



Ovarian Hyperstimulation Syndrome May be More Likely if Multiple Pregnancy Occurs Following Assisted Conception

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Abstract. Whereas modern assisted conception with such techniques as *in vitro* fertilisation now helps many subfertile couples to fulfil their ambition to have a child, it has not been without a price. The increased incidence of multiple pregnancies, with their attendant maternal and perinatal sequelae following assisted conception is well known, but perinatologists may be less familiar with the Ovarian Hyperstimulation Syndrome (OHSS) which is the other major complication when controlled ovarian hyperstimulation is used during assisted conception treatment. Mild forms of OHSS are common and require no more than symptomatic treatment. Severe forms of OHSS are uncommon occurring in 0.6% to 14% of IVF cycles [15, 5], but are nonetheless very important to identify as they may lead to thrombo-embolic disease, cardiorespiratory dysfunction, renal failure and even death [6]. This review considers whether OHSS may be related to multiple pregnancy by reviewing the available literature and local experience.

Key words: Ovarian Hyperstimulation Syndrome, *In vitro* fertilisation, Multiple pregnancy

Ovarian hyperstimulation syndrome is an iatrogenic potentially life threatening condition of unclear aetiology associated with supra-physiological stimulation of the ovary. The key features of the condition are ovarian enlargement due to multiple ovarian cysts and increased capillary permeability leading to a fluid shift out of the intravascular space, attributed to various possible vaso-active ovarian products including prorenin, prostaglandins, oestrogen, histamine and cytokines [1, 4, 10]. OHSS only develops following luteinisation initiated by luteinising hormone or human chorionic gonadotrophin (hCG) and once established is worsened by hCG, either endogenous or exogenous [11]. It is recognised that hCG levels are higher in multiple as opposed to singleton pregnancies from a very early period of gestation [13]. In addition, ovarian prorenin production has been shown to be positively related to levels of hCG and the number of conceptuses

[14]. It may thus be suspected that the higher levels of HCG associated with multiple pregnancy may increase the likelihood of OHSS, although curiously OHSS may resolve spontaneously despite continued HCG stimulation during early pregnancy [6].

Although it is generally agreed that there is a higher incidence of OHSS in conception versus non-conception assisted reproduction cycles [2, 8, 11], opinion is divided as to whether there is a specific relationship between OHSS and multiple pregnancy. The possibility has been raised that OHSS might favour pregnancy [2], although the more likely explanation for the observed association between OHSS and pregnancy is the effect of hCG from an implanting embryo [7]. A study [8] analysing 15 cases of OHSS occurring in 1302 patients undergoing ovarian stimulation for IVF reported a multiple pregnancy rate of 48% in women with moderate or severe OHSS as opposed to 24.9% in women without OHSS. Of the 21 cases of severe OHSS [12], 12 were pregnant including 6 multiple pregnancies. In contrast, a large multicentre study examining 128 cases of OHSS and 256 matched controls did not find that the proportion of multiple to singleton pregnancies was increased in the patients with OHSS [2]. Similarly in a smaller study there were only 2 twin pregnancies out of a total of 7 pregnancies in 8 women who had severe OHSS [3].

One explanation for the apparent discrepancy regarding a relationship between OHSS and multiple pregnancy between the various studies is that OHSS may present in two similar but distinct settings. "Early" OHSS presents 3 to 7 days following administration of exogenous hCG, whereas "late" OHSS occurs 12 to 17 days following hCG and is probably caused in large part by endogenous hCG from an implanting pregnancy [7]. It may be postulated that while early OHSS is not necessarily related to the presence or otherwise of a pregnancy and is wholly an iatrogenic consequence of the administered hCG, late onset OHSS may be caused or aggravated by the high levels of hCG produced by multiple pregnancies. This was first suggested in a study where all 4 women presenting with "late" OHSS had multiple pregnancies [7]. Since earlier studies do not take into account the time of onset of OHSS when analysing the proportion of multiple to single pregnancies it is possible that this may be a factor in their differing conclusions. In our experience of 30 women admitted to hospital with symptomatic OHSS following IVF either on the University IVF programmes of Sheffield or Bristol, 21 women presented within 10 days of oocyte retrieval (range 2 to 10 days), while 9 presented more than 10 days following oocyte retrieval (range 11 to 15 days). Of those presenting "early", 7 were pregnant (33%) with no multiple pregnancies. Among the "late" presenters all 9 were pregnant with 5 multiple pregnancies (3 sets of twins and 2 sets of triplets). Our experience would thus support the occurrence of OHSS in two distinct time frames [7], with the "late" form being more likely to be associated with multiple pregnancy.

It is important to consider whether the severity of OHSS is related to multiple pregnancy, and thus whether avoidance of multiple pregnancy may reduce the likelihood or severity of OHSS. A correlation might be expected between the severity of OHSS and the presence of multiple gestation sacs, given the primary role ascribed to hCG in the development of this condition [11]. Higher rates of multiple pregnancy were noted in cycles complicated by severe OHSS (71%) as opposed to those with moderate (43%) or no OHSS (24.9%) [8]. In our series of 30 patients, 6 had severe OHSS by the above criteria. All 6 were pregnant, with 4 multiple pregnancies. Attempts have been made to identify those patients most at risk of developing OHSS [2, 11] and in these cases consideration could be given to transferring fewer than three embryos although this is likely to reduce the overall pregnancy rates [9].

It is interesting to consider that the two most significant complications of assisted conception – multiple pregnancy and OHSS – may be inter-related and that in the future both of these problems may be reduced by single embryo transfer. This review thus further encourages fertility specialists to strive towards this important goal while maintaining good assisted conception pregnancy rates.

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