Reproductive BioMedicine Online (2014) **29**, 200–208

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ARTICLE

Quality of additional embryos transferred on pregnancy outcomes in IVF: predictions using a mathematical approach

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Abstract This study assessed the influence of adding embryos with different embryo quality on pregnancy rate and multiple pregnancy rate (MPR). The study included 1891 IVF transfers performed at two centres with different embryo transfer policies. Pregnancy rate and MPR were analysed following three models and then including embryo quality. A predictive mathematical model and two scatter plots were constructed. The model based on embryo independence was incompatible with the observed data, while both the ground and collaborative models provided excellent fits. The collaborative model, however, predicted multiple pregnancies, especially triplets, more accurately. Transfer of additional embryos, irrespective of embryo quality, always increased pregnancy rate and MPR. When implantation rate was low, there was a marked increase in pregnancy rate but only a relatively small increase in MPR. In contrast, with higher implantation rates, the increase in pregnancy rate was mainly due to the increase in MPR, with the same singleton pregnancy rate. Transfer of additional embryos, irrespective of embryo quality, follows a collaborative pattern and always results in an increase in pregnancy rate and MPR. The scatter plots accurately predicted the influence of the different combinations of number and embryo quality on pregnancy rate and MPR.

KEYWORDS: embryo quality, pregnancy rate, scatter plot

http://dx.doi.org/10.1016/j.rbmo.2014.04.020
1472-6483/

Introduction

Maximizing pregnancy and implantation rates has been one of the main aims of assisted reproduction programmes since the outset. In fresh cycles, increasing the number of transferred embryos increases pregnancy rate (McLernon et al., 2010; Pandian et al., 2009). Transferring more than one embryo is, however, associated with a substantial increase in multiple pregnancies (Bergh, 2005). Since multiple pregnancies, especially high-order multiples involve medical risks, as well as having economic consequences (Matorras et al., 2005; Strömberg et al., 2002), a number of strategies have been proposed to minimize multiple pregnancies. A previous study by the current study group showed that, at implantation, there is a collaborative effect between embryos (Matorras et al., 2005). Such collaborative action is responsible for the multiple pregnancy rate (MPR) being much higher than if the implantation of each embryo is an independent process. Specifically, the frequency of triplets was 3–40-times higher than would be expected if implantation were independent (Matorras et al., 2005).

Embryo quality is one of the most important prognostic factors in IVF, and embryo morphology has long been known to be strongly associated with IVF success (Van Royen et al., 1999; Rienzi et al., 2005; Scott et al., 2007). This has recently been confirmed in a large multicentre trial, which found that the association was independent of maternal age (Vernon et al., 2011). The current study group has described how the collaborative phenomenon is dependent on the implantation rate and described a formula to predict pregnancy rate and MPR based on the number of embryos transferred and the mean implantation rate obtained in each specific centre (Matorras et al., 2005). A more recent report (Williams et al., 2012) showed that the combination of the ground (Speirs et al., 1996) and the collaborative (Matorras et al., 2005) formulae into a combined formula increased the accuracy of pregnancy rate and MPR predictions. However, in both reports (Matorras et al., 2005; Williams et al., 2012), all transferred embryos were assumed to have the same implantation rate; thus, it was not possible to ascertain whether the collaborative pattern varied according to the different combinations of quality among the embryos present at the transfer.

Nowadays, the only concern regarding transfers of more than one embryo, if they are of the same quality, is multiple pregnancy, since the pregnancy rate is expected to increase. On the other hand, it could be speculated that additional embryos, if they were of poorer quality than the 'leading' embryo, could reduce the pregnancy rate. The aim of this study was to assess potential synergies and, in particular, the impact of the interaction between transferred embryos as a function of their quality on implantation and pregnancy rates. Additionally, scatter plots of pregnancy and multiple pregnancy rates according to implantation rates were obtained to intuitively visualize the expected increases in pregnancy rate and MPR according the number and quality of the embryos to be transferred.

Materials and methods

Study population

The study population consisted of all couples attending the assisted reproduction programmes in two centres who fulfilled the inclusion criteria. The first group corresponded to the IVF programme of a public centre (Hospital de Cruces, Bilbao; centre A) and the second to that of a private centre (Instituto Valenciano de Infertilidad, Bilbao; centre B). The study was approved by the Clinical Research Ethics Committee of our center (reference no. 4, approved 3 January 2010).

The study period ran from January 2005 to June 2007, and the study population consisted of all IVF cases in each centre in which at least one fresh embryo was available to transfer, provided that transfers were performed on day 2 or 3. When the study was performed, the standard policy in centre A was to transfer three embryos when available, and there were no cases of oocyte donation. In contrast, the standard policy in centre B was to transfer two embryos when available, and oocyte donation cycles were included. Because in previous work, the fit to the collaborative model was the same in oocyte donation cycles as in own oocyte cycles (Matorras et al., 2005), in centre B both kinds of cycles were at first studied together. In both centres, when patients received one embryo this was because no further embryos were available. For further details, see the Supplementary Materials and Methods (available online).

Results

In centre A, 987 embryo transfers were considered, with an implantation rate of 21% (562/2730) and a per transfer pregnancy rate of 44% (437/987). In centre B, 804 embryo transfers were analysed, 492 in own oocyte cycles and 312 in oocyte donation cycles, with an implantation rate of 39% (576/1472) and a per transfer pregnancy rate of 53% (425/804). There were three monozygotic twins, which, for the purpose of the study, were considered as two implanted embryos. In centre A, in single embryo transfers the implantation rate was 23% for good-quality embryos, 17% for fair-quality embryos and 8% for poor-quality embryos, while in centre B, these implantation rates were 36%, 34% and 15%, respectively. **Tables 1 and 2** report the transfers by embryo quality performed in centres A and B, respectively, and their outcomes.

Accuracy of predictive mathematical models

From fitting the different models to the observed data (**Tables 1 and 2** and Tables S1 and S2 in the online version at doi:10.1016/j.rbmo.2014.04.020), the following conclusions can be drawn. The goodness-of-fit test clearly indicates that the independent model is not valid. For centre A, chi-squared was 84.2 for 43 degrees of freedom (dof), which corresponds to an upper tail probability of 0.01% and means incompatibility even with a confidence level of 99%. For centre B, the results were even less compatible: chi-squared was 82.4

Table 1 Observed rates of singletons, twins and triplets in centre A, compared with the predicted rates according to different models.

Embryo quality[a]	Cycles	Pregnancies	Singletons				Twins				Triplets			
			Obs.	Coll.	Ground	Indep.	Obs.	Coll.	Ground	Indep.	Obs.	Coll.	Ground	Indep.
2G	32	18	14	10.5	10.8	12.0	4	2.5	2.8	2.0				
3G	128	67	43	44.8	42.8	54.1	18	19.4	22.1	18.1	6	5.3	3.8	2.0
2G + 1F	156	71	47	53.7	52.3	64.1	18	20.8	23.2	19.0	6	4.8	3.3	1.8
2G + 1P[b]	1	1	1	0.3	0.3	0.4	0	0.1	0.1	0.1	0	0.0	0.0	0.0
2F	76	24	18	20.5	21.1	23.2	6	3.4	3.4	2.7				
3F	137	63	53	43.6	43.2	50.9	10	13.3	14.0	11.8	0	2.4	1.5	0.9
2F + 1P	35	17	13	10.2	10.3	11.7	4	2.4	2.5	2.0	0	0.3	0.2	0.1
2P[b]	14	2	2	2.0	2.0	2.1	0	0.1	0.1	0.1				
3P[b]	9	0	0	1.7	1.7	1.8	0	0.2	0.2	0.2	0	0.0	0.0	0.0
1G + 1F	66	24	19	20.0	20.8	22.7	5	3.9	4.1	3.1				
1G + 2F	108	102	76	69.5	68.5	82.0	21	23.9	25.9	21.4	5	4.8	3.2	1.8
1G + 1F + 1P[b]	17	6	4	5.4	5.5	6.2	1	1.4	1.5	1.2	1	0.2	0.1	0.1
1G + 1P[b]	6	1	1	1.6	1.7	1.7	0	0.2	0.2	0.1				
1G + 2P[b]	3	2	2	0.9	0.9	1.0	0	0.2	0.2	0.1	0	0.0	0.0	0.0
1F + 2P[b]	18	2	2	4.5	4.6	5.0	0	2.5	2.8	2.0	0	0.1	0.0	0.0
1G	47	11	11	10.8	12.0	11.8								
1F	96	17	17	16.6	17.7	18.0								
1F + 1P[b]	25	6	4	5.4	5.6	6.0	2	0.5	0.5	0.4				
1P[b]	13	3	3	1.0	1.1	1.1								
Total	987	437	330	323.0	322.9	375.8	89	93.1	101.5	82.9	18	17.9	12.2	6.8

Values are *n*.
Obs. = observed; Coll. = collaborative model; Ground = ground model; Indep. = independent model.
[a]G, F and P = good, fair and poor, respectively.
[b]There were very few registered cases and are not statistically significant, being subject to large fluctuations.

Table 2 Observed rates of singletons and twins in centre B, compared with the predicted rates according to different models.

Embryo quality[a]	Cycles	Pregnancies	Singletons				Twins			
			Obs.	Coll.	Ground	Indep.	Obs.	Coll.	Ground	Indep.
1G	84	40	40	30.1	34.6	34.8				
2G	298	171	103	99.4	96.3	144.6	68	76.1	74.7	51.2
1G + 1F	209	122	63	70.1	6.5	100.4	59	50.3	49.7	33.3
1G + 1P[b]	17	5	4	5.9	6.4	7.5	1	1.8	1.8	1.2
1F	39	15	15	13.2	15.2	15.0				
2F	103	54	33	34.5	34.1	48.8	21	23.3	23.2	15.2
1F + 1P	31	10	8	10.4	11.3	13.2	2	3.1	3.0	2.0
1P[b]	13	2	2	1.9	2.2	2.2				
2P[b]	10	6	6	2.3	2.5	2.8	0	0.4	0.4	0.3
Total	804	425	274	268.0	271.2	369.4	151	155.0	152.8	103.3

Values are *n*.
Obs. = observed; Coll. = collaborative model; Ground = ground model; Indep. = independent model.
[a]G, F and P = good, fair and poor, respectively.
[b]There were very few registered cases and are not statistically significant, being subject to large fluctuations.

(14 dof), which corresponds to an upper tail probability of 0%. Given this, it can be concluded without any doubt that there is some kind of correlation between the implantation of different embryos.

In contrast, both the collaborative and the ground models provided excellent fits to the data. Specifically, the ground model gave chi-squared as 49.6 (41 dof) and 16.6 (13 dof) for centres A and B respectively, corresponding to upper tail probabilities of 16.8% and 21.8%; while the collaborative model gave chi-squared as 42.0 (41 dof) and 15.9 (13 dof) for centres A and B respectively, leading to upper tail probabilities of 42.7% and 25.5%. For the collaborative model, the best fits were obtained for values of the collaborative index (f) of about 1.5 (centre A) and 2 (centre B). This index is a parameter of the model that represents the increase in the implantation probability for the second and third embryos in such a way that, for example, 1.5 means that the second embryo is 1.5-times (50% more) and the third is 2.25-times (1.5×1.5) more

likely to become implanted. If the index is forced to be equal for both groups, a value of 1.7 is obtained, with a goodness-of-fit better than 20% in all cases. Absence of collaboration (or any other source of positive correlation) would be reflected in an index close to one, so this hypothesis can be rejected on the basis of these data. Although it could be argued that collaborative model fits the data slightly better, both models are statistically compatible with the data with a confidence of 90%, so neither can be ruled out. That is, at this stage, both hypotheses (association/collaboration or barrier-breaking) could be valid to explain the observed correlations (for further details, see Supplementary Results).

Influence of the addition of embryos

These models can be used to study how the addition of embryos, of equal or different quality and thus implantation rate, affects the pregnancy rate and MPR for the subset of cases with two or more implanted embryos. Some of the trends can be seen directly looking at the observed rates, but the modelling provides more flexibility and generality (specifically, results can be extrapolated to centres with different implantation rates). It is also less affected by fluctuations (some of the categories contain a very small number of cases and therefore their statistical significance is weak). Since both this study and previous work (Matorras et al., 2005) indicate that the collaborative model is the one that best reproduces the observations, in particular multiplet rates, this model is used as the basis for interpretation of the results. Several scenarios can be considered, depending on the number and quality of the transferred embryos. The influence of adding an embryo on the pregnancy rate and MPR can be studied for each case, illustrating the usefulness of this modelling as a tool to support decision making. This is done as a function of the quality of the embryos.

Influence of increasing from one to two transferred embryos

Table 3 summarizes the variation in pregnancy rate and MPR when a second embryo is transferred. The results are expressed as a function of the quality of the first and second embryos represented by their theoretical implantation rate for single-embryo transfer. Each row shows what would happen if a second embryo were to be added, always assuming that the second one is of the same or poorer quality. Note that along the diagonal the pregnancy and implantation rates for both embryos transferred are the same. The rate of multiple pregnancies (twins in this case) is shown in parentheses. It can be seen that for poor-quality embryos, adding another poor-quality embryo is associated with a remarkable increase in the pregnancy rate (close to 2-fold in many cases) while the MPR remains low. In contrast, for high implantation rates, the increase in pregnancy rate is much more modest, with a high rate of twins. These data are depicted graphically in **Figure 1**.

For an initial implantation rate of 40% or more, the improvement in pregnancy rate is equal to or smaller than the increase in the rate of twins (the singleton pregnancy rate is maintained or even reduced). It can be seen that this is not an artefact of the mathematical model, by checking the raw data from centre B. For this case, both G- and F-quality embryos had an implantation rate of 35–40%. The pregnancy rate for 1G embryos was 48%, which increased to 57% (2G) or 58% (1G + 1F) (Table S2 in the online version at doi:10.1016/j.rbmo.2014.04.020), while the multiple pregnancy rate changed from 0% to 23% and 28%, respectively (**Table 2**) and the singleton pregnancy rate reduced from about 50% to 20–30%. This is another observation that is consistent with the nature of the implantation process; if the first embryo has a high chance of becoming implanted, the probability for the second one is even higher.

Influence of increasing from two to three transferred embryos

Similarly, the pregnancy rate and MPR when a third embryo is transferred can be compared. Although the model can be applied to any combination of quality of the embryos, the interpretation is simplified by restricting the discussion here to the two extreme cases: (i) embryos 1 and 2 have the same quality; and (ii) there is the maximum difference in quality between embryos 1 and 2. It can be proved that these are the two limiting cases and any other combination yields intermediate results, and the predictions are very similar in most cases and the conclusions are the same. **Table 4** summarizes these comparisons. Each row represents what would happen if a third embryo were to be added to cases with a given pregnancy rate. Each column represents the addition of a third embryo with a given quality, with its individual implantation rate. The last column corresponds to the case

Table 3 Predicted pregnancy and multiple pregnancy rates for the collaborative model in the case of transferring of two embryos, as a function of implantation rate.

Implantation rate of the first embryo (i.e. pregnancy rate if only one embryo transferred)	*Implantation rate of the second embryo*				
	10%	*20%*	*30%*	*40%*	*50%*
10%	19.0 (1.5)				
20%	28.0 (3.0)	36.0 (6.0)			
30%	37.0 (4.5)	44.0 (9.0)	51.0 (13.5)		
40%	46.0 (6.0)	52.0 (12.0)	58.0 (18.0)	64 (24.0)	
50%	55.0 (7.5)	60.0 (15.0)	65.0 (22.5)	70 (30.0)	75 (37.5)

Values are % pregnancies (% multiple pregnancies).

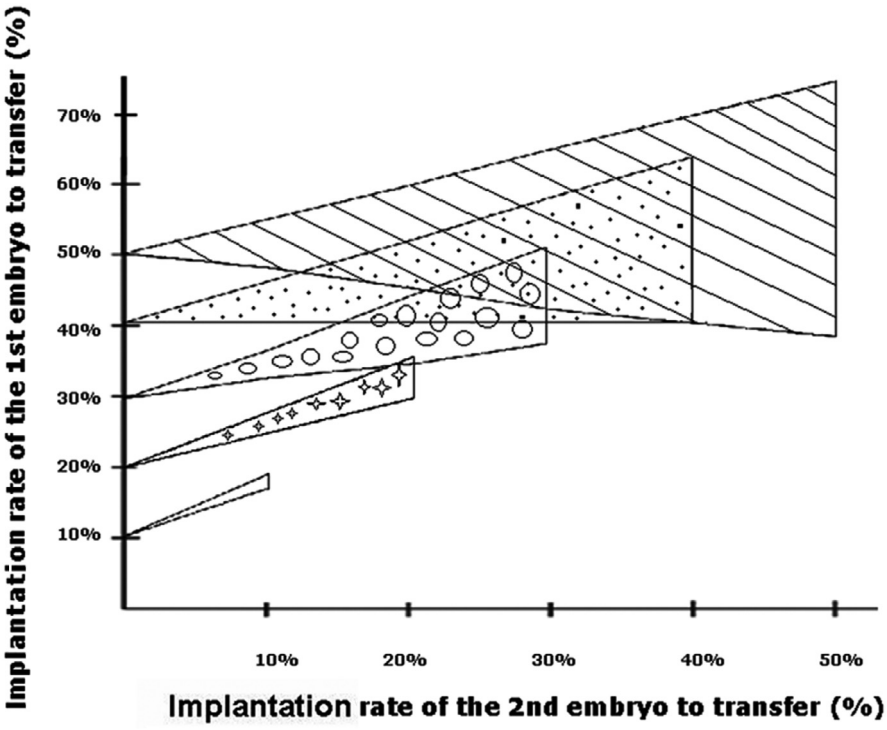

Figure 1 Predicted pregnancy and multiple pregnancy rates for the collaborative model for two transferred embryos, as a function of implantation rate. In each triangle, the lower line corresponds to singleton pregnancies, the upper line to the total pregnancies and the area to the multiple pregnancies.

Table 4 Predicted pregnancy and multiple pregnancy rates for the collaborative model for three transferred embryos, as a function of implantation rate.

Pregnancy rate (%) with the first two embryos	*Implantation rate of the third embryo*							
	10%		*20%*		*30%*		*Equal implantation rate for all three embryos*	
	PR	*MPR*	*PR*	*MPR*	*PR*	*MPR*	*PR*	*MPR*
20 (1.7)	28.0	(4.7) [0.5] (4.7) [0.5]					28.4	(4.9) [0.5]
30 (4.0)	37.0	(8.4) [1.1] (7.8) [0.9]					41.4	(11.0) [1.8]
40 (7.6)	46.0	(13.2) [2.1] (10.9) [1.4]	52.0	(18.3) [4.2] (18.2) [4.1]			53.5	(19.6) [4.7]
50 (12.9)	55.0	(19.5) [3.5] (14.0) [1.8]	60.0	(25.3) [7.0] (24.2) [6.1]			64.6	(30.7) [10.3]
60 (20.3)	64.0	(27.8) [5.5] (17.1) [2.3]	68.0	(33.9) [11.1] (30.1) [8.2]	72.0	(40.0) [16.6] (39.5) [15.8]	74.2	(44.2) [20.3]

Values are %; values in parentheses are % multiple pregnancies; values in square brackets are % triplets (already included in multiple pregnancies).
For MPR, upper cells in each row are based on the assumption that the first two embryos have the same implantation rate, while the lower cells are based on the assumption that there is the maximum difference in implantation rate between the first two embryos.
MPR = multiple pregnancy rate; PR = pregnancy rate.

of implantation of a third embryo of identical quality to the two other embryos. The fraction of multiple pregnancies is given in parentheses, while the triplet rates (already included in the MPR) are shown in square brackets. These are split between the two cases outlined above: ((i) embryos 1 and 2 have the same quality; and (ii) there is the maximum difference in quality between embryos 1 and 2): It can be seen that the pregnancy rate does not change in both cases, while some variation is observed in the rates of multiplets.

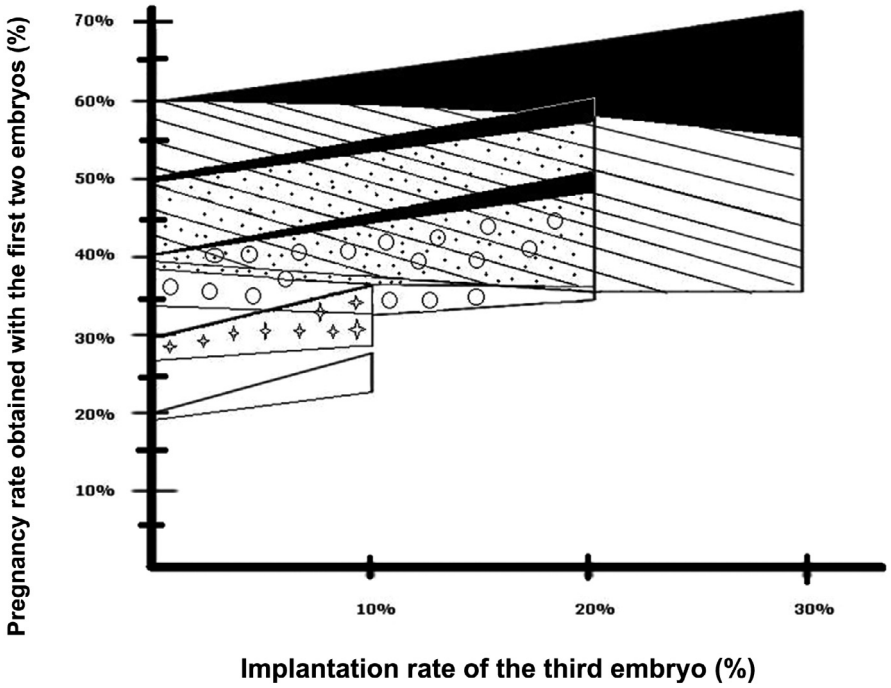

Figure 2 Predicted pregnancy and multiple pregnancy rates for the collaborative model for three transferred embryos, as a function of implantation rate. In each block, the lower line corresponds to singleton pregnancies, the upper line to the total pregnancies, the area to the multiple pregnancies and the black area to the triplet rate.

As in the previous scenario, as can be observed in **Figure 2**, for a high pregnancy rate the addition of an embryo only moderately increases the pregnancy rate, while greatly increasing the MPR. For example, adding a third equal-quality embryo when the first two have a pregnancy rate of 50%, improves the pregnancy rate to 64.6% but increases the rate of multiplets from 12.9 to 30.7% (**Table 4**). If the objective is to keep the multiple rate low, these data indicate that the inclusion of a third embryo is not recommendable if the pregnancy rate with transfer of two is higher than 30–40%. For an initial pregnancy rate of about 40% or more (implantation rate close to 25%, if both embryos are of the same quality), it can be observed that, as for the case above, the inclusion of an third embryo increases the pregnancy rate through multiplets, even reducing the singleton pregnancy rate (**Figure 2**). Moreover, for an initial pregnancy rate of 60% (implantation rate close to 40%, if both embryos are of the same quality), the inclusion of a third embryo increases the MPR, increasing triplets and decreasing twins (**Figure 2**).

Discussion

A number of individual and institutional recommendations have been issued to restrict the number of embryos transferred to prevent multiple pregnancy (JOINT SOGC-CFAS, 2008; Perez Milan et al., 2007; Association of Clinical Embryologists *et al.*, 2011; Kresowik et al., 2011). In the majority of these recommendations, the most important criteria are embryo quality and the age of the woman, but they also consider fresh versus cryopreserved embryos, number of IVF attempts and oocyte source (donor versus own). The quality of transferred embryos is a well-known factor in both pregnancy and implantation rates. Several criteria have been considered to analyse embryo quality. Embryo morphology has long been known to be strongly associated with IVF success (Rienzi et al., 2005; Scott et al., 2007; Van Royen et al., 1999). However, it is not always the case that the 'good' embryos based on classical morphological criteria are found to be normal embryos when preimplantation genetic diagnosis is performed (Alfarawati et al., 2011). On the other hand, even very poor-quality embryos based on classical morphological data can produce absolutely healthy newborn infants (Mendoza et al., 2014).

From a clinical point of view, in the presence of embryos of similar quality, the question of transferring more than one is only limited by the risk of multiple pregnancy, since the pregnancy rate will increase. However, it is not clear whether it is appropriate to combine one embryo with others of poorer quality. It could be speculated that poorer-quality embryos might impair the implantation of the best embryo, thus decreasing the pregnancy rate, or that perhaps the pregnancy rate would be the same but with an increase in multiple pregnancies, both situations being clinically undesirable.

In the late 1990s, the concept of the 'sponsoring embryo' emerged, this referring to the phenomenon that a good-quality embryo could make the rest of the embryos in a batch obtain higher pregnancy and implantation rates. Lightman et al. (1997) reported that this effect was larger the more good-quality embryos were transferred. Later on, Hu et al. (1998) added that not only the pregnancy rate but also the implantation rate was better when good-quality embryos were transferred. On the other hand, there is the problem of what to do when only additional poor-quality embryos are available: it could be speculated that their addition could have a positive effect, but the opposite could also be true (Lightman et al., 1997).

Concerning the number of transferred embryos and their potential synergies, in recent years, there have been several publications describing attempts to develop an equation that could predict both pregnancy rates and implantation rates. Torsky et al. (2005), employing an algorithm to predict pregnancy outcome after assisted reproductive technology in 281 transfers, reported a minimal embryo synergy regarding twins and concluded that a more detailed analysis of high-order multiple pregnancies was needed to clarify this phenomenon. The current study group's previous report (Matorras et al., 2005) showed how embryo implantation was indeed a collaborative phenomenon that could be predicted by a mathematical formula and that embryo synergy was much more evident in high-order multiple pregnancies. Williams et al. (2012) reported both a collaborative and a ground effect.

All of these studies (Matorras et al., 2005; Roberts et al., 2009; Williams et al., 2012) have, however, assumed the same implantation rate for all embryos transferred in the same transfer. However it could be speculated that the implantation pattern would not be the same with, for instance, two fair-quality embryos transferred together as one very good-quality embryo and one poor-quality embryo, even if the resulting mean implantation rate would be the same. This study attempted to ascertain whether this synergy was true for embryos, irrespective of their quality. The results revealed that such a synergy always appeared but its magnitude varied dramatically as a function of the quality of the embryos involved.

A recent paper reporting a study of live births resulting from the transfer of two fresh embryos described how a number of clinical and analytical parameters influences multiple (twin) pregnancy rate (Lannon et al., 2012). Further, Williams et al. (2012) indicated that the combination of the ground and collaborative formulae into a single formula increased the accuracy of pregnancy rate and MPR prediction. Consistent with these findings, this study's collaborative model does not imply a lack of influence of other parameters (such as endometrial factors, age of the woman, body mass index, antral follicle count, anti-Müllerian hormone concentration, stimulation protocol, serum peak oestradiol, sperm characteristics, and cause of infertility), but rather considers them as the average of a random variable.

One possible criticism of this work is that, due to its nonrandomized design, there could be some bias regarding single-embryo transfers. It is well known that pregnancy rate is much higher in elective single-embryo transfers than in single-embryo transfers when no additional embryos are available. The same is true for two embryo transfers (elective versus no additional available embryos) (Cai et al., 2011; Guerif et al., 2009). However, even in elective transfers, the larger the embryo cohort, the higher the pregnancy rate. In the present study's opinion, although the inclusion of the aforementioned parameters might improve the model to some extent, they probably act (at least in part) through their influence on implantation rate. In agreement with this, the behaviour of this collaborative model was very similar in the centre where double-embryo transfer was always performed when there were no further available embryos, than in the centre where the majority of double-embryo transfers were elective.

This work derived a mathematical equation based on the implantation rate in each centre for each quality of embryo to predict the expected increase in pregnancy rate and MPR if additional embryos are added, taking into account the quality of the additional embryo(s). Visual information can be easily obtained from **Figures 1 and 2**, facilitating the assessment of the most suitable embryo transfer scenario in each individual case. This study did not conduct separate analysis for clinical subgroups due to the size of the population under study.

This study has revealed that the addition of one or more embryos always increased the pregnancy and implantation rates, even if the additional embryos were of poorer quality than the leading embryo. The influence of the additional embryos was, however, markedly different, depending on their own quality. Specifically, when the leading embryo had an expected implantation rate of 50% (i.e. pregnancy rate of 50% and MPR of 0% if transferred alone), adding a similar-quality embryo can be expected to increase the pregnancy rate to 75% and the MPR to 37.5%; on the other hand, if the implantation rate of the second embryo were to be 30%, the pregnancy rate is predicted to be 65% and the MPR 22.5%, and if the implantation rate of the second embryo was only 10%, the pregnancy rate is estimated to be 55% and the MPR 7.5%. In contrast, if the leading embryo had an expected implantation rate of 20% (i.e. 20% pregnancy rate and 0% MPR if transferred alone), adding a similar-quality embryo should lead to a pregnancy rate of 36% and a MPR of 6%, and a second embryo with an implantation rate of 10% would lead to a pregnancy rate of 28% and MPR of 3%. A similar pattern was observed in transfers of three embryos. It is generally accepted, and supported by cumulative data from sources such as the Society for Assisted Reproductive Technologies (Sunderam *et al.*, 2012), that the inclusion of more than two embryos at transfer only increases the MPR, not the overall pregnancy rate, but these conclusions have been drawn without stratifying data based upon additional information, such as embryo quality. The current data indicate that when only poor-quality embryos (about 10% implantation rate) are available, transferring three instead of two would increase the pregnancy rate from 20 to 28%, with an increase in MPR from 1.7 to 4.7% (0.5% triplets). For further discussion, see the Supplementary Material.

This model provides a tool to define policies on the number of embryos to be transferred, making it possible to strike a balance between pregnancy rate and MPR, as a function of embryo quality. In general, for implantation rates >30%, the inclusion of embryos of similar or poorer quality increases the pregnancy rate through an increase in multiple pregnancies and tends to decrease the rate of singleton pregnancies. Clearly, the decision on which policy to adopt depends on how important it is considered to minimize the rate of twin pregnancies, but the transfer of two good-quality embryos seems a reasonable policy when the implantation rate is <30%. Interestingly, when the expected pregnancy rate with two embryos is 60% (e.g. an implantation rate of 40% in each embryo), adding a third embryo not only increases the pregnancy rate by increasing the MPR and decreasing singleton pregnancies, but also increases the triplet rate by decreasing the twin rate.

This study recommends that clinics calculate the implantation rate for each embryo quality based on their own data considering: (i) transfers of two or more embryos of the same quality; and (ii) single-embryo transfers of this quality (im-

plantation rate = number of implanted embryos/number of transferred embryos of one specific quality). Specific subanalysis combining embryo quality and woman's age would be likely to be worthwhile. If used in this way, this model could be very useful in decision making as an aggregated approach using a combination of embryo number, embryo quality and implantation rate for each embryo quality.

Certainly, many other factors should be taken into account when a transfer is planned but these results show that when trying to obtain the highest pregnancy and implantation rates, the addition of more embryos in cases with high implantation rate does not increase singleton pregnancies, but rather transforms nonpregnancies (or single pregnancies) into multiple pregnancies.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2014.04.020.

Further reading

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 21 February 2013; refereed 28 March 2014; accepted 1 April 2014.