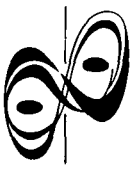

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Guidelines for the Prevention of Multiple Pregnancy in Treatment by in Vitro Fertilization

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Abstract. Within the same in vitro fertilization (IVF) program, treatment trials leading to single and multiple ongoing gestation were compared. Rates of cesarean delivery, prematurity and perinatal mortality were found much higher among twin and multiple IVF pregnancies. Our work thus attempts at defining characteristics of proneness to multiple gestation in IVF treatment, in order to try and avoid its occurrence. The mean vitality score of embryos replaced is the most reliable criterion for this purpose, enabling one to replace no more than two embryos when the average score is high. Age of the patient and cause of infertility are almost nondiscriminant in this respect. Ovarian stimulation parameters such as total dosage of gonadotropin treatment and level of estrogenic response, as well as numbers of oocytes and embryos obtained, may serve as secondary criteria for assessing the twinning risk.

Key words: In vitro fertilization, Ovarian stimulation, Embryos, Twinning risk

INTRODUCTION

In successful in vitro fertilization (IVF) programs twin and multiple pregnancies are far more frequent than among the normal population [2,5]. This difference clearly results from multiple embryo replacement which is applied by most teams in order to maximize pregnancy rates [13].

Although the majority of embryos replaced do not implant, in a significant number of treatment trials more than one will survive and prove capable of inducing a multiple gestation.

Twins are often considered as a bonus befalling previously infertile couples, but the well-known hazards linked to multiple pregnancy contradict this overoptimistic assumption [8].

The present report compares IVF trials entailing single and multiple pregnancies obtained in the same IVF program, with the aim of defining conditions that might favor the occurrence of multiple gestation. Such definition would help preventing twins and higher rank multiples and thereby avoiding complications such as high prematurity and perinatal death rates.

MATERIALS AND METHODS

Methods for IVF treatment applied in our clinic have been described in detail elsewhere [7,11]. They include ovarian stimulation aiming at collecting a series of oocytes and obtaining several embryos. Two stimulation methods have been used: 1) administration of clomiphene citrate followed by daily injections of human menopausal gonadotropin (hMG); 2) preliminary desensitisation of the pituitary by an analog of LHRH (Buserelin, Hoechst, Frankfurt) combined with hMG treatment.

Prior to intrauterine replacement or cryopreservation, embryos were given a vitality score based on developmental speed and on the amount of anucleate fragments extruded during early cleavage. The maximum score per embryo is 6 [11]. As a rule, no more than the three best embryos were replaced at each trial. However, in a few cases with antecedents of repeated IVF failure and consistently involving poor quality embryos, four were exceptionally replaced. Embryos in excess were frozen, provided their vitality score reached at least level 4. Numerical results are given with SEM values and were statistically evaluated by applying Pearson's χ^2 test and Student's two-tailed t test.

RESULTS

The present report deals with 169 completed pregnancies obtained by IVF treatment in our clinic. Only gestations that went beyond the 20th week after the last menstrual period were considered.

As shown in Table 1, twins and triplets represented 23% and 2.4% of these pregnancies, respectively. A case of quadruplets was observed after replacement of three embryos. Two of the four babies who were safely delivered at 35 weeks by elective cesarean section, proved to be MZ twins as demonstrated by examination of fetal adnexa and by blood groups and HLA antigen analysis.

Table 1 - Ongoing IVF pregnancies (%)

	Single	Multiple	
Total	125	44	(26)
Double		39	(23)
Triple		4	(2.4)
Quadruple		1	(0.6)

Table 2 - Outcome of ongoing IVF pregnancies (%)

	Single	Multiple
Cesarean section	17	60
Prematurity	3.4	57
Perinatal mortality	1.6	6.4
Twins		5
Triplets		17
Quads		0

Cesarean section was carried out 3.5 times more often for multiple than for single IVF pregnancies. The prematurity rate was likewise much higher in the former group (Table 2).

Two and six babies were lost among singletons and multiples, respectively. In only one double pregnancy, both twins died because of labor onset at 25 weeks of gestation. This patient has since delivered a single healthy baby conceived by IVF.

In two twin pregnancies one member of the pair was lost through intrauterine death in one case and because of multiple malformations in the other. In one set of triplets one baby died a few days before delivery while in another, one of the infants was lost because of acute neonatal respiratory distress.

Mean age of patients was not significantly different between groups of multiple and single IVF pregnancies nor was the distribution of different causes of infertility (Table 3). However, there was some tendency towards a smaller proportion of tubal cases among the group of multiple gestations.

Table 3 - Ongoing IVF pregnancies

	Single	Multiple
Age	31.5 ± 0.4	30.3 ± 0.6
Indications (%)		
Tubal	52.0	38.6
Idiopathic	25.2	25.0
Sperm defect	17.1	20.5
Others	2.4	11.4

Table 4 separates IVF pregnancies according to the method of ovarian stimulation. It appears, although not significantly, that in the group treated with buserelin and hMG, less ampoules of the latter were needed and higher peaks of estradiol (E^2) were reached among trials leading to multiple rather than to single pregnancy. Such difference does not appear in relation to classical clomiphene-hMG stimulation.

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Table 4 - Ongoing IVF pregnancies - Stimulation parameters

	Single	Multiple
hMG (N. amp.)		
Cl-hMG	15.1 ± 0.9	15.4 ± 1.4
Bus-hMG	25.8 ± 2.0	21.5 ± 1.8
E^2 peak (pg/ml)		
Cl-hMG	1724 ± 88	1780 ± 176
Bus-hMG	2566 ± 139	2816 ± 253

Cl: clomiphene citrate; Bus: buserelin; E^2: estradiol; hMG: human menopausal gonadotropin.

Table 5 - Ongoing IVF pregnancies

	Single	Multiple	
No. of oocytes			
Cl-hMG	7.0 ± 0.5	9.2 ± 0.9	P = 0.05
Bus-hMG	9.8 ± 0.6	12.4 ± 1.5	
No. of embryos			
Cl-hMG	4.5 ± 0.4	6.5 ± 0.5	P = 0.01
Bus-hMG	6.0 ± 0.5	7.5 ± 1.0	

Cl: clomiphene citrate; Bus: buserelin; hMG: human menopausal gonadotropin.

Numbers of oocytes and embryos that were obtained in IVF trials entailing an ongoing pregnancy were significantly higher in the group of multiple gestations that occurred after clomiphene-hMG treatment (Table 5). Greater numbers of eggs and embryos were generally obtained after using buserelin and hMG, but in this case, the difference between trials entailing single and multiple pregnancy was not found significant.

As shown in Table 6, the occurrence of a multiple pregnancy preferentially happened after replacing three rather than one, two or even four embryos. It should be recalled, however, that quadruple transfers were rare.

The mean vitality score of transferred embryos leading to multiple pregnancy, as well as that of all embryos obtained in the corresponding IVF trials, were significantly higher than observed in relation to single gestation (Table 7). Opportunities for cryopreserving embryos in excess were likewise double in the former group.

DISCUSSION

During the last decade increasing numbers of twin and multiple pregnancies have been induced by infertility treatment. In the East Flanders Prospective Twin Survey such pregnancies account for about 8% of the total population of twins and multiples born

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Table 6 - Ongoing IVF pregnancies – Numbers of embryos transferred (%)

	Single	Multiple	
Clomid-hMG			
1	10.1	0.0	
2	14.5	0.0	
3	73.9	100.0	P = 0.02
4	1.4	0.0	
Buserelin-hMG			
1	5.7	0.0	
2	11.3	5.3	
3	81.1	89.5	
4	1.9	5.3	

Table 7 - Ongoing IVF pregnancies – Mean embryonic scores and freezing of spare embryos

	Single	Multiple	
Score of transferred embryos	4.4 ± 0.1	5.1 ± 0.1	P = 0.001
Score of all embryos per trial	4.1 ± 0.1	4.8 ± 0.1	P = 0.04
Frozen spare embryos (% of trials)	26.4	52.3	P = 0.03

Maximal possible score per embryo = 6.

during the last years [4]. The majority of such cases, in particular high rank multiples, do not originate from extracorporeal fertilization but from treatment of anovulation with clomiphene and/or gonadotropic hormones, entailing natural conception [4,9].

However, as shown in the present report, twins and multiples are about 20 to 25 times more frequent among IVF pregnancies than in the overall population (Table 1). It should be emphasized that this difference exists in spite of the application of guidelines such as those suggested by the Voluntary Licensing Authority in the UK, recommending to replace no more than three embryos at each trial [16].

The increased cesarean section rate observed in our material versus that of the normal population (about 10% in our maternity and in the French-speaking part of the country), was partly due to the fact that IVF patients belong to a selected group which includes a high proportion of older primiparae and other pathological cases (Table 2). However, this difference also largely reflects the extreme cautiousness of obstetricians confronted with pregnancies which are hard to obtain and highly valued. The high prematurity rate observed among IVF multiples reinforces this attitude, thereby explaining why 60% of pregnancies belonging to this group underwent cesarean delivery.

The perinatal death rate among IVF singletons is not much higher than that observed in the overall population (9.6/1000 and 13.4/1000 in our maternity and in whole Belgium, respectively) [12]. Perinatal mortality among IVF twins was similar to that of all twins born in our maternity during the last five years (5.5%) [3]. In recent reports, perinatal loss of triplets is estimated to be around 10% [1,10]. In view of the above-mentioned figures and because of the pathological impact of prematurity and its high social cost [14], it becomes clear that special efforts should be devoted to avoid twin and multiple pregnancies induced through assisted procreation and ovulation induction. In IVF, a major difficulty arises. Indeed, reducing the risk of multiple pregnancy by systematically replacing only one or two embryos entails a drastic reduction of chances to obtain a baby [13].

Therefore, our work aims at reaching a definition of cases prone to develop multiple gestation after triple embryo transfer. On the basis of our data, Table 8 attempts at grading several parameters which are apparently involved in this risk. Although younger patients seem more prone to develop a multiple IVF gestation (Table 3) [6], the difference in age is so small that even if it became significant thanks to larger numbers of cases, it would still not be discriminant enough to be of any clinical help.

Table 8 - Relative value of risk criteria of multiple IVF pregnancy

Young patients	-
Non-tubal indication	±
Low dose of hMG	±
High E^2 peak	±
Many eggs and embryos	+
Triple transfer	+ +
High embryonic scores	+ + +

The same reasoning holds true as regards the general distributions of infertility causes (Table 4). However, a previous study of our IVF cases has shown that tubal indications include a subpopulation of patients who often exhibit a poor ovarian response leading to cycle cancellation and whose chances of pregnancy are markedly reduced even after completed trials [15]. In such patients the risk of multiple gestation is virtually nonexistent.

Total dosage of hMG and levels of estrogenic response tend to differ between IVF multiples and singletons obtained after buserelin-hMG management. However, the role of these parameters in a prognostic evaluation can only be subordinate to more discriminant criteria.

Numbers of eggs and embryos are significantly greater in IVF cycles leading to multiple gestation. By amplifying the ovarian response to hMG and oocyte harvests, the use of buserelin tends to erase these differences (Table 5). It remains that patients providing large numbers of oocytes of which a high proportion become fertilized and cleave, are to be considered at more risk of developing a multiple pregnancy.

It is logical that multiple gestations are more frequent after triple embryo replacement since, excepting the odd MZ case, IVF multiples are all plurizygotic (Table 6). However, the difference versus single and double transfer goes beyond mere proportionality to the numbers of embryos replaced. Its importance suggests that cycles leading to triple transfer also correspond to general conditions favoring multiple implantation [5,11,17].

The best prognostic criterion for evaluating the risk of twins and multiples in IVF treatment is obviously the embryonic vitality score, since its difference between single and multiple gestations in terms of transferred embryos, is highly significant (Table 7). Also the mean score of all embryos obtained in the same trial and the opportunity for cryopreservation may prove helpful in this respect.

In conclusion, we would suggest that when, in an IVF trial, at least three embryos endowed with scores higher than 5 are available, matters should be discussed with the couple prior to transfer, in order to convince patients to replace only two embryos and cryopreserve the remaining ones. Other factors of risk may also be taken into account but should be no more than adjuvants to the decision.

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