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RESEARCH ARTICLE

Predicting the chances of live birth for couples undergoing IVF-ICSI: a novel instrument to advise patients and physicians before treatment [version 1; peer review: 2 not approved]

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v1 First published: 04 Sep 2019, 8:1585
<https://doi.org/10.12688/f1000research.20038.1>
 Latest published: 22 Dec 2020, 8:1585
<https://doi.org/10.12688/f1000research.20038.2>

Abstract

Background: In developed countries, the prevalence of infertility ranges from 3.5% to 16.7%. Therefore, the number of *in vitro* fertilization technique (IVF) and its subtype intracytoplasmic sperm injection (ICSI) treatments has been significantly increasing across Europe. Several factors affect the success rate of *in vitro* treatments, which can be used to calculate the probability of success for each couple. As these treatments are complicated and expensive with a variable probability of success, the most common question asked by IVF patients is "What are my chances of conceiving?". The main aim of this study is to develop a validated model that estimates the chance of a live birth before they start their IVF non-donor cycle.

Methods: A logistic regression model was developed based on the retrospective study of 737 IVF cycles. Each couple was characterized by 14 variables (woman's and man's age, duration of infertility, cause of infertility, woman's and man's body mass index (BMI), anti-Müllerian hormone (AMH), antral follicle count (AFC), woman's and man's ethnicity, woman's and man's smoking status and woman's and man's previous live children) and described with the outcome of the treatment "Live birth" or "No live birth".

Results: The model results showed that from the 14 variables acquired before starting the IVF procedures, only male factor, man's BMI, man's mixed ethnicity and level of AMH were statistically significant. The interactions between infertility duration and woman's age, infertility duration and man's BMI, AFC and AMH, AFC and woman's age, AFC and woman's BMI and AFC and disovulation were also statistically significant. The area under the receiver operating characteristic (AUROC) curve test for the discriminatory ability of the final prediction model is 0.700 (95% confidence interval (CI) 0.660–0.741).

Open Peer Review

Approval Status

1

2

version 2

(revision)
22 Dec 2020

version 1

04 Sep 2019

view

view

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Any reports and responses or comments on the article can be found at the end of the article.

Conclusions: This model might result in a new validated decision support system to help physicians to manage couples' expectations.

Keywords

IVF, ICSI, prediction model, live birth, assisted reproduction, logistic regression

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Author roles: **Estácio da Veiga B:** Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Tavares DP:** Formal Analysis, Investigation, Methodology, Supervision, Writing – Review & Editing; **Metello JL:** Conceptualization, Data Curation, Supervision, Validation, Writing – Review & Editing; **Ferreira F:** Conceptualization, Supervision, Writing – Review & Editing; **Ferreira P:** Conceptualization, Data Curation; **Fonseca JM:** Conceptualization, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: We thank Portuguese Foundation for Science and Technology FCT/ MCTES - UID/EEA/00066/2019 (JF).

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How to cite this article: Estácio da Veiga B, Tavares DP, Metello JL *et al.* **Predicting the chances of live birth for couples undergoing IVF-ICSI: a novel instrument to advise patients and physicians before treatment [version 1; peer review: 2 not approved]** F1000Research 2019, 8:1585 <https://doi.org/10.12688/f1000research.20038.1>

First published: 04 Sep 2019, 8:1585 <https://doi.org/10.12688/f1000research.20038.1>

Introduction

Infertility is defined as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse¹. Taking this definition into account, it is a challenge to calculate the real prevalence or incidence rates for this condition².

According to the study performed by Boivin *et al.*³, the prevalence of infertility ranged from 3.5% to 16.7% in developed countries. Based on these authors' estimates, 72.4 million women are currently infertile and, of these, 40.5 million are currently seeking infertility medical care³. Most recent Portuguese data estimate that 9.8% of couples are infertile⁴.

Infertility is a multifactorial disease⁵. A male-related factor can be the cause, especially when there is a sperm or ejaculatory problem^{6,7} or it may be a female-related factor, namely when there is a disovulation or tubal dysfunction^{8,9}. Women's age, ovarian reserve, weight, and lifestyle factors – such as alcohol consumption and exercise habits – have also been related to this^{5,10–16}. Nonetheless, in up to 20% of cases, no cause can be found^{3,5}.

Several treatments have been proposed during the last century, with the most innovative bring *in vitro* fertilization (IVF), which was developed by Robert Edwards¹⁷ in 1978. After 41 years, the two most important medically assistant reproduction techniques (MAR) are *in vitro* fertilization (IVF) and its subtype intracytoplasmic sperm injection (ICSI)¹⁸. The number of IVF and ICSI treatments has been increasing across Europe¹⁹. According to the European Society of Human Reproduction and Embryology, the number of MAR cycles between 1997 and 2014 increased by 13%, reaching 776 556 cycles in Europe in 2015¹⁹.

Despite the increasing number of MAR treatments, IVF success is not guaranteed²⁰. In healthy young couples, the probability of achieving a live birth is between 20% and 25% per month. This probability may increase by up to 60% with MAR techniques²¹. The study by Malizia *et al.* also corroborates this finding, indicating that between 38% and 49% of couples who start IVF remain childless, even after undergoing up to six IVF cycles²². In Portugal, the last report of MAR showed that the treatments success rate is around 25–30%²³.

MAR treatments are expensive, time-consuming, stressful, and may lead to anxiety, depression, or marital problems^{24–28}. Also, these treatments have possible complications such as ovarian hyperstimulation syndrome, bleeding, and infection, as well as multiple or premature births²⁹.

The success rates fluctuate between studies and are dependent on several factors³⁰. If the chances of live birth are low and the risk or the cost is too high, the couple may consider other options such as adoption or to remain childless³¹. In other words, based on their specific probability of success, the couple may decide whether or not they proceed with the treatment. Therefore, the most common question asked by IVF patients is “What are my chances of conceiving?”

The answer to this tough question usually depends on the woman's age and infertility diagnosis³⁰. Nevertheless, many more parameters are known to affect IVF outcomes³² such as sperm quality, hormone doses, and physiological factors. Given this, a decision support system would be helpful to ensure that infertile couples are well informed regarding their chances of success with IVF³³.

There have been various efforts to build prediction models to assist physicians in predicting MAR success^{30,34–37}. To our knowledge, the first predictive model ever built in this context is from Templeton *et al.* in 1996 using a logistic regression model to predict the probability of live birth for an individual woman using the woman's age, number of previous live birth or pregnancies not resulting in a live birth, whether these were a result of previous IVF treatment, female causes of infertility, duration of infertility and the number of previous unsuccessful IVF treatments³⁰.

These authors found that the success of IVF decreased with female age and that women between 25 and 30 years were the most likely to have a live birth³⁰.

Considering the evolution of technology and the importance of other variables, Nelson and Lawlor developed a new model in 2011, using the same mathematical techniques, but including other factors such as the most prevalent causes of infertility, the source of the egg (donor or patient's own), type of hormonal preparation used (antioestrogen, gonadotrophin, or hormone replacement therapy), whether or not ICSI was used, and the number of previous cycles (1, 2 or 3)³⁶.

Taking into account that it is imperative to have validated models³⁸, in 2014, Velde *et al.* used their cohort to validate Templeton and Nelson and Lawlor's model's performance. They found that Templeton's model underestimated success rates while Nelson's model overestimated it³⁸.

Other relevant models of note include the one developed by Marca *et al.* which predicts live birth in assisted reproduction based on serum anti-Müllerian hormone (AMH) and women's age³⁵, and the Mc Leron *et al.* study³⁷ that estimated the cumulative personal chance of a first live birth over a maximum of six complete cycles of IVF using data from 23 417 women in the UK. The estimates of the last study³⁷ were only adjusted by the woman's age, infertility duration, previous pregnancies, infertility causes, and type of treatment.

Nonetheless, when Leijdekkers performed an external validation of Mc Leron's model³⁹ with Dutch women, it was found that there was an overestimation of the results and he decided to include biomarkers such as anti-Müllerian hormone (AMH), antral follicle count (AFC) and women's body weight. Other studies indicate it is important to include covariables such as body mass index (BMI), ethnicity and ovarian reserve³⁴ and corroborate that the use of variables such as BMI, AFC, AMH, ethnicity, and smoking status should be predictors in the model^{5,14,40,41}.

Furthermore, a machine learning approach was also proposed, which includes decision trees, genetic algorithms, and k nearest neighbors classifiers^{21,42–45}.

The main aim of this study was to integrate all the variables of interest referred in the literature to develop a validated model that estimates the chance of live birth for couples before they start their IVF non-donor cycle.

Methods

The present work is a retrospective study of data from IVF/ICSI cycles. The cycles were performed between 2012 and 2016 in the Centro de Infertilidade e Reprodução Medicamente Assistida (CIRMA) at Hospital Garcia de Orta, E.P.E., Almada, Portugal.

739 couples were considered once they met the criterion of being fresh non-donor cycles or cycles with live birth or without frozen embryos available.

The study was approved by the Hospital's Ethics Committee for Health, couples signed an informed consent document before treatment begins at the first infertility consultation. Patients were informed that, under complete anonymity, the data may be used in scientific papers for public presentation or publication⁴⁶.

The IVF result for each couple in the study was classified as 1 (if, at least, one baby was born alive and survived for more than 1 month) and 0 (otherwise), which is the model's dependent variable/primary outcome. This decision was based on other studies in this area^{30,34–37}.

In terms of the baseline characteristics used to develop this model and based on evidence from the published literature in this area^{30,32} the woman's and man's age (years), duration of infertility (months), cause of infertility (categorised as tubal factor, endometriosis, disovulation, male factor, both female and male factor - depending on whether the cause of infertility underlies the woman or the man - multiple female factors, unexplained infertility or other), woman's and man's BMI (kg/m²), AMH (ng/mL), AFC (antral follicle count), woman's and man's ethnicity (categorised as Asian, Caucasian, Gipsy, Indian, Black or Mixed), woman's and man's smoking status (never, previous, present) and woman's and man's previous live children (yes or no) were considered. Antral follicle count was obtained by transvaginal ultrasound, and serum anti-Müllerian hormone levels were measured by blood analysis. There should be no bias associated with this study, however, possible sources of bias may arise from couples responses during the consultation and the entry of the data in the database.

A summary statistical evaluation was performed for each variable. A univariate analysis was first performed. All continuous variables were compared using the t-student test and the categorical one using the Chi-square test. A p-value <0,05 was considered statistically significant⁴⁷.

A binary logistic regression⁴⁸ was developed using the primary outcome as binary (no=0 and yes=1) to achieve the aim of this study. An automatic backward selection process based on the Wald statistic was used to determine the final and the best logistic regression model⁴⁹. The model was based on the data from 737 couples (99,73%), because in 2 couples there was data missing (lack of BMI values in two couples) and as Iezzoni⁵⁰ indicated, it is not recommended to input missing values in health data.

As recommended by Hosmer and Lemeshow⁴⁸ the interactions between some variables were included, to increase the reliability of the model because as Fisher⁵¹ explained, the primary outcome can depend not only on one individual baseline characteristic but also on the relationship between baseline characteristics. The variables in interaction were: female's age and infertility duration⁵², BMI and oligospermia⁵³, AFC levels and women's BMI¹³ and AFC and AMH levels⁴⁰.

The model's performance was measured with the discriminative power assessed using the area under the curve (AUC) value^{34,55} and the model was internally validated using the bootstrapping technique with 1000 iterations⁵⁶. All statistical procedures were computed using IBM SPSS Statistics 25, and it was considered an α level of 0.05, which means that was assumed that there isn't statistical significance if the p-value of the test is above 0.05

The STROBE cross-sectional reporting guidelines were adopted in this article⁵⁷.

Results

A total of 737 cycles were evaluated. The overall rate of at least one live birth was 31.4%.

Baseline characteristics of couples are presented in [Table 1](#) and [Table 2](#).

The average age for female participants was 34.04 years ([Table 1](#)), and 36.14 for male participants. Younger women and men were more likely to achieve a live birth. The same was seen for men and women with lower BMI and shorter infertility durations. However, these results were only statistically significant for women's age, men's age, AFC and AMH (p<0.05).

[Table 2](#) shows that most women and men had never smoked. Most men and women were Caucasian and the male factor, which means male infertility, is the most prevalent infertility cause in this data. Most men and women had no previous live births (90,1% and 87,4%). Chi-square test revealed that no discrete characteristics have statistically significant differences for live birth (p>0.05). For this reason, interactions on different characteristics were considered.

In [Table 3](#), the binary logistic regression parameters computed with SPSS are presented. These parameters allow the assessment

Table 1. Baseline continuous characteristics of couples.

Characteristics	All couples (n=739)			Couples with live birth (n=232)			Couples without live birth (n=507)			T-student test p-value
	Mean $\pm$ Standard deviation	Minimum value	Maximum value	Mean $\pm$ Standard deviation	Minimum value	Maximum value	Mean $\pm$ Standard deviation	Minimum value	Maximum value	
Woman's age (years)	34.04 $\pm$ 3.74	18	39	33.13 $\pm$ 3.80	18	39	34.45 $\pm$ 3.64	19	39	p=0.000
Man's age (years)	36.14 $\pm$ 5.18	20	54	35.42 $\pm$ 4.90	21	52	36.47 $\pm$ 5.27	20	54	p=0.008
Woman's BMI (Kg/m ²)	24.35 $\pm$ 5.09	17	43	24.08 $\pm$ 4.21	17	41	24.47 $\pm$ 5.44	17	43	p=0.286
Man's BMI (Kg/m ²)	26.43 $\pm$ 7.29	18	47	25.97 $\pm$ 3.87	18	47	26.28 $\pm$ 3.85	19	47	p=0.619
AFC (number of follicles)	14.47 $\pm$ 9.24	2	52	17.03 $\pm$ 9.18	4	50	13.30 $\pm$ 9.03	2	52	p=0.000
AMH (ng/mL)	3.50 $\pm$ 3.74	0.09	30.70	4.24 $\pm$ 3.81	0.2	20	3.17 $\pm$ 3.66	0.09	30.7	p=0.000
Infertility Duration (months)	56.40 $\pm$ 28.68	10	180	55.17 $\pm$ 29.37	10	176	56.96 $\pm$ 28.34	12	180	p=0.437

BMI – body mass index; AMH - anti-Müllerian hormone; AFC – antral follicle count

Table 2. Baseline discrete characteristics of couples.

Characteristics		All couples (n=739)	Couples with live birth (n=232)	Couples without live birth (n=507)	Chi-square test p-value
Woman's smoking status	Smokes presently	200 (27.1%)	66 (28.4%)	134 (26.4%)	0.846
	Smoked previously	118 (16.0%)	36 (15.5%)	82 (16.2%)	
	Never smoked	421 (57.0%)	130 (56%)	291 (57.4%)	
Woman's ethnicity	Caucasian	662 (89.6%)	208 (89.7%)	454 (89.5%)	0.722
	African	29 (3.9%)	6 (2.6%)	23 (4.6%)	
	Asiatic	3 (0.4%)	1 (0.4%)	2 (0.4%)	
	Gipsy	11 (1.5%)	5 (2.2%)	6 (1.2%)	
	Indian	5 (0.7%)	2 (0.9%)	3 (0.6%)	
	Mixture	29 (3.9%)	10 (4.3%)	19 (3.7%)	
Woman's with previous children	Yes	73 (9.9%)	20 (8.6%)	53 (10.4%)	0.432
	No	666 (90.1%)	212 (91.4%)	451 (89.6%)	
Man's smoking status	Smokes presently	243 (32.9%)	82 (35.5%)	161 (31.8%)	0.379
	Smoked previously	124 (16.8%)	33 (14.2%)	91 (17.9%)	
	Never smoked	372 (50.3%)	117 (50.4%)	255 (50.3%)	
Man's ethnicity	Caucasian	678 (91.7%)	203 (87.5%)	475 (93.7%)	0.070
	African	21 (2.8%)	8 (3.4%)	13 (2.6%)	
	Asiatic	3 (0.4%)	1 (0.4%)	2 (0.4%)	
	Gipsy	12 (1.6%)	6 (2.6%)	6 (1.2%)	
	Indian	6 (0.8%)	3 (1.3%)	3 (0.6%)	
	Mixed	19 (2.6%)	11 (4.8%)	8 (1.6%)	
Man's with previous live children	Yes	93 (12.6%)	25 (10.8%)	68 (13.4%)	0.316
	No	646 (87.4%)	207 (89.2%)	439 (86.6%)	
Infertility cause	Endometriosis	87 (11.8%)	19 (8%)	68 (13%)	0.482
	Male factor	323 (43.7%)	86 (37%)	237 (47%)	
	Both female and male factor	83 (11.2%)	16 (16%)	67 (13%)	
	Unexplained infertility	216 (29.2%)	49 (21%)	167 (33%)	
	Multiple female factors	29 (3.9%)	6 (3%)	23 (5%)	
	Disovulation	78 (10.6%)	21 (9%)	57 (11%)	
	Tubal	147 (19.9%)	33 (14%)	114 (22%)	
	Other	8 (1.1%)	2 (1%)	6 (1%)	

of the chance of living birth on couples before they start their IVF non-donor cycle based on the variables previously mentioned.

The logistic regression results showed that from the 14 variables evaluated on the pre-treatment procedures, only male factor, the man's BMI, mixed ethnicity for men, and the level of AMH were statistically significant. Apart from these variables, the interactions between infertility duration and women's age, infertility duration and men's BMI, AFC and AMH, AFC and women's age,

AFC and women's BMI and AFC and disovulation were also statistically significant (p-value less than 0.05). The interactions between infertility duration and woman's age and man's BMI; AFC and AMH, woman's age, woman's BMI and disovulation were also statistically significant.

According to regression coefficients of the final model, an AMH unit increase raises the probability of IVF-ICSI success by 0.172 times, *ceteris paribus*. Similarly, the interaction between

Table 3. Final logistic regression model for live birth (n=737).

Variables	Regression coefficient	Standard Error	P-value	Odds ratio	95% I.C. Odds ratio	
					inf	sup
Male factor	0.445	0.180	0.013	1.561	1.097	2.222
Man's BMI	-0.155	0.034	<0.001	0.856	0.801	0.916
Mixed ethnicity on Man	1.330	0.496	0.007	3.781	1.430	9.996
Interaction between Infertility duration and Woman's age	-0.002	<0.001	<0.001	0.998	0.997	0.999
Interaction between Infertility duration and Man's BMI	0.002	<0.001	<0.001	1.002	1.001	1.003
Interaction between AFC and Woman's age	0.004	0.001	<0.001	1.004	1.002	1.006
Interaction between AFC and Disovulation	0.043	0.016	0.006	1.044	1.013	1.076
Interaction between AFC and Woman's BMI	-0.003	0.001	0.007	0.997	0.995	0.999
AMH	0.172	0.052	0.001	1.188	1.073	1.315
Interaction between AFC and AMH	-0.008	0.002	<0.001	0.992	0.989	0.996
Intercept	1.934	0.876	0.027	6.914	-	-

BMI – body mass index; AMH - anti-Müllerian hormone; AFC – antral follicle count

Figure 1. Receiver operating characteristic (ROC) curve of the final model. This shows the ROC curve test for the discriminatory ability of the final prediction model is 0.700 (95% confidence interval (CI) 0.660–0.741).

AFC and the woman's BMI decreases the same probability by 0.003 times and interaction between AFC and the woman's age increases it by 0.004 times. Male factor is the only infertility cause that enters individually into the final model raising the chances of success by 0.420 times.

Discussion

So far, providing an accurate prediction of the chances of achieving a live birth after FIV-ICSI treatments has not been an easy task³². In this study, a novel prediction model was built, including almost all clinical factors reported as important in the literature.

To our knowledge, this is the first model for live birth FIV-ICSI prediction that accounts for men's ethnicity. It also includes variables such as BMI and AFC, which were not included in many models before³⁴. This model includes all the characteristics that have been indicated as important in the literature to predict the chances of live birth in MAR^{5,30,32}.

The Templeton model³⁰ considers the existence of previous IVF cycles and has been externally validated by Nelson and Lawlor³⁶. Therefore, both these models can be applied before IVF is started and predict the success of IVF/ICSI treatment. During this study, it was not possible to obtain information about the number of previous cycles per couple, and so this factor was not included.

This model supports earlier findings in this scientific area such as the importance of AMH and AFC to predict live birth as predicted by other studies^{35,40} and indirectly corroborates the importance of woman's age to predict the result as shown by Templeton *et al.*³⁰. Nonetheless, it is crucial to refer that the increase of women's age, when in interaction with infertility duration, significantly decreases the probability of a living birth which is in accordance to Nelson's study³⁶.

Concerning the main reason for treatment, both male factor and disovulation (with AFC interaction) are the only causes that emerged in the final model. These causes raised the chances of success, which might be explained with the IVF-ICSI technique itself once the problem of sperm and ovulation anomalies are overcome¹⁸. In other words, women with ovulation problems and men with sperm anomalies have higher chances of success with IVF-ICSI technique because sperm and oocytes are medically collected and interact directly, although in an *in vitro* environment¹⁸.

Another notable finding is that an increase of the man's BMI (*per si*) or woman's BMI (with AFC interaction) decreased the chances of live birth, which is in accordance with the scientific literature. Women who are overweight are known to have ovulatory problems, and increased risks of miscarriage¹⁰ and obesity may adversely affect male reproduction by endocrine, thermal, genetic, and sexual mechanisms¹⁰. For instance, increased testicular temperature can result from prolonged periods of sitting in men with excessive lower abdominal fat deposited in the lower abdomen⁵⁸. Also, obesity tends to increase estrogen levels and reduce testosterone levels in men⁵⁹.

Concerning the man's ethnicity, we found that if the man is of mixed ethnicity, the odds of success are around 3.8. This finding must be interpreted cautiously as the sample is composed of 92% Caucasian males, with only 2.6% of males being of mixed ethnicity. Up to now, there doesn't seem to be any biological plausibility for this find, further researchers is required to validate this possible relationship between mixed ethnicity in men and increased success in IVF treatments.

A limitation of our model is that it is restricted to pre-treatment stages. Thereby, the physician must explain to patients when using our model that their success probability invariably changes during the cycles process. The resulting probability of our model should be considered a baseline one.

Many studies have accounted for the chances of live birth after IVF or ICSI treatment^{30,34–39}. When compared with other studies, the most similar one is Dhillon *et al.*'s model³⁴ due to the variables integrated into the model. However, in our study, there were no limitations on socioeconomic status since our data has been extracted from a public hospital with universal access⁶⁰ and so the results can be generalized to people of all socioeconomic backgrounds. This is an advantage over the Dhillon *et al.*'s model³⁴, where it is estimated that 75% of couples paid for their treatment and therefore their model could not be generalized to all social classes.

Predictive ability of the prediction models on medicine has been assessed by the AUC^{54,55}. In general, AUC for prediction models in reproductive medicine is rather low, ranging between 0.59 and 0.64⁵⁵. Table 4 shows the values of models' AUC predicting the chances of live birth for couples undergoing IVF-ICSI. Although McLernon *et al.*³⁷ have the highest value of the area under the receiver operating characteristic (AUROC) curve, that value decreased on Leijedekkers validation for 0.62³⁹. The model developed in this study has an AUC of 0.700, which is the second-highest value, and so has a comparable discriminatory ability with these previous models.

Taking into account that Coppus *et al.*'s systematic review concluded that prediction models in reproductive medicine would be limited to an AUC value of 0.65 due to the relatively

Table 4. Comparison of area under the receiver operating characteristic (AUROC) curve of existing models.

Model	AUROC curve of the model
Templeton <i>et al.</i> ³⁰	0.62
Nelson and Lawlor ³⁶	0.63
La Marca <i>et al.</i> ³⁵	0.66
Mc Lerno <i>et al.</i> ³⁷	0.73
Dhillon <i>et al.</i> ³⁴	0.62
This study	0.70

homogeneous group of subfertile patients⁵⁵, this study can be considered to improve upon the current available models.

The present model predicts the specific probability of a live birth based on easily acquirable couple characteristics before starting a treatment. It might help patients to understand the limitations of an IVF/ICSI in their particular case and also physicians to compare different treatment strategies. Furthermore, it might support institutions to predict the probability of the need for treatment repetition based on the specific characteristics of each couple.

We intend in the near future to perform an external validation with the developed model with a new dataset from Centro de Infertilidade e Reprodução Medicamente Assistida (CIRMA). Follow this, it is also planned to perform an external geographical validation to check if there is a geographical influence on chances of live birth for couples undergoing IVF-ICSI.

Conclusions

Many couples with fertility problems ask themselves if they should undergo an IVF-ICSI treatment. Our novel model

provides an estimated probability of their chances of live birth. This is the first model with Portuguese data and takes in account the important variables described in literature such as AFC, AMH, and woman's age. This tool may help physicians to shape couples' expectations conceding them the opportunity to plan their treatments and to prepare both emotionally and financially to them and so we are developing a user-friendly interface to help physicians in their clinical practice.

Data availability

Underlying data

The data that support the findings of this study are available on request from the author José Metello (jose.metello@hgo.min-saude.pt). The data cannot be made publicly available in accordance to paragraph d), number 2, Article 9 of the Regulation no. 2016/679 of the European Parliament and the Council of 27 April 2016 and due to the sensitive data containing information that could compromise the privacy of research participants. Informed consent was provided by patients who participated in the study for the use of their data for scientific purposes only and to safeguard their anonymity.

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Version 1

Reviewer Report 07 September 2020

<https://doi.org/10.5256/f1000research.21999.r69512>

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Jichun Tan

Center of Reproductive Medicine, Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang, China

This paper focused on an interesting topic of "What are my chances of conceiving?". However, the aim of this study is not clear. The logistic regression model is not enough to establish a novel prediction model. To the best of our knowledge, similar studies with larger sample size, more clinical variables, and advanced calculating models have been reported to predict the rates of live birth. In addition, more latest studies should be added in the introduction section.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Assisted reproduction

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Nov 2020

Bruna Estácio da Veiga, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Caparica, Portugal

Lisbon, November the 3rd 2020

We submitted an original research article entitled "Predicting the chances of live birth for couples undergoing IVF ICSI: a novel instrument to advise patients and physicians before treatment" for consideration by F1000Research journal that has been reviewed by two experts in the field, suggesting revisions to this paper. We want to thank their comments and we have done the following revisions accordingly for the second reviewer (all modifications can be seen through the "Track Changes" option):

Point 1: This paper focused on an interesting topic of "What are my chances of conceiving?". However, the aim of this study is not clear.

Response: We followed the reviewer's advice by modifying the abstract and introduction section, reinforcing the aim of our study: "The main aim of this study is to develop a validated model that estimates the chance of a live birth before the start of an IVF/ICSI non-donor cycle." and "The main aim of this study was to find a pre-treatment predictor for achieving a live birth before an IVF/ICSI treatment.", respectively.

Point 2: The logistic regression model is not enough to establish a novel prediction model. To the best of our knowledge, similar studies with larger sample size, more clinical variables, and advanced calculating models have been reported to predict the rates of live birth.

Response: Considering the size of the sample available and the reviewer's assessment of the model's evaluation, we added a table (Table 4) that lists 5 performance metrics (i.e., accuracy, F-score, precision, sensitivity and sensibility) and reflects our model performance, in order to respond to the reviewer's observation. Particularly about the sample size, we still achieved a ROC curve with a 95% Confidence Interval (CI) that is not very wide ("The ROC curve (...) had an AUC equal to 0.700 (95% CI 0.660–0.741)"). Although other important parameters are found in other studies, the 14 variables tested in our study were all the variables collected by CIRMA and made available for this study. Therefore, we can not follow the reviewer's suggestion and include more variables, because we did not collect and select the couple's data.

Point 3: In addition, more latest studies should be added in the introduction section.

Response: We thank the reviewer for this final comment and we tried to enrich the introduction section by adding more information about AI in predictive models, considering the recent study of Qiu et.al (reference 32) based on supervised learning algorithms.

Sincerely,

The authors.

Competing Interests: No competing interests were disclosed.

Reviewer Report 31 July 2020

<https://doi.org/10.5256/f1000research.21999.r68000>

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Charalampos Siristatidis

Assisted Reproduction Unit, Third Department of Obstetrics and Gynecology, Medical School, National and Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece

Authors developed a logistic regression model based on the retrospective study of 737 IVF cycles. They concluded that the model might result in a new validated decision support system to help physicians to manage couples' expectations concerning their possibility to have a live birth.

The introduction section is unreasonably extended, without providing the necessary information only, leading to the rationale of the study. Important similar models using more sophisticated networks, such as artificial intelligence, are missing.

Language and grammar need revision. The sample size is small. A proper power calculation is missing. Some important parameters that have been tested in other studies that contribute to live birth are missing. Limitations are not reported.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Assisted reproduction; methodology; artificial intelligence

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 03 Nov 2020

Bruna Estácio da Veiga, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Caparica, Portugal

Lisbon, November the 3rd 2020

We submitted an original research article entitled “Predicting the chances of live birth for couples undergoing IVF ICSI: a novel instrument to advise patients and physicians before treatment” for consideration by F1000Research journal that has been reviewed by two experts in the field, suggesting revisions to this paper. We want to thank their comments and we have done the following revisions accordingly for the first reviewer (all modifications can be seen through the “Track Changes” option):

Point 1: The introduction section is unreasonably extended, without providing the necessary information only, leading to the rationale of the study. Important similar models using more sophisticated networks, such as artificial intelligence, are missing.

Response: We followed the reviewer’s advice by modifying the introduction section, including more information about AI in predictive models, considering the recent study of Qiu et.al (reference 32) based on supervised learning algorithms.

Point 2: Language and grammar need revision.

Response: The reviewer asked for English changes and we reviewed the entire text.

Point 3: The sample size is small. A proper power calculation is missing.

Response: Considering the size of the sample available and the reviewer’s assessment of the model’s evaluation, we added a table (Table 4) that lists 5 performance metrics (i.e., accuracy, F-score, precision, sensitivity and sensibility) and reflects our model performance, in order to respond to the reviewer’s observation. Particularly about the sample size, we still achieved a ROC curve with a 95% Confidence Interval (CI) that is not very wide (“The ROC curve (...) had an AUC equal to 0.700 (95% CI 0.660–0.741)”).

Point 4: Some important parameters that have been tested in other studies that contribute to live birth are missing.

Response: Although other important parameters are found in other studies, the 14 variables tested in our study were all the variables collected by CIRMA and made available for this study. Therefore, we can not follow the reviewer’s suggestion and include more variables, because we did not collect and select the couple’s data.

Point 5: Limitations are not reported.

Response: We thank the reviewer for this final comment and we tried to enrich the discussion section by adding more clinical limitations found in our model to the limitation reported before: "A limitation of our model is that it is restricted to pre-treatment stages. Thereby, the physician must explain to patients when using our model that their success probability invariably changes during the cycles process. That is, the resulting probability of our model should be considered a baseline one. Taking into account that this study was performed with data from only one medical center, one limitation of these models is that only an internal validation was made. Moreover, the large temporal spectrum of the data (2012 to 2016) could mean that treatments made with older technology may have different results than those made with more recent ones (namely, vitrification procedures or culture media).".

Sincerely,
The authors.

Competing Interests: No competing interests were disclosed.

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