South Australian Perinatal Practice Guidelines

Ovarian Hyperstimulation Syndrome

Note:

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant woman. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of PPG

This guideline has been developed to assist in the assessment and management of women with ovarian hyperstimulation syndrome (OHSS).

Public-I4-A4

Government of South Australia
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Table of Contents

Summary of Practice Recommendations

- Ovarian hyperstimulation (OHSS) is an iatrogenic condition with the potential for uncommon, yet severe complications
- Initial assessment determines inpatient versus outpatient care
- Management focuses on provision of physiological and emotional support and prevention of morbidity
- The Gynaecology consultant on-call and the treating fertility specialist/ clinic must be notified of any case of moderate to severe OHSS
- RURAL & REMOTE WOMEN: Following oocyte retrieval of more than 17 oocytes, or if clinical suspicion of OHSS, it is recommended that women stay in the metropolitan area for at least 48 hours before travelling home

Abbreviations

AMH	Anti-mullerian hormone
ARDS	Adult respiratory distress syndrome
ART	Assisted reproductive technology
BMI	Body mass index
CBC	Complete blood count
CTPA	CT pulmonary angiogram
CVS	Central venous system
CXR	Chest X-ray
DVT	Deep venous thrombosis
FSH	Follicle stimulating hormone
hCG / HCG	Human chorionic gonadotropin
HDU	High dependency unit
ICU	Intensive care unit
IV	Intravenous
IVF	In vitro fertilisation
LFT's	Liver function tests
mg	Milligram(s)
mL	Millilitres
NSAID's	Non-steroid anti-inflammatory drugs
OHSS	Ovarian hyperstimulation syndrome
PCV	Packed cell volume
PCOS	Polycystic Ovarian Syndrome
K+	Potassium
PE	Pulmonary embolism
RCOG	Royal College of Obstetricians and Gynaecologists
Na	Sodium
TED	Thrombo-embolic stockings
USS	Ultrasound
VEGF	Vascular endothelial growth factor
V/Q scan	Ventilation / perfusion scan
>	Greater than
<	Less than

Definition

Ovarian hyperstimulation syndrome usually occurs as a complication of infertility treatment. Recent in vitro fertilisation (IVF) techniques have significantly reduced the incidence of OHSS, however the potential for severe illness remains and OHSS must be recognised and treated appropriately. Symptoms occur as an excessive response to ovarian stimulation with follicle stimulating hormone (e.g. Puregon, Gonal-F, Menopur, Elonva), or rarely Clomiphene – when hCG or luteinising hormone (LH) is also present.

Pathophysiology

Multiple ovarian follicles (>17) develop in response to FSH stimulation. When HCG or GnRH agonist is given to "trigger" release of these follicles, very high levels of vascular endothelial growth factor (VEGF) and other cytokines are produced by the ovaries. VEGF induces vascularisation of the multiple corpora lutea and also increases blood vessel permeability. There is leakage of fluid from the vasculature into the extravascular tissues – resulting in ascites, oedema and pleural or pericardial effusions. There is also a reduction in the circulating vascular volume - leading to haemoconcentration, thrombosis, reduced renal perfusion and oliguria (decreased urine output).

Aetiology

Almost always as a complication of infertility treatment, OHSS occurs in approximately 1% of antagonist IVF cycles, more so in agonist IVF cycles (approximately 3%, although some studies report an incidence of up to 8%).

Risk factors

- Polycystic Ovarian Syndrome (PCOS)
- Hypogonadotrophic hypogonadism
- Young age
- Low body mass index (BMI)
- Increased ovarian volume and high antral follicle count on baseline scan
- Elevated baseline measurements of anti-mullerian hormone (AMH)
- High treatment doses of FSH
- Rapidly rising / high oestrogen levels (>10,000pmol/L)
- Large number of oocytes collected (>17).

Clinical presentation

Early

Within 7 days of HCG “trigger” injection.

Late

10 days after HCG injection (usually associated with a positive pregnancy test)

- tends to be more prolonged and severe.

Clinical features

- Lower abdominal pain and bloating
- Nausea, vomiting and diarrhoea
- Shortness of breath, decreased exercise tolerance
- Vulval and peripheral oedema, ascites and pleural effusions.
- Cerebral Oedema (Confusion)

RCOG proposed classification of severity of OHSS

Table 3. Proposed RCOG classification of severity of OHSS

Category	Features
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually < 8 cm[a]
Moderate OHSS	Moderate abdominal pain Nausea ± vomiting Ultrasound evidence of ascites Ovarian size usually 8–12 cm[a]
Severe OHSS	Clinical ascites (± hydrothorax) Oliguria (< 300 ml/day or < 30 ml/hour) Haematocrit > 0.45 Hyponatraemia (sodium < 135 mmol/l) Hypo-osmolality (osmolality < 282 mOsm/kg) Hyperkalaemia (potassium > 5 mmol/l) Hypoproteinaemia (serum albumin < 35 g/l) Ovarian size usually > 12 cm[a]
Critical OHSS	Tense ascites/large hydrothorax Haematocrit > 0.55 White cell count > 25 000/ml Oliguria/anuria Thromboembolism Acute respiratory distress syndrome

[a] Ovarian size may not correlate with severity of OHSS in cases of assisted reproduction because of the effect of follicular aspiration. Women demonstrating any feature of severe or critical OHSS should be classified in that category.

Complications of OHSS

- Deep venous thrombosis (DVT)
- Pulmonary embolism (PE)
- Arterial thrombosis
- Internal jugular vein thrombosis and stroke
  - dizziness, neck pain, loss of vision
- Renal failure
- Adult respiratory distress syndrome (ARDS)/ Respiratory failure
- Cerebral Oedema
- Ovarian torsion
- Ileus
- Ascites
- Pericardial effusions (rarely)

Initial assessment

History

Examination

- General including weight and abdominal girth
- CVS
- Respiratory
- Abdominal

Consider differential diagnosis if severe pain or pyrexia (e.g. pelvic abscess, ovarian torsion, bowel perforation, ectopic pregnancy, appendicitis etc)

Investigations

Complete blood count (CBC)

- Haemoconcentration with PCV > 0.38
- White Cell Count (WCC) >16

Urea and electrolytes

- Hyponatraemia with Na+ <130
- Mildly elevated potassium
- Deranged Liver function tests (LFT's)

Coagulation profile

- Elevated Coagulation and D-dimers
- Elevated fibrinogen
- Reduced anti-thrombin III levels

HCG if >16 days after oocyte collection

Investigations to consider if clinically indicated

USS with Doppler's - if ovarian torsion suspected

- Enlarged ovaries with multiple cysts (+/- areas of small haemorrhage within the follicles) and small - moderate free fluid is usual following ovarian stimulation

Chest X-ray (CXR)

- Pleural or pericardial effusions
- Interstitial oedema

Suspected pulmonary embolism:

- Chest X-ray
- ECG/Electrocardiography
- Arterial blood gases
- Definitive diagnosis by either CT pulmonary angiogram (CTPA) or ventilation/ perfusion (V/Q) scan - depending on local availability
    - Ventilation/perfusion (V/Q) scan: Discuss with radiologist as a ventilation/ perfusion mismatch may occur secondary to pleural effusions and pulmonary oedema, limiting diagnostic capability of test.

Management

OHSS is a self-limiting condition, but is exacerbated by pregnancy. The treatment objectives are to support the woman and prevent complications, until vascular leakage resolves (days to weeks). The majority of women with OHSS are managed as outpatients, with daily communication. Outpatient management is suitable for women with mild to moderate OHSS.

Mild OHSS

Clinical presentation:

- Mild symptoms
- Able to maintain oral intake / no vomiting
- Maintenance of urine output
- No shortness of breath (or pleural effusions on examination)
- Not requiring opioid analgesia
- No evidence of significant haemoconcentration (PCV < 0.45)
- Supported at home.

Management of mild OHSS includes:

- Reassurance
- Encouragement of oral fluid intake (approx. 2L water daily)
- Education regarding symptoms and when to seek further help:
    - Increasing abdominal bloating / abdominal pain / leg pain
    - Nausea, vomiting, diarrhoea
    - Shortness of breath
    - Reduced urine output
- Arrange follow-up appointment in 2-3 days and provide 24hr emergency contact number. Follow-up will be provided by the treating ART clinician.
- Encourage to gently mobilise - but to avoid intercourse and strenuous activity
- Consider need for thromboprophylaxis with low molecular weight heparin (LMWH)
    - Decision regarding stat dose versus longer duration of treatment should be individualized and discussed with a consultant.

Admission and inpatient management is required if women present with:

- Pain requiring parenteral analgesia
- Moderate/severe dehydration and unable to maintain oral intake
- Tachycardia, hypotension
- Shortness of breath/ Pleural effusions
- Suspected thrombosis
- Oliguria
- Haemoconcentration/ Electrolyte disturbance:
    - PCV > 0.45 (haematocrit >45%)
    - WCC >16,000
    - Na+ < 135, K+ > 5.0
    - Abnormal liver function tests
    - Albumin < 26 – *although predictive value uncertain*
- Or if unsupported at home.

Inpatient Management

If a woman presents with OHSS to an emergency department, the gynaecological team should be notified and the gynaecological consultant on call must be advised of admission.

If the woman is under the care of a fertility clinic, please ensure that the On call consultant gynaecologist or clinical nurse at that clinic is also notified of the woman's presentation.

Notify consultant of any significant changes in condition. Transfer to a high dependency unit or intensive care unit may be required.

Ongoing assessment and management

OHSS requires ongoing assessment and careful management:

- Observations every 4 hours:
  - Temperature, pulse rate, blood pressure, respiratory rate, oxygen saturation
- Strict fluid balance chart
- Daily girth and weight
- Daily Examination:
  - Chest auscultation – looking for development of pleural effusions
  - Abdominal palpation – tenseness of ascites
  - Check calves – swelling and tenderness
- Daily blood tests (May be required every 12 hours if abnormal or if oliguria)
  - Complete blood count
  - Urea, electrolytes, liver function tests
  - +/- Coagulation studies – *not routinely recommended.*
- Thromboprophylaxis
  - TED stockings
  - Enoxaparin 40 mg subcutaneous daily
  - Mobilise as able
- Antiemetics
- Analgesia
  - Paracetamol and opioids as required
  - Avoid Non-Steroid Anti-Inflammatory Drugs (NSAID's) - due to effects on renal function and possibility of pregnancy

If pain is severe or unilateral → consider ovarian torsion →arrange Ultrasound with Doppler's +/- surgical intervention.

Remember that in the event of torsion, evidence suggests de-torsion over oophorectomy as most ovaries are salvageable (even if black).

Fluid management principles

Restrict fluid intake to 2.0-2.5 litres daily (oral plus IV)

- oral route is preferred where practical
- avoid potassium (K+) supplementation

Aim to keep urine output 30 – 50 mL / hour.

If oliguric (or unsure of urine output) - catheterize with hourly urine measurements and consider transfer of woman to a high dependency unit (HDU) or intensive care unit (ICU).

There is no indication for the routine use of diuretics.

IV Fluids

Initial bolus of 1L normal saline (sodium chloride 0.9%) intravenously, if significantly dehydrated

Normal saline (sodium chloride 0.9%) at 100 mL / hour initially, titrating to urine output.

If urine output < 30 mL / hour for 4 hours, then commence 4% albumin (500 mL at 100 mL / hour)

- Alternate with normal saline 0.9%
- *Albumin is often best utilized overnight as urine output is always reduced at night.*

If albumin is required, transfer woman to a HDU or ICU for close monitoring.

If remains oliguric (after 4% albumin) - start 20 % albumin (100 mL over 30 minutes).

If no improvement, and significant ascites is present consider paracentesis to improve renal blood flow.

Urinary tract infections may occur with prolonged catheterisation and should be treated with appropriate antibiotics.

Paracentesis (drainage of ascites)

Paracentesis is thought to decrease intra-abdominal pressure, therefore increasing renal blood flow and venous return. Use of paracentesis may reduce hospital stay. Consider for:

- Persistent oliguria
- Severe abdominal pain or tense ascites
- Respiratory compromise secondary to ascites.

Ascites drain to be inserted under ultrasound guidance (local anaesthetic or light sedation)

Drain 2 litres per 24 hours and clamp when daily drainage complete

- *It is uncertain as to how much ascitic fluid can be removed safely*

Albumin infusion may be required after repeated paracenteses.

Maintenance of respiratory function

If oxygen saturation decreased / respiratory compromise:

- Commence oxygen
- Arterial blood gases
- Consider draining ascites
- Physician review (suspected pulmonary embolism or infection)
- Consider drainage of pleural effusions
- Physiotherapy.

Management of concurrent pregnancy

HCG levels may not appear to double every 48 hours due to intravascular changes,

Avoid HCG injections - exacerbates OHSS, as longer-term stimulation of the corpus luteum

Progesterone pessaries are not contra-indicated.

Avoid medications that are harmful in early pregnancy.

Very occasionally termination of pregnancy is required for very severe OHSS.

Miscarriage risk does not appear to be increased by OHSS, however there may be a greater incidence of pre-eclampsia and prematurity.

Transfer to ICU

Transfer to ICU may be required if:

- Unable to maintain urine output / renal failure
- Significant pleural effusions and /or respiratory compromise
- Significant thromboembolic event.

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Acknowledgements

The South Australian Perinatal Practice Guidelines gratefully acknowledge the contribution of clinicians and other stakeholders who participated throughout the guideline development process particularly:

Write Group Lead
Dr Sally Reid

Write Group Members
Dr Bruno Radesic
Dr Kate Walsh
Dr Kris Bascomb

SAPPG Management Group Members
Sonia Angus
Dr Kris Bascomb
Lyn Bastian
Elizabeth Bennett
Dr Feisal Chenia
John Coomblas
A/Prof Rosalie Grivell
Dr Sue Kennedy-Andrews
Jackie Kitschke
Catherine Leggett
Dr Anupam Parange
Dr Andrew McPhee
Rebecca Smith
A/Prof John Svigos
Dr Laura Willington

Document Ownership & History

Developed by: SA Maternal, Neonatal and Gynaecology Community of Practice
Contact: HealthCYWHSPerinatalProtocol@sa.gov.au
Endorsed by: SA Safety and Quality Strategic Governance Committee
Next review due: 05/07/2023
ISBN number: 978-1-76083-018-2
PDS reference: CG300
Policy history: Is this a new policy? **N**
Does this policy amend or update and existing policy? **Y**
If so, which version? V2
Does this policy replace another policy with a different title? **N**
If so, which policy (title)?

Approval Date	Version	Who approved New/Revised Version	Reason for Change
05/07/2018	V3	SA Health Safety & Quality Strategic Governance Committee	Reviewed in line with scheduled review date of 5 years
30/12/2012	V2	SA Health Safety & Quality Strategic Governance Committee	Minor amendment
17/07/2012	V1	SA Maternal & Neonatal Network	Original approved version