Intrauterine insemination cycles: prediction of success and thresholds for poor prognosis and futile care

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Abstract

Purpose We aimed to define intrauterine insemination (IUI) cycle characteristics associated with viable birth, identify thresholds below which IUI treatments are consistent with very poor prognosis and futile care, and develop a nomogram for individualized application.

Methods This retrospective cohort study evaluated couples using fresh partner ejaculate for IUI from January 2005 to September 2017. Variables included female age, semen characteristics, and ovarian stimulation type. Using cycle-level data, we evaluated the association of these characteristics with the probability of viable birth by fitting generalized regression models for a binary outcome with a logit link function, using generalized estimating equation methodology to account for the correlation between cycles involving the same patient.

Results The cohort consisted of 1117 women with 2912 IUI cycles; viable birth was achieved in 275 (9.4%) cycles. Futile care (viable birth rate < 1%) was identified for women age > 43, regardless of stimulation type or inseminate motility (IM). Very poor prognosis (viable birth rate < 5%) was identified for women using oral medications or Clomid plus gonadotropins who were (1) age < 35 with IM < 49%, (2) age 35–37 with IM < 56%, or (3) age ≥ 38, and (4) women age ≥ 38 using *gonadotropins only* with IM < 60%. A clinical prediction model and nomogram was developed with an optimism-corrected c-statistic of 0.611.

Conclusions The present study highlights the impact of multiple clinical factors on IUI success, identifies criteria consistent with very poor prognosis and futile care, and provides a nomogram to individualize counseling regarding the probability of a viable birth.

Keywords Intrauterine insemination · Poor prognosis care · Futile care · Nomogram

Introduction

Intrauterine insemination (IUI) is a common approach for many women presenting for fertility treatment. It is the recommended

first-line approach for couples with unexplained infertility and for women without male partners using donor sperm for conception, as it is low-cost compared with other treatments, with reasonable success rates after repeated cycles [1]. Several factors have been found to impact the effect of IUI on pregnancy success. Female age, method of ovulation induction, duration and cause of infertility, income level, and smoking status have all been investigated and correlated with IUI success [2–9]. Many studies have investigated the role of semen parameters; however, there remains limited consensus on thresholds predictive of successful pregnancy and live birth.

In fact, some studies have found that semen parameters have no statistically significant impact on pregnancy rates, either pre- or post-processing [6, 10–12]. The majority of studies that report an effect have demonstrated the total motile sperm count in either the ejaculate or the inseminate to be predictive of IUI success [13–24]. However, a range of thresholds of 1–10 million motile sperm have been proposed. Concordantly, a meta-analysis evaluating 16 studies reporting

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total motile sperm counts in the inseminate found no cut-off value with both high sensitivity and specificity [25]. Other semen parameters including morphology and total progressive motility have shown similarly mixed results [13, 26–29]. A recent systematic review by Ombelet et al. identified a significant lack of standardization or identified threshold values for semen parameters known to impact IUI success [28]. Using data from 55 included studies, Ombelet et al. proposed threshold values of semen parameters in the inseminate, > 1 million total motile sperm and morphology > 4% with ejaculated total motile sperm counts of 5–10 million and motility > 30% as cut-off levels for pregnancy prediction, although with poor sensitivity and higher specificity [28]. Importantly, thresholds for semen parameters predictive of IUI success may vary depending on factors such as female age or type of ovarian stimulation, so a single threshold may not be generalizable to all populations.

While the aforementioned studies offer predictive value for pregnancy outcomes, many of the included studies lacked information or standardization of confounding factors for success such as female age or type of ovarian stimulation. In addition, there remain no identified thresholds below which IUI should not be offered. Thresholds for IUI which meet definitions of very poor prognosis and futile care, in accordance with the American Society of Reproductive Medicine (ASRM), remain unknown [30]. Using cycle-level data, the present study aims to add information about semen parameters and identify thresholds below which IUI should not be offered. Ultimately, we aim to strengthen available data for counseling couples on use of IUI as a means to achieve pregnancy, by providing a nomogram to estimate the probability of a viable birth based on couple characteristics.

Methods

This retrospective study included women who underwent IUI at Mayo Clinic, Rochester from January 2, 2005 to September 30, 2017. Eligible patients were identified from a clinical database maintained within the Division of Reproductive Endocrinology and Infertility. Women were excluded from the study if they declined access to their medical records for research purposes. The study was approved by the Mayo Clinic Institutional Review Board.

While some women underwent natural cycles with IUI, most completed one of three ovarian stimulation protocols: (1) oral medications, Clomid (50, 100, or 150 mg) or Letrozole (2.5, 5, or 7.5 mg), were started on cycle day 3 and continued until cycle day 7 with monitoring by either luteinizing hormone (LH) surge kits or follicle tracking ultrasounds. In women completing ultrasound monitoring, ovulation was triggered with human chorionic gonadotropin (hCG) when the lead follicle measured 20 mm. (2) Patients

undergoing combined Clomid plus gonadotropin cycles used Clomid 150 mg from cycle days 3–7 and took one dose of gonadotropins on cycle day 9. Patients using Clomid plus gonadotropins were monitored with ultrasound and triggered when the lead follicle measured 20 mm. (c) Lastly, patients undergoing *gonadotropin only* stimulation began daily injections on cycle day 3 and were monitored with both estradiol levels and ultrasounds for follicle tracking. Mature follicles were triggered at 18 mm with hCG.

Inseminations were performed approximately 24 h after a LH surge or 36 h after hCG trigger injection. The inseminate was prepared using a gradient technique [31]. Women were included in the present study if they used fresh partner ejaculate, rather than frozen or donor sperm, for their IUI procedure(s). Age at the time of insemination was calculated and categorized as < 35, 35–37, 38–40, 41–42, and 43+ years in accordance with The Society for Assisted Reproductive Technologies (SART) standardized reporting categories. The type of ovarian stimulation was categorized as natural, oral medications (Clomid or Letrozole), Clomid plus gonadotropins, or *gonadotropins only*. Semen parameters in the ejaculate and inseminate were evaluated for percent motility and number of total motile sperm. The primary outcome was a viable birth, defined as a delivery with a gestational age $\geq$ 24 weeks. A viable birth rate of 5% was used as a threshold for very poor prognosis care and viable birth < 1% was used as a threshold for futile care [30]. Viable birth was documented by review of obstetrical databases or manual chart review, as most patients seen for fertility treatments also deliver within our health system. Women in this cohort could have undergone multiple cycles of IUI before becoming pregnant or before discontinuing with IUI and could also have had multiple episodes of IUI (defined as a series of consecutive cycles with no more than 6 months between each cycle), during the time frame of this cohort.

Using data from individual cycles, univariate and multivariable generalized linear mixed regression models for a binary outcome with a logit link function were fit to evaluate the association of patient and sperm characteristics with the probability of viable birth. The models were fit using generalized estimating equation (GEE) methodology with an exchangeable correlation structure to derive empirical standard errors accounting for the correlation between outcomes from IUI cycles involving the same patient. Additional models were fit to evaluate the significance of two-way interactions between age group, type of ovarian stimulation, and inseminate motility and incorporating cubic splines to model the potential non-linear relationships for the continuous covariates. The associations were summarized using the odds ratios (OR) and corresponding 95% confidence intervals (CI) derived from model estimates.

A nomogram was created for the final prediction model that incorporated spline terms for age and inseminate motility

using the R ‘design’ package. Discrimination was assessed using the concordance (c) statistic, a measure of a model’s predictive accuracy that is analogous to the area under a receiver operating characteristic curve. The apparent performance of the model, as measured by the c-statistic estimated directly from the data used to develop the model, is a biased optimistic estimate of discrimination. Therefore, an optimism-corrected estimate of the c-statistic was derived using 500 bootstrap resamples, as a method of internal validation. Calibration was assessed by comparing the predicted probabilities estimated from the final model with the actual observed proportion with a viable birth.

All calculated *p* values were two sided and *p* values less than 0.05 were considered statistically significant. The statistical analysis was performed using the SAS version 9.4 software package (SAS Institute Inc., Cary, North Carolina, USA) and R 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1117 women with 2912 unique IUI cycles and 1335 episodes of care were included in the study. Mean age of first insemination was 32.8 (SD, 4.7; range, 22.1–47.6; median (IQR), 32.3 (29.3–35.9)) years. Most cycles involved ovarian stimulation with Clomid only (42.3%, 1231/2912). A total of 2226 cycles (76.4%) were completed with an hCG trigger. A viable birth was achieved after 275 (9.4%) of the 2912 IUI cycles.

Based on univariate analyses of the cycle-level data, younger age, ovarian stimulation with *gonadotropins only*, higher ejaculate motility, and higher inseminate motility were each significantly associated with an increased odds of a viable birth (Table 1). The panels in Fig. 1 depict the distribution of the inseminate sperm characteristics and their relationship with the probability of a viable birth upon modeling each characteristic using a cubic spline to

Table 1 Patient and sperm characteristics evaluated for an association with a viable birth using cycle-level data

Characteristic	Number (% of each row) with a viable birth	Univariate analysis		Full multivariable model [†]		Parsimonious multivariable model [†]	
		OR (95% CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value
Age at insemination (years)			0.029		0.009		0.007
< 35 (<i>N</i> = 2008)	210 (10.5%)	Referent		Referent		Referent	
35–37 (<i>N</i> = 455)	45 (9.9%)	0.90 (0.63, 1.28)		0.86 (0.60, 1.24)		0.86 (0.60, 1.23)	
38–40 (<i>N</i> = 296)	15 (5.1%)	0.46 (0.26, 0.80)		0.40 (0.22, 0.70)		0.39 (0.22, 0.70)	
41–42 (<i>N</i> = 96)	5 (5.2%)	0.48 (0.19, 1.22)		0.43 (0.17, 1.11)		0.41 (0.16, 1.06)	
43+ (<i>N</i> = 57)	0 (0.0%)	— [‡]		— [†]		— [†]	
Ovarian stimulation type			0.002		< 0.001		< 0.001
Oral only [^] (<i>N</i> = 1374)	116 (8.4%)	0.60 (0.45, 0.80)		0.50 (0.36, 0.70)		0.50 (0.37, 0.67)	
Clomid plus gonadotropins (<i>N</i> = 756)	60 (7.9%)	0.57 (0.40, 0.80)		0.51 (0.36, 0.72)		0.51 (0.36, 0.72)	
None/natural cycle (<i>N</i> = 66)	5 (7.6%)	0.52 (0.20, 1.33)		0.48 (0.18, 1.29)		0.49 (0.19, 1.25)	
Gonadotropins only (<i>N</i> = 716)	94 (13.1%)	Referent				Referent	
Trigger type			0.22		0.89		
LH surge (<i>N</i> = 686)	57 (8.3%)	0.83 (0.61, 1.12)		0.97 (0.67, 1.42)		N/I	
HCG trigger (<i>N</i> = 2226)	218 (9.8%)	Referent					
Total motile sperm in ejaculate*	—	1.05 (0.98, 1.14)	0.18	0.92 (0.78, 1.08)	0.31	N/I	
Motility of sperm in ejaculate (%)*	—	1.12 (1.03, 1.22)	0.006	1.06 (0.95, 1.18)	0.28	N/I	
Total motile sperm in inseminate*	—	1.06 (0.99, 1.13)	0.10	1.01 (0.88, 1.17)	0.87	N/I	
Motility of sperm in inseminate (%)*	—	1.21 (1.09, 1.34)	< 0.001	1.20 (1.05, 1.37)	0.009	1.19 (1.07, 1.32)	0.001

OR, odds ratio; LH, luteinizing hormone; HCG, human chorionic gonadotropin; N/I, not included

Results are bolded for odds ratios with a 95% confidence interval that do not contain 1

[†] The multivariable analysis was restricted to the 2855 cycles for women under 43 years of age since none of the women aged 43 and older had a viable birth. The full model included all of the patient and sperm characteristics listed in this table and the parsimonious model only included those characteristics with *p* < 0.05 in the full model

[‡] The odds ratio was not estimable since none of the women aged 43 and older had a viable birth

[^]Clomid only (*N* = 1231) or Letrozole only (*N* = 143)

*HR per doubling in total motile sperm (in millions) and per 10 unit (%) increase in motility of sperm

Fig. 1 Distribution of inseminate sperm characteristics (**a**, **b**) and their relationship with the probability of a viable birth (**c**, **d**), based on cycle-level data

accommodate a potential non-linear relationship. An increasing linear relationship was observed for motility across nearly the full range of values. However, for total motile sperm (TMS) an increasing linear relationship was only observed up to 10 million. The AUC or c-statistic for each sperm characteristic modeled using a cubic spline was 0.554 for motility and 0.529 for TMS. Age group, type of ovarian stimulation, and inseminate motility were each independently associated with an increased odds of a viable birth in a full multivariable model including all the characteristics in Table 1 and when considered together in a parsimonious multivariable model that included only the variables with $p < 0.05$ from the full model (Table 1). There were no statistically significant interactions between these three variables.

A total of 57 cycles were completed in women ages 43 and older and none of these cycles had a viable birth, meeting criteria for futile care. Of these 57 cycles, 40 (70.2%) involved stimulation with *gonadotropins only*, 11 (19.3%) with Clomid plus gonadotropins, 3 (5.3%) with oral medication only, and 3 (5.3%) were natural. The median (interquartile range, IQR) inseminate motility for these 57 cycles was 83% (79, 91).

The predicted probabilities of a viable birth, according to female age at first insemination, ovarian stimulation type, and inseminate motility, were estimated based on a multivariable main effects model restricted to non-natural cycle IUIs for women under 43 years of age. Both continuous age and motility were modeled using cubic splines to accommodate potential non-linear relationships. Cycles involving ovarian stimulation with oral medications or Clomid plus gonadotropins were combined for presentation purposes since the predictions were similar for the two groups. The nomogram for predicting a viable birth derived from the aforementioned multivariable model is shown in Fig. 2. For example, a 32-year-old treated with *gonadotropins only* with a partner's sperm motility of 70% would receive a total point value of 161, corresponding to a predicted probability of 0.14 for having a viable birth. On the other hand, if this same patient's partner has a sperm motility of 30%, their total point value would be 113, corresponding to a predicted probability of 0.05 for having a viable birth. The overall predictive ability of the model, as measured by the c-statistic, was 0.615 based on the original data and 0.611 corrected for optimism. The distribution of the predicted probabilities is displayed in Supplemental

Fig. 2 Nomogram for prediction of viable birth, based on cycle-level data restricted to non-natural IUI cycles for women under 43 years of age. Points are assigned for each of the predictors by drawing a line up from the scale for each predictor to the points bar at the top of the figure. The

points for all predictors are then added to determine the total points. A patient's predicted probability of having a viable birth is determined by drawing a line from the total points bar to the predicted probability bar

Fig. 1a. As shown in the calibration plot in Supplemental Fig. 1b, the observed proportion with a viable birth tracked fairly closely with the predicted probabilities, indicating that the model fit the data reasonably well.

The mean predicted probabilities are graphically presented in Fig. 3 along with 95% confidence bands. In each age group, the probability of a viable birth increased with increasing inseminate motility and was higher for cycles with *gonadotropins only* for ovarian stimulation. We further assessed the predictions using 0.05 as the threshold for very poor prognosis. As shown in Fig. 3, for those induced with *gonadotropins only* in the <35 and 30–35 age groups, the mean predicted probabilities were greater than 0.05 for those with inseminate motility above 17 and 24%, respectively. However, for cycles involving oral medications or Clomid plus gonadotropins, only cycles with an inseminate motility above 49% among those <35 years of age and with an inseminate motility above 56% among those 35–37 years of age had a mean predicted

probability above the 0.05 threshold. Among cycles induced with *gonadotropins only* for women in the 38–40 and 41–42 age groups, only cycles with an inseminate motility above 60 and 57%, respectively, had a predicted probability above this threshold. The mean predicted probabilities did not exceed 0.05 for cycles involving oral medications or Clomid plus gonadotropins in the 38–40 and 41–42 age groups.

Discussion

Despite the specific factors previously identified to influence pregnancy rates after IUI, there is varying evidence and limited standardization to guide patient counseling and management. We aimed to identify threshold values for sperm inseminate motility in conjunction with ovarian stimulation types and female age at which IUI provides a reasonable treatment approach or, alternatively, may be

Fig. 3 Predicted probability of a viable birth, according to age group at IUI, ovarian stimulation type, and inseminate sperm motility, based on cycle-level data restricted to non-natural IUI cycles for women under 43 years of age. The shaded areas represent the 95% confidence bands

considered to meet very poor prognosis or futile care. In addition, we created a clinical nomogram to support an individualized approach to patient decision-making and establishment of realistic patient expectations.

Multiple female factors have previously been identified to predict IUI success. Thijssen et al. evaluated women using donor sperm and found a negative correlation with increasing patient age, tobacco use, and obesity with successful pregnancy rates [2]. Liu et al. identified female age > 40 to be a threshold for poor prognosis after IUI [32]. Recently, previous parity was also identified to contribute significantly to IUI success [33]. We found that in our analysis, women aged ≥ 38 have a predicted probability of viable birth below 0.05, when using oral medications or Clomid plus gonadotropins for ovarian stimulation, regardless of inseminate motility. These results are not unexpected, and are explained by the known impact

of female aging on reproductive success. Even with *gonadotropins only* and optimal inseminate motility, the viable birth rate did not exceed 10% per cycle. For women ≤ 37 , per-cycle analysis showed that *gonadotropins only* stimulation was above the threshold for poor prognosis care, regardless of inseminate motility. However, for women using oral medications or Clomid plus gonadotropins, inseminate motility above 49% for women < 35 or above 56% for women 35–37 was required for a predictive probability of 0.05. The probability of viable birth per cycle supports current practices for unexplained infertility which recommend the use of ovulation/superoovulation and IUI for women ≤ 37 and proceeding directly to IVF for women of advanced reproductive age [34]. Lastly, the higher pregnancy rates with *gonadotropins only* must be interpreted in the context of known risk of multiple gestation, as has been previously published [35].

Semen parameters predictive of IUI success or failure have been previously evaluated. These studies offer inconsistent results and few comment on threshold values at which IUI should not be offered. Total motile sperm count greater than 1 million in the inseminate and greater than 5–10 million in the ejaculate have been positively correlated with clinical pregnancy rates [13, 15, 19, 20]. Conversely, individual studies have identified threshold values of both 5 and 10 million total motile sperm in the inseminate to be predictive of pregnancy outcomes, citing differences in pregnancy rates of 5.55 and 24.28% and 10.8 vs. 27.4%, below and above these thresholds, respectively [18, 21, 24]. Others have reported a threshold of 10 million total motile sperm as a differentiating factor in cost/success of treatment and use this to guide decisions about proceeding with IUI versus IVF [14]. Our study found the impact of inseminate motility to vary based on other clinical factors of ovarian stimulation type and female age. These conclusions support previous findings that found motility in the inseminate to be most predictive of IUI success [27, 36–39].

The nomogram developed from our findings adds a valuable clinical tool to guide patient decision-making and understanding of realistic success rates. In addition, validation of this tool on a large scale could be useful in supporting requests for insurance coverage of IVF without prior completion of IUI cycles to maximize the efficiency of ART, both in regard to time and financial resources.

The present study has multiple strengths including the large number of IUI cycles included for review and data on birth outcomes. As all cycles were completed at a single institution, variability in sperm preparation or procedure are minimized, although this may impact the generalizability of our findings. Additional limitations of our study include the lack of available infertility diagnosis and smoking status, which may impact patient specific recommendations, limited number of patients in the 41–42 age group, and generalizability of findings to other races and ethnic groups. While we believe the nomogram created is a valuable tool for patient counseling and decision-making, it does have modest predictive ability for viable birth with a c-statistic of 0.61. Validation of the prediction model in an external cohort is also needed. Finally, although IUI is a first-line treatment for same-sex female couples or women planning to single parent, the use of donor sperm was not evaluated in the present study and findings cannot be extrapolated to thawed parameters which are known to vary significantly from fresh samples.

Conclusion

The present study highlights the impact of multiple clinical factors on IUI success and identifies thresholds for very poor prognosis and futile care, using motility in the inseminate as

the primary determining factor. Considering other clinical factors of female age and ovarian stimulation type methods add nuanced conclusions predictive of patient success and allowed for creation of a nomogram to aid in patient counseling. These findings and graphical representations could aid in patient counseling and decision-making regarding use of IUI treatment for unexplained or male factor infertility.

Availability of data and material Data obtained from fertility database maintained in the Division of Reproductive Endocrinology and Infertility at Mayo Clinic.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not required in this retrospective cohort study. The study was approved by Mayo Clinic IRB.

Consent to participate Not applicable in retrospective cohort study.

Consent for publication Not applicable in retrospective cohort study.

Code availability Not applicable.

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