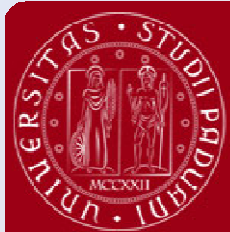Università degli Studi di Padova
Dipartimento di salute della donna e del bambino – SDB
U.O.C. Clinica Ginecologica ed Ostetrica
Scuola di Specializzazione in Ginecologia e Ostetricia
Direttore Prof. Giovanni Battista Nardelli

# DOSAGGIO SIERICO DI STEM CELL FACTOR IN PAZIENTI "POOR RESPONDER" SOTTOPOSTE A CICLI DI FECONDAZIONE IN-VITRO: UN NUOVO BIOMARKER PER STABILIRE SE E QUANDO INDURRE L'OVULAZIONE ED EFFETTUARE IL PRELIEVO OVOCITARIO

*Salvatore GIZZO*

UNIVERSITÀ DEGLI STUDI DI PADOVA

REPUBBLICA ITALIANA

**BOLLETTINO UFFICIALE**
**REGIONE DEL VENETO**

Venezia, venerdì 8 luglio 2011

Anno XLII - N. 49

- l'età di accesso delle coppie sia così determinato:
  - età femminile fino al compimento di 50 anni
  - età maschile fino a compimento di 65 anni
- il numero dei cicli sia così determinato:
  - 4 cicli di trattamento di 1° livello nei limiti di dosaggio previsti dalla nota AIFA 74.
  - 3 cicli di trattamento di 2° livello (pazienti arrivate ad eseguire il Pick up) nei limiti di dosaggio previsti dalla nota AIFA 74.

Circa l'età di accesso per le donne, essa viene determinata come sopra riportato in quanto si ritiene opportuno tener conto dell'aspettativa di vita in crescita, degli sviluppi della ricerca scientifica e quindi dare una maggiore opportunità alle donne.

### Variability of female reproductive ageing
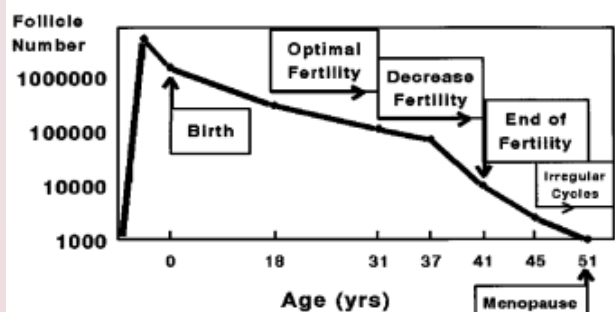


## Solar activity at birth predicted infant survival and women's fertility in historical Norway

Gine Roll Skjærvø†, Frode Fossøy and Eivin Røskaft

Department of Biology, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

Molecular Aspects of Medicine 38 (2014) 54–85

Contents lists available at SciVerse ScienceDirect

### Molecular Aspects of Medicine
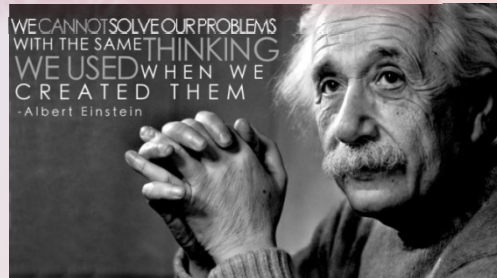
journal homepage: www.elsevier.com/locate/mam

Review

## The root of reduced fertility in aged women and possible therapeutic options: Current status and future perspects

Jie Qiao[a,1], Zhen-Bo Wang[b,1], Huai-Liang Feng[c,1], Yi-Liang Miao[d], Qiang Wang[e], Yang Yu[a], Yan-Chang Wei[b], Jie Yan[a], Wei-Hua Wang[f], Wei Shen[g], Shao-Chen Sun[h], Heide Schatten[i], Qing-Yuan Sun[b,*]

| Aged | |
|------|------|
| 20-24 | 86% |
| 25-29 | 78% |
| 30-34 | 63% |
| 35-39 | 52% |
| 40-44 | 36% |
| 45-49 | 5% |

# INTRODUCTION



WE CANNOT SOLVE OUR PROBLEMS WITH THE SAME THINKING WE USED WHEN WE CREATED THEM
-Albert Einstein

## The poor responder in IVF: is the prognosis always poor? A systematic review

J.F. Oudendijk[1], F. Yarde[1], M.J.C. Eijkemans[1], F.J.M. Broekmans[1], and S.L. Broer[1,*]

## Ovarian Reserve Test: An Impartial Means to Resolve the Mismatch Between Chronological and Biological Age in the Assessment of Female Reproductive Chances

Salvatore Gizzo, MD[1], Alessandra Andrisani, MD, PhD[1], Federica Esposito, MD[1], Alessandra Oliva, BS[1], Cecilia Zicchina, BS[1], Denise Capuzzo, MD[1], Michele Gangemi, MD[1], and Giovanni Battista Nardelli, MD[1]

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**NO BIOMARKERS TO PREDICT THE SUCCESS OF ART TREATMENTS
IN TERM OF QUALITATIVE / QUANTITATIVE OOCYTES AND EMBRYOS COLLECTION
ARE AVAILABLE**

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Reproductive BioMedicine Online (2011) 22, 140–147

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ARTICLE

## Circulating concentration of stem cell factor in serum of stimulated IVF patients

Ali Salmassi *, Sandy Zorn, Liselotte Mettler, Kerstin Koch, Walter Jonat, Andreas G Schmutzler

Centre for Reproductive Medicine, Women's Hospital, Christian-Albrechts-University, Arnold-Heller Str. 3, House 24, 24105 Kiel, Germany
* Corresponding author. E-mail address: asalmassi@email.uni-kiel.de (A Salmassi).
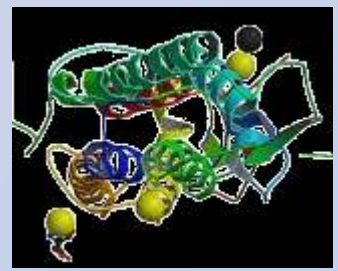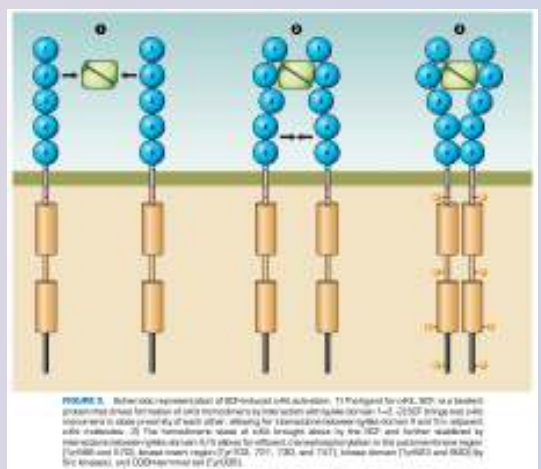
## SCF (STEM CELL FACTOR)

Pleiotropic cytokine with a molecular weight of 25–36 Kd that accomplish an effect on the target cells via the c-kit receptor, a tyrosine kinase receptor.

**ACTIONS**

Data from human experimental studies investigating the expression patterns of SCF and c-kit in the ovary, as well as the actions of SCF on oocytes and theca cells, suggested that SCF may be important for many stages of follicular development and oocytes maturation

SCF may be a candidate biomarker for the prediction of the success of a controlled ovarian hyperstimulation (COH) before ovulation induction and oocyte pick up?

Raffi F et al J Clin Endocrinol Metab, September 2012        Hu R et al Fertil Steril. 2014

# AIM OF THE STUDY

TRANSLATIONAL BIOMEDICAL RESEARCH

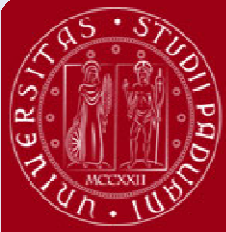**Effects of Recombinant Human AMH on SCF Expression in Human Granulosa Cells**

Rong Hu · Yan Lou · Fei-Miao Wang ·
Hui-Ming Ma · Xing Wu · Xiao-Mei Zhang ·
Juan Li · Ying-Pu Sun

## Antimüllerian hormone regulates stem cell factor expression in human granulosa cells

Rong Hu, Ph.D.,[a,b] Fei-miao Wang, M.D.,[a] Liang Yu, Ph.D.,[b] Yan Luo, M.D.,[a] Xin Wu, B.Sc.,[a] Juan Li, M.D.,[a] Xiao-mei Zhang, Ph.D.,[c] Sergio Oehninger, M.D., Ph.D.,[b] and Silvina Bocca, M.D., Ph.D.[b]

**TO EVALUATE IF THE SERUM CONCENTRATION OF STEM CELL FACTOR BEFORE OVULATION INDUCTION MAY BE CONSIDERED A NEW TOOL TO ESTABLISH WHETHER TO PERFORM FOLLICLE ASPIRATION OR NOT IN ELDERLY POOR RESPONDERS PATIENTS UNDERGOING IVF CYCLE**

**TO ACHIEVE THIS EVIDENCE, WE EVALUATED IF DIFFERENT PROTOCOLS OF OVARIAN STIMULATIONS MAY SIGNIFICANTLY INFLUENCE FOLLICULAR LEVELS OF SCF AND FURTHER IF THESE LEVELS MAY REFLECT THOSE OF SERUM**

# MATERIALS & METHODS

Pilot-observational-cohort study on 37 elderly infertile patients scheduled for IVF treatment at Padua University

**Inclusion criteria**

**43 to 50 years**
Estimated poor responders according to biochemical and sonographic features collected during ovarian reserve testing, as suggested by Bologna Criteria

**Exclusion criteria**

history of smoking within the previous 12 months, deep endometriosis/endometrioma, abnormal karyotype, mutations of the cystic fibrosis gene, acquired or inherited thrombophilia and immunological disorders, previous chemo and/or radio therapy for neoplasia, untreated uterine disease, patients who received low-dose aspirin during treatment and cases in which oocyte retrieval was cancelled due to insufficient ovarian response

**S-COH** group: Patients were firstly treated by standard-protocol - long-agonist-protocol and recombinant-FSH (starting dose of 300 IU) -

**LH-COH** group: (in case of treatment failure) patients were secondly treated by LH-protocol within 6 months after previous cycle - different from S-COH only for the rLH supplementation (150 UI starting from the fourth day of rFSH administration).
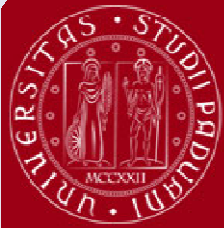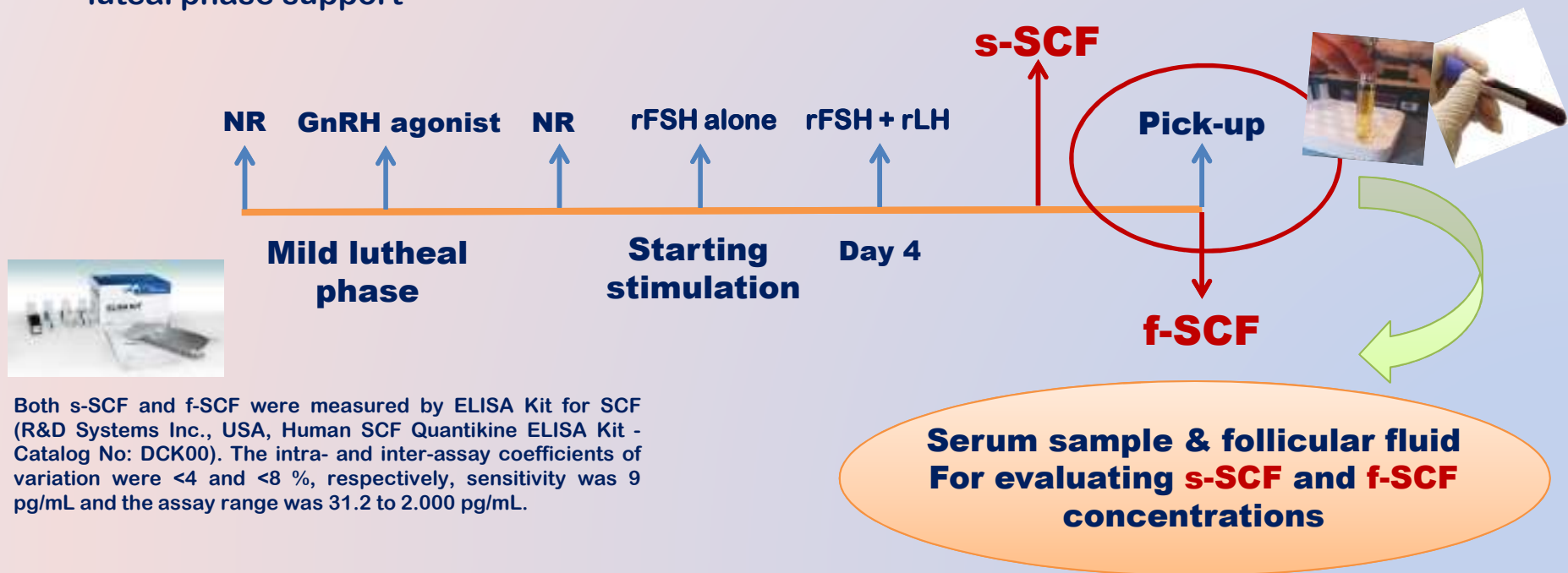
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# MATERIALS & METHODS

- Gonadotropin doses were adjusted according to biochemical and sonographic features of ovarian response beginning from stimulation day 5.

- When at least 3 follicles exceeded 16 mm in diameter (or at least 1 follicle larger than 18 mm) were observed on transvaginal sonography, we administrated rhCG 250 for ovulation induction

- All retrieved oocytes were fertilized by ICSI tecnique

- All patients received high dose progesterone supplementation (600mg vaginally and 100 mg intramuscular for day) in association with valerate E2 (2mg vaginal tablet twice daily) for luteal phase support

s-SCF

| NR | GnRH agonist | NR | rFSH alone | rFSH + rLH | | Pick-up |

**Mild lutheal phase**  **Starting stimulation**  Day 4

f-SCF

Both s-SCF and f-SCF were measured by ELISA Kit for SCF (R&D Systems Inc., USA, Human SCF Quantikine ELISA Kit - Catalog No: DCK00). The intra- and inter-assay coefficients of variation were <4 and <8 %, respectively, sensitivity was 9 pg/mL and the assay range was 31.2 to 2.000 pg/mL.

**Serum sample & follicular fluid For evaluating s-SCF and f-SCF concentrations**

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# RESULTS

| | NUMBER OF PATIENTS | MINIMUM | MAXIMUM | MEAN | STD. DEVIATION |
|---|---|---|---|---|---|
| Age | 37 | 44 | 48 | 45.32 | 1.12 |
| Basal FSH | 37 | 7.8 | 19.1 | 13.23 | 3.34 |
| Basal AFC | 37 | 1 | 7 | 4.01 | 2.12 |
| Basal AMH | 37 | 0.1 | 0.5 | 0.219 | 0,12 |

**Table 1.** Data regarding patients general features and ovarian reserve test before IVF treatments

**135 MII OOCYTES RETRIEVED**
**FERTILIZATION RATE OF 74.8%**
**TOTAL 101 EMBRYOS**
**OF WHICH**
**38 (37.6%) GRADE 1**
**45 (44.6%) AS GRADE 2**
**18 (17.8%) AS GRADE 3**

| | NUMBER OF PATIENTS | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| f-SCF pg/mL | 72 | 153 | 1068 | 658.64 | 232.120 |
| s-SCF pg/mL | 72 | 224 | 1097 | 753.39 | 245.055 |
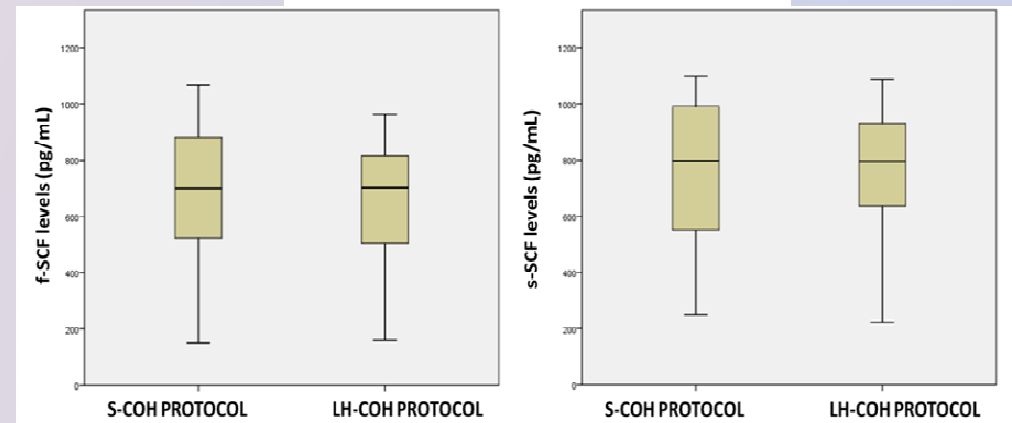


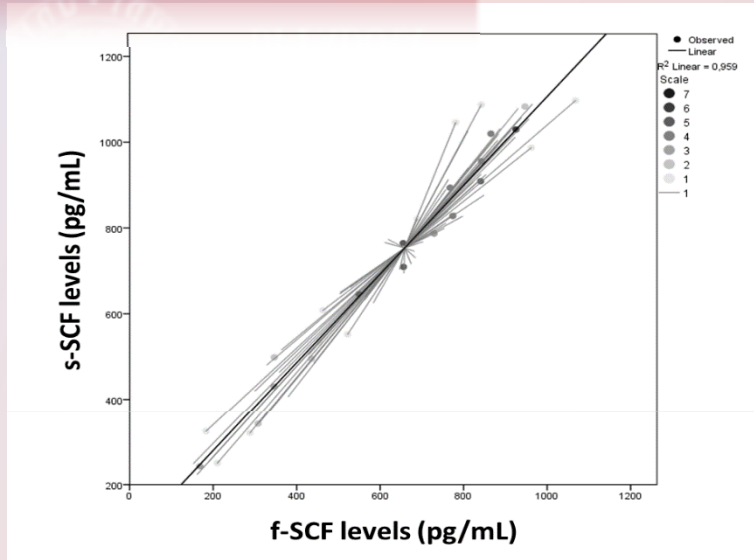**Figure 1.** Comparison between **S-COH** and **LH-COH** treatments in term of both **f-SCF** and **s-SCF** levels.
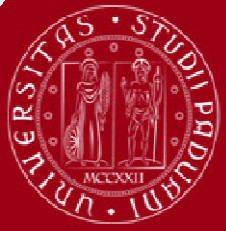
**Figure 2.** Comparison between f-SCF and s-SCF levels using a linear correlation (cases were paired using a chromatic grey scale for number of events).
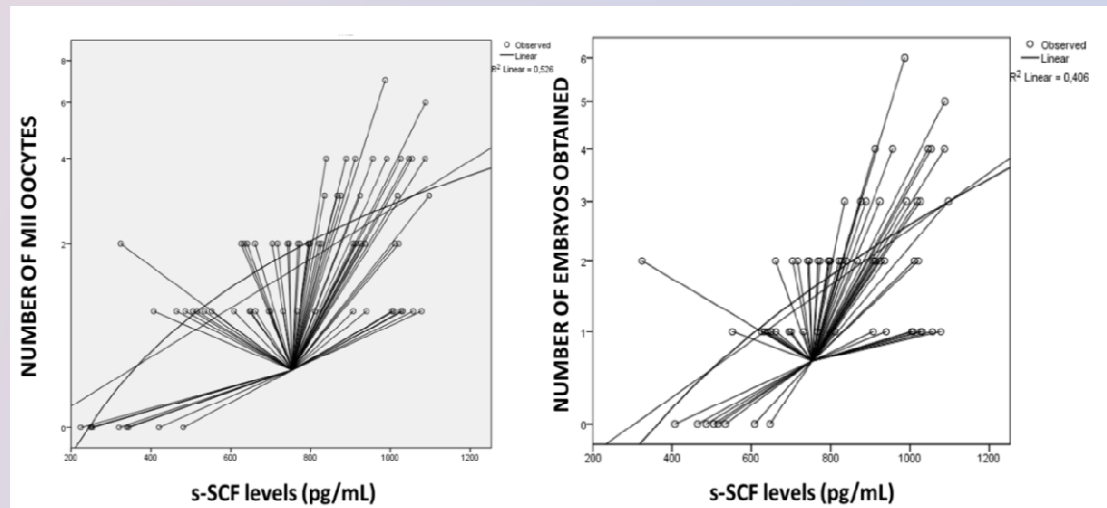


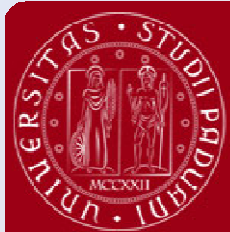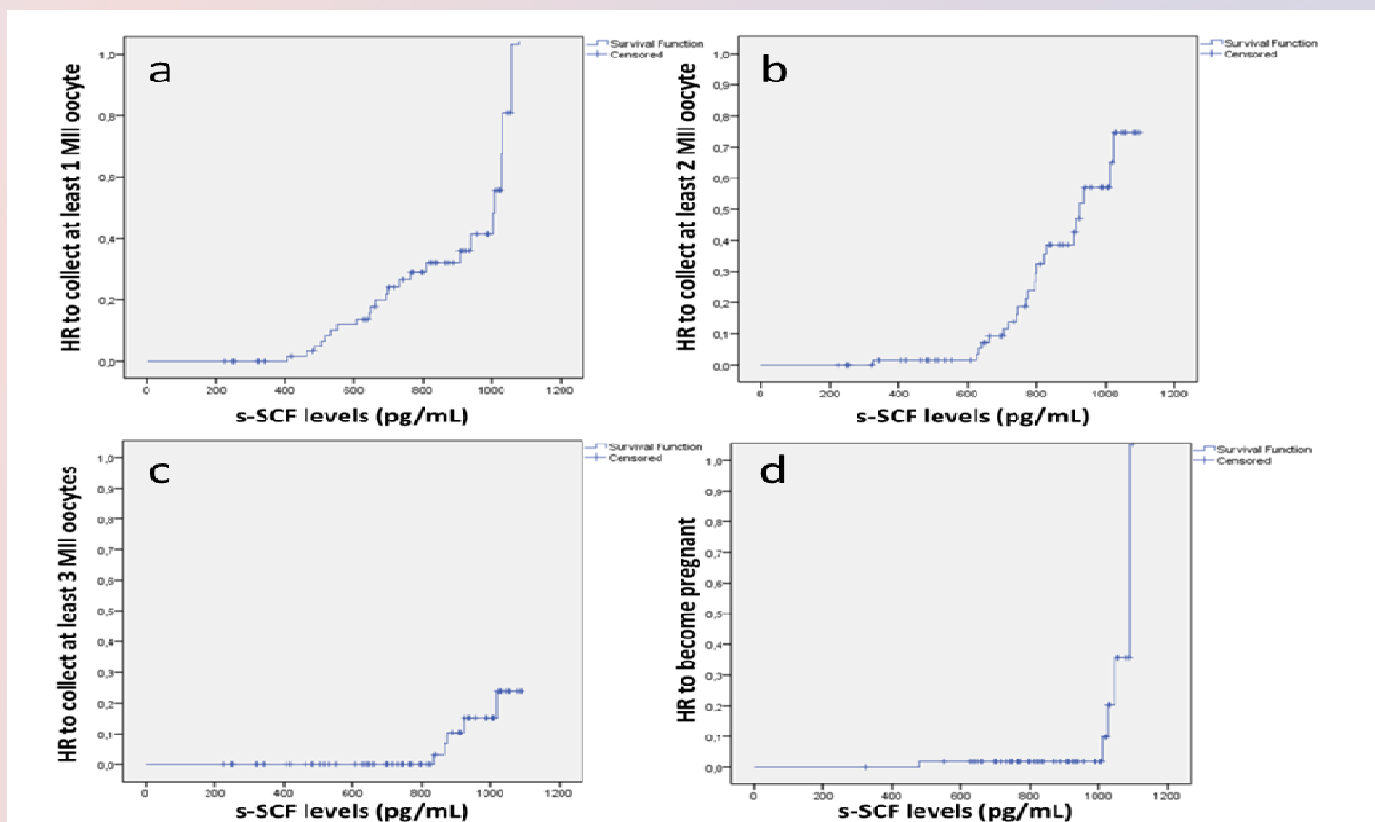**Figure 3.** Stratification of MII oocytes retrieved and embryos obtained for s-SCF value.
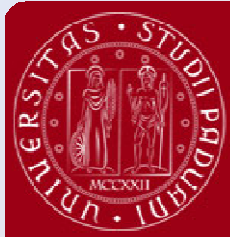
# RESULTS

**Figure 4.** Kaplan-Meier estimator curves for the estimation of events of
**at least 1, (fig 4a) 2 (fig 4b) or 3 (fig 4c) MII oocytes retrieved**
and **pregnancy establishment (fig 4d)**
(**s-SCF** levels were used as a time function factors).

## ...TO SUM UP

- **S-COH** and **LH-COH** did not show statistical differences in term of **f-SCF** and **s-SCF** concentrations.

- On the contrary **f-SCF** and **s-SCF** levels showed a strong linear correlation. [$p<0.001$]

- Estimating the chance of collecting MII-oocytes we found that:

  - At least **3 MII-oocytes** was collected with **s-SCF>800pg/mL**
  - At least **2 MII-oocytes** was collected with **s-SCF>600pg/mL**
  - At least **1 MII-oocytes** was collected with **s-SCF>400 pg/mL**
  - With **s-SCF<400 pg/mL** was not recovered MII-oocytes.

- Finally we found that all the **5 obtained pregnancies** (6.9% of all treatments and 8.9% of treatmentswith transfer of at least 1 embryo) occurred in patients with **s-SCF values >1000 pg/mL** at pick-up.

# CONCLUSIONS

**THE COHORT OF ELDERLY POOR RESPONDER PATIENTS ASKING FOR AUTOLOGOUS IVF WILL INCREASE IN THE NEXT FUTURE DUE TO**

➢ **THE EXPECTED INCREASING POPULAR TREND OF DELAYING FIRST PREGNANCIES**

➢ **THE PERSISTENCE OF LEGAL, POLITICAL, CULTURAL AND RELIGIOUS BARRIERS TO OOCYTE DONATION, (IN SOME COUNTRIES IS STILL UNAVAILABLE)**

**THE INTRODUCTION OF S-SCF ASSAY IN THE ROUTINE MANAGEMENT OF ELDERLY POOR RESPONDER PATIENTS MAY CONTRIBUTE TO SOLVE THE DILEMMA OF WHETHER TO CANCEL OR CARRY ON THE STIMULATION CYCLE**

**THIS IS CRUCIAL TO SAVE THE COUPLE AN UNNECESSARY FINANCIAL AND EMOTIONAL BURDEN**
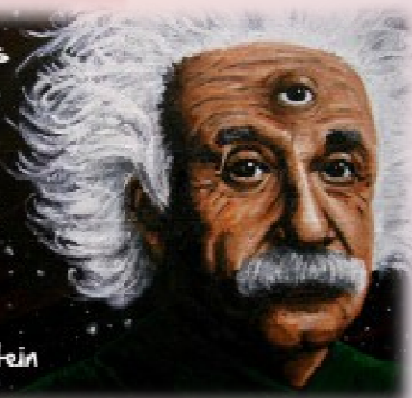
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**… THANKS FOR THE ATTENTION…**

"I believe in intuitions and inspirations...

I sometimes FEEL that I am right"

Albert Einstein

Prato Della Valle, Padova

Obstetrics and Gynecology Clinic, University of Padova