
- premedicate with combination antacid antihistamine prophylaxis, e.g. effervescent ranitidine 150mg
- rapid sequence induction

B - Breathing
Increased metabolic demand leading to accelerated hypoxaemia during periods of apnoea.

Recommendations:
- adequate pre-oxygenation prior to anaesthesia induction

Reduced functional residual capacity with increased ventilation/perfusion mismatch.

Recommendations:
- ventilation strategies to maintain oxygenation and minimise further lung injury; these include the use of lower tidal volume with limited plateau pressure to minimise overdistension, and positive end-expiratory pressure to prevent alveolar collapse at end expiration

C - Circulation
Maintenance of systemic blood pressure for adequate organ perfusion, including placental bed.

Recommendations:
- avoidance of aortocaval compression using a lateral uterine tilt
- adequate fluid resuscitation optimisation of Hb, platelets, fibrinogen and INR inotropic support – alpha adrenergic agonists (specifically noradrenaline) being agents of choice for maintenance of uteroplacental flow

9.5 Anaesthetic agent

No particular anaesthetic agent or technique is recommended for the septic patient. Commonly used intravenous and inhalation agents all cause hypotension from vasodilatation and /or myocardial depression. It is not the agent, rather the care with administration, judicious dose in a titrated manner; that ensures a smooth induction of anaesthesia.

When surgical procedures for sepsis control are necessary, the pregnant woman should be reassured that to date, no anaesthetic agent has been shown to be clearly harmful to the human fetus. When used in clinically relevant doses/ concentrations, there is no proof of teratogenicity in humans with the following [190, 191]:

- volatile agents
- barbiturates, ketamine, benzodiazepines
- opioids
- local anaesthetics
- muscle relaxants (these polarized molecules do not cross the placenta in significant amount)

Furthermore, it is uncertain whether results from animal studies suggesting anaesthetic agents influence early brain development by alteration of anatomical organization and functional consequences in the form of learning and memory deficit, can be extrapolated to the human fetal brain [192]. A systematic review and meta-analysis on the effects of general

anaesthetic during pregnancy on the neurocognitive development of the fetus (Bleeser et al, 2021) concluded that while neuronal injury is consistently found in all experimental models, there is limited translation of these results to human for the following reasons:

- difference in brain development between animal species and human
- some studies examined anaesthesia exposure without surgical stimuli
- monitoring and strict control of physiological homeostasis were below standards in many studies
- duration and frequency of exposure, and anaesthetic doses were often greater than used clinically[193]

It should also be noted these meta-analysis were only conducted on pre-clinical studies with no clinical studies identified.

Further research is needed to determine the effects of maternal anaesthetic exposure on fetal, neonatal and childhood neurocognitive outcomes due to multiple confounders, including maternal conditions. However, given only necessary surgery will be performed during pregnancy, research on the risks of various types of anaesthesia may be of more clinical utility.

9.6 Non-obstetric surgery in the pregnant patient with sepsis

There is a known association between epidural analgesia and maternal fever which is a non-infectious inflammatory response; maternal fever is furthermore associated with adverse neonatal consequences [194]. In addition to managing the elevated temperature, it is important to determine its aetiology in women receiving epidural analgesia to avoid confusion in diagnosing maternal sepsis.

While modern surgical and anaesthesia techniques have rendered non-obstetric surgery safe for the pregnant woman [195, 196], they carry a risk for adverse fetal outcomes (small for gestational age (SGA), premature labour, prematurity and fetal loss) which may be related to the underlying disease process rather than the warranted treatment. Moore *et al*[196] demonstrated no significant difference in overall mortality or 30 day mortality rates in pregnant and non-pregnant matched women undergoing similar surgical operations. Cohen-Kerem[195] *et al* reviewed pregnancy outcomes following non-obstetric surgery and their findings are summarised in Table 9.1.

It is estimated 1 to 2% of pregnant women undergo non-obstetric surgery during pregnancy [197]. A number of studies reported an increased risk of adverse pregnancy outcomes [198, 199], with a retrospective cohort study of 6.5 million pregnancies concluding that the attributable risk is however low [199].

Table 9.1: Pregnancy outcomes following non - obstetric surgery.

Event	Incidence
Maternal death	0.06%
Miscarriage	5.8% - all trimesters 10.5% - 1st trimester
Premature labour	3.5%
Fetal loss	2.5%
Prematurity	8.2%
Major birth defects associated with non-obstetric surgery in 1st trimester	3.9% (1 -3% in general population)

9.7 SARS-CoV-2 and anaesthesia

The principles of managing the SARS-CoV-2 infected patients undergoing anaesthesia are best summarised by the Australian and New Zealand College of Anaesthetists (ANZCA) professional document, ***PG68(A) Guideline on surgical patient safety for SARS-CoV-2 infection and vaccination.*** This is a frequently updated providing advice on safety concerns for surgery in patients with current or previous SARS-CoV-2 infection (attached as appendix).

Pandemic data demonstrated that pre-operative infection with SARS-CoV-2 was associated with increased peri-operative risks of morbidity and mortality which persisted for 2 to 3 weeks[200]. It is therefore recommended to delay non-urgent major surgery for at least 2 – 3 weeks if the patient is asymptomatic, or delay by 7 weeks for those with ongoing symptoms. For time sensitive / critical procedures, individualised patient risk assessment needs to be carefully balanced against the benefits of proceeding versus delaying the planned operation. This often involves shared decision making by a multidisciplinary team to determine the optimal timing of surgery.

When anaesthetising the SARS-CoV-2 infected obstetric patient for sepsis related urgent surgery, considerations should be given to meeting recommendations made by the PG68A guideline; in particular the multidisciplinary support from infectious diseases, intensive care, obstetric medicine specialist, obstetrician and neonatologist. A thorough pre-operative assessment should occur to optimise all vital organ system function. Infection with SARS-CoV-2 also confers an increased risk of deep vein thrombosis or pulmonary embolism, so appropriate thromboprophylactic measures should be instituted to mitigate risks.

9.7.1 Managing the suspected /confirmed SARS-CoV-2 infected patient for labour and delivery.

Khan et al eloquently summarised the anaesthetic issues relevant to managing the suspected/confirmed SARS-CoV-2 infected obstetric patient[201].

9.7.2 Labour analgesia

Neuraxial techniques should be offered to the obstetric patient as per usual practice. SARS-CoV-2 infection is not a contra-indication to regional analgesia and, or anaesthesia. It is strongly recommended that epidural analgesia be encouraged and instituted in those who are at increased risk of requiring medical interventions. Analgesia provided by a well functioning epidural provides multiple benefits:

- Reduce aerosol generation during labour
- Avoid nitrous oxide use
- Extension to anaesthesia for Caesarean delivery, thereby avoid general anaesthesia

Nitrous oxide / oxygen inhalation analgesia (Entonox) may be used with the correct equipment which includes a viral filter. The RANZCOG advises a cautious approach i.e. that nitrous oxide should not be routinely provided to women who are defined as suspected, probable or confirmed SARS-CoV-2 infected. If nitrous oxide is used in this setting, then all exposed staff must wear tier 3 PPE.

In the case of deterioration in the woman's symptoms, an individualised assessment regarding the risks of continuing the labour versus proceeding to emergency caesarean delivery in an effort to resuscitate the mother need to be made by the medical team.

9.7.3 Anaesthesia for Caesarean section

The anaesthetic considerations in managing the SARS-CoV-2 suspected / infected obstetric patient are the same as that of the non-pregnant population. Of relevance is the administration of general anaesthesia: airway interventions are aerosol generating procedures, so institutional policy /guidelines on protective measures need to be observed by all staff.

The basic principles of obstetric anaesthesia remain unchanged in patients with recent or peri-operative SARS-CoV-2 infection. The recommendation is to avoid general anaesthesia. As is in the uninfected population, neuraxial techniques will be the preferred choice of anaesthesia in the absence of contra-indications.

The logistics involved in the timely transfer of a suspected / confirmed SARS-CoV-2 infected woman from the birth suite to the operation room for an emergency delivery need to be borne in mind, in particular the donning of PPE consumes time which will impact on the decision to delivery interval. The importance of early communication between colleagues of the maternity team cannot be overstated.

Finally, workflow should be regularly rehearsed during pandemic wave in multidisciplinary team education / simulation sessions to minimise delay in carrying out emergency Caesarean deliveries.

10. Intensive Care for the Obstetric Patient

Fortunately, the need for maternal intensive care unit (ICU) admission is uncommon. The most common reasons for ICU admission in this patient population are the hypertensive disorders of pregnancy and obstetric haemorrhage[202]. Sepsis is also amongst the leading causes of maternal ICU admission[203].

Intensive care is a largely centralised resource and is often not immediately available in many healthcare settings caring for pregnant women. The low rates of ICU admission in these usually healthy women may cause uncertainty about referral criteria and recognition of the need for treatment escalation by maternity staff. Equally, many ICU staff (both medical and nursing) may be unfamiliar with obstetric patients and their particular diagnostic and management issues, leading to higher levels of uncertainty and anxiety about both the need for admission and subsequent management choices.

10.1 The deteriorating patient

Patients with sepsis may deteriorate rapidly and catastrophically. For hospitalised patients, the introduction of rapid response teams to intervene early in deterioration has been associated with a reduction in hospital mortality and cardiopulmonary arrest 204. However, even if recognition of deterioration occurs, activation of the rapid response team may not occur in up to 40% of instances 205. There is literature looking at both generic hospital rapid response teams attending obstetric patients,206 207and the development of obstetrics specific teams.208 Several specific obstetric early warning scores have been developed209, 210 and this position statement strongly recommends their use.

10.2 Triaging patients that require admission to the ICU

There is currently no well validated or absolute predictive scoring system that can reliably predict which of these patients will need ICU admission. The decision to admit to the ICU should be taken in consultation with the intensive care and the multidisciplinary obstetric teams. It should be recognised that the threshold for ICU admission may vary across settings, for reasons of skill mix and familiarity described above. Inter hospital transfer to a setting with greater capability or experience with these patients may be necessary.

The Royal College of Obstetricians Greentop Guideline on Bacterial Sepsis lists indications for transfer to ICU102. Most of these indications comprise either signs of worsening organ dysfunction or increasing clinical instability (refractory hypotension despite fluid resuscitation, worsening acidosis, renal failure etc). Intensive care input should aim to predate the development of these conditions if possible.

10.3 Indications for intensive care involvement

Adequate initial resuscitation and treatment may result in stabilisation and prevent progression and deterioration, averting the requirement for intensive care. However, as stated above it is preferable that an ICU opinion and /or admission occur before the development of any complication, let alone frank organ failure(s) or significant shock. If clinical concern exists then escalation of care should be considered early. Table 9.1 sets out in general terms when an ICU opinion should be obtained and ICU admission considered.

Depending on the woman's normal blood pressure, hypotension may be difficult to define but a reasonable starting point would be a systolic blood pressure of <90mmHg (mean arterial pressure <60-65mmHg): this cut-off may be higher if other signs of hypoperfusion exist.

Table 10.2: Indications for involvement of ICU.

Indications for ICU involvement if maternal sepsis considered	Signs or observations
Cardiorespiratory compromise	hypotension, tachycardia or other circulatory instability, tachypnoea, worsening hypoxia, increasing supplemental oxygen requirements
Evidence of organ dysfunction	oliguria, worsening renal failure, coagulopathy, others such as cytopenias, worsening hepatic function, altered mental status.
Other evidence of hypoperfusion	metabolic/lactic acidosis, signs of poor tissue perfusion, signs of inadequate placental perfusion
Other serious clinical concern, including potential for rapid deterioration	
Significant chronic maternal medical conditions	

10.3.1 Tachypnoea and hypoxia

There is evidence from the non-obstetric population that tachypnoea and a need for high concentrations of supplemental oxygen are the early warning criteria most strongly associated with life threatening adverse events [211]. Although the normal physiological changes of pregnancy result in a respiratory alkalosis, this does not result in an increased respiratory rate. It should always be remembered that aside from cardiorespiratory or thromboembolic causes tachypnoea may be the result of sepsis or a resultant or co-existent metabolic acidosis. Evaluation of a venous or arterial blood gas will help to discriminate causes as well as providing very important metabolic information. Hypoxia is a worrying sign, and warrants urgent

consideration of escalation of care and a full diagnostic workup. The potential for severe maternal and fetal compromise with worsening hypoxia, plus potentially difficult maternal airway management, mandates early recognition and action. Conditions where progressive hypoxia may be expected, such as severe COVID19 infection (see below), should be managed in an appropriate environment immediately with early referral to the ICU.

10.4 Intensive care management

Although mostly beyond the scope of this document, the management of obstetric sepsis in the ICU is similar to that of the non-obstetric patient. There is an extremely limited evidence base regarding intensive care management of obstetric patients in general, and no specific evidence available for the patient with sepsis.

As in the non-obstetric patient, ICU management in the obstetric population involves maintenance of physiological parameters and organ supports (supportive care) with directed care as and when possible (targeted antibiotic therapy, source control etc). Both invasive (e.g. intra-arterial access, central venous access) and non-invasive modalities such as echocardiography are used for close monitoring and to obtain detailed physiological data. Other invasive monitoring tools such as pulmonary artery catheterisation or intracranial pressure monitoring are used on a case by case basis. The normal physiological changes of pregnancy should be kept in mind when interpreting the data obtained.

In addition to the sepsis management and resuscitation described above, ongoing management principles include optimisation of volume status, maintenance of cardiac output, blood pressure and tissue perfusion, maintenance of metabolic homeostasis (including acid base and glucose status) and the provision of adequate oxygenation and ventilation. Every effort should be made to preserve tissue oxygenation and placental perfusion, with vasopressors (and less commonly inotropes) being utilised as in the non-pregnant population. Although there is a paucity of data, the recommended first line vasopressor in this situation is noradrenaline, aiming for a (titrated) mean arterial pressure of 65mmHg.[98, 212] Other organ supports employed will depend on the organ systems affected and the nature of the site/presentation/manifestation of sepsis and its subsequent complications.

COVID19 has been discussed elsewhere in this position statement. It has been noted that, at least early in the pandemic, all-cause mortality and ICU admission rates were significantly higher in pregnant/recently postpartum women with COVID19 than in pregnant/postpartum women without COVID19. [213] COVID19 illness requiring ICU management usually takes the form of hypoxic respiratory failure and the acute respiratory distress syndrome (ARDS). Like other ICU management, management of ARDS in pregnancy largely mirrors that of the non-pregnant patient, although greater care needs to be taken in maintaining adequate oxygenation and ventilation to avoid uteroplacental flow reduction and fetal hypoxia/acidosis. This results in aims that are often tighter than in the non-pregnant population: targets usually suggested are arterial partial pressures of oxygen of >70mmHg, and carbon dioxide <60mmHg[213] A recent study showed that ventilatory parameters in these women are similar to the non-pregnant ventilated COVID19 population.[214] Rescue therapies for refractory hypoxia in the non-pregnant population have been successfully used in pregnant and postpartum women. These include prone positioning[215] (which has a proven mortality benefit in non-pregnant ARDS[216]), inhaled nitric oxide[217] and extracorporeal membrane oxygenation (ECMO).[218]

Prone positioning in pregnancy provides logistical challenges: specifically managing the gravid uterus requires education and training. The following link provides guidance on how this can be undertaken safely and appropriately https://youtu.be/7orutHYuXFQ.

General ICU management of these patients includes deep venous thrombosis (DVT) prophylaxis, adequate analgesia, skin protection and care, stress ulcer prophylaxis, bowel care and the provision of adequate nutrition (oral, enteral or parenteral, being mindful of the increased demands of pregnancy).

In the case of the still pregnant patient, certain extra principles should be observed, see Table 10.3 below.

Table 10.3: Unique considerations when caring for pregnant ICU patients

Considerations/practice points when caring for the pregnant ICU patient
• Fetal wellbeing should be considered when setting physiological targets and monitoring should be undertaken by the obstetric team. There is minimal evidence available to guide practice.
• Care with medication prescribing
• Avoid supine positioning with maintenance of lateral tilt at all times.
• Delivery may be required for maternal or fetal indications.

10.5 Delivery in ICU

Delivery in the maternal ICU setting may need to be undertaken for maternal or fetal (obstetric) indications. This is a complex decision that requires multidisciplinary input from all members of the treating teams and is always made on a case by case basis.

In the case of the immediately postpartum woman midwifery care should be integrated to monitor perineal health, breast care and lactation issues, especially in the unconscious patient. It is important to facilitate contact between mother and newborn when appropriate to do so.

11. Midwifery and Nursing Care for Pregnant and Postnatal Women with Suspected or Proven Sepsis

KEY POINTS

In antenatal, birthing and postnatal women with suspected or proven sepsis:

- **Generate a multi-disciplinary, women-centred care plan**
- **Define the scope of practice for midwives and nurses caring for septic women**
- **Recognise the critical role of midwives, perinatal nurses and lactation consultants in the care and support of pregnant, birthing and postnatal women with suspected or proven sepsis**
- **Following delivery, facilitate mother-baby interaction and the woman's emotional response to birth including skin to skin contact with the baby and assistance with breastfeeding in the context of any additional monitoring or management required for management of sepsis**
- **Providing a timely and comprehensive written clinical handover to the woman's GP is required**

Antenatal, birthing and postpartum women with suspected or proven sepsis are experiencing an unexpected pathological event in the context of what should be a natural process of pregnancy. Midwives play a pivotal role in monitoring and co-ordination of the multi-disciplinary team, helping manage sepsis in parallel to the management of pregnancy, birthing and postnatal care. Midwives play an important role advocating for the patient and providing holistic care when sepsis occurs. Recognition of the special needs of this patient group will ensure appropriate consideration of their critical health issues as well as acknowledgement and recognition of the routine aspects of their care.

11.1 Developing a multi-disciplinary, women-centered approach to care

Appropriate planning for antenatal/birthing/postnatal women with suspected or proven sepsis involves ensuring that there is a co-ordinated multi-disciplinary women-centred plan in place. There is a spectrum of complexity and acuity of the care required and the site of care may vary from the antenatal ward to birthing unit, high dependency unit or intensive care unit. In clinical areas outside of maternity, it is essential to ensure the ongoing involvement of Midwives, Nurses and Lactation Consultants. A woman-centred care plan will highlight the wishes of the woman and her family as well as the needs of her baby. Additional allied health members may be required to assist with the care of a woman with sepsis including physiotherapists, social workers and perinatal mental health workers.

Some facilities may not have guidelines on managing high risk women outside of the maternity ward. All units are encouraged to participate in regular robust multidisciplinary care planning and simulation training for potential critical events.

Planning should consider the following issues:

11.1.1 Staffing

The scope of practice and expertise of staff needs to be considered when allocating who will care for septic maternity patients. Ideally staff who are dual trained as both Registered Nurses and Midwives care for these women with consideration taken into account on what specific skills will be required. Staff who are Registered Nurses or Registered Midwives alone may not be able to provide all aspects of clinical care for an unwell antenatal/birthing/postnatal woman with the scope of practice differing between professions (see Table 11). With no dedicated maternal ICU's it has become regular practice for facilities to send Midwives from maternity to attend to the care of a women in ICU, or for critical care Nurses to attend birth suite to monitor a patient. To ensure that the patient is safe in whatever environment they are cared for the following needs to be considered;

- The skill set of the Midwife and Registered Nurse. This may include the need for critical care nurses for invasive hemodynamic monitoring, or management of inotropes or respiratory support as well as midwifery staff for assessment of fetal well being, monitoring and management of labour.
- Ensuring safe patient ratios - critical care nursing as well as sufficient midwifery care in each location
- If possible - maintaining the continuity of carer from a midwifery perspective should be maintained. Knowing the patient wishes and gaining consent, reducing stress on the new parents being cared for by a known carer.

11.1.2 Location of care

Pregnancy and birth are family events with partners, other family members and friends frequently being part of the support team. Where appropriate, provision for more liberal visiting and family involvement should be encouraged and may be required to assist with care and maintain emotional support for the woman and her baby.

In each location ensure the availability of emergency equipment specific to antenatal/birthing/postnatal woman. This should include an emergency birthing set, particularly in non-maternity settings as well as breastfeeding assistance. Following delivery, consider optimising the care setting for postnatal woman to ensure opportunity for babies to "room-in" or ensure frequent visits whenever possible. When it is not logistically possible for a new mother to physically see her baby, a contingency plan should be present that allows virtual viewing of her baby and communication with staff caring for her baby through means such as video calls.

11.1.3 Care of the mother-baby relationship

If the woman is being cared for in a non-maternity setting, where rooming in is not possible, the needs of the mother-baby unit as well as other family members must be considered. If the baby is well, they may be admitted to the Special care Nursery as a "boarder baby" or even discharged home. Unwell or premature babies themselves will require specialized neonatal critical care. Neonatal Intensive Care or Special Care Nursery staff should be part of the care team to ensure the woman and her family are regularly updated on the baby's condition and wellbeing, and assist with regular contact depending on the mother's condition. Ideally this is regular physical contact but if not possible, regular 'virtual' contact is scheduled. There may be infection control concerns between mother and baby and other family members and these concerns should be discussed as part of the multi-disciplinary plan and prioritise the mother-baby relationship. Clear documentation and visible communication such as signage of what precautions are required including the use of personal protective equipment need to be advised.

If a miscarriage or stillbirth has occurred or it is not possible to have contact with the baby, the mother will still need follow up contact with a midwife or dedicated bereavement staff. To ensure a woman receives appropriate and seamless care in the community, providing a comprehensive and timely handover to the woman's general practitioner and potentially her maternal child health nurse is critical.

11.2 Support for women with suspected or proven sepsis after birth

11.2.1 Postpartum

Emergency births and complex maternal situations such as may occur with sepsis can be associated with ongoing trauma for many women. There is some evidence that supports mother-baby closeness to help prevent this trauma having a long term effect[219].

Table 11.1 Comparison of Scope of Practice for Critical Care Nurses and Midwives

Scope of Practice	Critical Care Nurse	Midwife
IV Cannulation	Yes	Yes*
Administration of IV Antibiotics	Yes	Yes
Basic Observations	Yes	Yes
Fetal Monitoring – Antenatal / Intrapartum	No	Yes
Administration of Inotropes	Yes	No
Ability to set up and monitor Telemetry	Yes	No
Invasive Blood Pressure Monitoring – Art Line	Yes	No
Basic Life Support	Yes	Yes
Advanced Life Support	Yes	No
Non-Invasive Ventilation	Yes	No
Mechanical Ventilation	Yes*	No
Establishing Breastfeeding	No	Yes
Maintaining Breastfeeding	No	Yes
Assisting with cares of the newborn	No	Yes
Obstetric Postnatal Observations	No	Yes
Breast and Perineal Care	No	Yes

* Indicates extended scope of practice

11.2.2 Skin to Skin Contact

Mother-baby closeness through immediate and undisturbed skin-to-skin contact after birth is a globally recommended practice for all women and their babies [220-222]. This activity has been shown to support the physiological release of maternal hormones that initiate the processes of separation and birth of the placenta, involution of the uterus and minimalizing of uterine blood loss[222]. Skin-to-skin contact also supports the newborn's physiological transition at birth by regulating their heart rate, respiratory rate and temperature. Once stable, the newborn has inbuilt capacity to seek, attach and suckle at the breast for their first feed. At the same time, maternal hormones are readying the colostrum for ejection as the baby carries out important breast-seeking behaviours resulting in breastfeeding.

Critical care settings are not routinely set up to achieve the quiet and safe environment which promotes these physiological and life-sustaining events. However, with planning and communication, between the multidisciplinary team members, consideration can be given as to whether the mother is well enough for regular opportunities for undisturbed skin-to-skin contact between herself and the baby. If possible, frequent breastfeeding should also be encouraged. If mother-baby contact is intermittent the mother may need to express breastmilk when the baby is not with her at the times when the baby would normally be feeding. It is important to note the following:

- Where possible, the woman's infant feeding plans should be discussed prior to birth and documented.
- The critically unwell postnatal woman who is breastfeeding may benefit from referral to a Lactation Consultant.
- If the woman wishes to breastfeed whilst being cared for in a critical care area a Midwife will need to be available to assist her with breastfeeding or expressing.
- The diagnosis and management of sepsis including intravenous fluids and first line antibiotics, even in the extremely unwell woman, is rarely a contraindication for breastfeeding. In the event that a specific antibiotic is required and there are concerns about compatibility with breastfeeding, suitable specialist advice should be sought, see appendix 4.

11.2.3 Fetal demise or minimal mother-baby contact

If fetal demise has occurred as a result of maternal sepsis, or it is not possible to have contact with the baby, the mother will still need midwifery care as well as psychosocial support and follow up with dedicated bereavement staff. Contacting her GP is essential to ensure ongoing community care.

Appendix 1:
Obstetrically Modified SOFA Score (omSOFA)

The obstetrically modified SOFA (omSOFA) score allows a score to be calculated based on the severity of various biochemical result, clinical signs and clinical interventions.

System Parameter	Score		
	0	1	2
Respiration PaO_2/FIO_2	≥400	300 - <400	<300
Coagulation Platelets,x10^6/L	≥150	100-150	<100
Liver Bilirubin (µmol/L)	≤20	20-32	>32
Cardiovascular Mean Arterial Pressure(mm Hg)	MAP≥70	MAP<70	Vasopressors required
Central Nervous System	Alert/Oriented	Rousable by voice	Rousable by pain
Renal Creatinine (µmol/L)	≤90	90-120	>120

Appendix 2: Page 1

Flowchart for Management of Maternal Patients with Sepsis

Management of Sepsis in Maternal Patients Summary

Early recognition and prompt management of the septic woman is key. Consider sepsis in women with signs or symptoms, risk factors and/or altered physiology or lab investigations. **Do not wait for Obstetric review to treat patient. Red Flags** may indicate sepsis in the pregnant woman and trigger empiric therapy: Pregnancy considerations are included below.

Sepsis management after 1 week postpartum is same as other non-pregnant women with additional considerations (breast feeding and potential sources of sepsis (Retained products of conception/mastitis/wound).

Recognise

Are there signs and symptoms of infection?

- Fevers/rigors
- Dysuria/urinary frequency
- Offensive vaginal loss
- Cough, shortness of breath
- Cellulitis (IVC sites, mastitis, wound)
- Vomiting, diarrhoea, abdominal/pelvic pain, peritonism
- Headache, neck stiffness, new confusion, change in behaviour, altered consciousness

Are there risk factors for sepsis?

- Indwelling devices (IV lines, IDC)
- Prolonged rupture of membranes
- Immunosuppression: Neutropenia, medication HIV, transplant, splenectomy
- Complicated Obstetric history, cervical cerclage
- Recent surgery or invasive procedure
- Co-morbidities: Obesity, diabetes
- Group B Strep positive

Are there abnormal vital signs?

Observation	Abnormal
HR (bpm)	>/=110 (or >15 over baseline)
SBP (mmhg)	<90
MAP (mmHg)	<65
RR (bpm)	>25
O2 saturation (%)	</=95
Temperature (°C)	>/=38 or <35.9

Are there abnormal lab investigations?

Normal Range in Pregnancy	Abnormal
pH [7.4-7.47]	<7.32
PaO2 [mmHg]	<93
PaC02 mm Hg [25-33]	>34
Bicarbonate mmol/L [16-22]	<16
Lactate mmol/L [<1.8]	>2
WCC x10^9/L [6-17]	<5 or >17
Platelets x10^9/L [150-420]	<100
Cr µmol/L [<80]	>90
ALT U/L [<33] AST [<33]	>33

- Tachycardia and tachypnoea occur earlier than hypotension. BP decompensation is a late sign and will demand more intensive resuscitative management.
- Fever and symptoms related to the gastrointestinal, respiratory and urinary tract are common with Group A Streptococcal (Strep pyogenes) sepsis from a pregnancy source.
- The earliest sign of fetal hypoperfusion may be an abnormal CTG, e.g. sustained fetal tachycardia, bradycardia, stillbirth.
- Recognition is a prompt to escalate care if able: Emergency Department > Urgent Senior Emergency Medical Team review; Ward > Rapid Response Team

Resuscitate

- Ensure Patent Airway
- Start SpO2 monitoring and supplemental SpO2 if </= 95%
- Ensure large bore IV access, Collect TWO sets of blood cultures (separate sites), FBE, EUC, LFTs, Coags, Lactate. Collect other cultures if required e.g. urine, stool, genital, wound swabs, viral resp swabs CXR unless alternate source is clear and no respiratory compromise

THIS MUST NOT DELAY ANTIBIOTICS

- Give IV crystalloid (0.9% Saline or CSL) — aim SBP >90mmHg. Monitor for fluid overload.
- If BP inadequate after 20mls/kg (up to 2L fluid), notify ICU and prepare for ionotropes
- CTG or Doppler of fetus +/- Fetal US

Appendix 2: Page 2

Flowchart for Management of Maternal Patients with Sepsis

Management of Sepsis in Maternal Patients Summary

Respond

GIVE ANTIBIOTICS: Empirical - Give in the following order:

- Aus: amoxicillin/ampicillin 2g IV q6h/ NZ: cefuroxime 1.5g IV q8h PLUS aminoglycoside* e.g. gentamicin 4-7me/kg (first dose} IV PLUS metronidazole 500mg IV q12h.
- If Penicillin allergic give Aus/NZ: Clindamycin 600mg IV q8h PLUS aminoglycoside e.g. gentamicin 4-7mg/kg (first dose)
- If at risk of MRSA sepsis ADD vancomycin 25-30mg/kg (loading dose) IV
- If at risk of Group A Streptococcal (GAS}(Strep Pyogenes) ADD: clindamycin 600mg IV q8h
- If at risk of Influenza ADD: Oseltamivir 75mg oral BD
- If suspected Covid: consult local guideline for management of Covid in pregnancy.

Inotropes: Noradrenaline as per local administration policy as first line +/- temporising with peripheral metaraminol 0.5mg aliquots IV. Femoral lines for administration ideally avoided due to increased infection risk, difficult access due to pregnant abdomen, increased DVT risk, difficulty tying flat with left pelvic tilt.

Source control: Seek source at all indwelling lines, urinary, genital and respiratory tract and surgical wounds including previous vascular access sites. Chorioamnionitis should be suspected with abnormal fetal observations, abdominal pain, gastrointestinal symptoms, ruptured membranes or PV discharge. Concems/suspicion re chorioamnionitis -> urgent O+G assessment and management.

Other Considerations

- Uterine displacement (wedge hip, manual displacement or left lateral positioning)
- Antipyretics: paracetamol 1g PO/IV - avoid Non-steroidal anti-inflammatories
- Thromboprophylaxis with Low Molecular Weight Heparin (e.g. enoxaparin 40mg SC daily) after renal function, platelets, coagulation and the likelihood for neuraxial anaesthesia or surgery has been assessed
- Corticosteroids may be indicated for fetal lung maturation in women at less than 34 weeks of gestation. Sepsis is not a contraindication to steroids.

Involvement of other teams

- Involve Obstetrics or Gynaecology, and if possible, an obstetric medicine physician at the earliest opportunity but do not delay management if awaiting review
- Infectious diseases, ICU and other specialty advice may be required depending on the cause and severity of sepsis
- ICU should be involved early if vital signs are outside normal range, if fluid resuscitation exceeds 2L, or inotropes are required, if mentation remains altered past initial resuscitation or if monitoring requirements exceed ward capabilities
- Liaise with nearest tertiary referral centre if retrieval and transfer of care is required
- Paediatrics/neonatology should be involved if viable delivery is being considered as an option

Reassess

Life-threatening maternal instability/cardio-pulmonary arrest

- In the event of an extremely unwell or rapidly deteriorating patient with pregnancy > 20 weeks, preparations should be made for the potential need for resuscitative hysterotomy, including identifying the most experienced clinician available who is capable of performing the procedure
- If cardio-pulmonary arrest occurs, in addition to standard resuscitation measures, the team should plan to commence resuscitative hysterotomy within 4 minutes. Do not delay waiting for an obstetrician or transfer to the operating theatre. The alm Is to deliver the fetus within 5 minutes of cardiac arrest.
- Indication for emergency Caesarean section for fetal distress (based on CTG / fetal US) should be guided by the obstetric service

*Use aminoglycoside advised by your local health service. BP - Blood Pressure; bpm - beats per minute; CRP - C-Reactive Protein; Cr – Creatinine; CSL - Compound Sodium Lactate (Hartmann's); CTG - Cardiotocography; EUC - Electrolytes, Urea, Creatinine; FBE - Full Blood Examination; HR - Heart Rate; ICU - Intensive Care Unit; IDC - Indwelling catheter; IV - Intravenous; kg - kilogram; LFTs - Liver Function Tests; mg – milligram; mls - milliliters; MRSA – Methicillin Resistant *Staphylococcus aureus*; NEURO - Neurological; NSAIDs - Non-Steroidal Anti-inflammatories; O & G - Obstetrics and Gynaecology; RR - Respiratory Rate – SBP - Systolic Blood Pressure; SpO2 - Saturation of peripheral oxygen; US - Ultrasound.

Appendix 3:

Pregnancy and Breastfeeding Medication Advisory Services

Australian Capital Territory
Canberra Health Services
Phone 02 5124 3333

New South Wales
MotherSafe at Royal Hospital for Women
Phone 02 9382 6539, **Toll free (NSW)** 1800 647 848

Queensland
Queensland Medicines Advice & Information Service
Royal Brisbane and Women's Hospital (NB: Queensland health professionals only)
Phone 07 3646 7098

South Australia
SA Pharmacy Medicines Information Service
Women's and Children's Hospital
Phone 08 8161 7555

Victoria
Monash Medicines Information
Phone 03 9594 2361
Royal Women's Hospital
Phone 03 8345 3190

Western Australia
Obstetric Medicines Information Service
King Edward Memorial Hospital
Phone 08 6458 2723

Written Pregnancy and Breastfeeding Medication Resources

- *Australian Medicines Handbook* 2020 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2020 July. Available from: https://amhonline.amh.net.au/
- Jones, W. (2018). *Breastfeeding and medication*.2nd edition Routledge/Taylor & Francis Group.
- Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501922/
- Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment edited by Christof Schaefer, Paul W.J. Peters, Richard K Miller, 3rd edition 2015
- Drugs in Pregnancy and Lactation 8th Edition: A Reference Guide to Fetal and Neonatal Risk
- Gerald G Briggs, Roger K Freeman and Sumner J Yaffe.
  ISBN: 978-0-7817787-6-3.
  Wolters Kluwer/Lippincott Williams & Wilkins.
- Mother to Baby Available: https://mothertobaby.org/
- Royal Women's Hospital Pregnancy and Breastfeeding Medicine Guide
- REPROTOX® Database: https://reprotox.org/
- UK Teratology Information Service: http://www.uktis.org/

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