The Weekly Probe

12th February 2016 **Volume 13 Issue 2**

New Heparin Charts- there are new heparin charts with a section for the anticoagulation of stroke patients (after discussing with the neurologist). There is also a place to write in the indication / protocol being used. Otherwise the principles of prescribing remain the same.

Message Centre- please remember to check the Message Centre for results of patients you have seen, in addition to orders that have been made under your name. At time results are amended or arrive well after the patient is discharged, so it helps you in terms of your education and feedback, and it helps the patient. If you do not know what to do with a result speak to one of the Staff Specialists.

THIS WEEK

OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

A 35yo lady with a presents with diffuse abdo pain and swelling 1 day after after having her eggs harvested as part of her IVF treatment. She is tachycardic, afebrile, BP 100/60 and is noted to have diffuse abdo tenderness with shifting dullness. On ED US she has small bilateral pleural effusions in addition to moderate amount of ascites. She is diagnosed as OHSS ? cyst rupture – her Fertility Clinic advice sheet advises lasix – she is later given saline, morphine and admitted under O&G.

25yo with hx of polycystic ovarian disease 7 weeks pregnant after course of clomiphene presents with acute abdomen – O/E BP 90 syst – peritonitic abdomen – taken to OT – found to have multiple ovarian cysts with ascitic fluid ++

What is OHSS? This is taken from 2 articles - Ovarian hyperstimulation Syndrome Budev, Critical care Medicine October 2005, pp S301-S306 & Ovarian Hyperstimulation Syndrome: Facts and Fallacies Beerendonk 53(7), July 1998, pp 439-449 Obstetrical and Gynaecological Survey

With an increasing maternal age and aggressive infertility treatment protocols including the development of IVF and cryopreservation (with the goal of obtaining sufficient numbers of oocytes and embryos), we have seen a rise in the incidence of OHSS.
Ovarian hyperstimulation syndrome (OHSS) is a potentially fatal, rare iatrogenic complication of ovarian stimulation usually occurring during the luteal phase or during the early part of pregnancy. Since the original descriptions of OHSS, it appears that OHSS is a potential complication of ovarian induction by almost every agent used for ovarian stimulation. OHSS is thought of as the loss of control over the intended therapeutic hyperstimulation of the ovaries. Severe or life-threatening forms of OHSS can lead to multiple complications necessitating ED presentations. The prevalence of the severe form of OHSS is small (0.5-5% of stimulated ovarian cycles) - however the incidence is increasing.
The most common form of OHSS occurs a few days after follicular rupture or follicular aspiration for IVF after follicular growth has been medically stimulated or induced with the administration of either gonadotropins, or rarely clomiphene (Clomid). Gonadotrophin-releasing hormore agonist or antagonists do not cause OHSS but are typically used in combination and may exacerbate the process. Rare cases have been described of a spontaneous form of OHSS, which may present in the absence of any treatment at the beginning of a spontaneous pregnancy.

The cardinal features of OHSS include marked ovarian enlargement due to ovarian stimulation leading to overproduction of ovarian hormones and vasoactive substances (especially vascular endothelial growth factor), which contribute to an increase in capillary membrane permeability and acute third space fluid sequestration in the form of ascites, hydrothorax, and anasarca. The fluid shift from the intravascular space to the interstitial spaces contributes most to the mortality associated with OHSS. The clinical manifestations are a result of the increased capillary membrane permeability resulting in a loss of protein-rich fluid. A massive extracellular exudative fluid accumulation in addition to severe intravascular volume depletion and hemoconcentration eventually leads to multiple organ failure.

The aetiology of OHSS is complex and many aspects remain unclear, but it appears that hCG, whether exogenous or endogenous (e.g., pregnancy derived), is a central factor in triggering OHSS.

Multiple risk factors have been implicated in the development of OHSS including age <35 yrs, low body mass, polycystic ovary syn, Hx of atopy or allergy, previous episodes of OHSS, increased numbers of developing follicles, higher or repeated doses of exogenous human hCG, gonadotrophin –releasing hormone agonist protocol and pregnancy.

There are multiple grades of OHSS based on the severity of symptoms, signs, and laboratory findings – alternatively we can divide the symptoms to mild-mod-severe.

OHSS

Grade	Mild	Moderate	Severe
1	Abdominal distension and discomfort		
2	Features of grade 1 plus nausea, vomiting, and/or diarrhea Ovaries are enlarged to 5–12 cm		
3		Features of mild OHSS plus ultrasonic evidence of ascites	
4			Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or breathing difficulties
5			All of the above plus change in blood volume, increased blood viscosity due to hemoconcentration, coagulation abnormalities, and diminished renal perfusion and function

The clinical symptoms and signs of OHSS are a result of marked circulatory dysfunction secondary to increased vascular permeability and marked arterial dilation leading to fluid shifts from the intravascular to the extravascular space. This fluid shift is considered the cardinal event of OHSS.

The first indication of OHSS is the formation of a small amount of ascites found on ultrasonographic evaluation. But massive accumulation of extravascular exudates can lead to tense ascites, pleural or pericardial effusions, electrolyte derangements, oliguric renal failure, haemoconcentration, and hypovolemia with or without hypovolemic shock.

Initial symptoms of early OHSS begin gradually with bloating and abdominal discomfort, which may progress to severe emesis, diarrhoea, shortness of breath, reduced urine output, and subsequent accumulation of palpable ascites after day 7, suggesting potentially severe OHSS. The cystic ovaries may enlarge and reach large sizes >12 cm with the potential to rupture or haemorrhage or lead to torsion and severe abdominal pain. Ultrasound examination of patients with OHSS usually reveals enlarged ovaries with numerous follicular cysts and ascites. Abdominal computed tomography can also be used to visualize ovarian enlargement and ascites in patients with OHSS. Physical exam in patients with severe OHSS may reveal weight gain and increased abdominal girth due to ascites and signs of hypovolaemia.

Several pathology changes may occur, including:

- increase in hematocrit indicating haemoconcentration (haematocrit >45%), leukocytosis, and thrombocytosis, which reflect a general inflammatory state as well as haemoconcentration.

- Ascites is often found in conjunction with oliguria with decreased urinary sodium excretion and hyponatraemia (with associated symptoms and complications) due to a low serum osmolality.
- Hyperkalaemia, metabolic acidosis, oliguria and renal dysfunction may be seen .
- Liver abnormalities in OHSS include elevated levels of AST & ALT in about 30% of patients with severe OHSS, which can sometimes be associated with an elevation in GGT or SAP.
- A relative immunodeficient state is present in patients with severe OHSS due to lower levels of immunoglobulins including IgG and IgA, potentially placing these patients at a higher risk for nosocomial infections. More than 83% of patients with severe OHSS will have at least one febrile episode for 24 hrs. In approximately one third of these cases, the fever can be attributed to infection (in most situations due to urinary tract infection), but in more than two thirds of cases no infectious agent can be identified. In febrile patients in whom infection was the aetiology, the causative responsible organisms included *Proteus mirabilis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *E. coli*, *Morganella morganii*, and *Proteus vulgaris*. Other sources of fever may include endogenous production of cytokines.
- OHSS can be complicated by thromboembolic events in up to 10% with severe cases. Remember this can be in uncommon locations such as arms or cerebral vessels.
- Pulmonary complications include pneumonia, PE, hydrothorax, collapse and ARDS.

Treatment
The treatment of OHSS is aimed at supportive conservative measures until the condition resolves.

Liaise with the treating O&G specialist / fertility centre or the O&G staff on-call. In most cases, the syndrome follows a self-limiting course that parallels the decline in serum hCG. Patients with mild manifestation of OHSS can be managed in the outpatient setting with oral analgesics and careful monitoring for syndrome progression. Worsening OHSS or escalation in symptoms and signs can still be monitored in the outpatient setting but with a low threshold for hospitalisation. Although the moderate form of OHSS usually subsides within 2–3 wks, patients may progress to severe or life-threatening disease rapidly, especially if pregnancy occurs. Close observation of these patients is recommended, and serial estimations of B-hCG should be followed to confirm conception.

In patients with moderate or severe OHSS, pelvic examination should be avoided to decrease the risk of ovarian cyst rupture and possible potential acute intra-abdominal haemorrhage. In severe OHSS, assessment of the hemodynamic and respiratory status is the initial step in the management of this high-risk condition with IDC (to monitor urine output + abdominal pressures().
An abdominal US is required to ascertain the size of the ovaries and to determine the presence of ascites. Look for and treat pulmonary complications – look for pericardial effusion (echo).

Medical therapy should be aimed at maintaining effective circulating volume and mobilizing fluid from the third space back into the vessels and preventing and countering haemoconcentration. Normal saline with or without dextrose is the crystalloid fluid of choice, but in severe cases albumin can be used as a plasma expander in cases of severe haemoconcentration (haematocrit >45%), severe hypoalbuminaemia (serum albumin level <3.0 g/dL), or tense ascites (note no randomised trials on albumin as a treatment (though of benefit as a prophylactic agent).
Prophylactic anticoagulation.
Abdominal paracentesis is the most common procedure performed in severe cases of OHSS. Paracentesis may be needed for symptomatic relief of tense ascites (especially if evidence of abdominal compartment syndrome- see below) but may also indicated in the setting of oliguria, increasing creatinine or decreasing creatinine clearance, and haemoconcentration refractory to medical therapy. Evacuation of a large volume of ascitic fluid allows for decreased abdominal pressure and improvement in renal blood flow, venous return, and cardiac output. In an effort to avoid puncture of the enlarged ovarian cysts, ultrasound-guided needle paracentesis (transabdominal or transvaginal) may be indicated. The volume of fluid removed at any one occasion or how often ascitic fluid should be removed has not been established. Note however that large volume ascites removal may lead to rapid accumulation of ascites and further depletes proteins lost from the intravascular compartment. In turn, this low intravascular protein concentration leads to further accumulation of fluid within the pleural and peritoneal space.
No large studies on NSAIDS
Surgical intervention for OHSS should be avoided unless haemorrhage of an ovarian cyst, cystic rupture, or torsion of the ovary is suspected.

ABDOMINAL COMPARTMENT SYNDROME & INTRA-ABDOMINAL HYPERTENSION

This is a topic we have not covered for a couple of years yet worth revising in the context of the above presentation. It is a topic of particular relevance to Liverpool with some world leaders on the topic having graced our corridors in the past and present– Sugrue, Balogh and Damours (from “Sidney”)- see WCACS link below.

Increased IAP has been increasingly recognized as both cause and consequence of many adverse events in critically ill patients especially trauma patients. However how is it relevant to the care of our patients especially considering the prolonged stay we have for some pretty sick patients?

Compartment syndrome (CS) refers to a fixed compartment that becomes subject to increased pressure, whether from injury or other means, leading to reduced capillary circulation and resultant ischemia and organ dysfunction. CS occurs most frequently in the extremities (eg crush injuries, trauma etc) and we see the 5Ps – pain, paresthaesias, pallor, paralysis, and pulselessness.

The same issues can apply in the abdomen where there is a rise in the intra-abdominal pressure (IAP) above that of the microvascular, venous or rarely, arterial circulations.

ACS is defined as the adverse physiologic consequences that occur with an acute increase in IAP. The consensus statement from the World Society of the Abdominal Compartment Syndrome defines intra-abdominal hypertension (IAH) as an IAP ≥ 12 mm Hg and ACS as a sustained IAP of ≥ 20 mm Hg associated with new organ dysfunction or failure. IAPs have the following usual ranges based on the patient's condition: healthy adults, 0-5 mm Hg; critically ill adults, 5-7 mm Hg. To get an idea of how frequently this happens, a recent multicenter, prospective epidemiologic study reported that the mean IAP in all intensive care unit (ICU) admissions was 10 ± 4.8 mm Hg. Normal IAP (< 12 mm Hg) wee seen in 68%, 32% had an IAH > 12 mm Hg, and 4.2% had ACS. The prevalence of ACS in patients with IAH was 13%. The mortality rate was significantly higher in the group with IAH group compared with the non-IAH group.

What happens with a rise in IAP? There is a fall in cardiac output and stroke volume (IVC compression); most importantly a decrease in coeliac, mesenteric, and renal artery blood flow / GFR - thus there is a clear link between IAH and the development of acute kidney injury – may also have a role in development of hepatorenal syn; an increase in oxygen consumption; and a decrease in pH and PaO2 - mechanical effects on ventilation (reduced TV, decreased compliance, increased work etc).

Abdominal perfusion pressure (APP) is used to assess the severity and adequacy of abdominal blood flow. It can be calculated by subtracting the IAP from the mean arterial pressure- aim > 50-60 mm Hg. APP is superior to IAP, arterial pH, base deficit, and arterial lactate in predicting organ failure and patient outcome.

ACS can be divided into primary, secondary, and chronic forms.

- Primary or acute presentations occur when an intra-abdominal pathology is directly responsible for the CS eg penetrating trauma, intraperitoneal haemorrhage, pancreatitis, pelvic fracture, ruptured AAA, and a perforated pelvic ulcer.
- Secondary presentations occur when no visible intra-abdominal injury is present, but injuries outside the abdomen cause fluid accumulation; examples of this include large-volume resuscitation (> 3 L), large areas of full-thickness burns, postoperative packing and primary fascial closure, and sepsis. Chronic ACS can develop in cases of cirrhosis with excessive ascites.

Conditions Associated With IAH and ACS

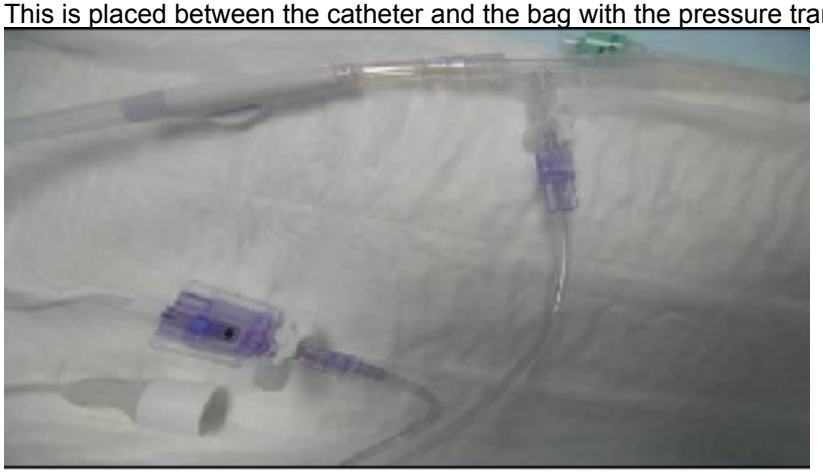
- Increased intra-abdominal volume
  - Gastrointestinal tract dilatation: gastroparesis and gastric distention, ileus, volvulus, colonic pseudo-obstruction
  - Intra-abdominal or retroperitoneal masses, eg, abdominal tumour
  - Ascites or haemoperitoneum
  - Pneumoperitoneum, eg, during laparoscopy
- Decreased abdominal wall compliance
  - Abdominal surgery, especially with tight abdominal closures
  - Abdominal wall bleeding or rectus sheath hematomas
  - Surgical correction of large abdominal hernias, gastroschisis, or omphalocele
- Combination of decreased abdominal wall compliance and increased intra-abdominal volume
  - Obesity
  - Sepsis, severe sepsis, and septic shock
  - Severe acute pancreatitis
  - Massive fluid resuscitation
  - Major burns (with or without abdominal eschars)
  - Complicated intra-abdominal infection

Investigations for ACS may include:
-an abdominal x-ray for free air or bowel obstruction and an

- abdominal CT scan to look for the "round-belly" sign (abdominal distension with an increased anteroposterior-to-transverse abdominal diameter (ratio > 0.80), collapse of the vena cava, or bowel wall thickening.

If suspected a IAP measurement should be performed. A quick technique is to hold the foley tubing straight up from symphysis pubis, height of urine column is the pressure. If there is no urine, instill 100 cc of saline. (1 mmHg = 1.36 cmH2O) Comparable accuracy to other standard techniques. (J Trauma 2002, 52:1169).

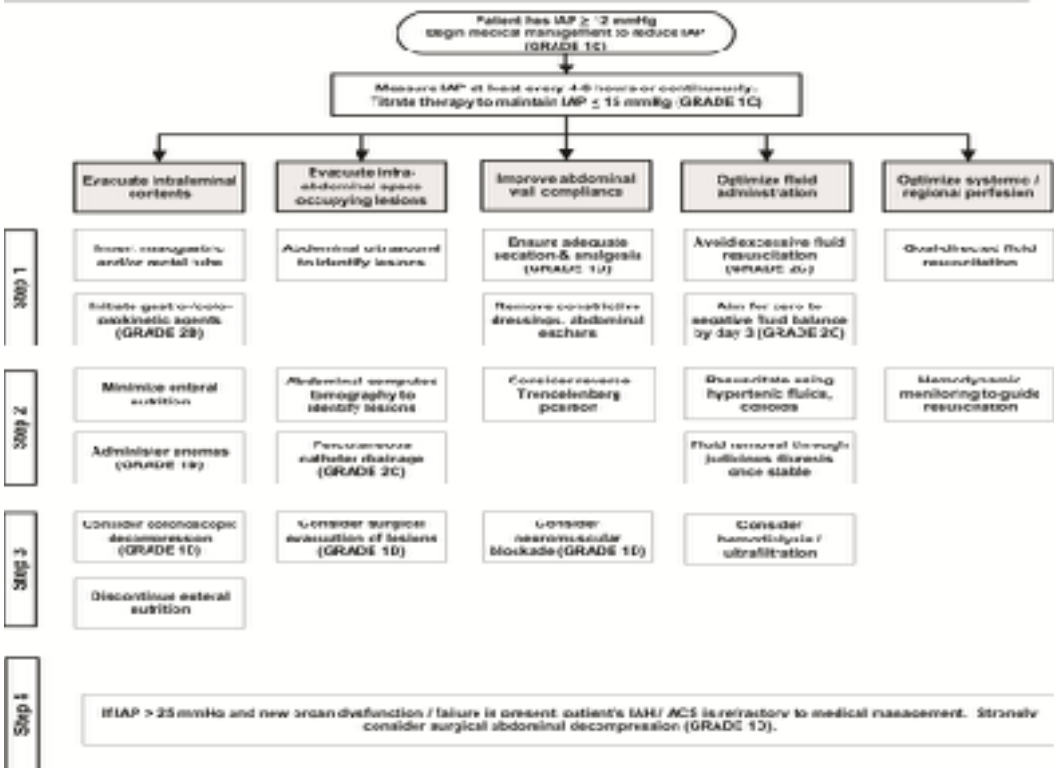
Bladder pressure can be monitored fairly easily with a pressure transducer as used for art lines and CVPs.
Have a look at the Liverpool ICU intranet page for the technique (only viewable if you are looking at this while at work) – the only specialised piece of equipment is a bladder T piece which you can obtain from Sutherland ICU.
This is placed between the catheter and the bag with the pressure transducer placed on the side arm.



Zero the transducer at the symphysis pubis. Empty the bladder then clamp it off.
Slowly inject 25mL sterile 0.9% sodium chloride into bladder via the injection port on the transducer.
Allow 30-60 seconds for equilibrium to occur, and allowing bladder detrusor muscle to relax.
Measure IAP at end expiration and ensure that abdominal muscle contractions are absent.

Management is based upon 3 principles: serial monitoring of IAP, optimization of systemic perfusion and organ function, and prompt surgical decompression for refractory IAH. Most patients with > 25mmHg and all patients with > 35mmHg should have surgical decompression. Nonsurgical strategies are appropriate, at least initially, for Grades I and II. These modalities may include body positioning, nasogastric and colonic decompression, fluid resuscitation, diuretics and dialysis.

Editor: Peter Wyllie



Medical interventions aimed at decreasing IAP target the 3 important contributors to IAH: (1) solid organ and hollow-viscera volume; (2) space occupying lesions, such as ascites, blood, fluid, or tumours; and (3) conditions that limit expansion of the abdominal wall
The WSACS proposed a medical treatment algorithm based largely on expert opinion that is aimed at both decreasing IAP and optimizing fluid resuscitation and systemic perfusion. Apologies re the size of the diagram but the medical treatment options discussed may be applied in a stepwise fashion. However note that the present level of evidence supporting these and other elements of this algorithm is limited, and the separate elements are not yet supported by clinical outcome data.

Refs – Medscape – up to date – World Society for Abdominal Compartment Syndrome (http://www.wsacs.org/) / Waele J et al, Intra-abdominal Hypertension and Abdominal Compartment Syndrome,; Am J Kidney Dis. 2011;57(1):159-169./ http://crashingpatient.com/intensive-care/abdominal-compartment-syndrome.htm/

JOKE / QUOTE OF THE WEEK

Editor: Peter Wyllie

Please forward any funny and litigious quotes you may hear on the floor (happy to publish names if you want)

THE WEEK AHEAD

Tuesdays - 12:00 – 13:45 Intern teaching -Thomas & Rachel Moore
Wednesday 0800-0900 Critical Care Journal Club. ICU Conf Room / 12.00-1.15 Resident MO in Thomas & Rachel Moore
Thursday 0730-0800 Trauma Audit. Education Centre / 0800-0830 MET Review Education centre / 1300-1400 Medical Grand Rounds. Auditorium.

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