Reducing multiples: a mathematical formula that accurately predicts rates of singletons, twins, and higher-order multiples in women undergoing in vitro fertilization

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Objective: To develop a mathematical formula that accurately predicts the probability of a singleton, twin, and higher-order multiple pregnancy according to implantation rate and number of embryos transferred.
Design: A total of 12,003 IVF cycles from a single center resulting in ET were analyzed. Using mathematical modeling we developed a formula, the Combined Formula, and tested for the ability of this formula to accurately predict outcomes.
Setting: Academic hospital.
Patient(s): Patients undergoing IVF.
Intervention(s): None.
Main Outcome Measure(s): Goodness of fit of data from our center and previously published data to the Combined Formula and three previous mathematical models.
Result(s): The Combined Formula predicted the probability of singleton, twin, and higher-order pregnancies more accurately than three previous formulas (1.4% vs. 2.88%, 4.02%, and 5%, respectively) and accurately predicted outcomes from five previously published studies from other centers. An online applet is provided (https://secure.ivf.org/ivf-calculator.html).
Conclusion(s): The probability of pregnancy with singletons, twins, and higher-order multiples according to number of embryos transferred is predictable and not random and can be accurately modeled using the Combined Formula. The embryo itself is the major predictor of pregnancy outcomes, but there is an influence from “barriers,” such as the endometrium and collaboration between embryos (embryo–embryo interaction). This model can be used to guide the decision regarding number of embryos to transfer after IVF. (Fertil Steril® 2012;■:■–■. ©2012 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, mathematical modeling, multiples, embryo transfer, outcome predictors

One of the greatest challenges in IVF is determining the number of embryos to transfer to the uterus. The decision is based on the need to balance the risk of no pregnancy, which may occur when too few embryos are transferred, with the risk of multiples if too many embryos are transferred (1–3). Making an informed decision requires the ability to determine the likelihood of a given outcome. We therefore sought to develop

Received November 23, 2011; revised and accepted August 8, 2012.
Z.W. has nothing to disclose. E.B. has nothing to disclose. M.B. has nothing to disclose. S.K.J. has nothing to disclose. R.E. has nothing to disclose. L.V. has nothing to disclose. Z.R. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2012 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.08.014

a mathematical formula that would predict the likelihood of single, twin, or multiple pregnancies according to the number of embryos transferred. Moreover, the ability to predict outcome according to a mathematical model would also inform our understanding of the biology of implantation and the relative contributions of both intrinsic embryonic and extraembryonic factors toward achieving pregnancy.

In 1994, Bouckaert et al. (4) reported that pregnancy probabilities largely followed a binomial distribution and could be estimated according to implantation rates and the number of embryos transferred. This model assumes that, like rolls of dice, each embryo is independent, and that pregnancy rates are only dependent on the implantation rate of the embryo. Martin and Welch (5) further elaborated on the implications of the binomial equation as it applied to implantation and demonstrated a trade-off between no pregnancy and the risk of twins. Trimarchi (6) applied probability math to outcomes data from Terriou et al. (7) to further support this model.

In 1996, Speirs et al. (8) postulated that a "barrier," representing factors external to the embryo, such as an endometrial factor, might impede implantation. He adjusted the Binomial Formula to account for this "barrier," and the resulting formula was known as the "Ground" Formula. Matorras et al. (9) predicted that a degree of collaboration exists between embryos and that the successful implantation of one embryo could increase the likelihood another embryo to implant. To incorporate this cooperativity, Matorras developed the Collaborative Formula to predict pregnancy outcomes according to the number of embryos transferred and demonstrated that the Collaborative Formula, and to a lesser extent the Ground Formula, better fit pregnancy data obtained from their center than did the Binomial Formula alone.

Because a "barrier" to implantation (8, 10, 11) and a degree of cooperativity between the embryos (9, 12) are both supported by evidence and not mutually exclusive, it is reasoned that both factors could play a role in implantation and pregnancy rates. We sought to determine whether a hybrid formula, incorporating aspects of the Binomial, Collaborative, and Ground Formulas would more accurately predict outcomes as compared with either formula alone. Such a formula would have implications for our understanding of factors affecting pregnancy rates and their relative number of embryos transferred and thereby inform the decision of how many embryos to transfer.

MATERIALS AND METHODS

Patient Population

The patient population was from a single IVF center from 1995 to 2008 (n = 12,003). We included IVF cycles that resulted in day-3 ET and did not involve preimplantation genetic diagnosis, testicular sperm extraction, or microsurgical epididymal sperm extraction.

Patients were grouped into the following categories: maternal ages 30–33 years with two or three embryos transferred; ages 34–36 years with two, three, or four embryos transferred; ages 37–39 years with three or four embryos transferred; ages 40–41 years with four or five embryos transferred; and age >41 years with five embryos transferred. These groups were selected because they constituted the vast majority of patients at our center. Implantation rates were calculated by dividing the total number of fetal hearts seen on week-7 ultrasound by the total number of embryos transferred for each group. The percentage represented by each outcome (no pregnancy, singleton, twins, more than twins) was determined by dividing the number of women with the specific outcome by the total number of women in the subject population and multiplying by 100 (i.e., percentage of twins represents percentage of twins out of total number of women in that demographic; not the percentage of women who were pregnant). Because analysis was done on deidentified catagoric grouped data, it was deemed nonhuman subjects research and exempted from institutional review board review.

In testing the Combined Formula against published data from other centers, the rates of singleton and twin gestations using two-embryo transfer were used to determine the implantation rates for each group. This implantation rate was then used to calculate the distribution of outcomes and was compared with the distribution of actual outcomes.

Formulas

The Binomial Formula is widely described and is given by:

$$A = \frac{n!}{m!(n-m)!} p^m (1-p)^{n-m},$$

where A is the probability of obtaining a given number of implanted embryos (m) when n number of embryos are transferred having an implantation rate of p.

The Ground Formula, described by Speirs et al. (8), adjusts the Binomial Formula by a factor to account for the barrier to implantation (b) of 0.2 (8) and is given by:

$$A = b \frac{n!}{m!(n-m)!} p^m (1-p)^{n-m}.$$

The Collaborative Formula described by Matorras et al. (9) assumes that the implantation of the first embryo predisposes additional embryos to implant (9). The Collaborative Formula is given by:

$$p_n^m = p_{n-1}^m . (1-\alpha_m) + p_{n-1}^{m-1} . \alpha_{m-1},$$

where P is the probability of having m number of implantations with n number of embryos transferred. Alpha (α) is $p + m \times d$ and is the probability of increasing success with each success and was determined to be 22% (9).

The Combined Formula was derived by coupling the Binomial, Ground, and Collaborative Formula:

$$P : x\left[b \frac{n!}{m!(n-m)!} p^m (1-p)^{n-m}\right] + y\left[P_{n-1}^{m*}(1-\alpha_m) + P_{n-1}^{m-1*}\alpha_{m-1}\right],$$

for which x and y represent the relative contribution of the Ground and Collaborative Formulas, respectively, and where x + y = 1. We named this formula the "Combined" Formula to reflect the fact that aspects of the previous models were being adapted to optimize the ability to predict pregnancy outcomes.

Measurements of Accuracy

For the purposes of this study, accuracy of the formulas were calculated as the average absolute difference between the observed and calculated percentage pregnant with singletons, twins, or higher-order multiples for a given number of embryos transferred. Therefore, the formula used to calculate accuracy (AC) was, $AC = \sqrt{(O - C)^2}$, where AC = accuracy, O = pregnancy rate as percentage observed for a given number of implantations observed, and C = pregnancy rate as a percentage calculated for a given number of implantation events. Accuracy for each age group and number of embryos transferred was averaged to determine the overall accuracy of a given formula.

Statistical Analysis

For a given formula, the Akaike information criterion (AIC) is computed for each combination of woman's age and number of embryos transferred. Assume an N-size sample having a particular age range and a certain number K of embryos transferred. Let n_k denote the number of cycles in this set having k fetal heartbeats (FH), where $0 \leq k \leq K$. We also denote by p_k the probability of each outcome $k \varepsilon \{0, \ldots, K\}$, as predicted by the formula in question.

On the basis of the above information, we compute the Pearson χ^2 statistic such that:

$$\chi^2 = \sum_{k=0}^{K} \frac{(O_k - C_k)^2}{C_k} = \sum_{k=0}^{K} \frac{(n_k - \mathrm{Np}_k)^2}{\mathrm{Np}_k},$$

where O_k is the observed number of women, and C_k is the expected number of women predicted from the formula in question.

Given the χ^2 statistic, the AIC can be computed as:

$$AIC = \chi^2 + 2M,$$

where M is the number of parameters used in the given formula. In particular, for the Binomial and Collaborative Formulas we let $M = 2$, and for the Ground and Combined Formulas we let $M = 3$.

Note that the AIC measures the goodness of fit of a certain statistical model such that smaller AIC implies a better model.

RESULTS

The Binomial, Ground, and Collaborative Formulas were compared for their ability to predict actual pregnancy rates. Representative results of a subset of patients are shown in Figure 1A. Averaged over all outcomes (no pregnancy, singleton, twin, and more than twin pregnancy) the Ground, Collaborative, and Binomial Formulas were able to predict the outcome to within 2.88%, 4.02%, and 5% of the observed outcomes, respectively. This is consistent with prior studies showing improved accuracy of the Ground and Collaborative Formulas compared with the Binomial Formula (9).

Initial inspection of the data revealed that although all three formulas roughly approximated outcomes, there was a general trend in the errors (Fig. 1A). This was confirmed by isolating the error of each formula in predicting a particular outcome (Fig. 1B). The Ground Formula overestimated rates of no pregnancy and singleton pregnancy (by 1.8% and 3.4%, respectively) but underestimated the rates of twins and higher-order multiples (by 2.4% and 2.6%, respectively). Conversely, the Collaborative Formula underestimated the rates of no pregnancy (by 7%) and overestimated the rates of twin and higher-order multiples (by 2.5% and 4.7%, respectively).

This result suggested that aspects of *both* the barrier and Collaborative Formulas were relevant in predicting pregnancy outcomes and that using only one formula failed to account for the effects shown in the other. Therefore, the Ground and Collaborative Formulas were merged to generate the Combined Formula. Mathematical modeling was used to vary the proportional contribution of the barrier and Collaborative Formulas. The best fit was determined to be 55:45 Ground:Collaborative (Fig. 2A). The final Combined Formula therefore is as follows:

$$P : .55\left[b\frac{n!}{m!(n-m)}p^m(1-p)^{n-m}\right] + .45\left[P_{n-1}^{m*}(1-\alpha_m) + P_{n-1}^{m-1*}\alpha_{m-1}\right].$$

An online version of this formula is available at https://secure.ivf.org/ivf-calculator.html (JAVA applet required to view).

When applied to data from our center, the Combined Formula more accurately predicted pregnancy outcomes across all population groups (Fig. 2B), with an average error of 1.4% compared with 2.88%, 4.02%, and 5% for the Ground, Collaborative, and Binomial Formulas, respectively (Fig. 3). This represents a 71% and 60% improvement compared with the Ground and Collaborative Formulas, respectively.

The Combined Formula proved to be a more accurate model in predicting a negative pregnancy or triplet gestation in the two young age groups (30–33 and 34–36 years old) when three embryos were transferred, as well as in the older age group (40–41 years old) when four or five embryos were transferred (Supplementary Table 1, available online). These are some of the most challenging clinical scenarios in which our formula can help determine the number of embryo to be transferred.

To evaluate the accuracy of each of the formulas (i.e., Binomial, Ground, Collaborative, and Combined) in predicting the likelihood of singletons, twins, and higher-order multiples, we computed the AIC (13). The results demonstrate that the Combined Formula achieves the lowest AIC compared with the other methods (Fig. 4), which makes it a better model for predicting the likelihood of singletons, twins, or higher-order multiples.

To determine whether this formula would accurately predict outcomes from outside centers, the published literature was searched for large, randomized, controlled studies from which implantation rates and pregnancy rates could be determined. A total of five such studies were found (1, 14–18). The

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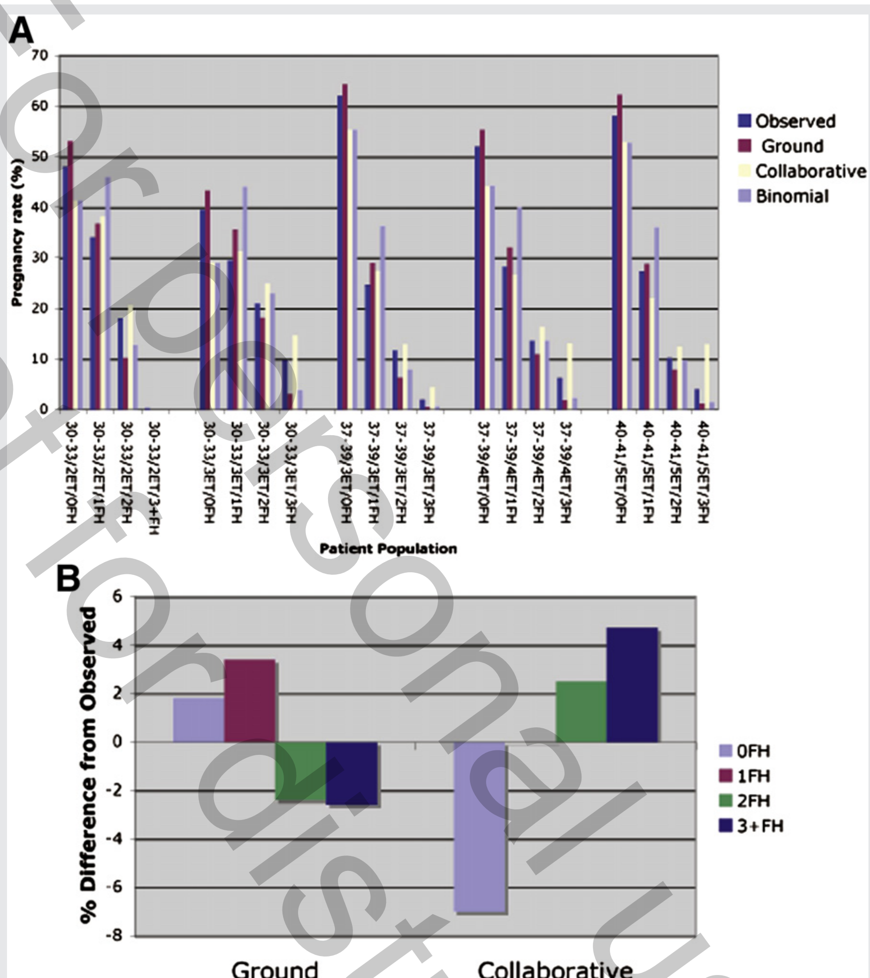
FIGURE 1



(A) Predicted and observed pregnancy rates. Comparison between observed pregnancy rates (*dark blue*) with rates calculated using the Ground (*burgundy*), Collaborative (*yellow*), and Binomial Formulas (*light blue*). Patient populations listed along the *x* axis were reported in an A/B/C format, whereby A describes the age of the subject population (e.g., 30–33-year-old women), B describes the number of embryos transferred (e.g., 3ET represents three embryos transferred), and C represents the outcome (e.g., 0FH = no pregnancy; 1FH = singleton pregnancy; 2FH = twin pregnancy; 3FH = more than two gestational sacs). (B) Difference between predicted and observed pregnancy rates using Ground and Collaborative Formulas. Average difference between the observed outcome rate of no pregnancy (*light blue*), singleton pregnancy (*burgundy*), twin pregnancy (*green*), and triplet or higher pregnancy (*dark blue*) and that outcome predicted by the Ground or Collaborative Formula.

Williams. Mathematical formula to predict IVF outcomes. Fertil Steril 2012.

Ground, Collaborative, and Combined Formulas were applied to the data from these five studies and the predicted results compared with the observed results (Supplementary Fig. 1A). Although all three models accurately estimated the rates of singleton pregnancy, the Combined Formula was the most accurate (Supplementary Fig. 1B, Supplementary Table 1).

DISCUSSION

The Combined Formula accurately predicted pregnancy outcomes using only implantation rates and the number of embryos transferred and did so with a higher degree of accuracy than previous formulas. The Combined Formula is consistent with a biological model in which implantation is primarily determined by the embryo (as modeled by the Binomial Formula) yet is also impacted by factors extrinsic to the embryo that may limit implantation (as predicted by the Ground Formula) and in which each implantation event predisposes another (as predicted by the Collaborative Formula). By incorporating these three models into the Combined Formula, we were able to significantly improve the ability to model pregnancy outcomes only on the basis of implantation rates and number of embryos transferred. Accounting for spontaneous loss rates for each pregnancy outcome will adjust for predicted delivery rates.

The formula was initially derived using modeling-based data from a single center. A concern may be raised regarding its generalizability. To address this limitation, we applied the formulas from five previously published studies and continued to observe an improved ability to model outcomes. For our

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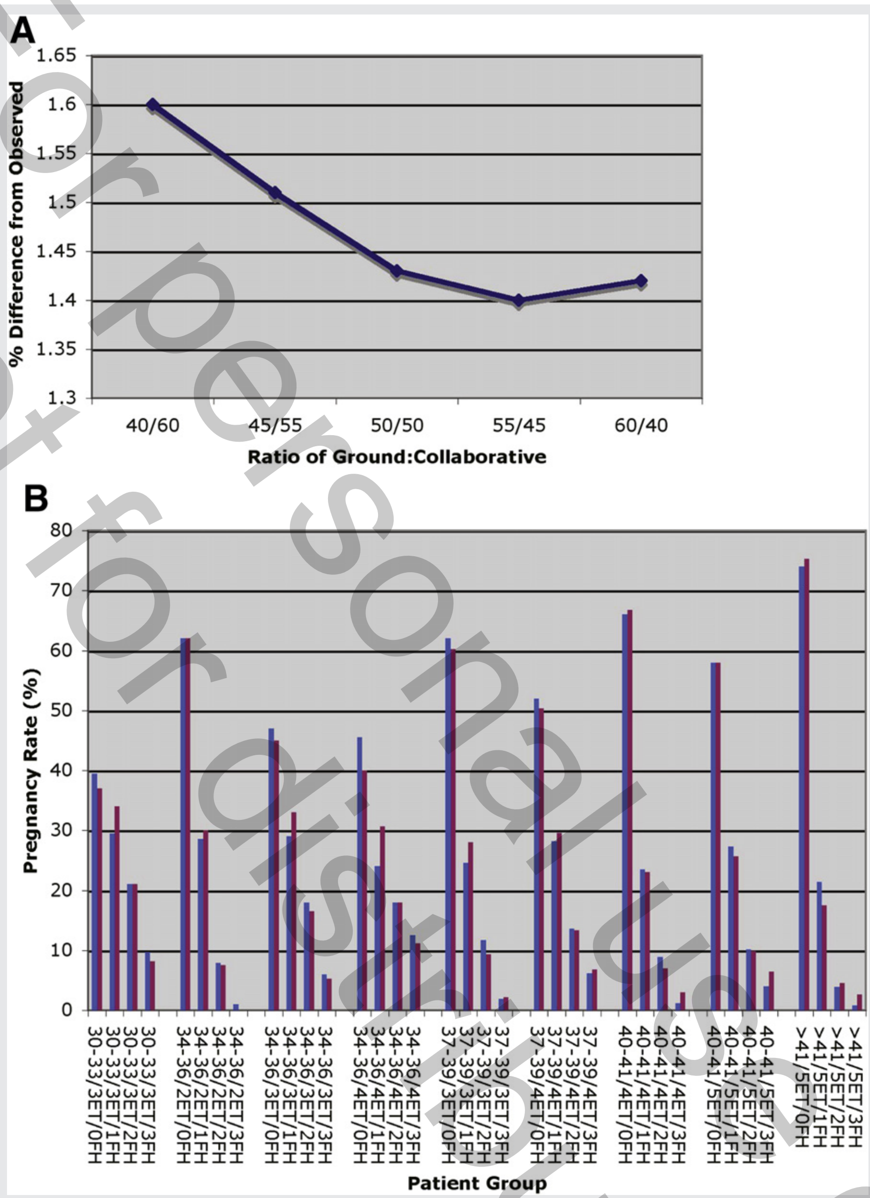
FIGURE 2



(A) Determining ratio of contribution of Ground and Collaborative Formulas to the Combined Formula. Graphic representation of mathematical modeling used to compare the difference of the observed pregnancy rates with those calculated by the Combined Formula while varying the relative weight of the ground vs. collaborative models. (B) Actual pregnancy rates compared with those predicted by the Combined Formula. Comparison of the observed pregnancy outcomes (*blue*) compared with those predicted by the Combined Formula (*burgundy*) for all groups studied. The *x* axis labels are in the same format as in Figure 1A.

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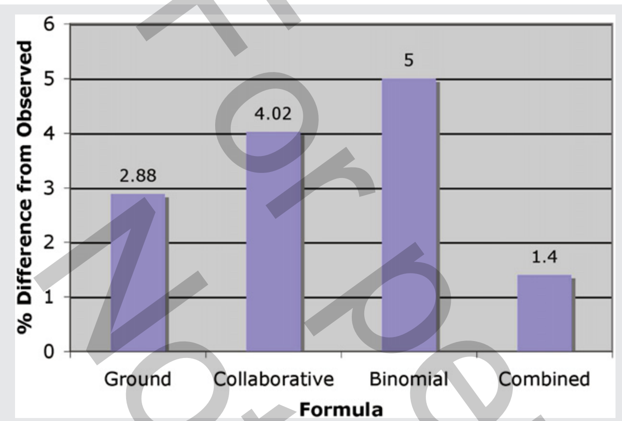
purposes, these published studies were limited by the fact that only one or two embryos were transferred. One of the strengths of the Combined Formula is the ability to predict outcomes when multiple embryos are transferred. It will be informative to expand future studies to look at data from other centers.

The Combined Formula is also dependent on an accurate estimation of implantation rates. For retrospective data, this can be directly determined. For use in counseling a patient or couple, historical data based on patient-specific factors or a second formula to calculate a predicted implantation rate are required. Although implantation rates vary between programs, it will need to be determined whether the difference is large enough to have a meaningful impact on predicted outcomes. Recent success in predicting implantation rates according to deep phenotyping of patient variables will aid in the application and accuracy of this formula (18).

A challenging yet critical decision in every IVF cycle concerns the number of embryos to transfer. This decision is made more difficult by the adeherence to general guidelines that may not reflect the particular circumstances of the patient

FIGURE 3



Difference between actual pregnancy rate and that calculated by the Ground, Collaborative, Binomial, and Combined Formulas. Values are expressed as percentages. Actual value is shown above the respective bar.

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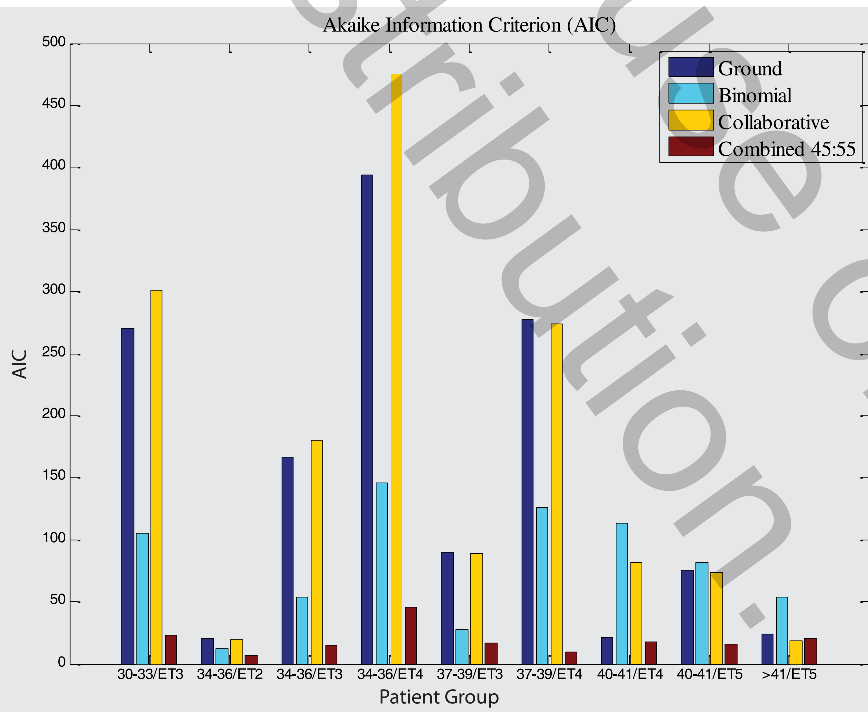
or that rely on imprecise approximations of outcomes (19). As demonstrated by Martin and Welch (5), in cases of a low implantation rate, increasing number of embryos transferred significantly improves likelihood of pregnancy while having minimal impact on risk of multiples. Conversely, in cases in which there is a high implantation rate, increasing the number of embryos transferred significantly increases the risk of multiples while having a minimal effect on the overall pregnancy rate.

This formula may be applied to three possible approaches toward managing the issue of multiple pregnancy. In the first approach, a consensus is reached regarding an acceptable rate of multiple pregnancies. For example, using the Combined Formula, we can determine that if there were a goal of an approximately 10% multiples rate, for a women with an implantation rate of 0.25, two embryos could be transferred (likelihood of multiples being 9%), whereas for a woman with an implantation rate of 0.1, four embryos could be transferred (likelihood of multiples being 9%).

In the second approach, instead of setting an acceptable rate of multiples determined by committee (20), this formula would allow an objective measure to be set. As the number of embryos increases, so too does the pregnancy rate. However, at a certain threshold, the increase in pregnancy rate is *primarily* due to an increase in multiples. The number of embryos required to reach this threshold is inversely related to the implantation rate. Therefore a less arbitrary way to set a recommended maximum number of embryos to transfer would be at the point where additional embryos would improve pregnancy rates primarily through increases in multiple rates.

In the third approach, the couple and their physician individually balance their medical, personal, and cultural preferences to make the decision. Using this formula would allow

FIGURE 4



The AIC for each of the prediction formulas. The AIC was calculated for each of the patient groups, as listed along the horizonal axis for the Ground (*purple*), Binomial (*blue*), Collaborative (*yellow*), and Combined (*maroon*) Formulas. Using the AIC, a lower number indicates a better model.

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a couple and their physician to determine the likelihood of having a pregnancy, singletons, twins, or higher-order multiples for any given number of embryos transferred. Thus this formula may be used to inform the discussion regarding number of embryos to transfer by adjusting the number of embryos to transfer and determining the predicted outcomes. The likelihood of the respective outcomes would inform the decision while allowing for accounting of each unique clinical and personal situation.

Pregnancy outcomes closely follow those predicted by the Combined Formula, in which the only variables used are implantation rates and the number of embryos transferred. The Combined Formula can therefore provide guidance and inform the decision regarding the number of embryos to transfer.

Acknowledgment: The authors thank their colleagues for their advice and helpful feedback.

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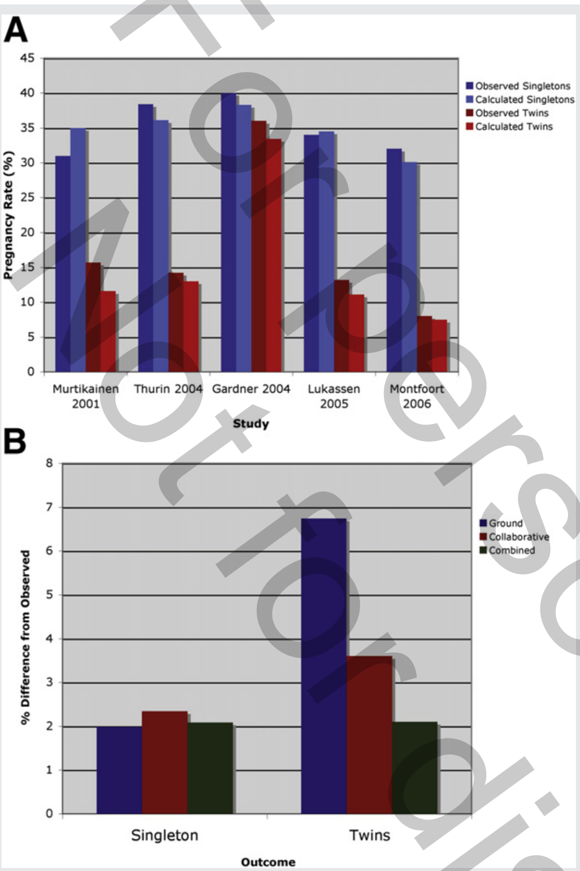
SUPPLEMENTARY FIGURE 1



(A) Application of the Combined Formula to previously published data from other centers. Comparison between actual pregnancy rates for singleton (*dark blue*) and twins (*dark red*) in previously published studies and the predicted pregnancy rates for singletons (*light blue*) and twins (*light red*) calculated using the Combined Formula. (B) Comparison of accuracy between Ground, Collaborative, and Combined Formulas. Difference between observed pregnancy outcome and that predicted by the Ground (*dark blue*), Collaborative (*burgundy*), and Combined (*dark green*) Formulas.

Williams. Mathematical formula to predict IVF outcomes. Fertil Steril 2012.

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SUPPLEMENTARY TABLE 1

Raw data showing observed outcomes and those calculated using the Ground, Collaborative, Binomial, and Combined Formulas.

		Formula			
Group	**Observed**	**Ground**	**Collaborative**	**Binomial**	**Combined (55:45)**
30-33/3ET/0FH	39.5	43.3	29.1	29	37
30-33/3ET/1FH	29.5	35.6	31.3	44	34
30-33/3ET/2FH	21	18.1	24.9	23	21
30-33/3ET/3FH	9.7	3.1	14.6	3.8	8.2
34-36/2ET/0FH	62	66.2	57.8	58	62
34-36/2ET/1FH	28.6	29.2	31.2	36.5	30
34-36/2ET/2FH	7.9	4.6	11	5.8	7.5
34-36/2ET/3FH	1	0	0	0	0
34-36/3ET/0FH	47	50.5	38.1	38	45
34-36/3ET/1FH	29	34.7	31.5	43	33
34-36/3ET/2FH	18	13.2	20.6	16.4	16.5
34-36/3ET/3FH	6	1.7	9.7	2	5.3
34-36/4ET/0FH	45.5	46.1	32.7	32.7	40
34-36/4ET/1FH	24	33.7	27.1	42	30.7
34-36/4ET/2FH	18	16.3	20.1	20.4	18
34-36/4ET/3FH	12.5	3.8	20.2	4.4	11.2
37-39/3ET/0FH	62	64.3	55.3	55.3	60.2
37-39/3ET/1FH	24.6	29	27.4	36.2	28
37-39/3ET/2FH	11.7	6.3	12.9	7.9	9.3
37-39/3ET/3FH	1.9	0.5	4.4	0.57	2.2
37-39/4ET/0FH	52	55.3	44.1	44.2	50.3
37-39/4ET/1FH	28.2	32	26.6	40	29.6
37-39/4ET/2FH	13.6	10.9	16.3	13.6	13.3
37-39/4ET/3FH	6.2	1.8	13.1	2.2	6.8
40-41/4ET/0FH	66	60.2	50.3	50.2	66.8
40-41/4ET/1FH	23.5	30.2	25.3	37.7	23
40-41/4ET/2FH	8.9	8.5	14.2	10.6	7
40-41/4ET/3FH	1.2	1.1	10.2	1.4	3
40-41/5ET/0FH	58	62.2	52.8	52.7	58
40-41/5ET/1FH	27.3	28.8	22	36	25.7
40-41/5ET/2FH	10.2	7.9	12.4	9.8	9.9
40-41/5ET/3FH	4	1.2	12.9	1.4	6.4
>41/5ET/0FH	74	77.8	72.2	72.2	75.3
>41/5ET/1FH	21.4	19.4	15.3	24.3	17.5
>41/5ET/2FH	3.9	2.6	6.9	3.3	4.5
>41/5ET/3FH	0.8	0.2	5.6	0.2	2.6

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1 **Reducing multiples: a mathematical formula that accurately predicts rates of singletons, twins, and higher-order multiples in women undergoing in vitro fertilization**

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A mathematical formula is developed that predicts the likelihood of singleton, twins, or higher-order multiples according to the number of embryos transferred and implantation rate.