



THE ROLE OF OESTRADIOL IN OOCYTE (EGG) MATURATION, IVF AND OHSS

THE ROLE OF OESTRADIOL IN FEMALE NATURAL MENSTRUAL CYCLES.

Oestradiol, also known as oestrogen, is a hormone which plays a central role in the oocyte maturation process, and also plays a secondary role in preparing the uterus for pregnancy. This hormone is found in both the blood and in the follicular fluid (around the oocytes). Levels of oestradiol vary throughout menstrual cycles, generally peaking at ovulation. Normal levels at ovulation are 500 to 1000 pmol/L¹ in the blood, and 2–3µmol/L in the follicular fluid.

In order for healthy oocytes (follicles) to develop, their environment must be predominantly oestrogenic. Normally in each menstrual cycle, initially between 10 to 20 follicles start to develop with this number varying from person to person and declining with age. In most natural menstrual cycles, only one of the follicles (oocytes) survives and is released at ovulation. This cell death of the other follicles (oocytes) is a natural process known as atresia and is due to the presence of relatively high levels of androgens compared to oestradiol in the follicular fluid of the oocytes.

OESTRADIOL AND IVF STIMULATION.

In order to increase each patient's chance of conception, IVF cycles aim to increase the number of eggs (oocytes) ovulated. Therefore, as part of the process of IVF, medications are used to stop or reduce the effect of atresia which leads to multiple follicle development and multiple oocytes ovulated. IVF stimulation, therefore leads to raised oestradiol levels with blood levels in a typical IVF procedure from 5000–15000 pmol/L with the average about 9000–10000pmol/L. Although this is about ten times greater than in a normal menstrual cycle, the level in the follicular fluid around each oocyte remains the same (2–3µmol/L). Consequently the follicles still all develop normally and the oocytes that are obtained fertilise and develop normally. However, more follicles are released at ovulation than in a normal menstrual cycle. For instance, the blood concentration of oestradiol may be ten times normal in an IVF cycle, but ten follicles may be collected.

During an IVF cycle, the patient's oestradiol levels are monitored by blood tests, and an assessment of when the optimum time to collect the follicles (oocytes) is undertaken. It is typical to assess follicular maturation (the best time to collect the oocytes) not by the oestradiol value, but by the ratio of oestradiol in the blood to the number of follicles seen, to be more than 10mm in size on ultrasound scan at the time that ovulation is to be triggered.

This value is 200–1000pmol/L per follicle more than 10mm. Values less than this are of concern because lower values may indicate that some follicles have not matured effectively, therefore resulting in poorer oocyte quality. In contrast, higher values of oestradiol, such as blood levels over 12 000 pmol/L have not been shown to result in poorer oocyte or embryo quality.

pmol = pico (million millionth) mole/Litre

µmol = micro (millionth) mole/Litre



OESTRADIOL AND OVARIAN HYPERSTIMULATION SYNDROME (OHSS).

The higher oestradiol blood levels associated with IVF treatment are a possible (but not proven) cause of OHSS, which is one of the more serious complications of IVF since its inception in the late 1970s. Unfortunately, there is no known way of predicting accurately which patients may suffer this complication or of preventing it from occurring. However, higher oestradiol levels have been linked to higher risk of OHSS. Nationally the risk of OHSS is 3% per stimulated cycle with a third of these requiring hospitalisation to manage the condition. The incidence of OHSS occurring at Canberra Fertility Centre has been 1.7% for 2008 and 1.8% for 2009. In that same period we only recorded two severe cases of OHSS for a rate less than 0.5%.

The link between oestradiol and OHSS is complicated by the fact that it does not just occur at a specific level of oestradiol. All that can be said is that the risk increases substantially over the range of 10 000 to 20 000pmol/L, but OHSS can occur at any level of oestradiol and has been reported in non stimulated natural cycles.

MEASURES TO REDUCE THE RISK OF OHSS.

At Canberra Fertility Centre we use a value of 17 000pmol/L as a cutoff level of oestradiol; other units have chosen 15 000 and some as high as 20 000pmol/L. If a patient's oestradiol reaches 17 000pmol/L oocyte collection is undertaken and all subsequent embryos produced are frozen. No embryos are replaced in that cycle because pregnancy is a known driver (but not a cause) of OHSS which can turn a mild case into a more severe case. Only in cases of very elevated oestradiol levels (greater than 30 000 pmol/L) would cancellation of the oocyte pickup be considered. Individual consultation with the specialist regarding high E2 levels, other requested blood levels and how the patient feels is considered when freezing all embryos.

Diagnosis of PCOS (Polycystic Ovarian Syndrome) is another risk factor taken into consideration by Canberra Fertility Centre and other fertility clinics. If a patient has been diagnosed with this condition her doctors will be more conservative in their stimulation and management as OHSS is more likely to occur.