Cost-effectiveness analysis comparing continuation of assisted reproductive technology with conversion to intrauterine insemination in patients with low follicle numbers

Bo Yu, M.D.,[a] Sunni Mumford, Ph.D.,[b] G. Donald Royster IV, M.D.,[c] James Segars, M.D.,[c] and Alicia Y. Armstrong, M.D.[c]

[a] Department of Obstetrics, Gynecology & Women's Health, Albert Einstein College of Medicine, Bronx, New York; and [b] Epidemiology Branch and [c] Program in Reproductive Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Objective: To compare the cost effectiveness of proceeding with oocyte retrieval vs. converting to intrauterine insemination (IUI) in patients with ≤4 mature follicles during assisted reproductive technology (ART) cycles.
Design: Probabilistic decision analysis. The cost effectiveness of completing ART cycles in poor responders was compared to that for converting the cycles to IUI.
Setting: Not applicable.
Patient(s): Not applicable.
Intervention(s): Cost-effectiveness analysis.
Main Outcome Measure(s): Cost effectiveness, which was defined as the average direct medical costs per ongoing pregnancy.
Result(s): In patients with 1–3 mature follicles, completing ART was more cost effective if the cost of a single ART cycle was between $10,000 and $25,000. For patients with 4 mature follicles, if an ART cycle cost <$18,025, it was more cost effective to continue with oocyte retrieval than to convert to IUI.
Conclusion(s): In patients with ≤4 mature follicles following ovarian stimulation in ART cycles, it was on average more cost effective to proceed with oocyte retrieval rather than convert to IUI. However, important factors, such as age, prior ART failures, other fertility factors, and medications used in each individual case need to be considered before this analysis model can be adapted by individual practices. (Fertil Steril® 2014;102:435–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Poor responders, intrauterine insemination, assisted reproductive technologies, cost effectiveness

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/yub-cost-art-iui-poor-responders/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received February 13, 2014; revised and accepted May 7, 2014; published online June 18, 2014.
B.Y. has nothing to disclose. S.M. has nothing to disclose. G.D.R. has nothing to disclose. J.S. has nothing to disclose. A.Y.A. has nothing to disclose.
The opinions and assertions contained in this article are the expressed views of the authors and are not considered official opinions of the Department of Health and Human Services, the Department of Defense, or the Albert Einstein College of Medicine.
This work was presented at the American Society of Reproductive Medicine's 67th Annual Meeting, Orlando, Florida, October 15-19, 2011.
Reprint requests: Bo Yu, M.D., Division of Reproductive Endocrinology & Infertility, Department of Obstetrics, Gynecology & Women's Health, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Block Room 621, Bronx, New York 10461 (E-mail: boyumich2@gmail.com).

Fertility and Sterility® Vol. 102, No. 2, August 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.05.015

Many patients undergoing assisted reproductive technology (ART) respond poorly to ovarian stimulation with gonadotropins, for a number of reasons (1–4). Patients with ART cycles resulting in ≤4 follicles over 14 millimeters are often referred to as poor responders (5–7). These ART cycles are usually associated with very low pregnancy

rates and high cancellation rates (8). Moreover, a large percentage of poor responders continue to respond poorly in subsequent ART cycles (9). Management options for poor responders include: cancellation, conversion to intrauterine insemination (IUI), or continuation with the ART cycle by proceeding to oocyte retrieval. This decision process is often difficult for both patients and physicians and involves clinical, financial, logistic, and emotional considerations.

The objective of this study was to identify which procedure is more cost effective in patients with ≤ 4 mature follicles during ART: conversion to IUI or continuation with oocyte retrieval. This study was conducted based on average outcome data in the literature and the average direct medical costs in clinics across the United States. However, the model used may be individualized to assist both patients and physicians in deciding whether to proceed with oocyte retrieval or convert to IUI in these patients.

MATERIALS AND METHODS

Since all probabilities and costs for the decision analysis were obtained from existing publications and publicly available information, this study was exempt from review by institutional review board. A decision-tree model (Fig. 1) was created to compare the societal costs of achieving an ongoing pregnancy with ART cycles that were converted to an IUI vs. with ART cycles that continued through oocyte retrieval in patients with 1–4 mature follicles. Patients with this number of mature follicles were assumed to have ART cycles that were either continued or converted to IUI; in addition, some of the ART cycles that proceeded through oocyte retrieval were assumed to have ended without an embryo for transfer. The cost and probability of each scenario contributed to the final cost analysis. One-way sensitivity analysis was conducted by varying either the ongoing pregnancy rates or the individual procedural costs.

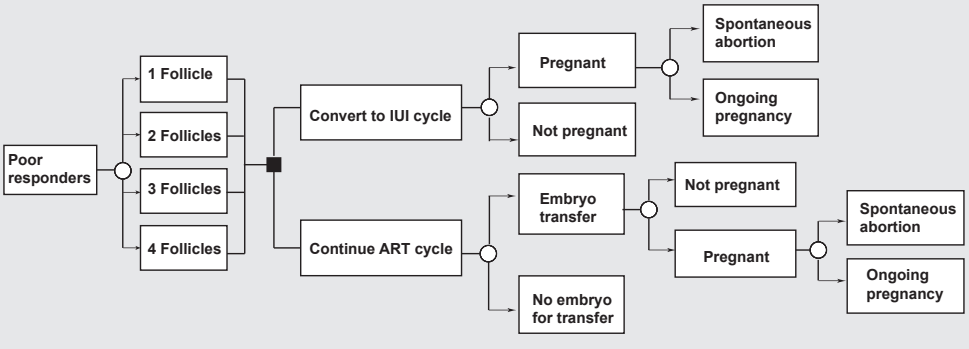
A computerized literature search in the MEDLINE, EMBASE, and randomized controlled trial registries, covering the period up to December 2013, on ART or IUI in poor responders or patients with low follicle numbers, was conducted. No language limitations were applied. The outcome data used in the decision-tree model originated from the published peer-reviewed articles identified in this literature review (8, 10–21). Costs were estimated by averaging the charges that were published on 21 fertility-center websites throughout the United States in various geographic regions. These 21 fertility centers were randomly chosen from the largest IVF clinics with estimated charges available online.

The charges included costs for: physician visits, ultrasounds, lab tests, and medications for both groups; and oocyte retrieval; embryo transfer (ET); and embryology lab in ART group, or IUI in IUI conversion group. Costs for gonadotropins and human chorionic gonadotropin (hCG) were estimated using the listed pricing of the Freedom Fertility Pharmacy. Clinic charges in 2010 US dollars were used as surrogates for direct costs and then converted to 2013 US dollars by adjusting for inflation using the US Department of Labor, Bureau of Labor Statistics consumer price index inflation calculator (www.bls.gov/data/inflation_calculator.htm). The ranges used in the sensitivity analyses were based on data from the same public sources.

Based on websites from clinics across the United States, the median cost of ART cycles up to and including the hCG trigger was estimated to be $9,000 in poor responders, with a range from $5,500 to $10,500. The median charges for remaining cycles were estimated to be $5,000 for completion of ART cycles, with a range from $3,500 to $10,000; and $500 for converted IUI cycles, with a range from $275 to $700. Therefore, the median cost for the continuation of the ART group was $14,000, which included the cost for ovarian stimulation ($9,000) plus oocyte retrieval and the rest of the ART cycle ($5,000); for the IUI conversion group, the median cost was $9,500, which included the cost for ovarian stimulation ($9,000) plus completion of the cycle with IUI ($500).

The cost analysis was conducted using the overall average cost to achieve one ongoing pregnancy, which is different from the healthcare cost for an individual patient. Using average pregnancy rates from published studies on poor responders, a calculation was made of the average total cost per ongoing pregnancy for ART patients that were converted to IUI vs. ART patients that proceeded with oocyte retrieval, grouped by the number of mature follicles at the time of the hCG trigger. One-way sensitivity analyses were completed for each follicle group to determine the average cost per

FIGURE 1



Decision-tree model. *Empty circle* denotes chance node. *Filled square* denotes decision node.

Yu. Cost effectiveness in poor responders. Fertil Steril 2014.

ongoing pregnancy, keeping constant the average pregnancy rates and median procedure costs for completed ART cycles, and varying the ongoing pregnancy rates for converted IUI cycles. In addition, sensitivity analyses were completed to determine whether decreasing ART costs would make IUI conversion more cost effective, keeping constant the average cost per ongoing pregnancy for converted IUI for each follicle group, and varying the cost of a single completed ART cycle across a range of costs for each follicle group from $10,000 to $20,000. Similar sensitivity analyses were done, with varying cost of converted IUI cycles.

RESULTS

For each patient group, continuation with ART resulted in higher ongoing pregnancy rates on average, and lower average total cost per ongoing pregnancy when compared with conversion to IUI (Table 1). For example, patients with 4 mature follicles had an average ongoing pregnancy rate of 12% if the cycles are converted to IUI, compared with 22% if the ART cycles are completed. This resulted in the difference in average cost per ongoing pregnancy: $79,167 vs. $63,636, respectively, for conversion vs. completion (Table 1).

Sensitivity analyses in which the average pregnancy rates and costs for completed ART cycles were kept constant, whereas the ongoing pregnancy rates for converted IUI cycles were varied, showed that for conversion to be more cost effective than completion, IUI needs to achieve ongoing pregnancy rates of 3%, 5%, 13.5%, and 15%, in patients with 1, 2, 3, or 4 mature follicles, respectively. These rates are much higher than the published average in each follicle group (Table 2).

When the cost per ongoing pregnancy for converted IUI is kept constant, and the cost of a single completed ART cycle is varied, in the 1–3 follicle groups, completing ART was more cost effective if the cost of a single ART cycle is $10,000–$25,000. In the 4-follicle group, if an ART cycle costs <$18,025, it is more cost effective to proceed with oocyte retrieval than to convert to an IUI. At amounts >$18,025, converting to IUI was more cost effective (Fig. 2).

Similar sensitivity analyses were done to determine the effect of varying the cost of converted IUI cycles. In the 1- and 3-follicle group, when the median total cost for the ART cycle is kept at $14,000 for each follicle group, then conversion to IUI is more cost effective than continuation with ART only when the cost for the converted IUI cycle is <$5,000. In the group with 4 mature follicles, if a converted IUI cycle costs <$7,650, it is more cost effective than continuation with ART.

TABLE 1

Average ongoing pregnancy rates and total costs per ongoing pregnancy for conversion to IUI vs. continuation with ART in patients with 1–4 mature follicles.

	Convert to IUI		Continue ART	
Mature follicle no.	Average ongoing pregnancy rate (%)	Cost per ongoing pregnancy ($)	Average ongoing pregnancy rate (%)	Cost per ongoing pregnancy ($)
1	1.6	614,488	4.5	321,977
2	1.7	578,341	7.6	190,644
3	7.0	140,454	20.0	72,445
4	12.0	81,932	22.0	65,859

Note: The ongoing pregnancy rates were based on estimates from the literature and were used to inform the decision-tree model cost estimates.

Yu. Cost effectiveness in poor responders. Fertil Steril 2014.

TABLE 2

Sensitivity analysis: varying ongoing pregnancy rates of converted IUI cycles, showing "threshold" ongoing pregnancy rates needed for converted IUI cycles to be more cost effective than completed ART cycles.

	Ongoing pregnancy rate (%)		
Mature follicle no.	Convert to IUI (published average)	Continue ART (published average)	Threshold rate at which IUI becomes more cost effective
1	1.6	4.5	3.0
2	1.7	7.6	5.0
3	7.0	20.0	13.5
4	12.0	22.0	15.0

Note: The ongoing pregnancy rates for both the IUI and ART groups were based on estimates from the literature and were used to inform the decision-tree model cost estimates.

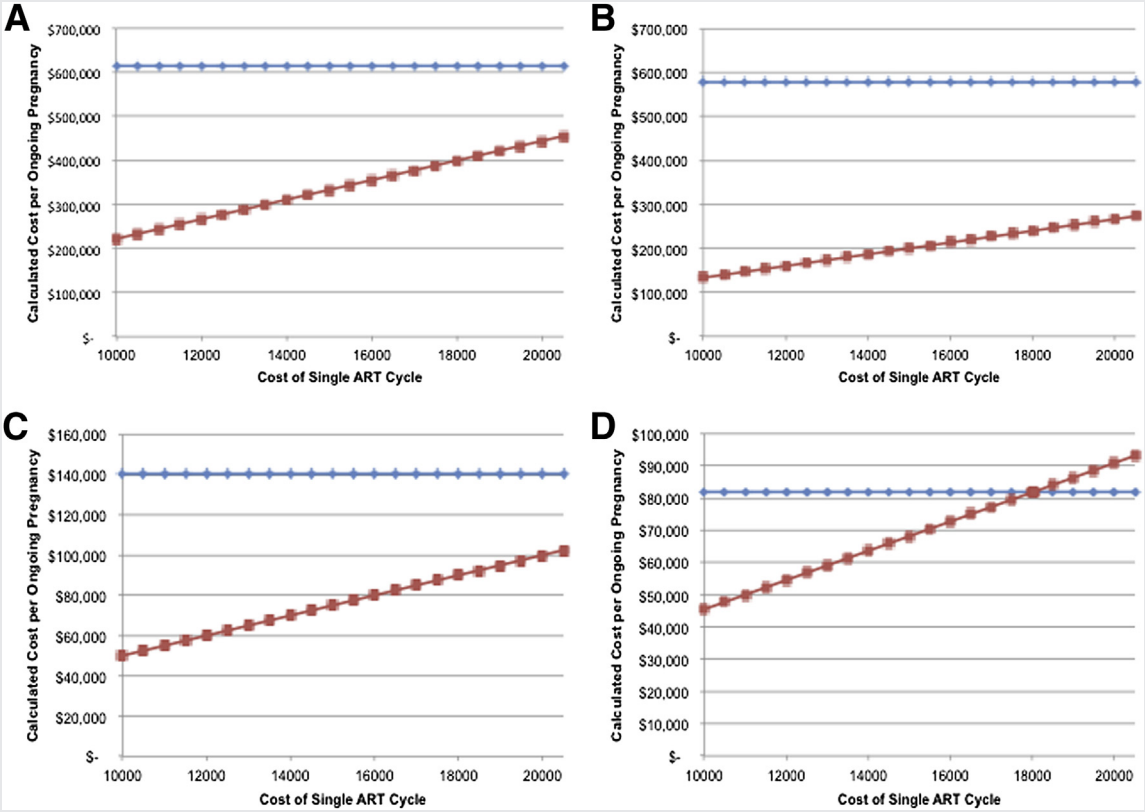
Yu. Cost effectiveness in poor responders. Fertil Steril 2014.

DISCUSSION

Based on the available public data, the current decision-tree model results suggest that continuation with ART is more cost effective than conversion to IUI in poor responders with ≤4 mature follicles. The current model was based on published information and involved a probabilistic decision analysis that does not factor in individual patient data such as age, prior poor response, hormonal status, or medication usage. The results of the decision-tree model could be adapted by individual practices to help with decision making for poor responders, based on the number of mature follicles and individual patient demographics. Individual practices could use their own pregnancy rates to identify the most cost-effective procedure specific to their own patient population.

The ability to predict pregnancy outcomes after ART is difficult for any patient, and especially for those with poor response to gonadotropin stimulation. ART is expensive, both financially and emotionally, and the decisions associated with ART become more difficult as follicle counts decrease. Very little guidance is available to assist clinicians and patients with making these difficult decisions during ART. The current literature is limited to retrospective cohort studies or case series. To answer the question of which treatment strategy is best in poor responders, a randomized controlled trial that considers various factors such as age, follicle numbers, infertility history, and prior treatments would be ideal. However, enrollment of patients into such a clinical trial could be difficult, owing to significant financial involvement and complex considerations in the decision-making process. A cost-effectiveness analysis is a major step toward providing physicians and patients with guidance when facing these difficult and individualized decisions.

FIGURE 2



Sensitivity analysis: varying the cost of ART while maintaining the cost of IUI conversion for the: (A) 1-follicle group; (B) 2-follicle group; (C) 3-follicle group; and (D) 4-follicle group. *Blue diamonds* represent the IUI group; *red squares* represent the ART group. In 1- to 3-follicle groups, completing ART was more cost effective if the cost of a single ART cycle was within the range $10,000–$25,000. In the 4-follicle group, if an ART cycle costs <$18,025, it was more cost effective than conversion to IUI. Above this cost level, converting to IUI was more cost effective.

Yu. Cost effectiveness in poor responders. Fertil Steril 2014.

In addition to age, there are biomarkers of ovarian reserve that may be useful in predicting outcomes in patients who are poor responders. Multiple publications have suggested that basal follicle-stimulating hormone plays a role in predicting pregnancy outcomes after IVF (3, 22). Since these early studies, there have been investigations of other biomarkers, such as antral follicle count (AFC), anti-müllerian hormone (AMH), and inhibin B. Unfortunately, the ability of any of these biomarkers alone to predict pregnancy outcomes has been variable (23). In a more recent study, investigators were able to significantly increase the accuracy of predicting ovarian response by combining age, AFC, and AMH (24). The ability of the markers to predict pregnancy outcome, however, was poor even when age, FSH, AMH, and AFC were considered. The authors concluded that the clinical usefulness of ovarian reserve testing prior to IVF is limited to the prediction of ovarian response (24, 25).

The difficulty of predicting ovarian response during ART, and a lack of large-scale and detailed studies of pregnancy outcomes in poor responders, led to several limitations. Individual patients were not evaluated; rather, a cost-analysis model was used to predict the financial burdens of conversion to IUI vs. oocyte retrieval for patients with 1–4 mature follicles. A high percentage of poor responses during ART occur as a result of age-related decline in fertility. Therefore, age is an important factor in counseling these patients and deciding whether to continue with the ART cycle or convert to IUI. However, age was not included as a factor in the current decision-tree model, owing to limited availability of publications that break down pregnancy outcomes in poor responders based on age groups.

The three articles that divided patients into two age groups did not investigate outcomes based on individual follicle numbers (14, 20, 26). One recent study did show that in patients age $\leq$40 years with $\leq$3 follicles, ART resulted in a statistically significantly improved live-birth rate compared with IUI conversion. The live-birth rates were comparable between the two groups if the patients were older than 40 years (21). Because this was the only study that analyzed pregnancy outcomes in poor responders grouped by both age and number of follicles, age was not included in the current decision-tree model. However, the sensitivity analyses cover a range of possible pregnancy rates to help overcome this limitation.

In addition, live-birth rates could not be used as the effectiveness measure, because the majority of articles on poor responders include ongoing pregnancy rates and not live-birth rates for their clinical outcome measure. Due to the same limitation in available data from existing publications, ovarian stimulation protocols, ovarian reserve status, and multiple pregnancies were not included in the decision-tree model. In addition, this study examined direct medical costs, and not indirect societal costs, such as medical leaves or decreased wages during treatment.

In conclusion, both patients and clinicians often have difficulty making the decision on whether to proceed with oocyte retrieval with only 1–4 mature follicles after ovarian stimulation during ART. The current cost-effectiveness analyses using average direct costs showed that it was more cost effective to proceed to oocyte retrieval than convert to IUI. Because this decision-tree model was based on published information, it did not factor in individual-level data, such as age, prior ART failures, other fertility factors, and medications used in each individual case. However, this model could be adapted by individual practices using their own patient demographic data and medical costs to help with decision making in their specific patient populations.

REFERENCES

1. Navot D, Rosenwaks Z, Margalioth EJ. Prognostic assessment of female fecundity. Lancet 1987;2:645–7.
2. Pellicer A, Lightman A, Diamond MP, Russell JB, DeCherney AH. Outcome of in vitro fertilization in women with low response to ovarian stimulation. Fertil Steril 1987;47:812–5.
3. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. Fertil Steril 1989;51:651–4.
4. Veleva Z, Jarvela IY, Nuojua-Huttunen S, Martikainen H, Tapanainen JS. An initial low response predicts poor outcome in in vitro fertilization/intracytoplasmic sperm injection despite improved ovarian response in consecutive cycles. Fertil Steril 2005;83:1384–90.
5. Surrey ES, Bower J, Hill DM, Ramsey J, Surrey MW. Clinical and endocrine effects of a microdose GnRH agonist flare regimen administered to poor responders who are undergoing in vitro fertilization. Fertil Steril 1998;69:419–24.
6. Surrey ES, Schoolcraft WB. Evaluating strategies for improving ovarian response of the poor responder undergoing assisted reproductive techniques. Fertil Steril 2000;73:667–76.
7. Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, te Velde ER. Predictors of poor ovarian response in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. Fertil Steril 2002;77:328–36.
8. Ulug U, Ben-Shlomo I, Turan E, Erden HF, Akman MA, Bahceci M. Conception rates following assisted reproduction in poor responder patients: a retrospective study in 300 consecutive cycles. Reprod Biomed Online 2003;6:439–43.
9. Centers for Disease Control and Prevention. Assisted reproductive technology success rates -national summary and fertility clinics reports 2011. Available from http://www.cdc.gov/ART/ART2011. Accessed on March 10, 2014.
10. Lashen H, Ledger W, Lopez-Bernal A, Barlow D. Poor responders to ovulation induction: is proceeding to in-vitro fertilization worthwhile? Hum Reprod 1999;14:964–9.
11. Biljan MM, Buckett WM, Dean N, Phillips SJ, Tan SL. The outcome of IVF-embryo transfer treatment in patients who develop three follicles or less. Hum Reprod 2000;15:2140–4.
12. Abusheikha N, Lass A, Burnley A, Brinsden P. In vitro fertilization cycles converted to intrauterine insemination because of poor follicular response have low success rates. Fertil Steril 2001;75:634–5.
13. Matorras R, Corcostegui B, Mendoza R, Ramon O, Aparicio V, Uriarte MT, et al. Converting an IVF cycle to IUI in low responders with at least 2 follicles. J Reprod Med 2003;48:789–91.
14. Wood S, Rahim R, Searle T, Sajjad Y, Troup S, Lewis-Jones I, et al. Optimal treatment for poor responders to ovarian stimulation: Does in vitro insemination offer any advantages to intrauterine insemination? Hum Fertil (Camb) 2003;6:13–8.
15. Galey-Fontaine J, Cedrin-Durnerin I, Chaibi R, Massin N, Hugues JN. Age and ovarian reserve are distinct predictive factors of cycle outcome in low responders. Reprod Biomed Online 2005;10:94–9.
16. Ng EH, Yeung WS, Ho PC. Patients with three or less dominant follicles may not be associated with reduced pregnancy rate of in vitro fertilization treatment. Eur J Obstet Gynecol Reprod Biol 2006;129:54–9.
17. Shahine LK, Lathi RB, Baker VL. Oocyte retrieval versus conversion to intrauterine insemination in patients with poor response to gonadotropin therapy. Fertil Steril 2009;92:1315–7.
18. Freour T, Dubourdieu S, Mirallie S, Langlois ML, Jean M, Barriere P. IVF conversion to IUI in poor responders: an observational study. Arch Gynecol Obstet 2010;282:445–9.
19. Norian JM, Levens ED, Richter KS, Widra EA, Levy MJ. Conversion from assisted reproductive technology to intrauterine insemination in low responders: Is it advantageous? Fertil Steril 2010;94:2073–7.
20. Nicopoullos JD, Abdalla H. Poor response cycles: When should we cancel? Comparison of outcome between egg collection, intrauterine insemination conversion, and follow-up cycles after abandonment. Fertil Steril 2011;95:68–71.
21. Reichman DE, Gunnala V, Meyer L, Spandorfer S, Schattman G, Davis OK, et al. In vitro fertilization versus conversion to intrauterine insemination in the setting of three or fewer follicles: How should patients proceed when follicular response falls short of expectation? Fertil Steril 2013;100:94–9.
22. Muasher SJ, Oehninger S, Simonetti S, Matta J, Ellis LM, Liu HC, et al. The value of basal and/or stimulated serum gonadotropin levels in prediction of stimulation response and in vitro fertilization outcome. Fertil Steril 1988;50:298–307.
23. Arce JC, La Marca A, Mirner Klein B, Nyboe Andersen A, Fleming R. Antimullerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients. Fertil Steril 2013;99:1644–53.
24. Broer SL, van Disseldorp J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, et al. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. Hum Reprod Update 2013;19:26–36.
25. Gizzo S, Andrisani A, Esposito F, Oliva A, Zicchina C, Capuzzo D, et al. Ovarian reserve test: an impartial means to resolve the mismatch between chronological and biological age in the assessment of female reproductive chances. Reprod Sci 2014;21:632–9.
26. De Sutter P, Dhont M. Poor response after hormonal stimulation for in vitro fertilization is not related to ovarian aging. Fertil Steril 2003;79:1294–8.