HOW CAN WE PREVENT IATROGENIC TWINS IN ART

Dr. Ramon Aurell, MD.

Reproductive Medicine Unit. Department of Obstetrics & Gynaecology. Institut Universitari Dexeus, Barcelona, Spain

ramaur@dexeus.com

Introduction

Iatrogenic Multiple Pregnancies and Ovulation Induction

The number of Multiple Pregnancies in southern Europe was reaching epidemic proportions in the late 1990s with the relevant consequences for the children, parents and the community in general.[1,2] Ovulation induction (OI) accounts for approximately 40% of the total of the high order multiple pregnancies.[2] In medical and social terms this pregnancies can have negative consequences. Recent studies have mentioned that the risk of an infertile couple from having a high order MP from ovulation induction or Insemination is greater than of having IVF.[3,4]

It seems then obvious the need for regulations and guidelines to avoid the increasing number of high order MP secondary to OI.

OI without ART is estimated to be responsible for 20% of twin birth and 30% of triplet and high-order MP. In Britain, OI alone is responsible for 67% of quadruplet and higher-order births.[6]

Recent work by us[5] and others[7] has suggested that certain factors are associated with high order MP, triplets or more, after gonadotrophin stimulation and if conservative limits for follicular development and oestradiol levels are applied the number of high order MP secondary to OI will be significantly reduced.

In our previous study[5] we analyzed retrospectively a large series of 1878 consecutive pregnancies from gonadotrophins stimulated cycles. We developed a three-variable model to identify patients at high risk for high order MP in OI cycles. We found the correlation between high order MP with increasing total number of follicles, oestradiol level >862pg/ml and age > or = 32 years.[5]

Strategies to prevent MP in OI and Insemination (IUI)

1. Alternative to gonadotrophin treatment
2. Strategies in OI
3. Alternatives to cancelled cycles
4. Cancelled cycles
5. Embryo reduction

1. Several alternatives with good results are used to reduce the number of MP from OI: Clomiphene Citrate (Imani, 1998, 1999, 2000; Eijkemans, 2003; Dickey 2002, 2004; Matorras, 2003.), Aromatase inhibitors (Mitwally, 2003; Fatemi, 2003), Diet and Exercise (Kiddy, 1998; Norman, 2004), Ovarian drilling (Farquhar, 2002; Bayram, 2004), or IVF.

2. The known strategies to avoid MP in OI, are : individualised treatment protocols, according to patients age, indication for treatment, number of antral follicles, basal FSH levels and BMI. Use of soft stimulation protocols, with small dose of gonadotrophins or low step-up protocols, and the use of careful monitoring of ovarian response with transvaginal USS and serum oestradiol levels.

3. Several alternatives are been used to reduce the number of cancelled cycles. Triggering of ovulation by GnRH agonist: Emperaire, 1991; Check, 1993; Balasch, 1994. Convert hiperstimulated cycles to IVF; Nisker, 1994; Bergh, 1998; Antman, 2002; Monzo, 2004. Puncture of supernumerary follicles: Belaisch, 1998; De Geyter, 1996, 1998; Albano, 2001.

Criteria for Cancellation: in our study, between June 2001 and December 2002, we looked at 849 consecutive patients receiving gonadotropin ovarian stimulation or OI without IVF for a total of 1542 treatment cycles.

Patients were administered highly purifies FSH (Neofertinorm: Serono) or recombinat FSH (Gonal-F: Serono). The regimen was chronic low-dose step-up protocol, with an starting dose of 75IU in >85% of women, 37.5IU in previous high responders and 150IU in women >40 years of age. Ovarian response was monitored by serial vaginal USS follicular measurement and serum E2 detreminations.

Couples were counselled about the risk of MP according to the prediction model established in our previous study (table 1, Ref 5).

Results are summarized in Figures 1 and 2 and in Table 2.

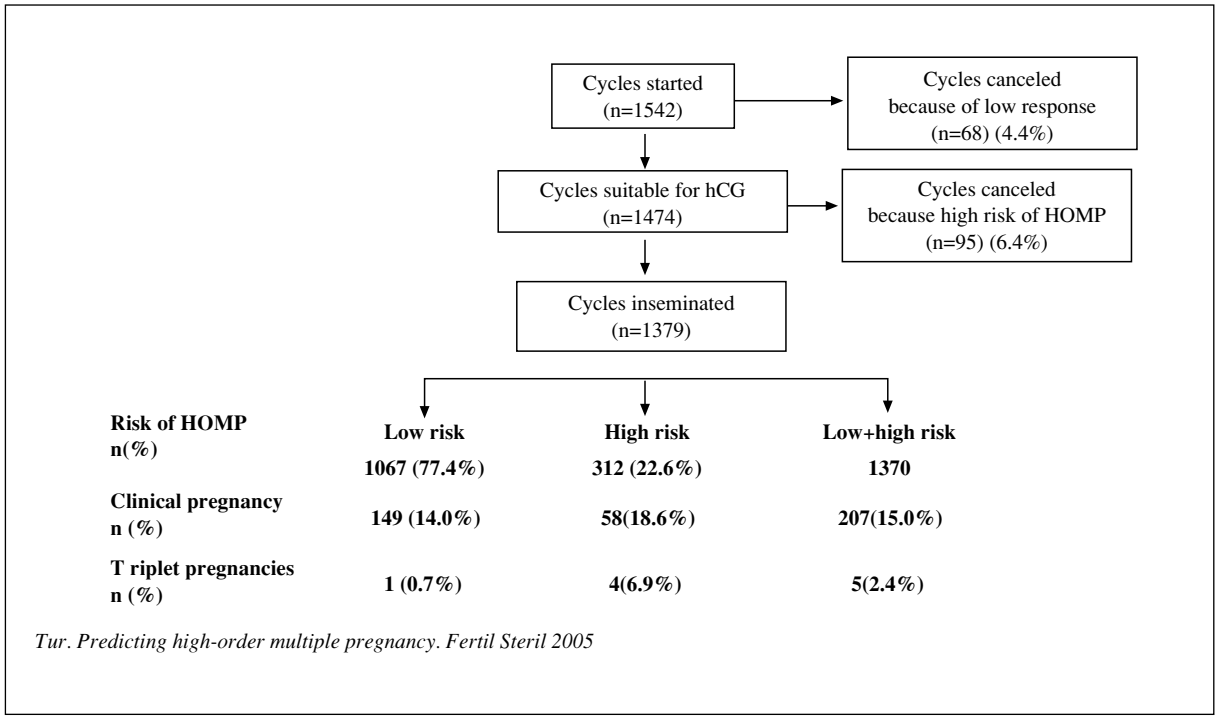

Figure 1. *Observed HOMPs in 1.542 ovulation induction cycles*

The main objective of any infertility therapy is to achieve a healthy single child: MP jeopardize that objective and high-order MP should be considered as an adverse outcome. As many as 2/3 of Iatrogenic MP, mainly involving triplets and more, may be attributable to OI drugs without IVF . There has been major control of IVF MP than with OI, therefore, identification of predictors of MP during OI cycles is clearly necessary.

In the present study we tested prospectively a three-variable prediction model for high-order MP.

Using this model is possible to maintain low risk high-order MP with good pregnancy rates. As many as 77.4% patients met the low-risk definition probably due to the conservative step-up treatment approach that we used in this study.

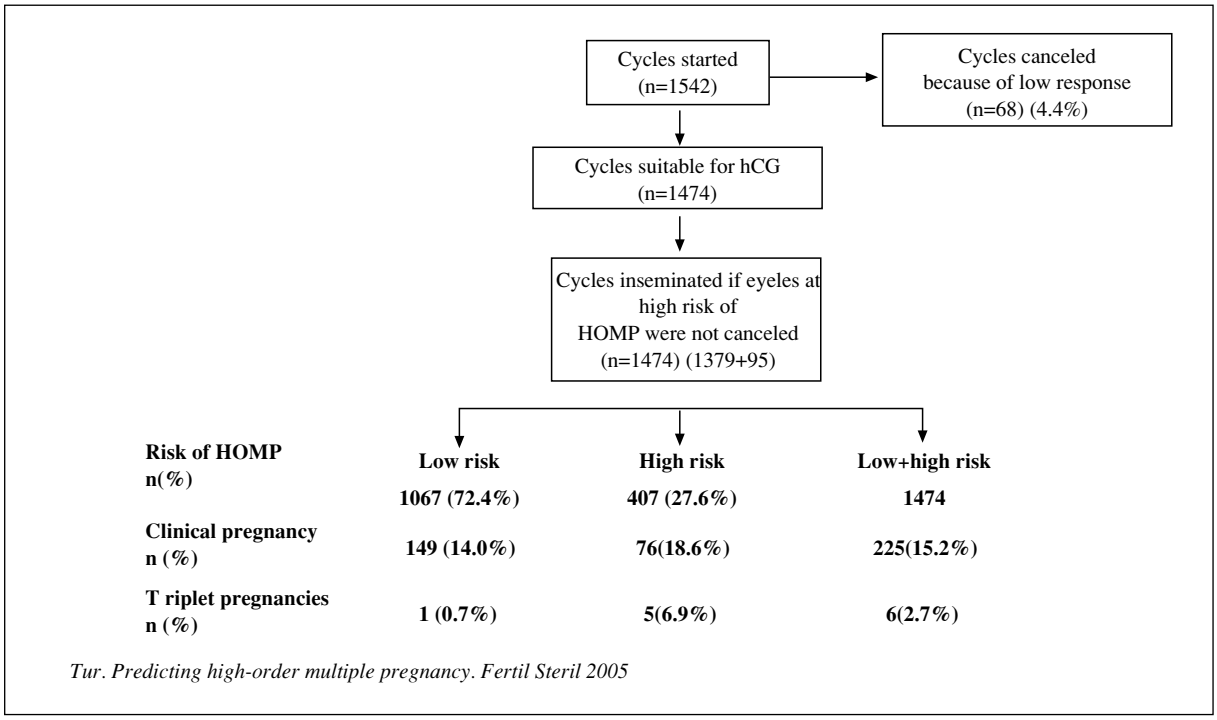

Figure 2. *Predicetd HOMPs with cancellation of cycles at high risk of HOMP.*

Table 1. *Observed numbers of cycles with low-order and high - order pregnancy and predicted probability of high-order pregnancy according to multivariate ordinal logistic regression analysis.*[a]

Total no. of follicles >10 mm on hCG day	Peak serum E_2 ≤862pg/ml		Peak serum E_2>862 pg/ml	
	Age > 32 y	Age ≤ 32 y	Age >32 y	Age ≤32 y
1 to 3 follicles				
Low-order pregnancy (n)	319	266	22	35
High-order pregnancy (n)	10	8	4	7
Probability	0.033	0.054	0.082	0.117
4 to 5 follicles				
Low-order pregnancy (n)	87	85	29	33
High-order pregnancy (n)	4	9	4	3
Probability	0.043	0.066	0.084	0.130
> 5 follicles				
Low-order pregnancy (n)	66	92	67	132
High-order pregnancy (n)	2	5	7	29
Probability	0.052	0.087	0.126	0.189

* From Tur et al.(7)

Tur. Predicting high-order multiple pregnancy. Fertil Steril 2005

Table 2. *Pregnancy rates and incidence of HoMP according to the use or not af a prediction model for HOMP*

	Prediction model for HOMP applied		
Variable	**Yes**	**No**	**P**
Pregnancy rate (%)	14	15.2	NS
HOMP (%)	0.7	2.7	<.001

Tur. Predicting high-order multiple pregnancy. Fertil Steril 2005

Prevention of MP in IVF

Introduction

During the past decade, in some countries, legislative guidelines targeted at limiting the number of embryos transferred have been promulgated in an effort to reduce the incidence of multiple gestations.[8] By limiting the number of embryos transferred per stimulated IVF cycles, the incidence of MP is reduced. However , when following this policy, a number of considerations are necessary in order to maintain an acceptable pregnancy rate: number of embryos available for transfer, embryo quality and womens, age.[9]

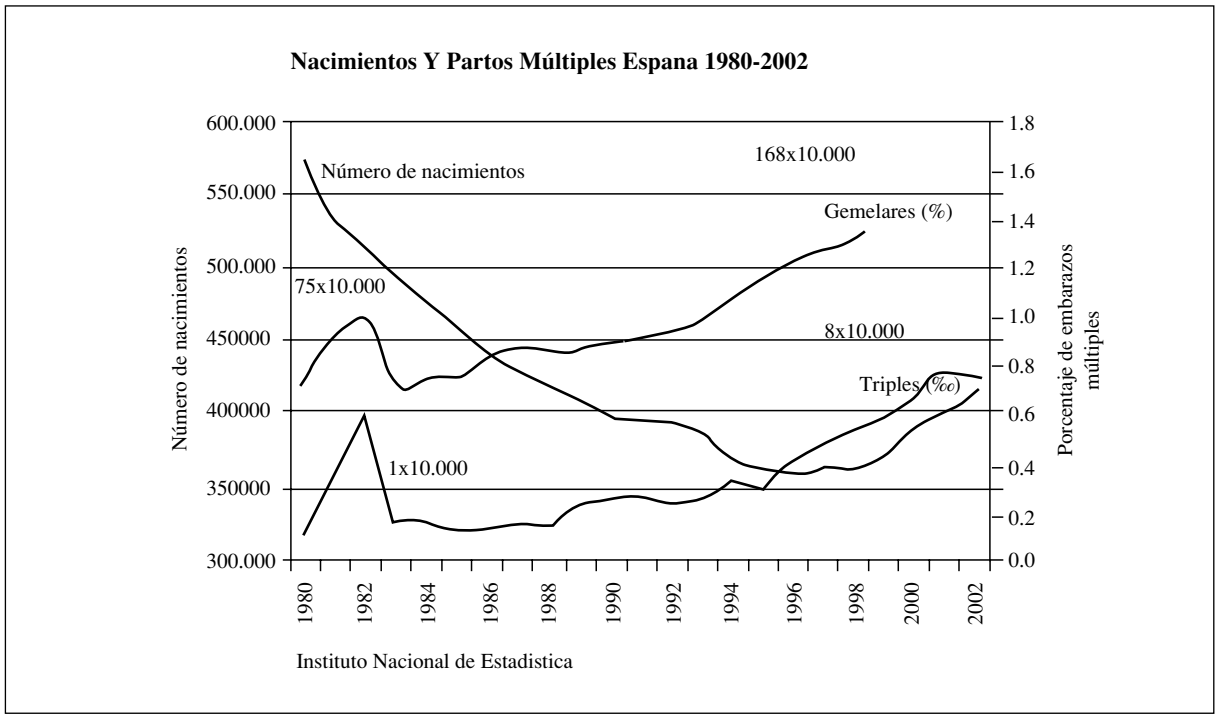

Figure 3. *MP and Births in Spain, 1980-2002.*

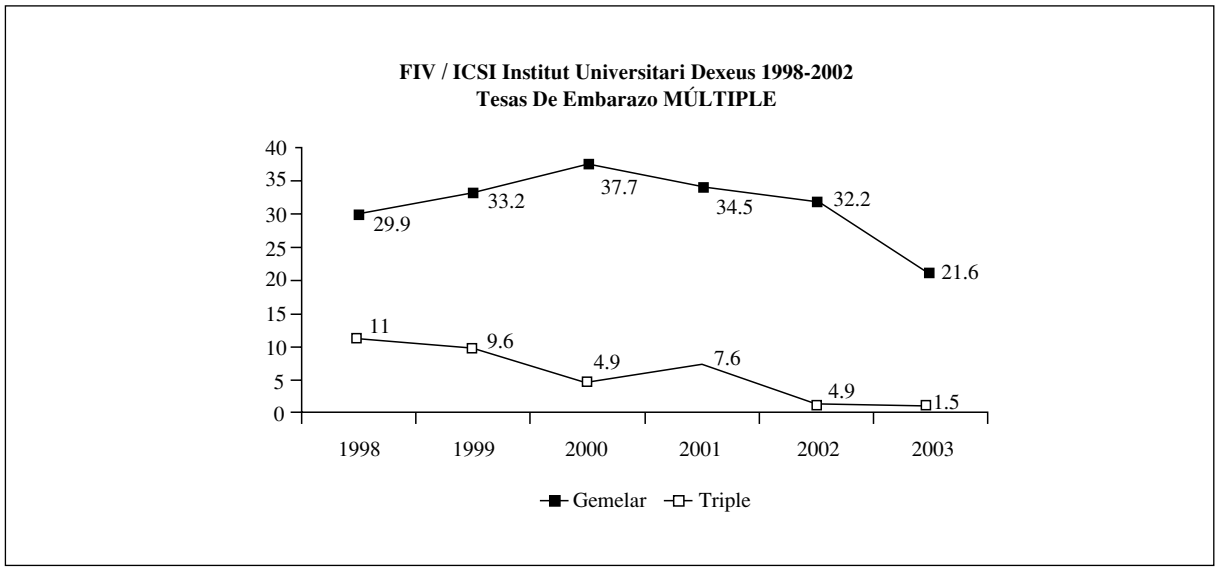

Figure 4. *MP in our institution from 1998-2003. We can see the evident decrease in MP, twins and triplets in our institution since the implementation of the MPS in 2001.*

Instituto Universitario Dexeus Multiple Pregnancy Score; MPS

In our unit we have been working towards reducing MP since late 90,s. We believe in Single ET (SET) and in Selective Single ET (sSET) trying to reduce the total number of MP and births. In Fig 2 is evident the increase in MP in Spain from the 90,s.

We worked towards the creation of a Embryo Transfer Score system trying to reduce the number of MP. For the last four years since the creation of the score we managed to reduce the incidence of MP without reducing substantially the pregnancy rates.

MATERIALS AND METHODS. CREATION OF MPS.

Retrospective analysis

A retrospective study was carried out on 377 cycles from our IVF/ICSI program between March and September 1999. As our main goal was to reduce triplets, only those patients with whom three embryos were transferred (day two post-puncture) were included in the study. A total of 227 cycles were analyzed, among which 120 resulted in pregnancy (64 singletons, 39 twins and 17 triplets) and 107 did not result in pregnancy.

The following parameters were analyzed: patient age, cause of infertility, number of cycle attempts, total number of embryos (number of available embryos at the moment of transfer) and total number of good quality embryos (number of good quality embryos available for transfer). A good quality embryo on day two was defined as one which, 48h after insemination or ICSI showed four regular blastomeres and less than 20% cytoplasmic fragmentation (Boiso et al., 2002).

No-pregnancy, singleton, twin and triplet cycles were compared according to the above parameters. Statistical analysis was performed with the SPSS® 10.0 software program for Windows ® (SPSS Inc., Chicago, IL, USA). Chi-square test, Fisher's test, Student's t test and analysis of variance were used to compare qualitative and quantitative variables. A further comparison was then made of singleton versus triplet pregnancies, and variables that were significantly associated with high-order multiple pregnancy were retained for testing in a multivariate logistic regression model. Receiver operating characteristic (ROC) curves were used to determine the cut-off point that best discriminated between high-order multiple pregnancy (* 3 gestational sacs) and single gestation (1 gestational sac). Significance was set at $p < 0.05$.

Prospective study

A prospective study was conducted with patients enrolled in our IVF/IVF-ICSI program between January and September 2002. Only those women who underwent embryo transfer on day two after oocyte retrieval and had three or more embryos available at the moment of transfer were included in the study. The number of embryos to be transferred was decided upon according to the MPS and patients who agreed with the proposed number of embryos (MPS-accepted group; n=301) were compared with those who requested more (MPS-not accepted group; n=92), the latter acting as the control group (Table IV). The sample was then stratified according to the number of embryos the MPS had recommended transferring (one, two or three), and patients accepting the recommendation were compared with those who did not (Table V). For example, if the MPS recommended transfer of one embryo, either one (1ET) or two embryos (2ET) were transferred, depending on whether the patient accepted the MPS or not (MPS=1, 1ET vs. 2ET).

Clinical pregnancy rates and multiple pregnancy rates were compared in all the groups using the chi-square or Fisher's test, where appropriate.

Pregnancy was diagnosed by positive urine and/or blood tests (Beta hCG) and the subsequent visualization of at least one intrauterine gestational sac by transvaginal ultrasonography at 6 weeks gestation. The order of the multiple pregnancy was classified according to the highest number of gestational sacs

observed by ultrasound imaging, including pregnancy sacs that did not contain an embryonic pole. Assessment of the outcome of pregnancy was not considered for the specific purpose of this study.

Table 1. *Comparison of study variables according to: 1) cycle results; and 2) single vs. triplet pregnancies*

	No pregnancy n=107	Singletons n=64	Twins n=39	Triplets n=17	P value(1)	P value (2)
Age (years)	35.8±4.5	34.6±3.6	33.2±3.6	32.7±2.6	<0.001	<0.05
No. of cycles attempts	1.9±1.1	1.6±0.9	1.7± 0.9	2.0±0.9	NS	NS
Total number of embryos available for transfer	6.6±3.8	6.7±3.8	6.9±3.5	9.9±5.8	<0.05	<0.001
Total number of good quality embryos for transfer	1.5±1.9	1.4±1.3	3.0±2.4	3.2±1.8	<0.001	<0.001

(1) comparison between all the groups
(2) comparison between singletons and triplets
- Data are given as mean ± SD
- NS = not significant

Table 2. *IVF Single, twin and triplet rates after transfer of three embryos, according to the number of good quality embryos available for transfer*

No. of good quality embryos	0	1	2	3	≥ 4
No. of transfers	69	49	39	35	35
No. of pregnancies (%)	25 (36.2)	24 (49.0)	29 (74.4)	20 (57.1)	22 (62.9)
Singletons (%)	18 (72.0)	18 (75.0)	16 (55.2)	8 (40.0)	4 (18.2)
Twins (%)	6 (24.0)	4 (16.7)	10 (34.5)	8 (40.0)	11 (50.0)
Triplets (%)	1 (4.0)	2 (8.3)	3 (10.3)	4 (20.0)	7 (31.8)

Comparison between singletons, twins and triplets <0.01 Percentages in parenthesis

Table 3. *MPS: Score given according to the number of good quality embryos and patient's age*

		Score
No. of good quality embryos	0	0
	1	1
	2	2
	3	3
	≥4	4
Patient age (years)	<30	2
	30-34	1
	35-39	0
	≥40	-1

Table 4. *Clinical pregnancy and multiple pregnancy rates: comparison between MPS-accepted group and MPS-not accepted group*

	MPS-accepted n = 301	MPS-not accepted n = 92	
No. of pregnancies (%)	152 (50.5)	62 (67.4)	< 0.01
No. of multiple pregnancies (%)	53 (34.9)	33 (53.2)	< 0.05
Twins (%)	50 (32.9)	30 (48.4)	<0.05
Triplets (%)	3 (2)	3 (4.8)	NS

NS = not significant
Percentages in parenthesis

Table 5. *Study variables comparing MPS-accepted and not-accepted groups with respect to MPS recommendation*

	MPS=1			MPS=2			MPS=3		
	1ET	2ET		2ET	3ET		3ET	4ET	
	n = 45	n = 70		n = 139	n = 16		n =117	n = 6	
Age of women (years)	31.1 ± 2.2	30.6 ± 2.3	NS	34.4 ± 3.8	37.1 ± 3.8	<0.05	35.3 ± 3.9	38.2 ± 4.9	NS
No. of attempts	1.1 ± 0.2	1.3 ± 0.6	<0.01	1.5 ± 0.9	1.9 ± 1.2	NS	1.6 ± 0.9	2.2 ± 1.2	NS
Oocytes recovered	16.7 ± 7.9	17.9 ± 6.6	NS	13.5 ± 6.8	12.7 ± 5.9	NS	10.6 ± 5.4	8.5 ± 4.0	NS
Oocytes inseminated	13.6 ± 6.5	14.9 ± 6.0	NS	11.1 ± 5.9	10.2 ± 5.5	NS	8.7 ± 4.5	6.2 ± 2.3	NS
Oocytes fertilized	11.2 ± 5.4	11.5 ± 5.1	NS	8.6 ± 4.7	8.1 ± 4.7	NS	6.4 ± 3.3	4.8 ± 1.0	NS
No. of good quality embryos	6.2 ± 2.8	5.8 ± 1.8	NS	4.4 ± 2.4	4.2 ± 2.2	NS	1.5 ± 1.4	0.3 ± 0.5	<0.05

Data are given as mean ±SD
NS = not significant

Table 6. *Clinical pregnancy rates and multiple pregnancy rates: comparison between MPS-accepted group and MPS-not accepted group, stratified by MPS*

	MPS=1			MPS=2			MPS=3		
	1ET	2ET		2ET	3ET		3ET	4ET	
	n = 45	n = 70		n = 139	n = 16		n =117	n = 6	
No. of pregnancies (%)	19 (42.2)	48 (68.6)	<0.01	82 (59.0)	11 (68.8)	NS	51 (43.6)	3 (50.0)	NS
No. of multiple pregnancies (%)	-	26 (54.2)	-	30 (36.6)	5 (45.4)	NS	23 (45.1)	2 (66.7)	NS
Twins (%)	-	26 (54.2)	-	30 (36.6)	3 (27.3)	NS	20 (39.2)	1 (33.3)	NS
Triplets(%)	-	-	-	-	2 (18.2)	-	3 (5.9)	1 (33.3)	NS

NS = not significant
Percentages in parenthesis

RESULTS

Results of the retrospective analysis:

Table I shows the comparison between no-pregnancy and single, twin and triplet pregnancies. Univariate analysis found no significant differences between the four groups with respect to cause of infertility or number of cycle attempts. There were, however, significant differences in terms of age, total number of embryos available for transfer and number of good quality embryos.

The same differences were found when comparing only single and triplet pregnancies. When the three significant variables were entered simultaneously into the logistic regression model, only two of them remained significant: age and number of good quality embryos. Of these, the number of good quality embryos was the most significant. Analysis of ROC curves produced the following cut-off values: two good quality embryos (Sensitivity 81.3, with 95% CI=69.5-89.9; Specificity 64.7, with 95% CI=38.4-85.7, area under the ROC curve 0.785); 34 years of age (Sensitivity 50.0, with 95% CI=37.2-62.8; Specificity 76.5, with 95% CI=50.1-93.0, area under the ROC curve 0.665). Table II shows that the rate of triplet pregnancies increases along with the number of good quality embryos available.

Multiple pregnancy score:

The MPS was developed on the basis of the two cut-off values identified above: age=34 years and two good quality embryos. As Table II shows, the rate of triplet pregnancies increased notably when more than two good quality embryos were available. Therefore, it was decided to award one point for each good quality embryo (Table III). In terms of age, one point was awarded for the cut-off value of 34 years, but the overall scoring range also took into account that the risk of multiple pregnancy has been shown to be higher for women under

30 and lower for those over 40. Consequently, the final scoring system was as shown in Table III. We then proposed the following criteria: one embryo would be transferred when the final MPS was 5 or 6, two embryos when the MPS was 3 or 4 and 3 embryos when it was less than 3.

Results of the prospective study

Of the 393 women with at least three available embryos at the moment of transfer, 301 accepted transfer of the number of embryos recommended by the MPS (76.6%, MPS-accepted group) and 92 requested more embryos (23.4%, MPS-not accepted group).

The overall clinical pregnancy rate per embryo transfer was significantly different: 50.5% in the MPS-accepted group (152 pregnancies / 301 transfers) vs. 67.4% in the MPS-not accepted group (62 pregnancies / 92 transfers) ($p<0.01$). However, the overall multiple pregnancy rate was significantly lower in the MPS-accepted group (34.9% vs. 53.2% in the MPS not-accepted group; $p<0.05$) (Table IV).

The number of embryos proposed by the MPS compared with the number actually transferred is shown in Table V. The MPS recommended transfer of one embryo (MPS 1) in 29.3 % of women (115/393); 45 accepted (MPS 1-1ET) and 70 requested two embryos (MPS 1-2ET). In 39.4% (155/393) of women, the MPS indicated transfer of two embryos (MPS 2); 139 accepted (MPS 2-2ET) and 16 requested three embryos (MPS 2-3ET). Finally, the MPS recommended transfer of three embryos (MPS 3) in 31.3 % (123/393) of women; 117 accepted (MPS 3-3ET) and 6 requested four embryos (MPS 3-4ET).

As seen in Table VI, there was a significant difference between the MPS 1-1ET and MPS 1- 2ET groups in terms of the clinical pregnancy rate (42.2% and 68.6%, respectively) ($p<0.01$). However, there were no significant differences in either the MPS 2 (MPS 2-2ET, 59%; MPS 2-3ET, 68.8%) or MPS 3 (MPS 3-3ET, 43.6%; MPS 3-4ET, 50%) groups, although the difference in the size of their respective sub-groups makes statistical comparison impossible. Nevertheless, the overall multiple pregnancy rate was always higher when more embryos than recommended by the MPS were transferred. For the MPS 1 group transfer of two embryos led to 54.2% of twin pregnancies, for the MPS 2 group transfer of three embryos led to 18.2% of triplets, and this figure rose to 33.3% when four embryos were transferred in the MPS 3 group.

DISCUSSION

The risks of multiple gestation are well recognized and there is general agreement among the medical community that multiple pregnancy needs to be reduced (Land and Evers, 2003). However, despite various guidelines and recommendations (ASRM,1999; ESHRE, 2001) multiple pregnancy rates have continued to rise over the last twenty years along with the increasingly widespread use of ART (Tur et al., 2001).

Studies have shown that no more than two embryos should be transferred in young women with good quality embryos (Dean et al., 2000). More recently, some authors (Vilska et al., 2001; De Neubourg et al., 2002) have suggested that in the first attempt only one embryo should be transferred in such circumstances. However, the prognosis is not always so favourable, and rather than limiting the number of embryos transferred across all patients, we believe it is better practice to decide selectively, according to individual characteristics.

Several authors have analyzed risk factors for multiple pregnancy and the following have been identified: young age of women (Svendsen et al., 1996), embryo quality (Basil et al., 1997), both these factors (Minaretzis et al., 1998), and number of embryos available for transfer (Engmann et al., 2001) - when several embryos develop, there is an increased likelihood that good quality embryos can be selected for replacement. Templeton and Morris (Templeton and Morris, 1998) found that older age, tubal infertility, longer duration of infertility and a higher number of previous attempts were all associated with a significant decrease in multiple pregnancy, and, furthermore, the number of eggs fertilized and the number of embryos available for transfer were important factors in determining outcome. When more than four embryos were fertilized and available, transfer of only two embryos did not decrease the likelihood of pregnancy, but it did reduce the chance of multiple pregnancy.

Our retrospective study found the number of good quality embryos and age of women to be the most important parameters related to the multiple pregnancy rate, whereas the total number of embryos available, number of previous cycle attempts and cause of infertility bore no relationship. Thus, the quality of the embryo transferred in a given cycle is the factor that most influences outcome. Other studies (Devreker et al., 1999) have shown better embryo quality for patients with more than five available embryos, regardless of maternal age. Our results suggest, however, that age also has an influence, with the multiple pregnancy rate being lower in older women. Moreover, these women tend to have fewer available embryos and show a higher rate of chromosomal abnormalities. A correlation has been reported between maternal age and chromosomal abnormalities (Munne et al., 2002), and a relationship between morphological criteria and the ability of an embryo to develop to the blastocyst stage with chromosomal abnormalities (Sandalinas et al., 2001). These studies show that a morphologically normal embryo may have chromosomal abnormalities, and since the implantation rate can be lower in such cases, the transfer of more embryos may well be justified.

Most authors recommend that transfer be carried out according to factors associated with good prognosis (age, cycle number, embryo quality etc.). However, our aim was to develop a standardized procedure (MPS) that took into account the two factors identified in the multivariate study (age and number of good quality embryos on the day of transfer). By assigning different cut-off values the MPS enables a decision to be made regarding the number of embryos to be transferred according to the specific characteristics of each cycle.

The overall results of the prospective study show that 76.6% (301/393) of women accepted transfer of the number of embryos recommended by the MPS. However, while a majority of those with recommended transfer of two (89.7%,139/155) or three (95.1%,117/123) embryos accepted this proposal, only 39% (45/115) of women with recommended transfer of one embryo did so. Thus, couples generally accepted the risk of multiple pregnancy, particularly twins. In a survey of women who had had twins, either spontaneously or after IVF/ICSI techniques (Pinborg et al., 2003), only 17-24% said they would accept single embryo transfer; the possibility of free treatment and having had complications associated with twin pregnancy were factors related to acceptance. In Spain, eSET is still rarely used. ESHRE data from 1999 (Nygren and Andersen, 2002) show that only 8.6% of embryo transfers involved a single embryo (although it is not specified in the data, it is safe to assume that this figure refers predominantly to non-eSET). This contrasts sharply with the same data for Scandinavian countries, the figure for Finland being 21.6%.

Although use of the MPS enabled us to reduce the rate of triplets to 2% (in 1999 the figure was 9.8% - unpublished data for our centre), there was no significant change in the rate of twin pregnancies (32.9% in the present study compared with 33.2% in 1999). However, overall results show that when the number of embryos transferred was greater than that recommended by the MPS, the resulting increase in the pregnancy rate (67.4% vs. 50.5% in MPS-accepted) was accompanied by a higher multiple pregnancy rate (4.8% of triplets and 48.4% of twins). Similar results were found for the MPS 1 group, the one most appropriate for evaluation because of the comparable number of cycles in the 1ET vs. 2ET subgroups. However, as was pointed out above, a similar comparison cannot be made for the MPS 2 and MPS 3 groups, since the relative number of cycles in each of their subgroups makes them impossible to compare statistically; the large majority of women in both groups accepted the MPS recommendation.

Most comparative studies of eSET vs. eDET have shown a higher pregnancy rate for the transfer of two embryos, although the difference is not significant (Martikainen et al., 2001; Vilska et al., 2001; Gerris et al., 1999; Gerris et al., 2002). In contrast, we did achieve a significantly higher pregnancy rate when transferring two embryos, although this was accompanied by an unacceptably high twin pregnancy rate (54.2%). However, given that the pregnancy rate after eSET (42.2%) was more than acceptable, the increased risk of multiple pregnancy associated with the transfer of two embryos seems an unacceptable price to pay. In order to evaluate these outcomes further, we would need to consider the cumulative clinical pregnancy rate after the transfer of frozen-thawed embryos (Martikainen et al., 2001; Tiitinen et al., 2001), as well as the cumulative live birth rate per couple (Ozturk et al., 2001).

Although many authors (Engmann et al., 2001; Templeton and Morris, 1998) argue that the number of attempts is a factor to take into account when deciding how many embryos to transfer, our results, in accordance with those of Basil et al. (Basil et al., 1997), suggest that this is not an important variable. Nevertheless, the number

of attempts may be a factor leading couples to request transfer of more embryos. As our centre is private, it is the couples themselves who bear the cost of IVF cycles and this fact, combined with their desire to achieve pregnancy, may be decisive. Indeed, IVF centres also want to achieve high pregnancy rates and the couples, whose priority is to achieve pregnancy, are usually willing to accept the risks of multiple pregnancy (Gleicher et al., 1995). Therefore, extensive counselling should be available regarding ongoing pregnancy rates and the potential consequences for both mother and child of multiple pregnancies, not only those of a higher order but also twins. In our opinion, the number of embryos to be transferred should be decided jointly with the couple after they have been fully informed of the risk involved, the aim being to achieve the greatest likelihood of pregnancy and the lowest risk of multiple gestation.

In our view, a strict policy aimed at limiting the number of embryos to be transferred (for example, no more than two in all cases) would excessively reduce the pregnancy rate. Thus, the purpose of the MPS is to achieve a similar pregnancy rate when transferring one, two or three embryos while avoiding - as much as possible - triplet pregnancies and keeping the number of twins to an acceptable minimum.

In conclusion, these preliminary results on the use of the MPS are a first step towards reducing multiple pregnancy rates, especially for triplet pregnancies. Although this scoring system can help to decide how many embryos to transfer in order to minimize multiple pregnancy, a twin pregnancy rate of 32.9% is still unacceptably high, and the MPS will need to be improved to reduce it.

References

1. The ESHRE Capri Workshop Group. Hum, Reprod 2000;15:1856-64
2. Jones HW. Multiple Births: how are we doing?. Fertil Steril 2003;79:17-21
3. Guzick DS et al. Efficacy of superovulation in IUI in the treatment of infertility. N Engl J Med 1999;340:177-83.
4. Gleicher N et al. Reducing the risk of HOMP after stimulation with gonadotropins. N Engl J Med 2000;343:2-7.
5. Tur R. et al. Risk factors for HOMP implantation after OI. Hum Reprod 2001;16:2124-9
6. Levene MI et al. HOMP births and modern management of indertility in Britain. Br J Obstet Gynaecol 1992;99:607-13
7. Dickey RP et al. Follicle numbers and estradiol levels …Fertil Steril 2001;75:69-78
8. Owen K. Elective Single ET. N Engl J Med 2004.
9. Proceedings of an expert meeting. MP. New York. April 2003. Bertarelli Foundation.

— Adonakis, G., Camus, M., Joris, H., Vandervorst, M., Van Steirteghem, A. and Devroey, P. (1997) The role of the number of replaced embryos on intracytoplasmic sperm injection outcome in women over the age of 40. Hum. Reprod 12, 2542-2545.

— American Society for Reproductive Medicine. (1999) A practice Committee Report. Guidelines on Number of Embryos Transferred. Birmingham, AL: American Society for Reproductive Medicine.

— Azem, F., Yaron, Y., Amit, A., Yovel, I., Barak, Y., Peyser, M.R., David, M.P. and Lessing, J.B. (1995) Transfer of six or more embryos improves success rates in patients with repeated in vitro fertilization failures. Fertil Steril 63, 1043-1046.

— Basil, S., Wyns, CH., Toussaint-Demylle, D., Abdelnour, W. And Donnez, J. (1997) Predictive Factors for Multiple Pregnancy in in Vitro Fertilization. J Reprod Med 42, 761-766.

— Bergh., T., Ericson, A., Hillensjo, T., Nygren, K.G. and Wennerholm, U.B. (1999) Deliveries and children born after in-vitro fertilisation in Sweden 1982-95: a retrospective cohort study. Lancet 354, 1579-1585.

— Boiso, I., Veiga, A. and Edwards, R.G. (2002) Fundamentals of human embryonic growth in vitro and the selection of high quality embryos for transfer. Reprod Biomed online 5, 328-350.

— Coroleu, B., Carreras, O., Veiga, A., Martell, A., Martínez, F., Belil, I., Hereter, L. and Barri, PN. (2000) Embryo transfer under ultrasound guidance improves pregnancy rates after in-vitro fertilization. Hum Reprod 15, 616-620.

— Coroleu, B., Barri, P.N., Carreras, O., Martínez, F., Parriego, M., Hereter, L., Parera, N., Veiga, A. and Balasch, J. (2002) The influence of the depth of embryo replacement into the uterine cavity on implantation rates after IVF: a controlled, ultrasound-guided study. Hum Reprod 17, 341-346.

— De Neubourg, D., Mangelschots, K., Van Royen E., Vercruyssen, M., Ryckaert, G., Valkenburg, M., Barudy-Vasquez, J. and Gerris, J. (2002) Impact of patients' choice for single embryo transfer of a top quality embryo versus double embryo transfer in the first IVF/ICSI cycle. Human Reprod 17, 2621-2625.

— Dean, N.L., Phillips, S.J., Buckett, W.M., Biljan, M.M. and Tan, S.L. (2000) Impact of reducing the number of embryos transferred from three to two in women under the age of 35 who produced three or more high-quality embryos. Fertil Steril 74, 820-823.

— Devreker, F., Pogonici, E., De Maertelaer, V., Revelard, P., Van den Bergh, M. and Englert, Y. (1999) Selection of good embryos for transfer depends on embryo cohort size: implications for the "mild ovarian stimulation " debate. Human Reprod 14, 3002-3008.

— Elster, N. (2000) Less is more: the risks of multiple births. Fertil Steril 74, 617-623.

— Engmann, L., Maconochie, N., Tan, S.L. and Bekir, J. (2001) Trends in the incidence of births and multiple births and the factors that determine the probability of multiple birth after IVF treatment. Human Reprod 16, 2598-2605.

— ESHRE Campus Course Report (2001) Prevention of twin pregnancies after IVF/ICSI by single embryo transfer. Human Reprod 16, 790-800.

— Garel, M. and Blondel, B. (1992) Assessment at 1 year of the psychological consequences of having triplets. Human. Reprod., 7, 729-732.

— Gerris, J., De Neubourg, D., Mangelschots, K., Van Royen, E., Van de Meerssche, M. and Valkenburg, M. (1999) Prevention of twin pregnancy after in vitro fertilization or intracytoplasmatic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. Human Reprod 14, 2581-2587.

— Gerris, J., De Neubourg, D., Mangelschots, K., Van Royen, E., Vercruyssen, M., Barudy-Vasquez, J., Valkenburg, M. and Ryckaert, G. (2002) Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. Human Reprod 17, 2626-2631

— Gleicher, N., Campbell, D.P., Chan Ch. L., Karande, V., Rao, R., Balin, M. and Pratt, D. (1995) The desire for multiple births in couples with infertility problems contradicts present practice patterns. Human Reprod 10, 1079-1084.

— Keith, L.G., Oleszczuk, J.J. and Keith, D.M. (2000) Multiple gestation: Reflections on Epidemiology, Causes, and Consequences. Int. J Fertil 45, 206-214.

— Land, J.A. and Evers, J.L.H. (2003) Risk and complications reproduction techniques: Report of an ESHRE consensus meeting. Human Reprod 18, 455-457.

— Martikainen, H., Tiitinen, A., Tomás, C., Tapanainen, J., Orava, M., Tuomivaara, L., Vilska, S., Hydén-Granskog, C.H., Hovatta, O. and the Finnish ET Study Group (2001) One versus two embryo transfer after IVF and ICSI: a randomized study. Human Reprod 16, 1900-1903.

— Matorras, R., Ballescá, J.L., Viscasillas, P., Peinado, J.A., Romeu, A., Coroleu, B., Bernabeu. R., Cuadrado, C., Martínez, L. and Palumbo, A. (2002) Registro FIV-ICSI. Sociedad Española de Fertilidad. Año 1999. Iberoamericana de Fertilidad, 19, 33-40.

— Minaretzis, D., Harris, D., Alper, M.M., Mortola, J.F., Berger, M.J. and Power, D. (1998) Multivariate analysis of factors predictive of successful live births in in vitro fertilization (IVF) suggests strategies to improve IVF outcome. J Assist Reprod. Genet 15, 365-371

— Munne. S., Sandalinas, M., Escudero, T., Marquez, C. and Cohen, J. (2002) Chromosome mosaicism in cleavage-stage human embryos: evidence of a maternal age effect. Reprod Biomed online, 4: 223-232

— Nijs, M., Geerts, L., Van Roosendaal, E., Segal-Bertin, G., Vanderzwalmen, P. and Schoysman, R. (1993) Prevention of multiple pregnancies in an in vitro fertilisation program. Fertil Steril 59, 1245-1250.

— Nygren, K.G. and Andersen, A.N. (2002) Assisted reproductive technology in europe,1999. Results generated from European registers by ESHRE. Human Reprod 17, 3260-3274.

— Oztuurk, O., Bhattacharya, S. and Templeton, A. (2001) Avoiding multiple pregnancies in ART. Evaluation and implementation of new strategies. Human Reprod 7, 1319-1321.

— Pinborg. A., Loft, A., Schmidt, L. And Andersen, A.N. (2003) Attitudes of IVF/ICSI-twin mothers towards twins and single embryo transfer. Human Reprod 18, 621-627.

— Qasim, S.M., Karacan, M., Corsan, G.H., Shelden, R. and Kemmann, E. (1995) High-order oocyte transfer in gamete intrafallopian transfer patients 40 or more years age. Fertil Steril 64, 107-110.

— Sandalinas, M., Sadowy, S., Alikani, M., Calderon, G., Cohen, J. and Munne, S. (2001) Developmental ability of chromosomally abnormal human embryos to develop to the blastocyst stage. Hum Reprod 16, 1954-1958.

— Scholz, T., Bartholomäus, S., Grimmer, I., Kentenich, H. and Obladen, M. (1999) Problems of multiple births after ART: medical, psychological, social and financial aspects. Human Reprod 14, 2932-2937.

— Staessen, C., Janssenswillen, C., Van Den Abbeel, E., Devroey, P. and Van Steirteghem, A. (1993) Avoidance of triplet pregnancies by elective transfer of two good quality embryos. Hum Reprod. 8, 1650-1653.

— Svendsen, T. O., Jones, D., Butler, L. and Muasher, S. (1996) The incidence of multiple gestations after in vitro fertilization is dependent on the number of embryos transferred and maternal age. Fertil Steril 65, 561-565.

— Templeton, A. and Morris, J. K. (1998) Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization, N Engl J Med 339, 573-577.

— Tiitinen. A., Halttunen, M., Härkki, P., Vuoristo, P. and Hyden-Granskog, C. (2001) Elective single embryo transfer: the value of cryopreservation. Human Reprod 16, 1140-1144.

— Tur, R., Barri, P.N., Coroleu, B., Buxaderas, R., Martínez, F. and Balasch, J. (2001) Risk Factors for high-order multiple implantation after ovarian stimulation with gonadotrophins: evidence from a large series of 1878 consecutive pregnancies in a single centre. Human Reprod 16: 2124-2129.

— Van Royen, E., Mangelschots, K., De Neubourg, D., Valkenburg, M., Van de Mersche, M., Ryckaert G., Eestermans, W. and Gerris, J (1999) Characterization of a top quality embryo, a step towards single-embryo transfer. Human Reprod 14, 2345-2349.

— Vilska, S., Tiitinen, A., Hyden-Granskog, C. And Hovatta, O. (1999) Elective transfer of one embryo results in acceptable pregnancy rate and eliminates the risk of multiple births. Hum Reprod 14, 2392-2395.

— Vilska, S., Hydén-Granskog, C.H., Hovatta, O. and the Finnish ET Study Group (2001) One versus two embryo transfer after IVF and ICSI: a randomized study. Human Reprod 16, 1900-1903.