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Ovarian Hyperstimulation Syndrome

Fact Sheet 32

Updated August 2013

Ovarian Hyperstimulation Syndrome (OHSS) is an uncommon but very important problem associated with attempts to stimulate ovulation. It is encountered in its most clinically significant forms in 'controlled' ovarian hyperstimulation used in high technology Assisted Conception, notably IVF, although it can be seen associated with any form of ovulation stimulation. The reported incidence varies between 1 in 250 IVF cycles up to 1 in 20 but this wide range might well be related to recording and to differing thresholds for concern.

In its mildest and most common form it causes little more than mild lower abdominal discomfort but severe forms can cause clotting disorders (even stroke) and be life threatening so they necessitate vigorous therapy. The methods of classifying the stages of OHSS are still controversial as is the exact pathophysiology (i.e. the underlying mechanism or cause). It is easiest to use the oldest classification of mild, moderate and severe.

It is important to note that the syndrome is not directly caused **by** the drugs but by the excessive hormones and other substances produced by the ovaries in **response** to them. To add to the difficulties we find that whilst one person may develop significant problems at a certain hormone (oestrogen) level others may suffer no ill effects – the disorder is therefore complex biochemically and appears to involve a number of compounds, particularly Vascular Endothelial Growth Factor (VEGF) and Interleukin 6, which are involved in inflammatory and blood vessel permeability changes that causes a 'leakage' of fluids out from the blood vessels, leaving the blood concentrated and fluid building up in places where it shouldn't normally be!

Despite the difficulties in defining the exact causes we can limit the occurrence by identifying the population at risk and then modifying their management.

Who is at risk?

Most at risk is the young (less than 35), lean woman with previously diagnosed polycystic ovarian syndrome (PCOS; see fact sheet number 24) who, with stimulation, rapidly develops very high oestrogen levels and shows excessive ovarian response on ultrasound. Anti-Mullerian Hormone (AMH) levels can also be used to predict the likelihood of an excessive ovarian response so the doctor can then tailor hormone stimulation dosages with this in mind.

The use of GnRH **analogues** (leuprorelin acetate/Lucrin and nafarelin acetate/Syneral) in the Assisted Conception treatment protocols allows prolonged stimulation and as such potentially increases the risk of OHSS so the medical team need to be careful when needing to use this treatment strategy. Less ovarian stimulation and more use of GnRH **antagonists (cetrolrelix/Cetrotide),** to suppress early LH surges, can decrease the occurrence. We can expect 'gentler' stimulation in the future particularly with advances in embryology meaning we have more high quality embryos and less need for more ovarian stimulation to get more eggs (**quality** at last over-riding **quantity**). 'Support' of the luteal phase (after egg collection) with injectable human Chorionic Gonadotrophin (hCG /Ovedril/Pregnyl) was used routinely in the past but should now only be given with great care and

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progesterone (vaginal or by injection), being safer, is preferred. HCG, whether exogenous (given by injection) or endogenous (from an early pregnancy) is a significant factor in the development of the syndrome.

For those women at increased risk we have now developed a number of strategies some of which remain controversial. Reducing the stimulating hormone dosage is necessary and reducing the ovulatory (trigger) dose of hCG from 10,000 IU to 5000 IU has some small theoretical advantage. Withholding completely the ovulatory dose of hCG was a mainstay of prevention when the ovaries were thought to be over responding but a variation known as 'coasting' where the hCG is still given but only when the oestrogen levels have fallen back to an 'appropriate' level is now preferred by many clinicians.

Should the ultrasound appearances (i.e. excessive follicular development) be grounds for concern during the oocyte retrieval some advocate the immediate use of intravenous albumen (a protein rich blood product). However, initially encouraging reports have been questioned and albumen carries its own risks. The more established approach is to completely empty all the ultrasonically visible follicles and then to use embryo cryopreservation (freezing) to avoid the possibility of pregnancy in that cycle (and hence avoiding any pregnancy-produced hCG causing OHSS) and watching the woman carefully until she has settled completely. The embryos, after freezing then later thawing, can be replaced in a later 'natural' cycle.

Treatment

Treatment of the established case of OHSS will depend very much upon the severity of symptoms and whether the problem arises early after egg collection or later as a sign of endogenous hCG production indicative of an early pregnancy.

Mild to moderate lower abdominal discomfort and nausea can be treated by reduction in activities and attention to an adequate fluid intake (some advocating electrolyte-rich solutions such as 'sports drinks'). In severe cases increasing abdominal discomfort often associated with vomiting will require hospitalisation with meticulous monitoring of changes in abdominal girth, blood electrolytes, haemodynamic stability (blood pressure etc.) and signs of haemoconcentration (blood thickening) and most importantly signs of impending coagulation (clotting), liver and kidney failure. Treatment will be directed towards pain relief and maintenance or restoration of normality in all these areas. This is usually achieved by the use of anticoagulants and intravenous colloid solutions (albumen is often used but is controversial) coupled with paracentesis (drainage of the abdominal fluid) if distension (bloating) is painful or oliguria (low urine output) persists despite the other treatment. There is some recent support in the medical literature for the **early** use of paracentesis. Rarely 'intensive care' in an appropriate hospital will be required (beyond the scope of this review) and very rarely consideration given to termination of an early pregnancy if all other treatments fail.

OHSS is a potentially life-threatening disorder. Although we remain uncertain of its exact pathophysiology there are steps that can be taken to predict those at risk and minimise the occurrence, and effects.

Professor Geoffrey Driscoll