A multicentric, prospective test of Cap-Score's™ ability to predict a man's probability of generating pregnancy

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Abstract

OBJECTIVE: Semen analysis lacks an evaluation of fertilizing ability, and fails to diagnose many cases of male factor infertility. Previously, Cap-Score™, the percentage of sperm that can capacitate, showed strong correlations with male fertility (retrospective and cohort comparison studies), and prospectively identified low versus normal fertility using a simple cut-off. However, male fertility is a continuum; logistic regression based on clinical pregnancy outcomes revealed how Cap-Score relates to the probability of generating a pregnancy (PGP) in 3 cycles (Schinfeld et al, 2018; n=124; 5 clinics). Here, we prospectively tested the relationship between the predicted PGP and actual intrauterine insemination (IUI) outcomes.

DESIGN: A multicentric prospective test of the PGP model's ability to predict pregnancy. IUI was used as the experimental model to ensure collection of outcomes and provide control over number and timing of inseminations relative to ovulation. For inclusion, men had to have ≥ 3 million cells post-wash, and female partners could not have factors precluding IUI, e.g., tubal occlusion, hydrosalpinges.

MATERIALS AND METHODS: Studies were approved by Weill Cornell's IRB or WIRB. Cap-Score and outcomes were obtained from 6 clinics (n=292). A total of 128 finished treatment (pregnant or ≥ 3 IUIs). The previously published PGP model was tested in three ways. First, new outcomes were added to the prior 124 and the model recalculated to determine change. Second, the Akaike Information Criterion identified whether Cap-Score alone, or in combination with traditional semen analysis metrics, produced the best model. Third, to test the model prospectively, the 128 new outcomes were divided into rank-ordered Cap-Score quintiles of roughly equal size. The original model was used to predict the number pregnancies per group and a chi-squared statistic determined if predicted and observed outcomes differed. All statistics were independently confirmed regarding appropriateness and accuracy.

RESULTS: Only a slight change ($\bar{X}$=2.4%), from the original model (PGP=1/[1+exp[-[-2.86+0.08*Cap-Score]]]; n=124; p<0.01) was noted when new data were added ((PGP=1/[1+exp[-[-2.30+0.06*Cap-Score]]]; n=252; p<0.001), and fit improved. Further, no change in model parameters was detected (p>0.05). Cap-Score alone produced the best model. The pregnancies prospectively predicted by the original model were consistent with those observed (chi-square: 2.28; 5 degrees of freedom; p=0.809, showing no difference between predicted and observed pregnancies).

CONCLUSIONS: Despite the potential for introducing noise when using "real world" cases from diverse settings, there was no significant change upon doubling the dataset. The number of pregnancies observed were consistent with those predicted by the published model. These results further demonstrate the strong relationship between Cap-Score, sperm function/fertilizing ability, and the ability to generate pregnancy.

Introduction

Sperm must mature functionally through the process of capacitation to become able to fertilize. Capacitation depends on membrane lipid changes, and can be assessed by redistribution of the ganglioside G_{M1}, the basis of the Cap-Score™ male fertility assay. Based on clinical pregnancy outcomes from IUI, the relationship between Cap-Score and the probability of generating pregnancy (PGP) was previously defined using data from 5 clinics (**Figure 1**). Here, we tested the relationship between the predicted PGP and actual intrauterine insemination (IUI) outcomes in three ways, including a prospective assessment.

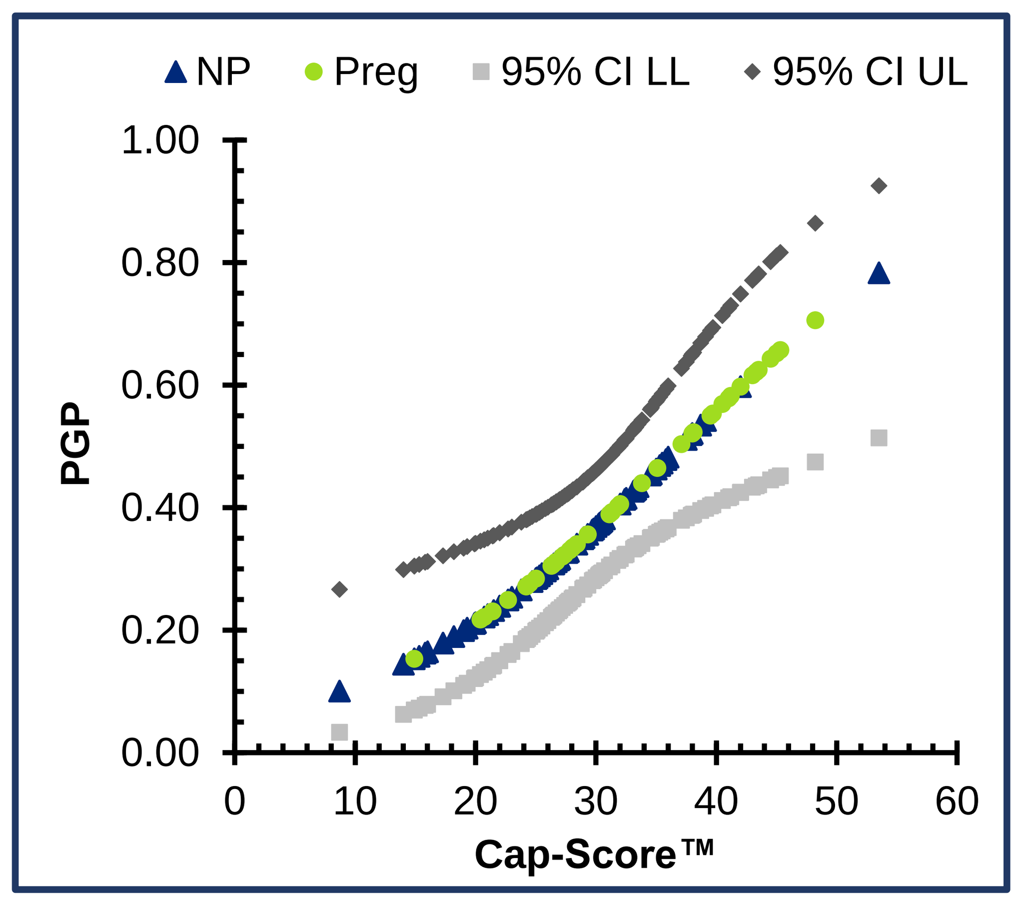

Figure 1. Cap-Score™ and its association with pregnancy. Logistic regression generated an equation explaining the relationship between Cap-Score™ and Probability of Generating a Pregnancy (PGP). All individuals completed at least 3 rounds of IUI or generated pregnancy. Data were obtained from 5 clinics and across a wide age range of women undergoing IUI (n=124; PGP range: 10-78%; Schinfeld et al., 2018). Non-pregnant cycles (NP); Cycles resulting in pregnancy (Preg); lower limit confidence interval (CI LL); upper limit confidence interval (CI UL).

Results

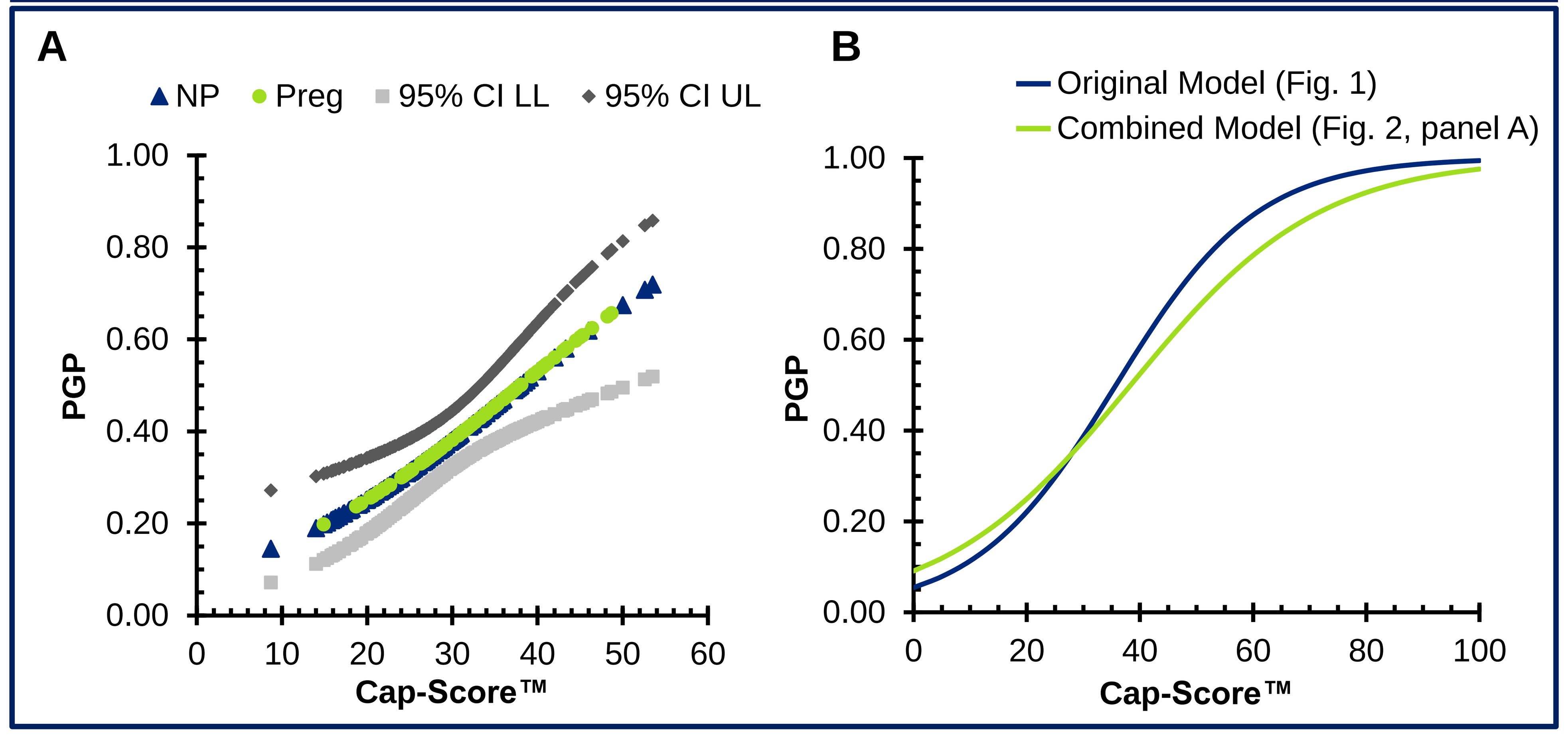

Figure 2. Original and new logistic regression models defining the relationship between Cap-Score and the Probability of Generating Pregnancy (PGP) within 3 cycles. Only a slight change in the predicted PGP ($\bar{X}$=2.4%), was noted from the original model when the new data were added and fit improved (**A** logistic model including all data ($n=124_{original}+128_{new}$)). Further, no change in model parameters was detected (p>0.05). The greatest divergence from the original model occurred in the lower and higher range of Cap-Scores where there were not only fewer observations, but also some differences in practice based on the Cap-Score results (**B** overlapping models**)**. Non-pregnant cycles (NP); Cycles resulting in pregnancy (Preg); lower limit confidence interval (CI LL); upper limit confidence interval (CI UL).

Model	AIC
Cap-Score	318.6
Motility	331.1
Concentration	333.7
Volume	333.1
Cap-Score + Motility	319.1
Cap-Score + Concentration	320.6
Cap-Score + Volume	319.1
Motility + Concentration	333.0
Motility + Volume	332.0
Concentration + Volume	334.7
Cap-Score + Motility + Concentration	320.6
Cap-Score + Motility + Volume	319.4
Cap-Score + Concentration + Volume	321.1
Concentration + Motility + Volume	333.9
Cap-Score + Concentration + Motility + Volume	320.8

Table 1. Akaike Information Criterion (AIC; (Akaike 1974). Model: shows the measures considered. AIC was performed to test whether the inclusion of one or more traditional SA parameters would improve PGP fit. Briefly, the AIC penalizes increasing model complexity without a reciprocal increase in fit. Lower AIC values reflect the most appropriate models. Cap-Score alone was found to provide the optimal model, underscoring that capacitation served as the primary metric of male fertility.

Cap-Score™ Quintile	N	Observed pregnancies	Predicted pregnancies ± σ
1st	26	8	5.46 ± 2.07
2nd	25	7	6.98 ± 2.24
3rd	26	11	8.84 ± 2.24
4th	25	8	10.40 ± 2.46
5th	26	15	14.58 ± 2.49

Table 2. Prospective test of observed versus predicted pregnancies based on probability of generating pregnancy (PGP). The 128 new outcomes were rank-ordered by Cap-Score and divided into quintiles (25-26/group). The observed and predicted pregnancies within 3 cycles were determined per group. Predicted pregnancies were calculated by summing quintile PGP values, with PGP being predicted by the original logistic regression model (Fig. 1). A chi-square statistic revealed no difference between observed and predicted pregnancies (chi-square=2.279 ; p=0.809; five degrees of freedom).

Age range	N	Observed pregnancies	Predicted pregnancies ± σ
≤29	34	12	11.85 ± 2.68
30-34	115	46	42.55 ± 4.99
35-39	66	22	22.64 ± 3.73
≥40	16	4	5.22 ± 1.78

Table 3. Test of impact of maternal age on the relationship between Cap-Score and male fertility. First, we added maternal age as a term in the logistic regression; the coefficient of age was not significant (p=0.42). We next disaggregated outcomes data into age groups. No difference was observed between predicted and observed pregnancy outcomes, across maternal age groups (chi-square=0.585; p=0.965; four degrees of freedom).

Conclusions

- Addition of 128 new clinical outcomes had only minor impact on the relationship between Cap-Score and male fertility/PGP.
- Cap-Score alone was the best predictor of the probability of generating a pregnancy
- The number of pregnancies observed was consistent with the prospective predictions made by the model relating Cap-Score and a man's ability to generate pregnancy within 3 cycles.
- Although female age and fertility are clearly linked, if a woman was eligible for IUI, then Cap-Score accurately predicted pregnancy across maternal ages.

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