Archives of Gynecology and Obstetrics (2019) 300:441–446
https://doi.org/10.1007/s00404-019-05156-2

A predictive formula for selecting individual FSH starting dose based on ovarian reserve markers in IVF/ICSI cycles

Mengchen Zhu[1] · Shanshan Wang[1] · Shanling Yi[1] · Xiaomin Huang[1] · Junan Meng[1] · Li Chen[2] · Haixiang Sun[1] · Jianjun Zhou[1]

Received: 29 October 2018 / Accepted: 6 April 2019 / Published online: 11 April 2019

Abstract

Background Although exogenous follicle-stimulating hormone (FSH) has been used for decades and millions of cycles have been performed worldwide until now, criteria for selecting the proper FSH starting dose have not been clearly identified. The aim of this study was to elaborate a formula based on markers of ovarian reserve for the calculation of the appropriate starting dose of FSH.

Methods A total of 931 patients underwent in vitro fertilization (IVF) treatment using long GnRH agonist protocol was retrospectively identified and reviewed. 673 cases of them with a normal ovarian response (4–14 retrieved oocytes) were used to analysis the predictive formula. All follicles 4–7 mm in diameter were counted in the same day of blood sample in both ovaries using transvaginal ultrasound scan. The modified protocol of each patient was recorded and analyzed in the same center. In another center were the numbers of retrieved oocytes of 750 validated patients recorded and analyzed.

Results A formula model based on age, AMH, and antral follicle count (AFC) was able to accurately predict the ovarian sensitivity and accounted for 57.2% of the variability of ovarian response to FSH. When tested in the same total population used to elaborate the model it predicts a high 46.88% rate of step-down protocol in higher-starting FSH dose group and about 57.92% of patients had their dose step-up modified in lower-starting FSH dose group during their treatment, respectively. And when tested in different population from another center used to elaborate the model it predicts a high 64.40% rate of ≥ 15 retrieved oocytes in higher-starting FSH dose group and about 22.50% of patients had ≤ 7 retrieved oocytes in lower-starting FSH dose group during their treatment, respectively.

Conclusions In the present study we demonstrated that the individualized FSH starting dose may be calculated on the basis of a woman's age, AMH and AFC. The formula model might be a useful, immediate, and easily applicable tool for clinicians to predict the tailored starting dose of FSH during their daily clinical practice.

Keywords Age · AMH · AFC · Ovarian reserve · Starting FSH dose

Introduction

The aim of controlled ovarian stimulation (COS) in vitro fertilization and embryo transfer (IVF-ET) is mainly to stimulate multiple follicle development for achieving the optimum number of oocytes in a single cycle, which is defined as 8–14 [1–3]. A poor ovarian response will cause higher

Mengchen Zhu and Shanshan Wang have contributed to the work equally and should be regarded as co-first authors.

Haixiang Sun and Jianjun Zhou should be regarded as co-corresponding authors.

✉ Haixiang Sun
zhou6jj@126.com

✉ Jianjun Zhou
zhou6jj@hotmail.com

[1] Reproductive Medicine Center, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Zhongshan North Road 53, Nanjing 210008, Jiangsu, People's Republic of China

[2] Reproductive Medical Center of Nanjing Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, Jiangsu, People's Republic of China

cycle cancellation rate and lower pregnancy rate, a hyper-ovarian response may contribute to higher risks of ovarian hyperstimulation syndrome and fresh embryo transfer cancellation rate. Ovarian response to gonadotrophin stimulation differs from each other [4]. In clinical practice, it is the most important decision in the planning of IVF cycles to choose suitable gonadotrophin doses for each patient [5–7]. The individualized therapy tailored on patients' own characteristics allows a high chance of good pregnant outcome and minimizes risks of ovarian stimulation. The use of exogenous follicle-stimulating hormone (FSH) to promote multiple follicle development is important in ART. Although exogenous FSH has been used for decades and millions of cycles have been performed worldwide until now, criteria for selecting the proper FSH starting dose have not been clearly identified [5].

Clinicians usually choose the FSH starting dose according to their clinical experience. Age of patient, body mass index (BMI) and markers of ovarian reserve will be mostly considered if there was no precious IVF perform [4, 8]. Serum FSH, anti-Müllerian hormone (AMH), and antral follicle count (AFC) are currently accepted predictive markers for ovarian reserve. AMH and AFC have the best performance in predicting ovarian response to exogenous FSH [9–13]. AMH is synthesized by granulose cells located on ovarian follicles and a good marker of predicting ovarian response because of low intercentres' variability [14–16]. AFC could reflect the remaining ovarian follicle pool as the pool of primordial follicles is related to the number of growing antral follicles [17–19]. Basal FSH will increase to force the aging ovary to respond as a woman ages and measurable increase of FSH can be detected 5 years earlier than menopause in some women [20].

The aim of this article was to investigate whether it was possible to develop a formula based on characteristics of IVF patient and markers of ovarian reserve that would be able to make an appropriate exogenous FSH starting dose suggestion for patients undergoing IVF treatment.

Methods

In this retrospective observation study, 931 randomly selected women who underwent IVF treatment from January 2015 to December 2016 at the Reproductive Medicine Center of Nanjing Drum Tower Hospital were recruited. 673 cases of them with a normal ovarian response (4–14 retrieved oocytes) were used to analyze the predictive formula model. This study was approved by the Nanjing Drum Tower Hospital Research Ethics Committee. Additionally, another 750 women who underwent IVF treatment from April 2015 to December 2016 at the Reproductive Medical Center of Nanjing Jinling Hospital were recruited in this study to verify the feasibility of this formula model. Informed consent was provided by all subjects at recruitment.

All patients were treated with a long GnRH agonist protocol and stimulation with recombinant FSH for controlled ovarian stimulation. The starting FSH dose was chosen based on clinician's clinical experience. Follicular growth was monitored and FSH doses were adjusted using transvaginal ultrasound and estradiol (E2) measurement. The dose was increased on day 5 or 7 of stimulation if a lower ovarian response (low serum E2 level or less follicles) was observed. This is considered as a step-up protocol. Similarly, step-down protocol was considered as dose decrease if follicular growth continued fast in patients with high serum E2 levels on day 5 or 7 of stimulation thereafter. Constant FSH doses were sustained until the day human chorionic gonadotropin (hCG) induce final follicular maturation based on normal follicular growth, which was considered a constant protocol. Then 5000–10,000 IU hCG was administered to induce final follicular maturation when two or more follicles reaching ≥ 18 mm in diameter were observed. The oocyte retrieval procedures were performed under transvaginal ultrasound guidance 34–36 h after hCG administration. The IVF/intracytoplasmic sperm injection (ICSI) performances were carried out 4–6 h after oocyte retrieval. One or two embryos at 2 pronuclei (PN) embryo stage, 18–20 h after insemination, 7–12 cells stage at day 3, and $< 15\%$ fragmentation stage were selected to transfer into the uterine cavity under ultrasound guidance on day 3 after oocyte retrieval. Luteal support was carried out for 10 weeks from the day of oocyte retrieval with progesterone. Patients with high risk of OHSS were cancelled for fresh embryo transfer. Clinical pregnancy was defined as vaginal ultrasound check of the fetal cardiac activity after 4 or 5 weeks of oocyte retrieval and a live birth was defined as a birth accompanying any sign of life irrespective of the weeks of gestation according to the World Health Organization.

Hormone assay and AFC measurement

Blood samples were taken in the early follicular phase (day 3) prior to any IVF-related drug administration. Serum AMH was measured using the Elecsys® AMH electro-chemiluminescence immunoassay on an automated analyzer (cobas; Roche Diagnostics International, Ltd.). The standards cover a range of 0–23 ng/ml. The assay sensitivity was 0.01 ng/ml. Serum FSH was measured by an automatic chemiluminescence immunoassay analyzer (Beckman Coulter UniCel DXI800, Brea, CA, USA) and the corresponding reagents, calibration materials, and quality control materials. For the FSH assay (Access hFSH, cat. no. 33520; Beckman Coulter), the intra-assay and total coefficients of variation were below or equal to 4.3% and 5.6%, respectively. All follicles 4–7 mm in diameter were counted in the same day of blood

sample in both ovaries using transvaginal ultrasound scan. The total counts of follicles in both ovaries were considered as the AFC.

Statistical analyses

The SPSS 21.0 was used for statistical analysis. Normally distributed variables were presented as mean and standard deviation. Categorical variables were depicted by frequency and percentage. Ratios were compared using Chi-squared tests. Binary correlation was used to identify the independent factors that affect the starting FSH dose. Then the variables predictive of the starting FSH dose were analyzed by backwards stepwise multiple linear regression. Backward selection of parameters was applied using Wald $P < 0.05$ for entry and $P > 0.1$ for removal. Then the variables reaching the statistical significance in multiple linear regression analysis were used in calculation for the final formula model elaborated to suggest the appropriate starting dose of FSH needed to achieve the desired response. Regression coefficients for each variable were incorporated in a multiple linear regression equation.

Results

Among 931 women who underwent IVF–ET treatment with a long GnRH agonist protocol were enrolled in this retrospective study, 673 of them with a normal ovarian response (4–14 oocytes retrieved) were used to access a multiple linear regression analysis equation. Total 931 patients' characteristics are reported in Table 1.

Results of binary correlation and multiple linear regression analysis with the starting FSH dose as a dependent variable are shown in Tables 2 and 3. The binary correlation analysis showed that the starting FSH dose was significantly predicted by AMH, AFC, age of female and basal FSH levels; however, in multiple linear regression analysis the statistical significance was reached only for AMH, AFC, and age. The model based on multiple linear regression analysis accounts for 57.2% of the variability of starting FSH dose ($R^2 = 0.574$; R^2-adjusted: 0.572). Formula was concluded from the multiple linear regression analysis as follows: $S = 2.398A_1 - 7.653A_2 - 1.994A_3 + 252.062$, where S is the starting FSH dose, A_1 is age of female, A_2 is antral follicle count (AFC) and A_3 is anti-Müllerian hormone (AMH).

According to the predicted formula model, the dose of starting FSH will be increased with decrease of AFC and AMH, increasing age of female. Total 931 patients were divided into three groups depending on the difference between the practical starting FSH dose and the formula-derived starting FSH dose. Higher-starting FSH dose group (group A1), the practical-starting FSH dose – the formula-derived starting FSH dose ≥ 37.5 IU; appropriate-starting FSH dose group (group B1), − 37.5IU < the practical-starting FSH dose – the formula-derived starting FSH dose < 37.5 IU; lower-starting FSH dose group (group C1), the practical-starting FSH dose – the formula-derived starting FSH dose ≤ − 37.5 IU. In higher-starting FSH dose group (group A1), there was a high rate of step-down protocol (46.88%), and step-up protocol only accounted for 19.79%. And in lower-starting FSH dose group (group C1), there was a high step-up protocol rate (57.92%) and a low step-down protocol rate (16.83%). Three gonadotrophin therapy protocols accounted for about 30–40% in appropriate-starting FSH dose group (group B1) equally (Table 4).

Table 1 Patients characteristics

Variables	$n = 931$
Age (years)	29.73 ± 4.34
BMI (kg/m^2)	22.41 ± 3.12
AMH	4.68 ± 3.53
AFC	17.29 ± 6.19
Basal FSH levels (IU/L)	6.92 ± 2.28
Basal LH levels (IU/L)	5.85 ± 4.59
Duration of stimulation (days)	10.95 ± 2.59
Total FSH administered (IU)	2076.61 ± 842.40
No. of retrieved oocytes	11.72 ± 4.82
No. of good-quality embryos	4.39 ± 2.50
Clinical pregnancy rate (%)	74.13% (490/661)
Live birth rate (%)	62.34% (399/640)

Table 2 Predictors of starting FSH dose in binary correlation analysis

	R	*P*
AMH	− 0.529	< 0.001
AFC	− 0.741	< 0.001
Age (years)	0.351	< 0.001
Basal FSH levels (IU/L)	0.209	< 0.001
BMI (kg/m^2)	0.020	NS

NS difference not statistically significant ($P > 0.05$), *BMI* body mass index

Table 3 Predictors of starting FSH dose in multiple linear regression analysis

	Regression coefficient	*P*
AMH	− 1.994	0.009
AFC	− 7.653	< 0.001
Age (years)	2.398	< 0.001
Basal FSH levels (IU/L)	0.032	NS

NS difference not statistically significant ($P > 0.05$)

Table 4 Comparison of patients' gonadotrophin therapy protocol of three groups derived from formula

	Step-up protocol	Step-down protocol	Constant protocol	*P*
Group A1	19.79% (38/192)	46.88% (90/192)	33.33% (64/192)	< 0.001
Group B1	40.11% (215/536)	30.78% (165/536)	29.10% (156/536)	< 0.001
Group C1	57.92% (117/202)	16.83% (34/202)	25.25% (51/202)	< 0.001

Table 5 Patients' characteristics for verification of the feasibility of starting FSH dose formula

Variables	*n* = 750
Age (years)	29.30 ± 3.99
BMI (kg/m^2)	22.92 ± 3.33
AMH	5.11 ± 3.65
AFC	19.93 ± 9.12
Basal FSH levels (IU/L)	6.95 ± 3.01
Basal LH levels (IU/L)	5.34 ± 5.96
Duration of stimulation (days)	9.38 ± 1.41
Total FSH administered (IU)	1747.40 ± 754.37
No. of retrieved oocytes	13.97 ± 5.84
No. of good-quality embryos	4.55 ± 3.18

Then another 750 randomly selected women who underwent IVF treatment from April 2015 to December 2016 at the Reproductive Medical Center of Nanjing Jinling Hospital were recruited to verify the feasibility of this formula model. These patients were also treated with a long GnRH agonist protocol and stimulation with recombinant FSH for controlled ovarian stimulation. Total 750 patients' characteristics are shown in Table 5. Then total 750 patients were also divided into three groups according to the difference between the practical-starting FSH dose and the formula-derived starting FSH dose. Higher-starting FSH dose group (group A2), the practical-starting FSH dose—the formula-derived starting FSH dose ≥ 37.5 IU; appropriate-starting FSH dose group (group B2), − 37.5 IU < the practical-starting FSH dose – the formula-derived starting FSH dose < 37.5 IU; lower-starting FSH dose group (group C2), the practical-starting FSH dose – the formula-derived starting FSH dose ≤ − 37.5 IU. The higher-starting FSH dose group (group A2) has the highest rate of ≥ 15 retrieved oocytes (64.40%) and lowest rate of ≤ 7 retrieved oocytes (6.2%) among these three groups. And the ≤ 7 retrieved oocytes rate was 22.5% in lower-starting FSH dose group (group C2), which was highest in these three groups. The rate of optimal number of retrieved oocytes (8–14) was 46.5% in appropriate-starting FSH dose group (group B2). (Table 6).

Discussion

GnRH agonist protocol is widely used in clinical practice in both normal and abnormal ovarian responsders. To accommodate modern trends of milder stimulation, individualization of IVF treatment strategies in women undergoing their IVF cycles seems to be more crucial. Several observations clearly indicate that a standard fixed dose of FSH is not be suitable for all women undergoing IVF treatment [21–26] and the starting dose of FSH in IVF cycles should be individualized. Results of the present study of recombinant FSH have clearly shown that ovarian response to FSH mainly depends on female age and the status of ovarian reserve [27, 28]. Indeed, in our present study starting-FSH dose formula was based on three common markers of ovarian reserve: age, serum AMH and AFC. With age increase, the quantity and quality of oocytes decline, which contributes to decreased clinical pregnancy and obvious increased incidence of infertility in IVF treatment, correspondingly [29]. AFC is related to the number of growing antral follicles which are linked with IVF success [17–19]. Additionally, AMH is currently the most commonly used serum biomarker to predict ovarian reserve because of good stability and low variability [14–16].Therefore an accurate measurement of ovarian reserve and selection of appropriate-starting FSH dose are clearly two important points for the individualization of IVF treatment strategies. An accurate measurement of ovarian reserve will give the clinicians a useful tool to make individual IVF treatment, while tailored therapy based on age and markers of ovarian reserve seems to be an agreed-upon approach by the majority.

Table 6 Comparison of patients' oocytes retrieved of three groups derived from formula

No. of retrieved oocytes	≤ 7	8–14	≥ 15	*P*
Group A2	6.2% (11/177)	29.4% (52/177)	64.4% (114/177)	< 0.001
Group B2	10.1% (41/404)	46.5% (188/404)	43.3% (175/404)	< 0.001
Group C2	22.5% (38/169)	61.5% (104/169)	16.0% (27/169)	< 0.001

Several complex models have been described to estimate the starting dose of FSH with patient characteristics such as age and ovarian reserve [4, 22, 27, 30]. However, the formula model we designed may be considered more useful than those preciously created for following several reasons: a Poppler score of ovarian stromal blood flow was included in the nomogram by Poporic-Todororic et al. [22], which was not easily measured in daily clinical practice. The nomogram by La Marca et al. [27] allows clinicians to modulate the starting FSH close according to the number of retrieved oocytes. Actually, the number of retrieved oocytes could be largely affected by many factors, and different races differ in genetic background. Nevertheless, not only do AMH and AFC have good stabilities, but also the formula we created is only based on three common markers of ovarian reserve: age, AMH and AFC. The R^2-adjusted of model by La Marca et al. was only 0.30. However, the R^2-adjusted in simple formula model we created reached 0.57. This result means that our formula model seems to have a higher accuracy. Additionally, when tested in the same total population used to elaborate the model it predicts a high 46.88% rate of step-down protocol in higher starting-FSH dose group and about 57.92% of patients had their dose step-up modified in lower-starting FSH dose group during their treatment. All these figures indicate that the formula model we created not only has a higher efficacy for predicting the starting FSH dose but also is a simply tool including only three common markers measured easily. They also indicate that the proposed formula seems to be a possible tool for personalizing IVF treatment with reducing patients' gonadotrophin therapy protocol variability derived from clinical experience.

The number of retrieved oocytes is a relevant prognostic indicator in women undergoing in IVF cycles, and the optimal rather than maximum number of oocytes is the preferred achievement after controlled ovarian stimulation in a single cycle. The optimal number of oocytes was defined as the range of 8–14 in some large trials [3, 31, 32]. To elaborate a formula based on markers of ovarian reserve for the calculation of the appropriate starting dose of FSH so as to get a normal ovarian response, only the normal response women group was included to develop the predictive algorithm. However, when verifying the feasibility of this formula model all the kinds of ovarian response women were included: normal ovarian response, poor ovarian response and high ovarian response. In this study, when tested in different total 750 population from another center used to elaborate the formula model it predicts a highest 64.40% rate of ≥ 15 retrieved oocytes and a lowest 6.2% rate of ≤ 7 retrieved oocytes in higher-starting FSH dose group among these three groups. Even the rate of 8–14 retrieved oocytes was lower in appropriate-starting FSH dose group than in lower-starting FSH dose group (46.5% vs. 61.5%), a highest 22.50% rate of ≤ 7 retrieved oocytes were found in lower-starting FSH dose group among three groups during their treatment. These data indicate that clinicians may choose individual FSH starting dose to achieve optimal oocytes retrieved, reducing the rate of high or low ovarian response using the formula model we created.

In conclusion, all the evidences above make the formula model we developed a useful, immediate and easily applicable tool to predict the tailored starting dose of FSH in clinical daily practice. Of course, a good model should assist clinicians to choose appropriate starting-FSH dose with a view to accommodate modern trends of milder stimulation, while maintaining better pregnant outcomes, but minimizing or even removing the complication of ovarian stimulation. The further model validation is needed to clearly demonstrate in larger, prospective, randomized controlled trials whether the use of the formula model can give significant advantages in the outcome of IVF cycle patients.

Author contributions HS protocol/project development. JZ protocol/project development, manuscript correction and revision. MZ protocol/project development, data collection and management, manuscript writing and editing, data analysis. SW data collection and management, manuscript editing, data analysis. SY data collection and management. XH data collection and management. JNM: data collection and management. LC validated data collection and management.

Funding This study was supported by Chinese National Natural Science Foundation (81771537, 81571504, 81200450), Nanjing Medical Science and technique Development Foundation (QRX11166), Maternal and fetus medicine Key Lab of Jiangsu Province (XK 201102, BL2014003).

Compliance with ethical standards

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

References

1. Macklon NS, Stouffer RL, Giudice LC et al (2006) The science behind 25 years of ovarian stimulation for in vitro fertilization. Endocr Rev 27(2):170–207. https://doi.org/10.1210/er.2005-0015
2. Ji J, Liu Y, Tong XH et al (2013) The optimum number of oocytes in IVF treatment: an analysis of 2455 cycles in China. Hum Reprod 28(10):2728–2734. https://doi.org/10.1093/humrep/det303
3. Allegra A, Marino A, Volpes A et al (2017) A randomized controlled trial investigating the use of a predictive nomogram for the selection of the FSH starting dose in IVF/ICSI cycles. Reprod Biomed Online 34(4):429–438. https://doi.org/10.1016/j.rbmo.2017.01.012
4. Howles CM, Saunders H, Alam V et al (2006) Predictive factors and a corresponding treatment algorithm for controlled ovarian stimulation in patients treated with recombinant human follicle stimulating hormone (follitropin alfa) during assisted reproduction technology (ART) procedures. An analysis 1378 patients.

Curr Med Res Opin 22(5):907–918. https://doi.org/10.1185/030079906X104678
5. Fauser BCJM, Diedrich K, Devroey P (2008) Predictors of ovarian response: progress towards individualized treatment in ovulation induction and ovarian stimulation. Hum Reprod Update 14(1):1–14. https://doi.org/10.1093/humupd/dmm034
6. La MA, Sunkara SK (2014) Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update 20(1):124–140. https://doi.org/10.1093/humupd/dmt037
7. Moolenaar LM, Broekmans FJ, Van DJ et al (2011) Cost effectiveness of ovarian reserve testing in in vitro fertilization: a Markov decision-analytic model. Fertil Steril 96(4):889–894. https://doi.org/10.1016/j.fertnstert.2011.06.072
8. Fleming R, Broekmans F, Calhaz-Jorge C et al (2013) Can anti-Mullerian hormone concentrations be used to determine gonadotrophin dose and treatment protocol for ovarian stimulation? Reprod Biomed Online 26(5):431–439. https://doi.org/10.1016/j.rbmo.2012.02.027
9. La MA, Sighinolfi G, Radi D et al (2010) Anti-Mullerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 16(2):113–130. https://doi.org/10.1093/humupd/dmp036
10. Lan VT, Linh NK, Tuong HM et al (2013) Anti-Müllerian hormone versus antral follicle count for defining the starting dose of FSH. Reprod Biomed Online 27(4):390–399. https://doi.org/10.1016/j.rbmo.2013.07.008
11. Al-Azemi M, Killick SR, Duffy S et al (2011) Multi-marker assessment of ovarian reserve predicts oocyte yield after ovulation induction. Hum Reprod. 26(2):414–422. https://doi.org/10.1093/humrep/deq339
12. Broekmans FJ, Kwee J, Hendriks DJ et al (2006) A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 12(6):685–718. https://doi.org/10.1093/humupd/dml034
13. Broekmans FJM, Ziegler DD, Howles CM et al (2010) The antral follicle count: practical recommendations for better standardization. Fertil Steril 94(3):1044–1051. https://doi.org/10.1016/j.fertnstert.2009.04.040
14. Fleming R, Seifer DB, Frattarelli JL et al (2015) Assessing ovarian response: antral follicle count versus anti-Mullerian hormone. Reprod Biomed Online 31(4):486–496. https://doi.org/10.1016/j.rbmo.2015.06.015
15. Iliodromiti S, Anderson RA, Nelson SM (2015) Technical and performance characteristics of anti-Mullerian hormone and antral follicle count as biomarkers of ovarian response. Hum Reprod Update 21(6):698–710. https://doi.org/10.1093/humupd/dmu06
16. Iliodromiti S, Nelson SM (2015) Ovarian response biomarkers: physiology and performance. Curr Opin Obstet Gynecol 27(3):182–186. https://doi.org/10.1097/GCO.0000000000000175
17. Carvalho BRD, Silva JCRE, Reis RMD et al (2008) Ovarian reserve evaluation: state of the art. J Assist Reprod Genet 25(7):311–322. https://doi.org/10.1007/s10815-008-9241-2
18. Broer SL, Mol BW, Hendriks D et al (2009) The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. Fertil Steril 91(3):705–714. https://doi.org/10.1016/j.fertnstert.2007.12.013
19. Broer SL, Dólleman M, Opmeer BC et al (1900) AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 17(1):46–54. https://doi.org/10.1093/humupd/dmq034
20. Lenton EA, Sexton L, Lee S et al (1988) Progressive changes in LH and FSH and LH: FSH ratio in women throughout reproductive life. Maturitas 10(1):35–43
21. Todorovic BP, Loft A, Bredkjæer HE et al (2003) A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. Hum Reprod 18(11):2275–2282
22. Todorovic BP, Loft A, Lindhard A et al (2003) A prospective study of predictive factors of ovarian response in 'standard' IVF/ICSI patients treated with recombinant FSH. A suggestion for a recombinant FSH dosage normogram. Hum Reprod 18(4):781–787
23. Popovic Todorovic B, Loft A, Ziebe S et al (2004) Impact of recombinant FSH dose adjustments on ovarian response in the second treatment cycle with IVF or ICSI in "standard" patients treated with 150 IU/day during the first cycle. Acta Obstet Gynecol Scand 83(9):842–849. https://doi.org/10.1111/j.0001-6349.2004.00573.x
24. Andersen AN, Devroey P, Arce JC (2006) Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum Reprod 21(12):3217–3227. https://doi.org/10.1093/humrep/del284
25. Devroey P, Polyzos NP, Blockeel C (2011) An OHSS-free clinic by segmentation of IVF treatment. Hum Reprod 26(10):2593–2597. https://doi.org/10.1093/humrep/der251
26. Lainas TG, Sfontouris IA, Zorzovilis IZ, Petsas GK et al (2010) Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). Hum Reprod 25(3):683–689. https://doi.org/10.1093/humrep/dep436
27. Marca AL, Papaleo E, Grisendi V et al (2012) Development of a nomogram based on markers of ovarian reserve for the individualisation of the follicle-stimulating hormone starting dose in in vitro fertilisation cycles. BJOG 119(10):1171–1179. https://doi.org/10.1111/j.1471-0528.2012.03412.x
28. Karlsson MO, Wade JR, Loumaye E et al (1997) A population model for the follicular growth in women treated with follicle stimulating hormone. Clin Pharmacol Ther 62(6):665–674. https://doi.org/10.1016/S0009-9236(97)90086-2
29. Abdalla HI, Burton G, Kirkland A et al (1993) Age, pregnancy and miscarriage: uterine versus ovarian factors. Hum Reprod 8(9):1512–1517
30. Olivennes F, Howies CM, Borini A et al (2011) Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study. Reprod Biomed Online 22(Suppl 1):S73–82. https://doi.org/10.1016/S1472-6483(11)60012-6
31. Arce JC, Andersen AN, Fernández-Sánchez M, Visnova H, Bosch E, García-Velasco JA et al (2014) Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 102(6):1633–1640.e5. https://doi.org/10.1016/j.fertnstert.2014.08.013
32. Bosch E, Nyboe AA, Barri P et al (2015) Follicular and endocrine dose responses according to anti-Müllerian hormone levels in IVF patients treated with a novel human recombinant FSH (FE 999049). Clin Endocrinol (Oxf) 83(6):902–912. https://doi.org/10.1111/cen.12864