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Serum and follicular fluid Stem Cell Factor assay in IVF poor responder and normal responder patients: a predictive biomarker of oocyte retrieval

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Abstract

Objective The aim of the study is to investigate serum stem cell factor (SCF) concentrations as potential biomarker for oocyte retrieval efficiency in IVF patients with poor prognosis.

Methods A pilot case–control study was performed on 30 poor and 30 normal responders that were stimulated with antagonist protocol. SCF concentrations were evaluated in samples of serum and follicular fluid obtained by all patients on the day of oocyte retrieval. At the time of oocyte retrieval, follicular fluid from at least two follicles ≥ 14 mm and two follicles < 14 mm was collected for SCF determination.

Results We did not find any statistical difference when comparing serum and follicular fluid levels of SCF in both poor- and normal-responder patients, the same results were achieved when poor-responder patients were stratified according to the number of MII oocytes retrieved. Moreover, levels of SCF (OR 1.000, 0.994–1.006) or in follicular fluid from ovarian follicles ≥ 14 mm (OR 0.995, CI 0.989–1.001) or from ovarian follicles < 14 mm (OR 1.003, CI 0.999–1.0069), were not significantly associated with the chances of ongoing pregnancies in poor-responder patients.

Conclusion SCF was unable to predict oocyte retrieval efficiency or the chances of reaching embryo transfer.

Keywords Stem Cell Factor · Normal responder · Poor responder · Follicular fluid · In vitro fertilization (IVF)

Introduction

Although the incidence of poor ovarian response (POR) during in vitro fertilization (IVF) cycles have been classically described within a range of 9–24% according to different studies [1], this number has increased in the last few years [2, 3]. Anti-Müllerian hormone (AMH) and antral follicle count (AFC) appear to be valuable markers mainly for ovarian reserve, then as an indicator of response during IVF treatment in POR. The measurement of AMH is a useful marker for selecting the starting dose of recombinant follicle-stimulating hormone (rFSH) and prediction of POR. Serum AMH level and AFC numbers are significantly associated with the number of retrieved oocytes. Normally, AMH measurement is proposed to women before starting an IVF cycle with a clear definition of cut-off values for the prediction of poor- and hyper-response. To date, no biochemical markers have been able to predict oocyte retrieval success in terms of the quality and numbers of oocytes or the rate of metaphase II oocytes that may be recovered prior to performing oocyte pick-up, which could avoid empty retrievals or failed cycles even before embryo transfer, especially in poor-responders.

Stem cell factor (SCF) is a cytokine growth factor produced in the human follicular phase immediately prior to the ovulatory phase. It has been recently shown to play an important role in folliculogenesis and ovulation [4]. SCF triggers the recruitment of the primordial follicle pool and oocyte maturation. In the human ovary, SCF is secreted by granulosa cumulus cells (GCs) can directly stimulate growth

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and differentiation of oocytes and theca cells, and increase steroid hormone production [5–8].

Follicle-stimulating hormone (FSH) is involved in the release of SCF with the regulation of several paracrine factors from the oocytes, which interact with GCs during follicular development. The function of FSH in primordial folliculogenesis seems to occur through SCF because the number of FSH-stimulated primordial follicles is lower in the presence of an SCF antibody [9]. It has been actually shown that follicles cultured with SCF increase significantly the mean diameter from primordial, early primary, primary, and growing primary follicles in the mouse, whereas these effects were inhibited by treatment with SCF neutralizing antibody [10]. Thus, it has been proposed that follicular fluid SCF levels may affect folliculogenesis and later ovulation, while serum SCF could reflect successful stimulation with a large follicular maturation. Remarkably, a recent report has shown that in IVF cycles, SCF levels in follicular fluid were significantly higher in follicular fluid of patients in which at least one oocyte was retrieved in comparison to those in which no oocyte was found [11]. These data led to conclude that SCF might be used as a predictor of IVF outcome [4], especially in the management of poor-responder patients [11].

In order to confirm this challenge, we designed a pilot study to compare SCF levels in both serum and follicular fluids between normal-and poor-responder patients. Additionally, we also demonstrated a possible relationship between SCF levels and the number of MII oocytes retrieved during follicular retrieved in order to propose serum SCF as a new serum biomarker to predict the efficiency of oocyte retrieval in poor ovarian responders.

Materials and methods

Study design and population

We conducted a pilot study by enrolling 30 normal- and 30 poor-responder patients according to Bologna criteria who underwent ovarian stimulation for IVF/ICSI at IVI Madrid from June 2015 to August 2015, consecutively selected. The study was approved by the Ethics Committee of Hospital "Puerta del Hierro" with number 1506-MAD-044-JG.

The inclusion criteria were: (group A—poor-responders) women who underwent IVF/ICSI treatment who met Bologna criteria [3], BMI 18–30 kg/m^2 and at least two follicles of $\geq$ 14 mm and two follicles of < 14 mm at oocyte, were excluded cases of male infertility; (group B—the control group) volunteers aged 18–35 years who met the criteria to be oocyte donors. Oocyte donors were healthy women with regular menstrual cycles of 21–35 days, no family history of hereditary or chromosomal diseases, normal karyotype, body mass index (BMI) of 18–29 kg/m^2, no more than two previous miscarriages, or gynecological or medical disorders, and a negative screening result for sexually transmitted diseases [12]. Donors should have at least six antral follicles per ovary at the beginning of the cycle.

The exclusion criteria in both groups were patients with abnormal karyotype, cystic fibrosis mutation, acquired or inherited thrombophilia and immunological disorders, patients who underwent chemotherapy or radiotherapy, ovarian endometrioma, dermoid or any functional cyst, previous ovariectomy, patients operated for any ovarian mass, endometrial intra-cavitary disease or patients with any new diagnosed chronic infectious disease, such as human papilloma virus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV). In the control group women with basal antral follicle count > 20 or < 6 per ovary, women with comorbidities that may interfere with ovarian stimulation treatment, the presence of ovarian cysts or thosewith polycystic ovary syndrome based on Rotterdam criteria, were excluded [13].

Ovarian stimulation protocol

Patients were stimulated with recombinant FSH (rFSH, Gonal F; MerckSerono, Geneva, Switzerland), either alone or in combination with highly purified hMG (HP-hMG, Menopur, Ferring). The starting dose was 150 UI rFSH with 75 UI HP-hMG in poor-responder patients, and 150 UI of rFSH in normal-responder patients. In both groups, monitoring follicle development by ultrasound scans, serum estradiol concentration was performed from day 5 of stimulation until the day of triggering. Gonadotropin doses were not modified on the basis of sonographic features of ovarian response beginning from stimulation day 5. Daily doses of 0.25 mg GnRH antagonist (Cetrotide®; Merck Serono, Spain) were started when one follicle reached a mean diameter of 13 mm. When at least two follicles measured $\geq$ 17 mm in mean diameter, 6500 UI recombinant hCG (Ovitrelle®; MerckSerono, Spain) was administered subcutaneously in the poor-responder patients. A single dose of 0.2 mg of triptorelin (Decapeptyl®; Ipsen Pharma, Spain) was administered to trigger final oocyte maturation when at least two follicles reached a mean diameter $\geq$ 17 mm in the normal responders. The number of follicles was determined on the day of triggering. Follicles were aspirated 36 h after administering hCG or GnRHa. After embryo transfer on day 3 or day 5, group A patients were supplemented with vaginally progesterone, 400 mg daily (Progeffik®; Effik Laboratories, Spain or Utrogestan®; SEID, Spain), for luteal support. Clinical pregnancy was confirmed by beta hCG determination 14 days after embryo transfer, ongoing pregnancy was defined as an uncomplicated pregnancy over 12 gestational weeks.

Collection of biological samples

Blood samples and follicular fluid (FF) were collected on the day of oocyte retrieval. Blood was withdrawn by venipuncture and collected in 10 ml sterile tubes, centrifuged at 1000*g* at 5 °C for 30 min. Serum aliquots were stored at − 80 °C until further analysis. Follicular fluids were individually aspirated without flushing from selected follicles of ≥ 14 mm and < 14 mm after being measured in both dimensions at the day of oocyte retrieval. The needle was withdrawn and completely emptied prior to each puncture, no culture media were used in collection tubes. After removing oocytes, follicular aspirates were centrifuged for 5 min at 200*g* and the supernatant was stored at − 80 °C.

The SCF concentrations in serum and FF were measured in duplicate by solid-phase ELISA using the R&D Diagnostic SCF kit (R and D, Wiesbaden, Germany). This immunoassay is calibrated against highly purified *Escherichia coli*-expressed recombinant human soluble SCF produced by R&D Systems. A two-fold dilution for serum and FF was performed with Calibrator Diluent RD 11. This assay used the quantitative sandwich enzyme immunoassay technique. The SCF concentrations ranged from 31.2 to 2000 pg/ml, with a sensitivity of 9 pg/ml. The intra- and the inter-assay SCF precision was < 4% and < 10%, respectively.

Serum AMH levels were determined by a single measurement through the Elecsys AMH assay in an e411 Cobas automated device (Roche). The limit of functional sensitivity was 0.03 ng/ml and the coefficient of variation was 3.5%, as determined for the control samples during the study. The estradiol levels on the day of ovulation induction were determined by chemo luminescence in an automatic analyzer Architect i100 (Abbot Diagnostics). The intra-and inter-assay coefficients of variation were below 6% in both cases. For estradiol, the limit of detection was < 10 pg/ml.

Statistical analysis

The data from the clinical outcomes were presented as descriptive statistics (mean ± standard deviation). For comparisons, *t* test or Chi-square tests were used whenever appropriate, after the Shapiro–Wilk-test to check normal distribution. Logistic regression was used to analyze the impact of several variables (age, number of oocytes, number of oocytes MII, poor responder condition, embryo transfer, embryo freeze, SCF and SCF < 14 mm or > 14 mm) on the ongoing pregnancy rate. Receiver operating characteristic (ROC) curves were used to analyze the predictive value of the SCF levels on ongoing pregnancy rate. This test was also used specifically in poor responders to predict the probability of have embryo transfer and the number of retrieved oocytes according to the SCF levels. A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences 19.0 (IBM Corporation, New York, USA).

Endpoints

The primary end point was to evaluate whether there were differences in the concentration of SCF in serum and follicular between normal and poor responders. Secondary end points were to evaluate if SCF's concentration in serum and FF in poor responders might be predictive of the number of total oocytes and metaphase II oocytes, in addition demonstrated if SCF in serum or FF could be able to predict the ongoing pregnancy in POR. Tertiary end point was to evaluate whether existed a correlation between the concentration of SCF in serum and FF with the age of patients.

Results

Thirty poor-responder patients (group A) and normal-responder patients (group B) were enrolled in our study. Their socio-demographic and health characteristics are reported in Table 1.

When comparing the serum and follicular fluid (FF) levels of SCF, we were unable to find statistical differences between normal- and poor-responders (Table 2). Similar results were obtained when analyzed the probability of obtain oocytes during follicular retrieval in the serum SCF levels (OR 1.000, CI 0.994–1.006), in the FF from mature follicles ≥ 14 mm (OR 0.856, CI 0.825–1.125) or from immature follicles < 14 mm (OR 1.008, CI 0.999–1.006).

The logistic regression analysis showed that age, number of oocytes MII, normal/poor responders and embryo-freeze

Table 1 Patients' characteristics

	Normal responders	Poor responders	*p*
Age (years)	26.9 ± 1.4	40.8 ± 1.0	< 0.001
BMI (kg/m^2)	21.7 ± 0.2	21.8 ± 0.8	0.843
Estradiol (pg/ml)	2500 ± 495	1279 ± 317	< 0.001
Dose FSH (UI)	1810 ± 170	1789 ± 230	0.876
Days of stimulation	11.0 ± 0.3	11.6 ± 0.8	0.157
AFC	12.6 ± 1.2	3.9 ± 0.6	< 0.001
Number of oocytes	16.7 ± 2.3	4.4 ± 1.0	< 0.001
Number of oocytes MII	11.6 ± 1.5	3.5 ± 0.7	< 0.001
Embryos transferred	1.4 ± 0.3	0.4 ± 0.2	< 0.001
Embryos day 3	2 ± 0.19	1.4 ± 0.63	
Embryos day 5	1.3 ± 0.23	1 ± 0.0	
Embryos frozen	3.4 ± 1.0	0.03 ± 0	< 0.001

BMI body mass index, *FSH* follicle stimulating hormone, *AFC* antral follicle count, *MII* Metaphase II, *UI* unit international

Table 2 SCF concentration in serum and follicular fluid in the follicles larger or smaller than 14 mm in normal and poor responders

	Normal responders (mean ± SD)	Poor responders (mean ± SD)	*p*
SCF (pg/ml)	1567 ± 75	1614 ± 68	0.339
SCF (pg/ml) (follicles > 14 mm)	1486 ± 102	1439 ± 147	0.593
SCF (pg/ml) (follicles < 14 mm)	1278 ± 190	1107 ± 249	0.259

Table 3 Regression model for ongoing pregnancy

	OR and CI	*p*
Normal/poor responder	0.068 (0.011–0.432)	0.004
Age	0.822 (0.710–0.950)	0.008
Number of oocytes	1.077 (0.974–1.190)	0.147
Oocytes MII	1.314 (1.068–1.617)	0.010
Embryos transferred	1.820 (0.443–7.477)	0.406
Embryos freeze	1.937 (1.147–3.270)	0.013
SCF (serum)	0.999 (0.995–1.002)	0.455
SCF-FF (> 14 mm)	1.001 (0.999–1.003)	0.442
SCF-FF (< 14 mm)	1.001 (0.999–1.002)	0.470

OD odds ratio, *CI* confidence interval

were correlated with the probably of ongoing pregnancy, while retrieved oocytes, embryo transfer, SCF in serum and in FF did not significantly affect the probability of ongoing pregnancy (Table 3). We analyzed the SCF levels in serum and FF in the poor-responder patients depending on whether the day of retrieved oocytes they had oocytes or not (Fig. 1) and depending on the number of MII oocytes retrieved (Fig. 2). In both cases, we did not find statistical differences between groups. The logistic regression analysis in the poor-responder patients showed that neither serum SCF levels (OR 1.000, CI 0.994–1.006), nor the FF SCF concentration from follicles ≥ 14 mm (OR 0.995, CI 0.989–1.001) or from follicles < 14 mm (OR 1.003, CI 0.999–1.0069),

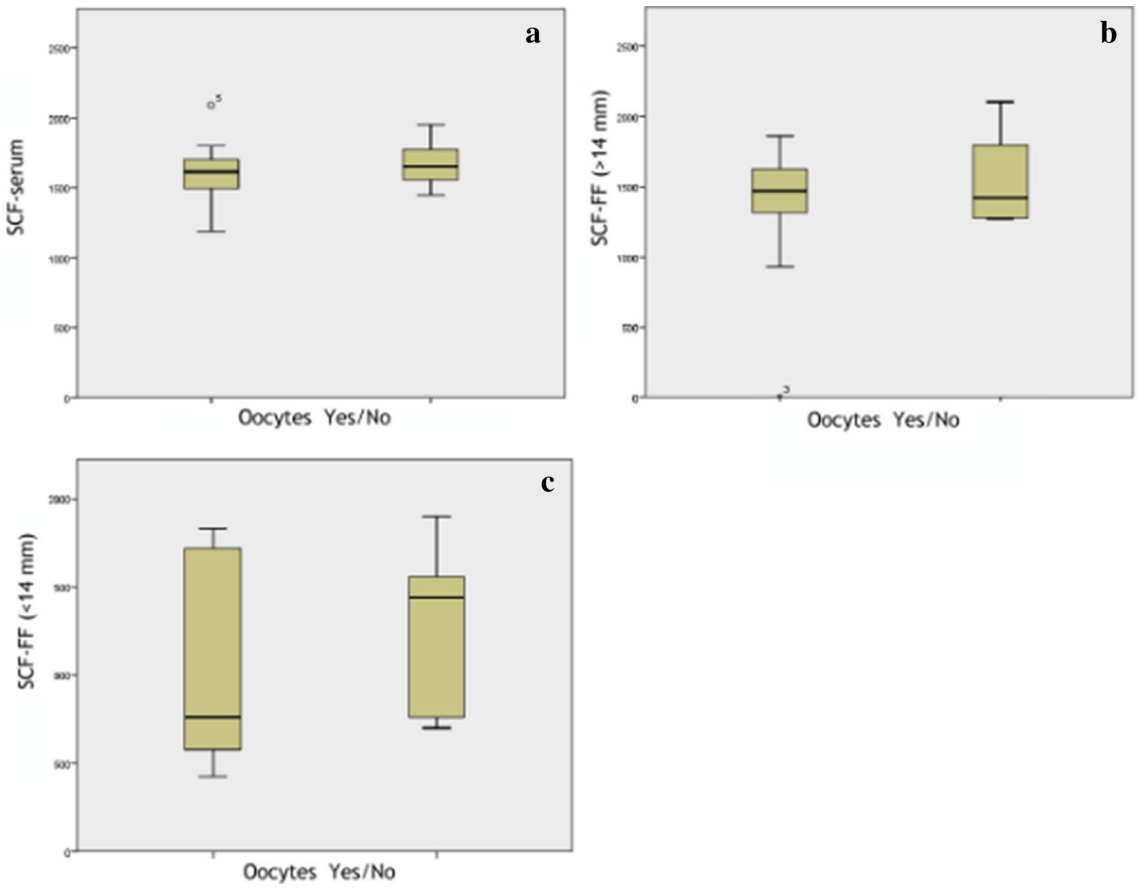

Fig. 1 Measuring the SCF concentration in serum and follicular fluid of poor responders along with or without oocyte recovery. **a** Presence or absence of oocytes versus SCF serum; **b** presence or absence of oocytes versus SCF in follicular fluid (follicle > 14 mm); **c** presence or absence of oocytes versus SCF in follicular fluid (follicle < 14 mm)

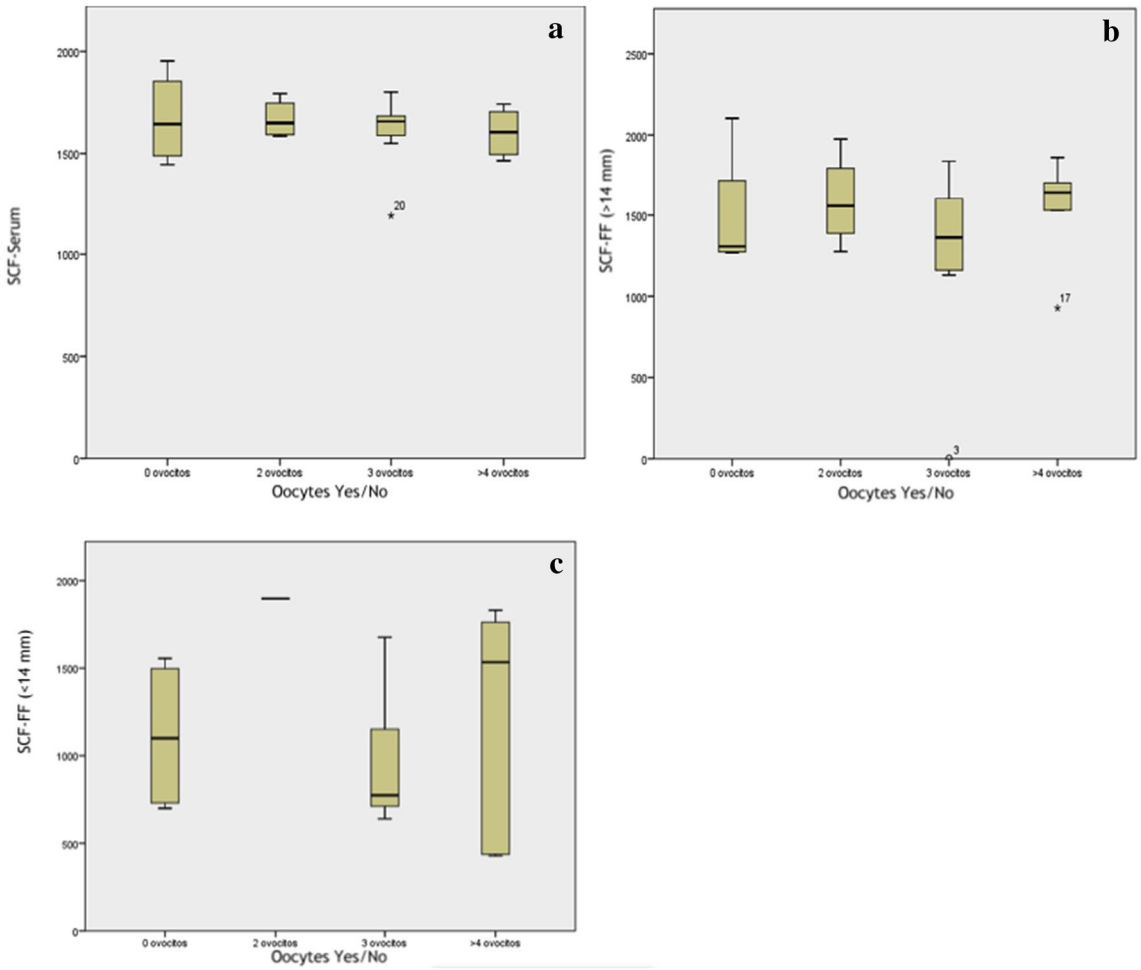

Fig. 2 Measuring the SCF concentration in serum and follicular fluid in poor-responder patients based on number of recovered oocytes. **a** Number of oocytes versus SCF serum; **b** number of oocytes versus SCF in follicular fluid (follicle > 14 mm); **c** number of oocytes versus SCF in follicular fluid (follicle < 14 mm)

significantly affected the odds of having embryo transfer. Finally, we did not find any relationship between the age of the normal and poor responder patients and the SCF in serum and FF, according to the size of the aspirated follicles (Fig. 3).

Discussion

To our knowledge, this is the first study that compares SCF level in serum and FF between a healthy populations of normal-responder patients who undergoing ovarian stimulation with a good prognosis and a selected population of poor-responder patients. In consideration of the different characteristics of patient population, if any difference existed at these two extremes, it would be evidently apparent.

The main finding of our study was the absence of significant differences in the SCF levels in serum and FF between normal responders and poor-responder patients after taking into account the largest differences between these two patient populations. We choose two different patient groups (young egg donors with good ovarian reserve and women with ovarian already compromised reserve, mainly due to advanced maternal age) to detect any differences in serum or FF.

Recently, some groups have linked SCF activity to AMH synthesis because the hormone plays a role as a negative modulator on the SCF pathway [14, 15]. Interestingly, a more recent study presented a negative correlation between AMH concentration and oocyte viability in follicular fluid. The authors measured the concentration of AMH in FF collected from patients undergoing in vitro fertilization, showing that compared with the high AMH group, the low AMH group showed significantly higher percentage of top quality oocytes, fertilization, clinical pregnancy, and embryo implantation rates, which indicated a positive association

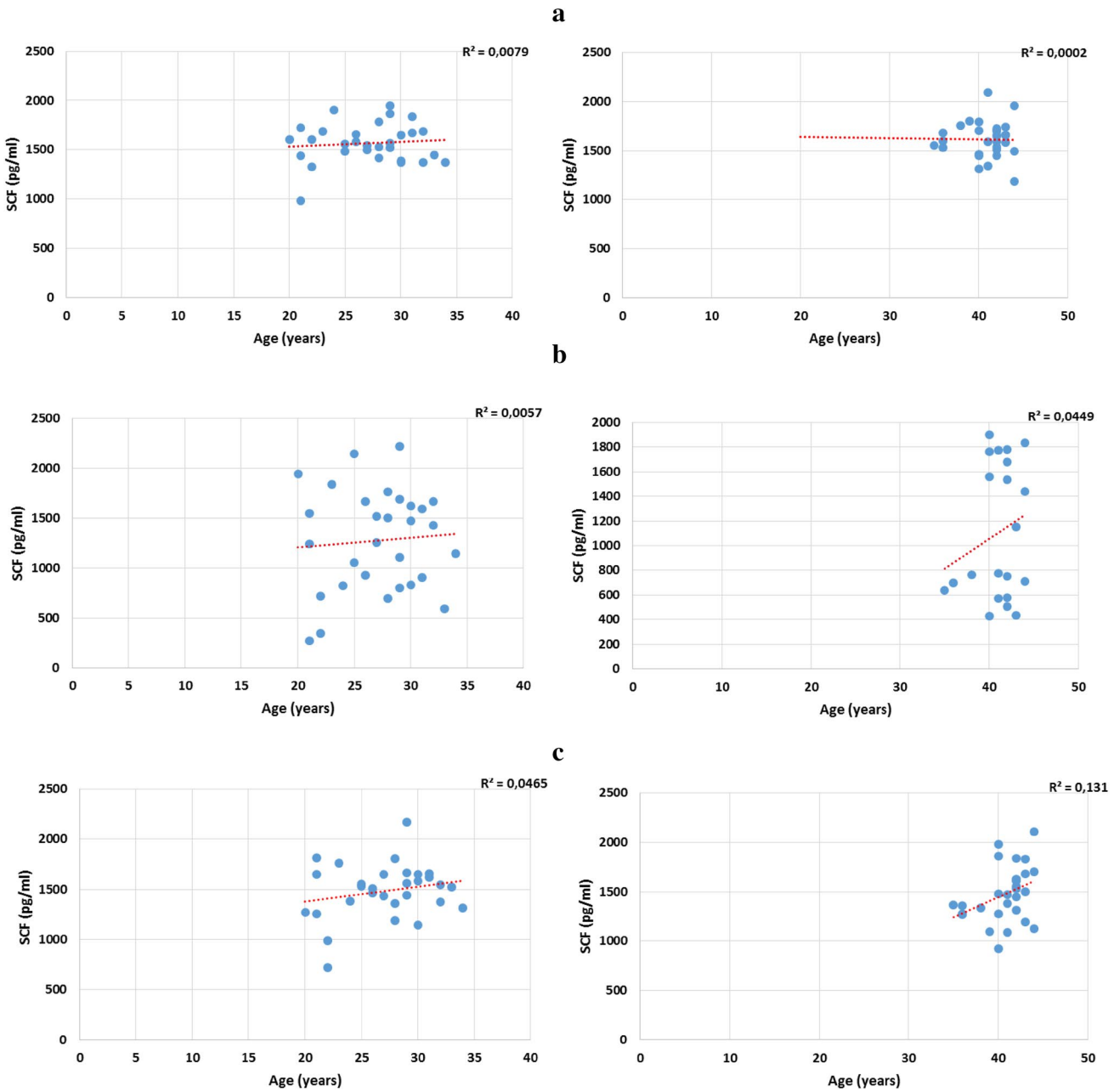

Fig. 3 **a** Normal responders (age versus serum SCF) and poor responders (age versus serum SCF); **b** normal responders (age versus SCF follicular fluid, follicle > 14 mm) and poor responders (age versus SCF follicular fluid, follicle > 14 mm); **c** normal responders (age versus SCF follicular fluid, follicle < 14 mm) and poor responders (age versus SCF follicular fluid, follicle < 14 mm)

between SCF expression and oocyte viability [16]. Since patients with poor ovarian response have very low or undetectable levels of AMH [3], they hypothesized that serum SCF may be a new relevant biomarker in ART.

However, other studies have shown differences that can be attributable to SCF kinetics. Some authors have been reported that SCF concentration was reduced from the day of hCG administration to the day of oocyte retrieval [4]. The maximum SCF concentration was reached on the day of trigger, with a progressive reduction from the day of oocyte retrieval. On the day of embryo transfer SCF levels gradually increased again and reached a plateau between 3–4 weeks of pregnacy [4]. In our study we were not able to gain this difference because measured serum SCF levels only on the day of oocyte retrieval.

Some studies have shown that SCF kinetics in serum and FF can be influenced by the amount of gonadotropins administered for ovarian stimulation. Several groups have

demonstrated a positive correlation between the total dose of gonadotropins administered, serum estradiol levels and SCF concentrations in serum and FF [4, 17]; contrarily, others have noticed that different gonadotropins or pituitary inhibition does not significantly modify SCF concentrations [18]. A recent report [5] did not find any differences between SCF concentrations and different gonadotropin administration protocols. However, this issue remains controversial, our study found no correlation between the dose of gonadotropins or serum estradiol levels and SCF concentrations. In Gizzo et al. study although the starting dose was adjusted according to the biochemical and sonographic features of ovarian response, the total FSH dose was significantly higher than used in our population, which remained unchanged throughout ovarian stimulation. Gizzo et al. [11] has been recently suggested that serum SCF could be a promising biomarker, especially in poor-responder patients, for clinical decision making on whether to cancel or proceed to oocyte retrieval. It could contribute to avoid empty retrievals or follicular aspirations where no MII are obtained, and to reduce costs and frustration. Our study failed to identify a correlation between SCF serum or FF concentrations at the time of oocyte retrieval and the number of MII oocytes retrieved, as well as no predictively for the chance to achieve ongoing pregnancy. Tan et al. found that levels of SCF in FF and GCs were positively associated with oocyte developmental potential. The authors showed that SCF's levels in FF and GCs from the group with high-quality embryos were significantly greater than those from the group without high quality embryos [19]. Although, they included patients < 37 years, considered as normal responders who underwent ICSI for male infertility, were not included a control group [19].

Hammadeh et al. [20] concluded that ICSI outcome was not related to SCF concentrations in serum or FF, and therefore, this parameter could not be used as a prognostic factor in ICSI program. As mentioned before, our results did not match previous reports [11], which have shown a positive correlation between SCF levels and number of mature oocytes, in fact Gizzo et al. showed only difference SCF's serum in patients with different number of MII oocytes. These differences could be due to different patient samples since SCF could undergo wide inter-individual variability depending on the patient's age.

Our study has some limitations, mainly represented by the different types of triggering in the two groups, poor-responder patients received hCG, while normal-responder patients received tryptorelin, in this way we cannot exclude that the use of different ovulation inductors may cause a different SCF response. Although, there are no published studies that indicate this possible occurrence. In addition, patients in the group of poor responders were stimulated only with rFSH without hMG that was used in poor responders. The current literature in this sense seems to be controversial and again we can not exclude a potential confounding influence with the existing studies. Probably these points could resolve with larger study cohort with the following subgroups: poor responder with/without hMG and normal responder with/without hMG.

In conclusion, we did not find any significant differences in the SCF serum and FF levels between normal- and poor-responder patients. In our experience, follicular and serum SCF values at the time of oocyte retrieval showed no difference between normo and poor responder patients. Moreover, no correlation was found between follicular fluid SCF concentration and the rate of MII oocyte in poor responders, independently from follicle size.

Our findings suggest that the assessment of SCF concentration in serum and follicular fluid at the time of oocyte retrieval is not useful to predict oocyte retrieval efficiency. In a poor responder patients referred to IVF was not able to predict the chances of reaching embryo transfer and achieving ongoing pregnancy.

Author contributions MC conceptualization: equal, validation: lead, writing—original draft: lead, writing—review and editing: equal; MC data curation: equal, formal analysis: lead; AP data curation: equal, investigation: equal; JP data curation: supporting, investigation: equal; AP data curation: equal; JAG-V conceptualization: lead, validation: equal, writing— review and editing: equal.

Compliance with ethical standards

Conflict of interest All authors declare that they have not conflict of interest.

Ethical approval All procedures performed in the studies that involved human participants were in accordance with the ethical standards of the Institutional and National Research Committee, with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all the individual participants enrolled for the study.

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