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Paper

Are Pregnancy Rates Compromised Following Embryo Freezing to Prevent OHSS?

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ABSTRACT

Objective: To compare pregnancy rates with fresh and frozen embryo transfer in patients admitted to Royal Jubilee Maternity Service (RJMS), Belfast between January 1st 2004 and December 31st 2005 with ovarian hyperstimulation syndrome (OHSS).

Method: A retrospective analysis of all ART cycles (2,283) carried out in RJMS between January 1st 2004 and December 31st 2005 and of all patients admitted to RJMS within 3 weeks of assisted reproduction therapy (ART).

Results: The incidence of OHSS requiring admission was 2.01%, which represented 80.70% of post-ART emergency admissions. The eventual pregnancy rate was 52.27% in all women admitted with OHSS. The pregnancy outcome in OHSS patients who received fresh embryo transfer was 56.52% and with frozen embryo transfer 50%. The main indications for fertility treatment in OHSS cases were male factor (31%) and polycystic ovarian syndrome (14%). Two distinct incidence peaks of OHSS were identified – early and late. 77.77% of women who suffered from late onset OHSS had a concurrent positive pregnancy test.

Conclusion: The pregnancy rate in OHSS cases, both with fresh and subsequently with frozen embryo transfer, was exceptionally high. There was no statistically significant difference between fresh and frozen embryo transfer pregnancy rates. An elective embryo freezing policy to moderate the severity and duration of OHSS does not compromise outcome for women at risk of OHSS.

INTRODUCTION

OHSS is a major complication of fertility treatment occurring in between 0.6% and 10% of ovarian stimulation cycles for assisted reproduction (ART)[1]. Whilst the primary aetiological factor is a largely unpredictable and excessive response to follicle stimulating hormone (FSH), in fact, the syndrome will not occur without the administration of human chorionic gonadotrophin (hCG) either exogenously, to induce the final maturation of the follicle prior to oocyte retrieval, or endogenously, from an establishing pregnancy[2].

The exact pathogenesis of OHSS is still not fully understood but the involvement of cytokines, particularly vascular endothelial growth factor (VEGF), and the ovarian renin-angiotensin system (RAS) are clearly central to the pathogenesis of the condition[2,3].

Clinically, OHSS results in ovarian enlargement and a shift of protein-rich fluid from the vascular compartment into the third space compartments (particularly the peritoneal and pleural cavities), leading to the potentially fatal complications of renal failure, through hypoperfusion, and thromboembolism by haemoconcentration and increased viscosity[4,5].

A variety of approaches has been taken to help prevent OHSS including "coasting" whilst on treatment (the suspension of FSH stimulation to allow the ovarian response to quieten) and, once the oocytes have been retrieved, the freezing of all embryos for transfer subsequent to the ovaries quietening down: the condition is clearly aggravated and prolonged by both the degree of ovarian stimulation and by pregnancy[1,2].

In the Regional Fertility Centre (RFC), Royal Jubilee Maternity Service (RJMS), Belfast there is an active policy of freezing all embryos if the patient is deemed clinically to be at high risk of developing OHSS. The definition of "high risk" is arbitrary and includes the number of oocytes obtained, the amount of ascites and the size of the ovaries at oocyte retrieval as well as the age of the patient and any previous history of OHSS. However, as the prediction of OHSS is imprecise, a significant number of cases will still occur in patients who have undergone fresh embryo transfer. As a result, there tend to be two peaks of incidence of OHSS: the first occurs within a week of the ovulatory hCG injection whilst the second occurs in response to pregnancy, typically around two weeks after the injection.

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It has been postulated that as OHSS occurs in those women with the most florid response to stimulation, their pregnancy rates should be significantly greater than the overall pregnancy rates for both fresh (24%) and frozen embryo transfer (22%) in any one unit. In this study fresh and frozen embryo transfer pregnancy rates will be determined for patients who developed OHSS and compared with pregnancy rates in the unit as a whole.

MATERIALS AND METHODS

Charts were reviewed for all women admitted to RJMS with a diagnosis of OHSS after ART between January 1st 2004 and December 31st 2005 at the RFC, Belfast. In all 2,283 ART cycles were performed and 57 charts were identified for women subsequently admitted to RJMS with OHSS. As the RFC serves the geographically small region of N. Ireland, all patients are advised to attend RJMS if they have any complication of treatment. It is the experience of the unit that patients are very infrequently admitted elsewhere with OHSS arising from treatment in the RFC.

The following information was recorded: the woman's previous medical history; the primary indication for ART; the date of oocyte retrieval; the date of embryo transfer and whether this was with fresh or frozen embryos; the date of presentation with OHSS and the management. Pregnancy outcomes were also noted.

All patients had previously given written consent to allow their charts to be audited.

RESULTS

A total of 1,123 fertility treatments were carried out in 2004 and 1,160 in 2005. The distribution between in-vitro fertilisation (IVF), intra-cytoplasmic sperm injection (ICSI), and frozen embryo transfer (FET) is given in Table I.

TABLE I:

The overall number of ARTs undertaken in 2004 and 2005.

Fertility Treatment:	2004:	2005:	TOTAL:
IVF	484	515	999
ICSI	405	412	817
FET	234	233	467
TOTAL:	**1123**	**1160**	**2283**

In 2004, there were 29 (2.58%) emergency admissions to RJMS following fertility treatment whilst in 2005 there were 28 (2.41%) emergency admissions. In total, therefore, for the two years, 52 patients were admitted with 57 admissions (5 patients were admitted on two separate occasions). Of these 57 admissions, 46 (80.70%) were due to OHSS - two patients were admitted twice with OHSS. Of the remaining 11 admissions: 5 were due to an ovarian cyst; 2 to an ovarian abscess; 2 to miscarriage; 1 to an ectopic pregnancy; and 1 to unspecified abdominal pain.

The primary indications for ART for the 44 patients admitted with OHSS are compared with the primary indications for treatment amongst the general population of N. Ireland attending the RFC in Table II.

TABLE II.

Comparison of primary indication for treatment in those undergoing ART in the RFC vs OHSS patients

Indication for treatment:	General Population in N. Ireland:	OHSS Group:	% Difference:
Male Factor	43.86%	31%	**- 12.86%**
Unexplained	19.02%	25%	**+ 5.98%**
Tubal Disease	14.34%	14%	**- 0.34%**
Multiple Factors	8.02%	0%	**- 8.02%**
Ovulatory Disorder	7.24%	14%	**+ 6.76%**
Endometriosis	4.03%	11%	**+ 6.97%**
Multiple Female Factors	3.2%	0%	**- 3.2%**
Other	0.27%	5%	**+ 4.73%**

The degree of OHSS was classified as moderate in 37 (80%) and severe in 9 (20%) cases (OHSS Classification, National Collaborating Centre for Women's and Children's Health)[1]. Where the OHSS was classified as mild it was routinely managed as an outpatient and, therefore, not identified in this study. Of the 44 patients admitted with OHSS, 3 experienced severe complications: one deep vein thrombosis (DVT) and two pleural effusions.

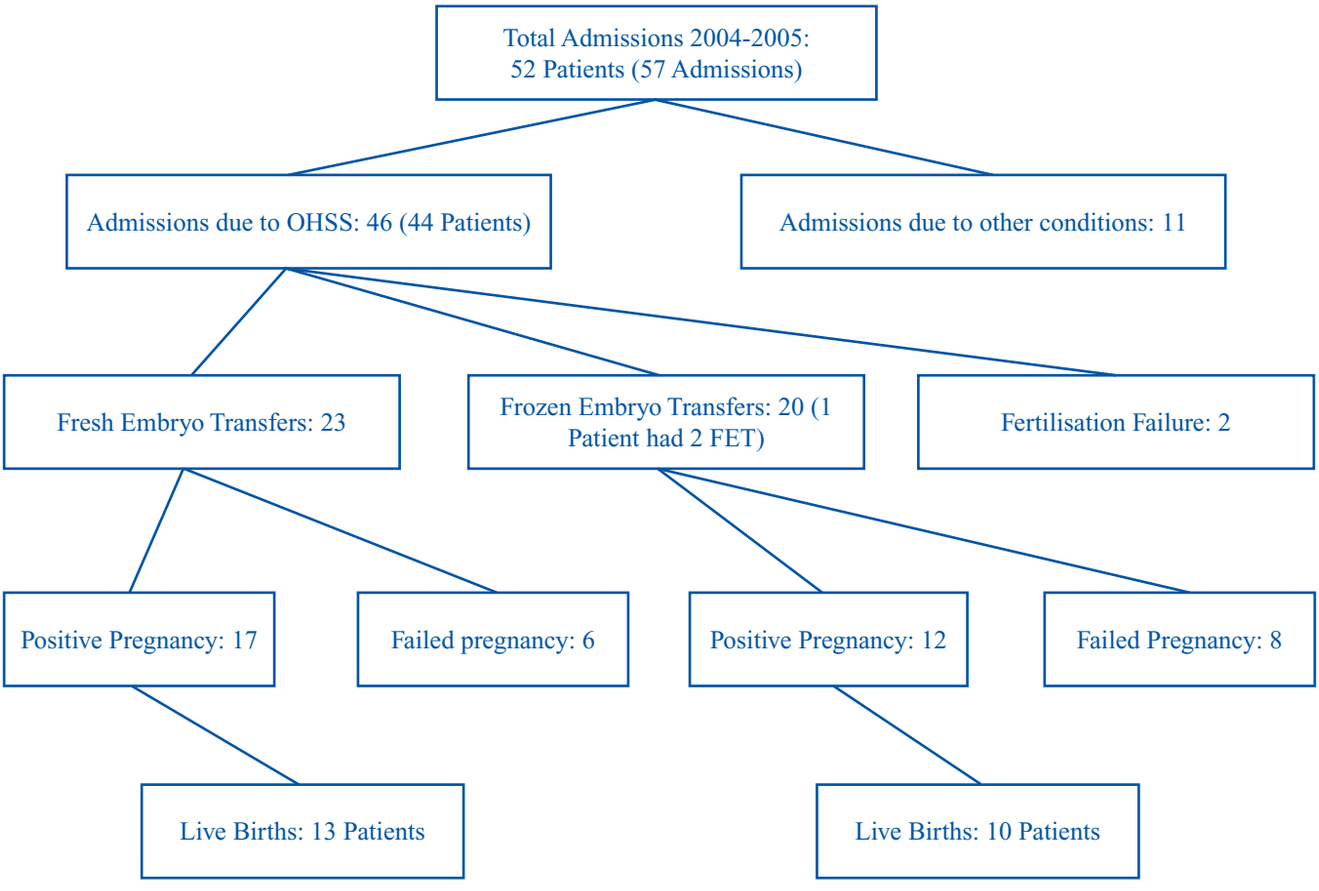
Of the 44 patients admitted, 23 (52%) had undergone fresh embryo transfer, whilst 20 (45%) had had all their embryos frozen. Two patients had fertilisation failure and, therefore, no embryo transfer from the stimulation cycle. One patient had two separate frozen embryo transfer cycles in the year 2005. Of the 23 patients who had a fresh embryo transfer, 17 (74%) became pregnant of whom 13 (76.5%) went on to give birth (10 singletons and 3 twin pregnancies). Of the 20 frozen embryo transfers, 12 (60%) patients became pregnant of whom 10 (83%) went on to give birth (8 singletons and 2 twin pregnancies).

Overall, for all patients admitted with OHSS, 29 conceived of whom 6 (21%) miscarried, 18 (62%) had a singleton live birth and 5 (17%) had twins. This demonstrated a positive pregnancy outcome in patients who were admitted with OHSS of 52.27% overall – 56.52% with fresh embryo transfer and 50% with frozen embryo transfer. This difference was not statistically significant (χ^2=0.183, dof=1, p>0.2).

Amongst the 23 patients admitted as an emergency for OHSS who received fresh embryo transfers, only one patient was admitted twice due to OHSS – an early admission and a late admission. The majority, 13 (57%), were admitted early and 9 (39%) were admitted late. Of those women who

TABLE 3:

Total Number of Admissions to the RJMS following ART, Fresh vs Frozen Embryo Transfers for OHSS Patients, and the Pregnancy Outcome



were admitted with early OHSS, 6 (46.15%) had a positive pregnancy outcome and of those with late OHSS, 7 (77.77%) had a positive pregnancy outcome. Early OHSS was defined as patients who presented within 9 days of oocyte retrieval and late OHSS was defined as patients who presented 10 or more days following oocyte retrieval.

DISCUSSION

In this study the incidence of complications arising from ART in the RFC, Belfast necessitating admission between January 1st 2004 and 31st December 2005 was 2.5%. This is in keeping with national figures of between 2.04% and 15%[4,6,7]. Of these 57 admissions, 46 (80.70%) were due to OHSS, which represented an incidence of 2.01%. This again was in keeping with the published incidence rates for OHSS of between 0.6% and 10%[6,8].

Within the patient population admitted for OHSS, the main indication for ART was male factor infertility (31%), with unexplained infertility representing 25% and PCOS only 14% of cases. This distribution contrasts with the literature, where PCOS is the commonest indication for ART in OHSS patients[9]. A study by Abramov, Elchalal, and Schenker in 1998 reported that 35.6% of those admitted with OHSS and receiving fertility treatment had anovulatory infertility, while 23.3% had male factor infertility and only 8% had unexplained infertility[10]. Within this unit overall, the major indication for ART was male factor infertility whilst the indication was PCOS in only 7.24% of ART patients. However, a 14% incidence of PCOS in OHSS patients is twice that in the ART population at large in N. Ireland suggesting that PCOS predisposes to this condition.

In the Regional Fertility Centre, Belfast there is an active but arbitrary policy of deferring embryo transfer and performing embryo freezing if a woman is deemed to be at significant risk of OHSS. Clearly, the unit's policy does not result in a reduced pregnancy rate per oocyte retrieval. However, the significantly small number of OHSS patients with elective embryo freezing highlights the importance of this approach.

The pregnancy rates reported in this study were significantly greater than those reported by the National Institute of Clinical Excellence (NICE), which suggested an average live birth rate per fresh embryo transfer of 17.6% based on figures from January 1995 to March 1999[1]. In comparison, NICE found that the average live birth rate per frozen embryo transfer was 11.5% based on national figures from January 1995 to March 1999[1]. OHSS patients are by definition patients whose ovaries respond excessively to gonadotrophin stimulation. Therefore, these women should have an increased chance of oocyte production and an increased number of

oocytes compared to other women and, consequently, it is not unreasonable that they would have an increased chance of successful fertilisation and pregnancy.

In addition to various degrees of severity of OHSS, patients that received a fresh embryo transfer are at risk of experiencing both an early and a late occurrence of OHSS. Early onset OHSS is thought to be due primarily to the administration of exogenous hCG whilst late onset OHSS is induced primarily by endogenous hCG from the implanting embryo[8,11]. To support the theory that late OHSS results from endogenously produced hCG from the implanting embryo and that it confers a better pregnancy outcome, our study found that 77.77% of the women who suffered from late OHSS had a positive pregnancy outcome. That is over 60% higher than the average birth rates following fresh embryo transfer and over 50% higher than the overall birth rates amongst our unit's general patient population. A study by Papanikolaou *et al* in 2006 found that all patients with severe OHSS became pregnant; a study by Abramov, Elchalal, and Schenker in 1998 found that 73% of women with severe OHSS had positive pregnancy outcomes; and Schenker in 1999 described a clinical pregnancy rate of 73.2% in women with severe OHSS[8,10,12].

Our results, in conjunction with the published literature, appear to support strongly the assumption that OHSS is predictive of a successful outcome and that an active policy of embryo freezing and deferment of embryo transfer is not disadvantageous to the patient in terms of pregnancy.

CONCLUSION

OHSS represented 80.70% of emergency admissions following ART. This remains both a major burden on hospital services and a significant risk to patients. OHSS in its severe form is potentially fatal. However, OHSS is an indicator of high fertility with an ultimate pregnancy rate of 52.27% in those who develop OHSS. This compares to an average pregnancy rate of 11.5% - 17.6% in the ART population nationally.

In conclusion, it is essential to counsel patients about the risks of OHSS prior to initiating fertility treatment. It is always disappointing to be told that embryo transfer is not to take place as planned in order to prevent OHSS. However, significant comfort may be derived from the excellent frozen embryo transfer pregnancy rates in this unit.

The authors have no conflict of interest.

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