Volume expanders for the prevention of ovarian hyperstimulation syndrome

MA Youssef, Selma Mourad

**Background:** Ovarian hyperstimulation syndrome (OHSS) is a serious and potentially fatal complication of ovarian stimulation which affects 1% to 14% of all in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles. A number of clinical studies with conflicting results have reported on the use of plasma expanders such as albumin, hydroxyethyl starch (HES), mannitol, polygeline and dextran as a possible intervention for the prevention of OHSS. Women with very high estradiol levels, high numbers of follicles or oocytes retrieved, and women with polycystic ovary syndrome (PCOS), are at particularly high risk of developing OHSS. Plasma expanders are not commonly used nowadays in ovarian hyperstimulation. This is mainly because clinical evidence on their effectiveness remains sparse, because of the low incidence of moderate and severe ovarian hyperstimulation syndrome (OHSS) and the simultaneous introduction of mild stimulation approaches, gonadotropin-releasing hormone (GnRH) antagonist protocols and the freeze-all strategy for the prevention of OHSS.

**Objectives:** To review the effectiveness and safety of administration of volume expanders for the prevention of moderate and severe ovarian hyperstimulation syndrome (OHSS) in high-risk women undergoing IVF or ICSI treatment cycles.

**Search methods:** We searched databases including the Cochrane Gynaecology and Fertility Group Specialised Register of controlled trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and trial registers to September 2015; no date restrictions were used as new comparators were included in this search. The references of relevant publications were also searched. We attempted to contact authors to provide or clarify data that were unclear from trial or abstract reports.

**Selection criteria:** We included randomised controlled trials (RCTs) comparing volume expanders versus placebo or no treatment for the prevention of OHSS in high-risk women undergoing ovarian hyperstimulation as part of any assisted reproductive technique.

**Data collection and analysis:** Two review authors independently selected the studies, assessed risk of bias and extracted relevant data. The primary review outcome was moderate or severe OHSS. Other outcomes were live birth, pregnancy and adverse events. We combined data to calculate pooled Peto odds ratios (ORs) and 95% confidence intervals (CIs) for each intervention. Statistical heterogeneity was assessed using the I² statistic. We assessed the overall quality of the evidence for each comparison, using GRADE methods.

**Main results:** We included nine RCTs (1867 women) comparing human albumin (seven RCTs) or HES (two RCTs) or mannitol (one RCT) versus placebo or no treatment for prevention of OHSS. The evidence was very low to moderate quality for all comparisons. The main limitations were imprecision, poor reporting of study methods, and failure to blind outcome assessment. There was evidence of a beneficial effect of intravenous albumin on OHSS, though heterogeneity was substantial (Peto OR 0.67 95% CI 0.47 to 0.95, seven studies, 1452 high risk women; I² = 69%, very low quality evidence). This suggests that if the rate of moderate or severe OHSS with no treatment is 12%, it will be about 9% (6% to12%) with the use of intravenous albumin. However, there was evidence of a detrimental effect on pregnancy rates (Peto OR 0.72 95% CI 0.55 to 0.94, I² = 42%, seven studies 1069 high risk women, moderate
quality evidence). This suggests that if the chance of pregnancy is 40% without treatment, it will be about 32% (27% to 38%) with the use of albumin. There was evidence of a beneficial effect of HES on OHSS (Peto OR 0.27 95% CI 0.12 to 0.59, I² = 0%, two studies, 272 women, very low quality evidence). This suggests that if the rate of moderate or severe OHSS with no treatment is 16%, it will be about 5% (2% to 10%) with the use of HES. There was no evidence of an effect on pregnancy rates (Peto OR 1.20 95% CI 0.49 to 2.93, one study, 168 women, very low quality evidence). There was evidence of a beneficial effect of mannitol on OHSS (Peto OR 0.38, 95% CI 0.22 to 0.64, one study, 226 women with PCOS, low quality evidence). This means that if the risk of moderate or severe OHSS with no treatment is 52%, it will be about 29% (19% to 41%) with mannitol. There was no evidence of an effect on pregnancy rates (Peto OR 0.85 95% CI 0.47 to 1.55; one study, 226 women, low quality evidence). Live birth rates were not reported in any of the studies. Adverse events appeared to be uncommon, but were too poorly reported to reach any firm conclusions.

**Authors’ conclusions:** Evidence suggests that the plasma expanders assessed in this review (human albumin, HES and mannitol) reduce rates of moderate and severe OHSS in women at high risk. Adverse events appear to be uncommon, but were too poorly reported to reach any firm conclusions, and there were no data on live birth. However, there was evidence that human albumin reduces pregnancy rates. While there was no evidence that HES, or mannitol had any influence on pregnancy rates, the evidence of effectiveness was based on very few trials which need to be confirmed in additional, larger randomised controlled trials (RCTs) before they should be considered for routine use in clinical practice.