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ASSISTED REPRODUCTION

The clinical analysis of poor ovarian response in in-vitro-fertilization embryo-transfer among Chinese couples

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Abstract

Purpose To explore the prevalence, predictor of clinical pregnancy and possible aetiology of poor ovarian response (POR) in in vitro fertilization–embryo transfer (IVF–ET) in Chinese.

Methods A total of 4,600 retrieval oocyte cycles were finished between July 1, 2004 and April 30, 2006. Poor ovarian responses were observed in 426 patients of 472 cycles undergoing IVF, which were selected on the same retrieve oocyte day as the control group. The outcome of IVF–ET and the common markers of ovarian reserve were compared.

Results The patients had previous ovarian surgery in 64 cycles of 472 poor ovarian response cycles. The group with poor ovarian response has significant differences in comparison with the control group in age (36.6±4.2 vs 33.3±4.04), ovarian surgeries (13.6 vs 2.8%), dose of gonadotrophin (58.5±15.8 vs 40.6±17.0), fertilization rate (71.5 vs 86%) and pregnancy rate (14.8 vs 36.7%). In the group with poor ovarian responses, clinical pregnancy rate declined significantly in women aged >40 years than in those aged ≤40 years (2.8 vs 18.5%, $P<0.001$). The age, basal serum follicle stimulating hormone (FSH), basal serum luteinizing hormone (LH), basal oestradiol (E2) concentrations, FSH to LH ratio and the antral follicle count (AFC) are the common markers of ovarian reserve in our center. We found that there were significant differences in age, basal FSH, FSH-to-LH ratio and the antral follicle count. But no statistical significant differences were observed in basal oestradiol concentration and basal serum LH when comparing the two groups. Binary logistic regression analysis was used to study the relation among age, FSH, LH, E2, AFC and clinical pregnancy, and the age (odds ratio, 0.863; 95% confidence interval, 0.805–0.925; $p=0.000$) was the only variable selected.

Conclusion Our data show that the prevalence of poor ovarian response in Chinese is 11.9%. Previous ovarian surgery is associated with poor ovarian responses. The pregnancy rate of women with poor ovarian response is low in IVF–ET, especially the decline in clinical pregnancy rate of women aged >40 years became accelerated. Correct identification of those who are at risk for POR prior to stimulation is helpful in tailoring the best stimulation protocol to individual patients. Chronological age significantly improved the prediction of clinical pregnancy of poor ovarian responders.

Keywords In vitro fertilization–embryos transfer · Poor ovarian response · Pregnancy outcome · Predictor

Introduction

Delayed childbearing warrants a continuous focus on the phenomenon of reproductive aging. Aging of the ovary seems to play a key role in this process, which comprises both primordial follicle reduction and oocyte quality deterioration [1]. Poor ovarian response is a significant problem in modern fertility treatment. It is associated with a significant decline in the success rate of fertility treatment.

The remaining follicle pool and its quality are usually referred to as ovarian reserve. Correct controlled ovarian stimulation is of paramount importance in assistant reproductive technologies. Before starting ovarian stimulation, a

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prospective analysis of the ovarian reserve of the patient, correct identification of patients who are at risk for poor response can help physicians to individualize counseling and permit the patients to decide whether to undergo a demanding infertility treatment. Definition of the goals of the ovarian stimulation and selection of the correct stimulation protocol are mandatory [2]. Although it is difficult to standardize the characteristics that categorizes a patient as 'poor responder,' several factors are associated with poor ovarian response, such as age, previous ovarian surgery, pelvic adhesions [3]. The reported prevalence of poor responders amongst patients undergoing IVF–ET is 9–24% [5]. However, it is very difficult to make a more accurate estimation because there is no common definition of poor response [3, 4].

When the standard dose of gonadotrophins fails to induce a proper multifollicular growth, the obvious clinical approach is to increase the dose of gonadotrophins. The daily dose of gonadotrophin increased from 300 to 450 IU can results in an increased pregnancy rate and reduced cancellation rate [6]. But some studies failed to significantly improve ovarian response and clinical outcome [7, 8].

The aim of this study is to investigate the incidence, possible aetiology, and then management about poor ovarian response in in vitro fertilization–embryo transfer (IVF–ET) and the prediction of ongoing pregnancy in Chinese.

Materials and methods

Subjects

Between July 1, 2004 and April 30, 2006, a total of 4,600 retrieval oocyte cycles were finished. Data on 426 subjects who had an ovum pickup in a total of 472 IVF/ICSI cycles were collected from the IVF UNIT of Peking University Third Hospital. Data were obtained on a retrospective analysis. At present, there is no consensus on the definition of poor ovarian response. The most widely used classification is based on the number of collected oocytes and therefore we also used the same criteria. At a mean fertilization rate of 50–60% in IVF, we defined poor ovarian response as: collection of fewer than 4 oocytes at retrieval and the dose of gonodortrophins higher than 3,000 IU in this study, The patients were selected on the same day of oocyte pick-up and the collection of more than 4 oocytes and less than 15 oocytes at retrieval as the control group.

The patients were analyzed in groups based on their main cause of infertility: tubal factor, male factor, unexplained infertility, endometriosis. There are no significant difference in the causes of the two groups. The main characteristics of patients for each group are summarized in Table 1.

Ovarian stimulation

A long GnRH agonist (GnRH-a) protocol or A short GnRH agonist protocol was used for pituitary down-regulation. Briefly, GnRH-a was started on days 21–23 of the previous cycle or commenced on day 2 of the treatment cycle in both groups, ovarian stimulation was performed with urinary and/or recombinant gonadotropins. Just before administration of the first gonadotropins dose, the total number of antral follicles measured 2–8 mm in both ovaries was counted. Four hundred seventy-two cycles of poor ovarian response adopted short GnRH agonist protocol, the poor ovarian group discontinued GnRH-a on day 6–7 after stimulation. In the control group, short GnRH agonist protocol was used for pituitary down-regulation in 390 cycles whereas long GnRH agonist in 82 cycles.

The two groups started gonadotropins on day 3 of their treatment cycle. The choice of gonadotropins, i.e. recFSH and hMG, was taken by the patient and was entirely

Table 1 Characteristics of subjects, stimulation, and outcome variables

Variable	Poor responders (n=472)	Normal responders (n=472)
Mean(±SD) age	36.6±4.2	33.3±4.04*
Mean (±SD)duration of infertility	7.23±4.9	7.02±4.8
No.(%) of patients with primary infertility	287(60.8%)	282(59.7%)
No.(%) of patients with indicated infertility diagnosis		
Tubal factor	254(53.8%)	261(55.3%)
Male factor	99(21%)	112(23.7%)
Unexplained	49(10.4%)	59(12.5%)
Endometriosis	70(14.8%)	40(8.5%)
Previous ovarian surgery(%)	64(13.6%)	13(2.8%)*
Mean (±SD) day 2 FSH level (IU/l)	11.8±5.14	8.33±2.89*
Mean (±SD) day 2 LH level (IU/l)	4.41±2.78	4.67±2.75
Mean (±SD)day 2 FSH/LH	3.32±2.56	2.19±1.44*
Mean (±SD) day 2 E2 level (pmol/l)	112.4±87.7	108.6±43.7
Mean (±SD) day 2 antral follicle count (n)	4.09±2.49	10.1±7.2*
Mean (±SD) no. of total ampules	58.5±15.8	40.6±17.0*
Mean (±SD) duration of stimulation (day)	10.8±2.0	10.2±1.7
Mean (±SD) peak E2 level (pmol/l)	3615±2021	9042±5674*
Mean (±SD) no. of oocytes	3.45±1.74	14.2±6.5*
Mean (±SD) fertilization rate (% of oocytes)	71.0%(1,326/1,867)	86%(4,919/5,720)*
Clinical pregnancy rate (%)	70(14.8%)	173(36.7%)*

*p<0.05

voluntary. Combined with recFSH and hMG were administered in the patients with poor ovarian response, Day 1 was defined as the first day of menstruation in both groups. Human chorionic gonadotropin (10,000 IU, profasi; Serono) was administered when the follicles with a diameter of 18 mm were present, combined with appropriately rising estradiol levels. Oocyte pick-up was performed under transvaginal ultrasonographic (US) guidance 36 h later.

The embryo-transfer (ET) was followed by 14 days of luteal phase support with 3,000 IU of hCG three times per week (on days 1, 3, 5 after oocyte pick-up) and with 60 mg/day oiled progesterone. After a positive pregnancy test, clinical pregnancies were confirmed by the presence of a gestational sac on transvaginal US scanning at 7 weeks of gestation.

Ultrasonographic measurements

Follicular diameters were measured during transvaginal US scanning, the follicular diameter was calculated as the average of the length of the longest follicular axis and that of the axis perpendicular to it in the same scanning plane. ALOCKA SD-100 was used with a 7.5-MHz vaginal transducer.

Assays

Estradiol, follicle-stimulating hormone (FSH), luteinization hormone (LH) were measured in plasma specimens with the Immulite (Diagnostic Products Corporation, DPC) according to the instructions of the manufacturer. The assays are based on the microparticle enzyme immunoassay technology (MEIA). The inter assay coefficient of variation was less than 10% and the intra assay variation was less than 15%.

Outcome measures

A primary outcome measure was the pregnancy rate/cycle and the total gonadotropin dose. Days of stimulation and fertilization rate were secondary outcome measures. The third measures were age and previous ovarian surgery.

Clinical pregnancy was defined as an intrauterine gestational sac detected by first trimester US examination.

Statistical analysis

Statistical analysis was performed with the SPSS 10.1 package. For normally distributed continuous variables, Student's two-tailed t test was used. For categorical data, the chi-square test or Fisher's exact test was used. Values of $p<0.05$ were considered to be statistically significant. Data are presented as mean ± SD unless otherwise indicated. Binary logistic regression analysis was used to study the relation among age, FSH, LH, E2, AFC and clinical pregnancy. Backward selection of parameters was applied with $p<0.05$ and $p<0.10$ for deletion, the results are given in terms of odds ratio (OR) and 95% CI which is the measure of effects immediately given by the logistic regression with OR>1.0 corresponding to positive associations and OR<1.0 corresponding to negative associations (Table 2).

The area under the receiver operating characteristic curve (ROC AUC) was computed to assess the predictive accuracy of the logistic models, yielding values from 0.5 (not predictive) to 1.0 (perfect prediction).

Results

Eighty-seven cycles were cancelled to retrieve oocyte because of poor ovarian response between July 1, 2004 and April 30, 2006. The patients had previous ovarian surgery in 64 cycles and previous IVF attempts in 46 cycles of 472 poor ovarian response cycle. The group with poor ovarian response has significant difference in comparison with the control group in age (36.6±4.2 vs 33.3±4.04), ovarian surgeries (13.6 vs 2.8%), gonadotrophin (58.5±15.8 vs 40.6±17.0), fertilization rate (71.0 vs 86%) and pregnancy rate (14.8 vs 36.7%). The causes and duration of infertility were similar between the two groups. In the group of poor ovarian responses, clinical pregnancy rate declined significantly in women aged >40 years compared with those aged ≤40 years (2.8 vs 18.5%, $P<0.001$), that is to say, only 3 patients have pregnancy in 109 women aged >40 years.

The age, basal serum FSH, basal serum LH, basal oestradiol concentrations, FSH to LH ratio and the antral follicle count are the common markers of ovarian reserve in our center. We found that there were significant differences in age, basal FSH, FSH-to-LH ratio and the antral follicle count, and no statistically significant differences in basal

Table 2 Binary logistic regression analysis with odds ratios and area under the receiver operating characteristic curve (ROC AUC) of common markers for the prediction of clinical pregnancy of poor ovarian response

	OR (95%CI)	P	ROC AUC
Age	0.863(0.805–0.925)	0.000	0.332
LH	Not selected	0.218	0.469
FSH/LH	Not selected	0.211	0.480
AFC	Not selected	0.313	0.590
E2	Not selected	0.588	0.487
FSH	Not selected	0.814	0.438

oestradiol concentration and basal serum LH when comparing the two groups.

Binary logistic regression analysis was used to study the relation among age, FSH, LH, E2, AFC and clinical pregnancy. Backward selection of parameters was applied with $p<0.05$ and $p<0.10$ for deletion. When we performed a binary logistic regression analysis, the age (odds ratio, 0.863; 95%confidence interval, 0.805–0.925; $p=0.000$) was the only variable selected. AFC, BFSH, E2, BFSH/LH, BLH were not selected, which means that chronological age significantly improved the prediction of clinical pregnancy of poor ovarian response.

Discussion

In in vitro fertilization (IVF), the association of poor ovarian response due to diminished ovarian reserve with cycle cancellation and a significant decline in success rates is well known. The variable number of mature follicles on the day of human chorionic gonadotrophin (HCG) administration noted on ultrasound and the number of oocytes retrieved has been used as criteria to define poor ovarian response. Other parameters widely used are peak serum oestradiol concentrations and the total gonadotrophin dose and/or the daily stimulation dose and/or prolonged duration of gonadotrophin stimulation. Our inclusion criteria were collection of fewer than 4 oocyte at retrieval, and the dose of gonodortrophins higher than 3,000 IU. In our study, 87 cycles were cancelled to retrieve oocyte because of poor ovarian responses. The cancellation rate is lower because the patients were reluctant to give up retrieval even if there were fewer than 3 follicles. The rate of poor ovarian response varies from 9 to 24% in IVF/ICSI cycles [3]. The data reported here about the prevalence of poor ovarian response is 11.9% in Chinese according to our standard, which consists with previous studies.

The reproductive potential of a woman decreases as she advances in age, ovarian aging is characterized by lowered pregnancy rates and decreased ovarian responsiveness to gonadotropin administration. In this study, the group with poor ovarian response has significant difference in comparison with the control group in age (36.6±4.2 vs 33.3± 4.04), ovarian surgeries (13.6 vs 2.8%) and pregnancy rate (14.8 vs 36.7%). The pregnancy rate significantly declined in the group of poor ovarian response. The so-called poor responders are likely to suffered from diminished ovarian reserve and consequently have impaired pregnancy prospects due to loss of oocyte quality, Correct identification of patients who are at risk for poor response can help physicians to individualize counseling and allow the patients to decide whether or not to undergo a demanding infertility treatment. Accurate assessment of ovarian response potential before the patient entering an IVF program is, therefore, of pivotal importance. Poor ovarian response is a significant problem in modern fertility treatment. It is associated with a significant decline in the success rate of fertility treatment. Poor ovarian response is more common in older women, but younger women also sometimes exhibit a poor response to stimulation [9]. However, it is very difficult to make a more accurate estimation because of the lack of common definition of this group of patients.

Although several possible aetiologies have been associated with poor ovarian response, it seems that a diminished ovarian reserve is the principal factor in poor ovarian response [10]. Genetic mechanisms regulate the rate of follicular atresia. It can be speculated that poor response, such as the age of menopause, is genetically determined. Possible acquired factors such as obesity, chemotherapy, radio therapy, pelvic surgery, pelvic infections or tubal disease, severe endometriosis, and heavy smoking can also be associated with a poor ovarian response [11–15]. In our study, the patients had previous ovarian surgery in 64 cycles of 472 poor ovarian response cycles. The group with poor ovarian response has significant difference in comparison with the control group in ovarian surgeries (13.6 vs 2.8%), which means that previous ovarian surgery is associated with poor ovarian responses.

One of the most important problems in the management of poor ovarian responder patients is the difficulty in predicting poor ovarian response to ovarian stimulation in order to tailor the correct stimulation regimen. As a prognosticator of individual ovarian potential, chronological age is of limited value because women of the age can be at different stages in the process of follicular depletion. Basal FSH values obtained during the infertility work-up were significantly higher in the poor responders. Basal FSH has been shown to be a better marker of individual ovarian reserve than age. Measuring basal E2 along with basal FSH in patients who undergo IVF cycles is of great importance. Although there is inconsistency among investigators [16–18], cancellation rate was significantly increased in patients with basal E2 levels of >80 pg/ml. Although the AFC appears to be the best predicators of ovarian responses during IVF treatment to date [9, 19], this test is obviously not perfect. Despite of the low AFC, one-third of the patients had a normal response to the hyperstimulation. The clomiphen citrate challenge test was first introduced by Navot et al. in 1987 to determine follicle reserve in women aged 35 years or older. It showed that the level of FSH after administration of clomiphen from day 5 up to the ninth IVF cycle. An FSH elevation compared with basal level in the tenth day indicated a greater ovarian reserve [20, 21]. Evaluation of serum inhibin-B shows that reduced day 3 serum inhibin-B concentration correlates with reduced fertility rate [22]. Many investigators do not mention serum

inhibin-B because its reduction always correlates with increased basal FSH and E2 [23]. A study by Syrop et al. [24] shows a relation between ovarian volume and its response to exogenous gonadotropin. The authors consider this relationship more important than increased basal FSH levels. However, until now, there is no exact measure for ovarian volume. But a volume less than 2–3 cm is consistent with experience. Unfortunately, although several attempts have been tried, no accurate predicative test is available to assess ovarian response. In our study, we found that there were significant differences in age, basal FSH, FSH-to-LH ratio and the antral follicle count. But it is important to emphasize that no test is absolutely predictive and the best test is of course ovarian response to ovarian stimulation.

Other authors have found that increasing the gonadotropin dose, decreasing the duration of GnRH agonist and using GnRH antagonist may increase the number of oocytes and pregnancy rate [25, 26], In our study, the total gonadotropin dose is significantly higher in the poor ovarian response group and poor ovarian response patients discontinued GnRH agonist on 6–7 days of stimulation. The patients will afford the cost of IVF by themselves in China currently and recFSH is very expensive and the start dose of gonadotropin is higher, therefore we have combined the recFSH and hMG in the treatment of poor ovarian response.

When we performed a binary logistic regression analysis to study the relation among age, FSH, LH, E2, AFC and clinical pregnancy, the age (odds ratio, 0.863; 95% confidence interval, 0.805–0.925; $p=0.000$) was variable selected. AFC, BFSH, E2, BFSH/LH, BLH were not selected, which means that chronological age significantly improved the prediction of clinical pregnancy of poor ovarian response. Pregnancy rate after assisted reproduction is significantly lower in older patients than in younger patients. In addition to a gradual decrease in the number of oocytes that can be retrieved, nuclear and cytoplasmic quality of oocytes declines with increase of age. In the group of poor ovarian responses, clinical pregnancy rate declined significantly in women aged >40 years compared with those aged ≤40 years (2.8 vs 18.5%, $P<0.001$), that is to say, only 3 patients have pregnancy in 109 women aged >40 years. Our data show that pregnancy rate of poor ovarian responses is lower than that of the control group, especially for women aged >40 years became accelerated. Women aged >40 years of poor ovarian response can be considered to have donor oocytes or to undergo natural IVF cycle. Natural IVF cycle without/with minimal stimulation can be considered as an easy and cheap approach in the management of poor responder patients [27, 28].

In conclusion, our data show that the prevalence of poor ovarian response in Chinese is 11.9% and previous ovarian surgery is associated with poor ovarian responses. The pregnancy rate of poor ovarian response women is low in IVF–ET, especially for women aged >40 years become accelerated. Women aged >40 years of poor ovarian response can be considered to have donor oocytes or to undergo natural IVF cycle. Chronological age significantly improved the prediction of clinical pregnancy of poor ovarian response.

References

1. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implication for forecasting menophause. Hum Reprod. 1992;7 (10):1342–6.
2. Kailasam C, Keay SD, Wilson P, Ford WC, Jenkins JM. Defining poor ovarian response during IVF cycles, in women aged <40 years, and its relationships with treatment outcome. Hum Reprod. 2004;19 (17):1544–7.
3. Lashen H, Ledger W. Management of poor responders in IVF. Hum Reprod. 1999;14(7):1919, Jul.
4. Bancsi LF, Broekmans FJ, Mol BW, Habbema JD, te Velde ER. Performance of basal follicle-stimulating hormone in the prediction of poor ovarian response and failure to become pregnant after in vitro fertilization: a meta-analysis. Fertil Steril. 2003;79 (5):1091–100, May.
5. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol. 1997;14(5):521–7.
6. Hofmann GE, Toner JP, Muasher SJ, Jones GS. High-dose follicle-stimulating hormone (FSH) ovarian stimulation in low-responder patients for in vitro fertilization. J In Vitro Fertil Embryo Transf. 1989;6(5):285–9, Oct.
7. Karande VC, Jones GS, Veeck LL, Muasher SJ. High-dose follicle-stimulating hormone stimulation at the onset of the menstrual cycle does not improve the in vitro fertilization outcome in low-responder patients. Fertil Steril. 1990;53(3):486–9, Mar.
8. Land JA, Yarmolinskaya MI, Dumoulin JC, Evers JL. High-dose human menopausal gonadotropin stimulation in poor responders does not improve in vitro fertilization outcome. Fertil Steril. 1996;65(5):961–5, May.
9. Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, te Velde ER. Predictors of poor ovarian responses in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. Fertil Steril. 2002;77(2):328–36.
10. Pellicer A, Ardiles G, Neuspiller F, Remohi J, Simon C, Bonilla-Musoles F. Evaluation of the ovarian reserve in young low responders with normal basal levels of follicle-stimulating hormone using three-dimensional ultrasonography. Fertil Steril. 1998;70(4):671–5, Oct.
11. Dechaud H, Ferron G, Anahory T, Arnal F, Humeau C, Hedon B. Obesity and assisted reproduction techniques. Contracept Fertil Sex. 1998;26(7–8):564–7, Jul–Aug.
12. Tulandi T, Sammour A, Valenti D, Child TJ, Seti L, Tan SL. Ovarian reserve after uterine artery embolization for leiomyomata. Fertil Steril. 2002;78(1):197–8, Jul.
13. Keay SD, Liversedge NH, Jenkins JM. Could ovarian infection impair ovarian response to gonadotrophin stimulation? Br J Obstet Gynaecol. 1998;105(3):252–3, Mar.
14. El-Nemr A, Al-Shawaf T, Sabatini L, Wilson C, Lower AM, Grudzinskas JG. Effect of smoking on ovarian reserve and ovarian

stimulation in in-vitro fertilization and embryo transfer. Hum Reprod. 1998;13(8):2192–8, Aug.
15. Nargund G, Cheng WC, Parsons J. The impact of ovarian cystectomy on ovarian response to stimulation during in vitro fertilization cycles. Hum Reprod. 1995;11(1):81–3.
16. Raga F, Bonilla-Musoles F, Casan EM, Bollina F. Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome. Hum Reprod. 1999;14:1431–4.
17. Fratterelli JL, Bergh PA, Drews MR, Sharara FI, Scott RT. Evaluation of basal estradiol levels in assisted reproductive technology cycle (Part 2). Fertil Steril. 2000;74:518–24.
18. Smotrich DB, Widra EA, Gindoff PR, Levy MJ, Hall JL, Stillman RJ. Prognostic value of day 3 estradiol on in vitro fertilization outcome. Fertil Steril. 1995;64:1110–36.
19. Ng EH, Tang OS, Ho PC. The significance of the number of antral follicles prior to stimulation in predicting ovarian responses in an IVF programme. Hum Reprod. 2000;15:1937–42.
20. Loumaye E, Billion JM, Mine JM, Psalti I, Pensis M, Thomas K. Prediction of individual response to controlled ovarian hyperstimulation by means of a clomiphen citrate challenge test. Fertil Steril. 1990; 53:295–301.
21. Scott RT, Leonardi MR, Hofmann GE, Illions EH, Neal GS, Navot D. A prospective evaluation of clomiphene citrate challenge test screening in the general infertility population. Obstet Gynecol. 1993;2:539–45.
22. Seifer DB, Lambert-Messerlian G, Hogan JW, Gardiner AC, Blazar AS, Berk CA. Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. Fertil Steril. 1997;67:110–4.
23. Hughes EG, Robertson DM, Handlesman DJ, Hayward S, Healy DL, de Kretser DM. Inhibin and estradiol responses to ovarian hyperstimulation: effects of age and predictive value for in vitro fertilization outcome. J Clin Endocrinol Metab. 1990;70:358–64.
24. Syrop CH, Willhoite A, Van Voorhis BJ. Ovarian volume: a novel outcome predictor for assisted reproduction. Fertil Steril. 1995; 64:1167–71.
25. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Comparison of agonistic flare-up-protocol and antagonistic multiple dose protocol in ovarian stimulation of poor responders: results of a prospective randomized trial. Hum Reprod. 2001;16(5):868–70, May.
26. Fasouliotis SJ, Laufer N, Sabbagh-Ehrlich S, Lewin A, Hurwitz A, Simon A. Gonadotropin-releasing hormone (GnRH)-antagonist versus GnRH-agonist in ovarian stimulation of poor responders undergoing IVF. J Assist Reprod Genet. 2003;20(11):455–60, Nov.
27. Bassil S, Godin PA, Donnez J. Outcome of in-vitro fertilization through natural cycles in poor responders. Hum Reprod. 1999;14 (5):1262–5, May.
28. Morgia F, Sbracia M, Schimberni M, Giallonardo A, Piscitelli C, Giannini P, Aragona C. A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization. Fertil Steril. 2004;81(6):1542–7, Jun.