Defects in sperm capacitation and fertilizing ability are highly prevalent in men undergoing fertility examination, even if normozoospermic

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Abstract

OBJECTIVE: Semen analysis (SA) fails to evaluate fertilizing ability and best identifies extreme infertility cases. Cap-Score™ functionally assesses sperm capacitation/male fertility and prospectively predicts pregnancy. Here, we examine the association of SA, Cap-Score, and Cap-Score's relationship with the probability of generating pregnancy in 3 cycles (PGP; Schinfeld et al., 2018), in men questioning their fertility vs fertile men.

DESIGN: Cohort comparison: Cap-Score, PGP and SA metrics were compared in 1,948 men questioning fertility vs 76 fertile men (pregnant partner or recent father).

MATERIALS AND METHODS: Semen was collected from 2,155 men having SA and Cap-Score because of fertility concerns (22 clinics; 11/2016 to 7/2019). Volume, concentration and motility were available for 1,948 and were assessed (WHO criteria; morphology omitted due to variable methods). Fixed samples were shipped to Androvia for Cap-Score and PGP determination. Fertile men were assessed previously (WIRB approval). Table 1 was designed with even PGP bins and evaluated by Chi-square.

RESULTS: 61% (1,183/1,948) of men having SA were normozoospermic (volume, concentration, motility). Compared to fertile men (p<0.001), more men having fertility exams had Cap-Scores ≤ 31 (PGP bins of ≤ 19, 20-29 and 30-39). Fewer than expected had Cap-Scores ≥ 32 (PGP bins of 40-49, 50-59 and ≥ 60). This distribution revealed a high prevalence of reduced capacitation/fertilizing ability in men having fertility exams. Defects in sperm function were equally prevalent regardless of passing any single or multiple SA metrics, or those having >10 million total motile cells (TMC; p=0.987).

CONCLUSIONS: Of normozoospermic men having fertility exams, 64% (757/1,183) had Cap-Scores ≤ 31 (PGP ≤ 39%); in contrast, only 25% of fertile men (19/76) scored in this range. Conversely, only 36% (426/1,183) of normozoospermic men questioning their fertility had Cap-Scores ≥ 32, in contrast to 75% of fertile men. These data support reports that reduced sperm function/fertilizing ability is common in men questioning their fertility and cannot be detected by traditional SA, contributing to the high percentage of men diagnosed with idiopathic infertility. In men having fertility exams, reduced Cap-Scores were detected equally in normozoospermic men vs all men examined. These data show that a test of sperm capacitation offers a powerful complement to traditional SA, capable of identifying normozoospermic men with reduced sperm fertilizing ability.

Introduction

Semen analysis (SA) does not assess sperm fertilizing ability and fails to diagnose most cases of male infertility. Sperm functional maturation is known as capacitation and is required for fertilization. Cap-Score™, which quantifies capacitation status, functionally assess fertilizing ability and prospectively predicts the probability of generating pregnancy in 3 IUI cycles (PGP; Schinfeld et al., 2018). Here, we examine the association of SA, Cap-Score, and Cap-Score's relationship with PGP, in men having fertility exams vs fertile men.

Material and Methods

Semen was collected from men questioning their fertility (MQF; 22 clinics; 10/2016 to 7/2019 n=2,155). Volume, concentration and motility were available for 1,948 and were assessed according to WHO criteria (morphology omitted due to methods varying among clinics). Fixed samples were shipped to Androvia for Cap-Score and PGP determination. Cap-Score data from fertile men was reported previously (Cardona et al., 2017).

Results

Cap-Score (%)	PGP (%)	% of all men questioning fertility	% normozoospermic men questioning fertility	% men questioning fertility >10M TMC	% fertile men
≤ 18	≤ 19	8% (151/1,948)	6% (69/1,183)	7% (128/1,809)	1% (1/76)
19 - 25	20 - 29	28% (551/1,948)	27% (322/1,183)	28% (499/1,809)	9% (7/76)
26 - 31	30 - 39	31% (611/1,948)	31% (366/1,183)	32% (573/1,809)	14% (11/76)
32 - 36	40 - 49	17% (330/1,948)	19% (224/1,183)	18% (320/1,809)	36% (27/76)
37 - 42	50 - 59	10% (186/1,948)	10% (124/1,183)	10% (176/1,809)	24% (18/76)
> 42	≥ 60	6% (119/1,948)	7% (78/1,183)	6% (113/1,809)	16% (12/76)

Table 1. Distribution of data relating Cap-Scores, PGP, and traditional SA metrics. Of the 2,155 MQF, accompanying SA data were available for 1,948. 61% (1,183/1,948) of all MQF were normozoospermic based on WHO criteria. Of these normozoospermic men, 64% (757/1,183) had PGPs ≤39; in contrast, only 25% of fertile men (19/76) scored in this range. Conversely, only 36% (426/1,183) of normozoospermic men questioning their fertility had Cap-Scores ≥ 32, in contrast to 75% of fertile men. Compared to fertile men (p<0.001), more men having fertility exams had Cap-Scores ≤ 31 (PGP bins of ≤ 19, 20-29 and 30-39). Fewer than expected had Cap-Scores ≥ 32 (PGP bins of 40-49, 50-59 and ≥ 60).

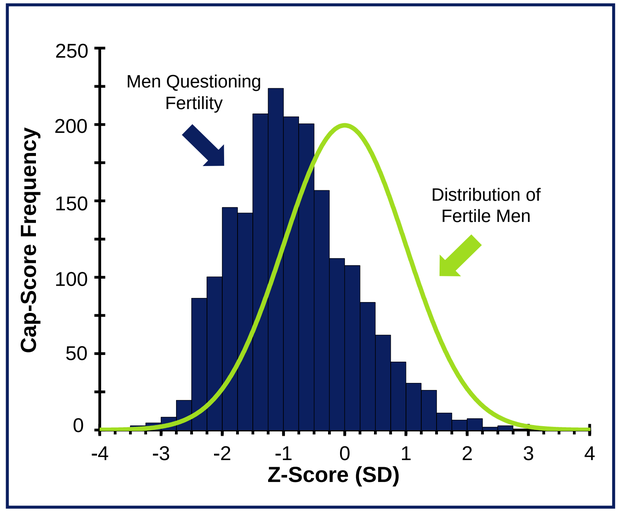

Figure 1. Data generated from men questioning their fertility (MQF) (n = 2,155 men, 22 clinics) were compared to a cohort of men with known fertility (n = 76 men, 187 samples; Cardona et al, 2017). The distribution of Cap-Scores in MQF (blue histogram) was significantly different from that in fertile men (green curve, p<0.001), with 81% (1,741/2,155) falling below the fertile mean of 35.3. The x-axis shows Z-scores, with the mean of 35.3 set to 0, and every unit equal to one standard deviation of 7.7.

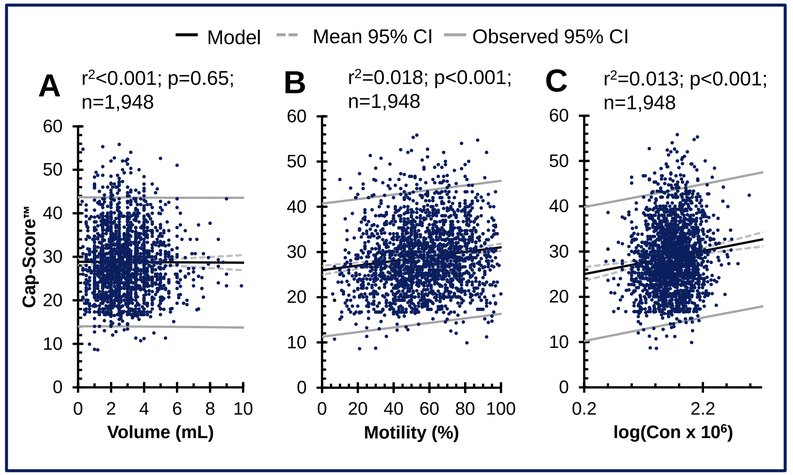

Figure 2. Scatterplots showing no relationship between volume and Cap-Score (r^2<0.001, p=0.65), and minimal relationships between motility and Cap-Score and concentration and Cap-Score. Small, but statistically significant relationships were found for motility and concentration (p<0.001 for each). Motility was found to contribute ~2% to the Cap-Score (r^2 = 0.018) and concentration was found to contribute ~1% to the Cap-Score (r^2 = 0.013) Note that one outlier data point (volume = 15 ml; Cap-Score = 17.9%) was removed from plot **A** to facilitate visual discrimination of the majority of the data points. The outlier was included in the analysis of relationship between volume and Cap-Score.

Conclusions

- Significantly more men questioning their fertility had lower Cap-Scores when compared to fertile individuals.
- In men having fertility exams, reduced Cap-Scores were detected equally in normozoospermic men vs all men examined.
- Minimal/no relationship was found between Cap-Score and sperm concentration, motility, or volume.
- All together, these data demonstrate that capacitation is a highly sensitive indicator of male fertility.

Future directions

- Capacitation can provide important information about male fertility, directly impacting a couple's chances of conception. Cap-Score can provide a functional complement to the traditional SA, potentially helping reduce the high percentage of men diagnosed with idiopathic infertility.

Funding