Role of the proportion of dominant follicles in patients with polycystic ovary syndrome undergoing in vitro fertilization-embryo transfer

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Abstract

Background: There is no absolute consensus for the best time for triggering. The aim of this study was to investigate the effect of different proportion of dominant follicles (PDF) on the human chorionic gonadotropin (HCG) day for the clinical outcomes in patients with polycystic ovary syndrome (PCOS) of different ovarian stimulation protocols.

Methods: A total of 371 cycles of the gonadotropin-releasing hormone (GnRH) agonist long protocol and 347 cycles of GnRH antagonist protocol from January 2014 to December 2016 were included in this retrospective study. Based on the PDF on the day of the HCG administration, the included patients were divided into three groups: Group A (low PDF), PDF <20%; Group B (medium PDF), 20%≤ PDF <40%; Group C (high PDF), PDF ≥40%. The measurements regarding ovarian stimulation characteristics, fertilization rate, top quality embryo rate, clinical pregnancy rate, and ovarian hyperstimulation syndrome (OHSS) rate were compared in different PDF groups with different protocols.

Results: In both the GnRH antagonist protocol and GnRH agonist long protocol, the characteristics such as mean age, anti-Mullerian hormone, antral follicle count (AFC), and body mass index were comparable between groups. The number of oocytes retrieved decreased statistically significantly as the PDF and rate of matured oocytes increased. In the GnRH agonist long protocol, the rate of normally fertilized oocytes was highest in Group A (59.74 ± 31.21 vs. 49.70 ± 37.95, 49.67 ± 36.62; P = 3.743, P = 0.025). There were no significant differences in the rate of top-quality embryos and the clinical pregnancy rate between the groups. The clinical pregnancy rate was similar in the three groups (63.6%, 62.5%, 67.5%, respectively, χ² = 0.989, P = 0.911). The moderate and severe OHSS rate increased statistically significantly when the PDF increased, which was highest in group C (1.4%, 3.1%, 6.7%, respectively, χ² = 12.014, P = 0.017). In the GnRH antagonist protocol, there were no significant differences in the rate of top-quality embryos, the rate of normally fertilized oocytes, the clinical pregnancy rate, and the moderate and severe OHSS rate between the groups. The clinical pregnancy rate in Group C was higher than that in Group A (57.9% vs. 46.6%, χ² = 10.850, P = 0.093).

Conclusions: In the GnRH antagonist protocol, PDF on the HCG day of less than 20% may be unfavorable to the clinical pregnancy rate in PCOS. In the GnRH agonist long protocol, delaying the HCG trigger timing has no good effect on clinical pregnancy and the risk of OHSS might increase in patients with PCOS.

Keywords: Proportion of dominant follicles; GnRH antagonist protocol; GnRH agonist long protocol

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female reproductive disorders affecting approximately 10% of reproductive age women. This population is at an extremely high risk of ovarian hyperstimulation syndrome (OHSS). With the development of assisted reproductive technology (ART), there are more and more issues concerned about how to decrease or avoid OHSS. Currently, a gonadotropin-releasing hormone (GnRH) antagonist protocol is strongly recommended in PCOS, which became an important part of the guideline for OHSS prevention from the American Society for Reproductive Medicine as Grade A evidence level.[1,2]

The GnRH antagonist protocol was undertaken for nearly 20 years in China. However, the clinical pregnancy rate was lower than that in the classic GnRH agonist long protocol by 8% to 10%.[3,4] There are many factors which affect the outcome, including ovarian response, protocol selection, trigger timing, and luteal phase support.[5,6] Some professors have proposed that the human chorionic gonadotropin (HCG) administration criteria in the GnRH antagonist protocol should be different from the GnRH
agonist long protocol. The question as to whether it is better to delay or put forward the time of HCG administration in the different protocols remains elusive.

HCG administration for triggering the final oocyte maturation is the last and key procedure for controlled ovarian hyperstimulation (COH), but the optimal criteria of the HCG trigger for all patients in a variety of protocols is not available. Previously, HCG was administered when there was one or two leading follicles ≥18 mm or three follicles ≥17 mm in diameter. The number of dominant follicles was preferred as an important item for HCG administration. The number of pre-ovulatory follicles available at the end of ovarian stimulation may be not a reliable reflection of cycle prognosis. Obviously, it is not suitable for all patients with different ovarian reserve especially in PCOS with a high ovarian reserve and in different COH protocols.

PDF was proposed as it can reflect the overall follicle development. This study was based on the previous study after the advantage of PDF on HCG day. We retrospectively analyzed the different PDFs and clinical outcomes in PCOS of the different protocols and explored the role of PDF in the HCG triggering decision.

Methods

Ethical approval

This study was approved by the Institutional Review Board at Sun Yat-sen Memorial Hospital (2016, No. 44). The data in this study were collected from the reproductive center of Sun Yat-sen Memorial Hospital between January, 2014 and December, 2016. There were a total of 371 cycles of the GnRH agonist luteal long protocol and 347 cycles of GnRH antagonist protocol in patients with PCOS. The PCOS diagnosis was according to the Rotterdam criteria in 2003. The baseline characteristics were compared including age, antral follicle count (AFC), anti-Mullerian hormone, baseline serum follicle stimulation hormone (FSH). The items such as the number of leading follicles ≥18 mm, the number of follicles ≥10 mm on HCG day, the mature oocytes rate, the fertilization rate, the clinical pregnancy rate, and moderate/severe OHSS. We also analyzed the individual characteristics of cycles.

GnRH agonist long protocol

Long-acting GnRHa (0.93–1.25 mg intramuscular [i.m.] once; IPSEN, Paris, France) or a short-acting GnRHa (0.1 mg i.m. per day until HCG day; IPSEN) was usually administered on the 18th to 22nd days of menstrual cycle (5–7 days after ovulation) after the corpus luteum detected on the vaginal ultrasound, if necessary, we measured serum progesterone level to determine the ovulation. Two to 3 weeks later, the vaginal ultrasound and blood hormones test (FSH, luteinizing hormone [LH], estradiol [E2]) were necessary. Gonadotropin 100 to 300 U/day can be administered when the results fully reached the pituitary complete down-regulation criteria. Every 3 to 5 days, the ultrasound and blood hormones were monitored to evaluate follicular development, when at least one follicle ≥18 mm or 3 follicles ≥17 mm in diameter emerges, HCG (Livon, China) 4000 to 10,000 U or GnRHa (IPSEN) 0.2 mg can be used as a trigger. Thirty-six to 38 h later, the vaginal oocyte retrieval was performed, embryos were cultured until the 3rd to 5th day, and then the embryo transfer was performed. Corpus luteal support began from the oocyte recovery with a progesterone intramuscular injection 60 mg/day or progesterone capsules 600 mg/day trans-vaginal until the day of pregnancy test.

GnRH antagonist protocol

On the 2nd or 3rd day of menstrual cycle, the sex hormones FSH, LH, E2, and the vaginal ultrasound were performed to evaluate the bilateral ovarian follicular condition. Gonadotropin 75 to 300 U/day was administered for ovarian stimulation, every 3 to 5 days to monitor ultrasound and blood hormones to evaluate follicular growth. GnRH antagonist was added according to the flexible or fixed protocol. When at least one follicle ≥18 mm or 3 follicles ≥17 mm in diameter merged, HCG (Livon) 4000 to 10,000 U or GnRHa (IPSEN) 0.2 mg was administered to trigger the oocyte final maturation. The oocyte retrieval, embryo transfer, and a luteal support regime were the same as in the GnRH agonist long protocol.

Measurements

PDF was obtained by the number of ≥18 mm follicles/ number of ≥10 mm follicles on the HCG day. We divided the cycles into three sub-groups according to PDF in the GnRH agonist long protocol and the GnRH antagonist protocol, respectively. The tertile borderline of ≥18/ ≥10 mm follicles proportion was 20% and 40%, respectively. Proportion of leading follicles more than 18 mm on HCG day more than 40% was set high PDF, and medium PDF: between 20% and 40%, low PDF was less than 20%.

The primary outcome of interest was the clinical pregnancy rate. The secondary measurements were the mature oocyte rate, the normally fertilized rate, and the rate of moderate and severe OHSS. We also analyzed the individual characteristics of cycles.

Statistical analysis

The data was subjected to a normality test using the one-sample Kolmogorov-Smirnov method. The variance homogeneity test was performed on the measurement data. Normal distribution data were presented as mean ± standard deviation (SD), and non-normal distribution data were presented by median (Q1–Q3). The variance homogeneity data were analyzed by analysis of variance (ANOVA); the comparison between the two was analyzed by least significant difference and Tamhane method. The Chi-square test is used for qualitative data and is expressed as a percentage. Baseline and demographic characteristics were analyzed by ANOVA, the results were showed with mean ± SD, and a Chi-square test was used for categorical data such as clinical pregnancy rate. Non-normal distribution data were analysed by Kruskal-Wallis test. Logistic regression analysis, forward Likelihood ratio (LR), and indicators related to clinical pregnancy were observed. All data were tested at the
Table 1: Analysis of basic characteristics of patients in GnRH agonist long protocol.

| Characteristics          | Group A (PDF <20%) (n = 148) | Group B (20%< PDF ≤40%) (n = 161) | Group C (PDF >40%) (n = 60) | F or H | P         |
|--------------------------|------------------------------|-----------------------------------|-----------------------------|--------|-----------|
| Age (years)              | 29.68 ± 3.23                 | 30.03 ± 3.59                     | 30.31 ± 4.03                | 0.746  | 0.475     |
| BMI (kg/m²)              | 22.07 ± 3.49                 | 22.59 ± 3.39                     | 23.10 ± 3.52                | 2.025  | 0.134     |
| Infertility (years)      | 6.34 ± 1.74                  | 6.49 ± 1.83                      | 6.88 ± 1.39                 | 0.070  | 0.932     |
| Serum baseline FSH (U/L) | 8.48 ± 7.27                  | 7.97 ± 5.08                      | 8.59 ± 5.65                 | 0.566  | 0.568     |
| Serum baseline LH (U/L)  | 1.82 ± 1.18                  | 1.65 ± 0.82                      | 1.47 ± 0.62                 | 1.863  | 0.157     |
| AMH (ng/mL)              | 10.40 ± 4.11                 | 9.36 ± 4.04                      | 9.48 ± 4.45                 | 1.762  | 0.174     |
| AFC                      | 32.42 ± 12.01                | 29.72 ± 10.44                    | 31.29 ± 11.98               | 1.848  | 0.159     |
| Initiation dose of Gn (U)| 133.63 ± 35.92               | 135.52 ± 39.18                   | 127.14 ± 27.18              | 1.107  | 0.332     |
| Total dosage of Gn (U)   | 1572.03 ± 818.52             | 1582.25 ± 707.51                 | 1535.75 ± 758.62            | 0.077  | 0.926     |
| Days of Gn               | 10.73 ± 3.73                 | 10.86 ± 5.34                     | 10.68 ± 3.76                | 0.045  | 0.956     |
| E2 on HCG day (pg/mL)    | 3760.83 ± 1270.50            | 3388.05 ± 1362.28*               | 2994.96 ± 1329.02*          | 6.084  | 0.003     |
| P on HCG day (ng/L)      | 0.83 ± 0.36                  | 1.28 ± 1.12                      | 1.10 ± 0.66                 | 1.328  | 0.219     |

Normal distribution data were presented as mean ± standard deviation. Non-normal distribution data were presented by median (Q1–Q3). AFC: Antral follicle count; AMH: Anti-Mullerian hormone; BMI: Body mass index; E2: Estradiol; FSH: Follicle stimulation hormone; Gn: Gonadotropin; HCG: Human chorionic gonadotropin; LH: Luteinizing hormone; P: Progesterone; PDF: Proportion of dominant follicles; T: Testosterone.

Table 2: Analysis of basic characteristics of patients in GnRH antagonist protocol.

| Items                  | Group A (PDF <20%) (n = 148) | Group B (20%< PDF ≤40%) (n = 141) | Group C (PDF >40%) (n = 58) | F or H | P         |
|------------------------|------------------------------|-----------------------------------|-----------------------------|--------|-----------|
| Age (years)            | 30.59 ± 3.67                 | 30.62 ± 3.85                     | 31.06 ± 4.34                | 0.352  | 0.704     |
| BMI (kg/m²)            | 21.95 ± 3.01                 | 21.95 ± 3.59                     | 23.01 ± 3.98                | 2.395  | 0.093     |
| Duration of infertility| 4.0 (2.9–5.0)               | 4.0 (2.0–6.0)                    | 5.0 (2.0–6.0)               | 0.438  | 0.803     |
| Serum baseline FSH (U/L)| 6.95 ± 1.71              | 6.99 ± 1.86                      | 7.19 ± 2.06                 | 0.359  | 0.699     |
| Serum baseline LH (U/L)| 7.81 ± 6.12                 | 6.84 ± 4.47                      | 7.21 ± 4.55                 | 1.319  | 0.269     |
| Serum baseline T (nmol/L)| 1.53 ± 0.92          | 1.59 ± 0.71                      | 1.61 ± 0.76                 | 0.286  | 0.752     |
| AMH (ng/mL)            | 8.79 ± 4.15                 | 7.95 ± 3.79                      | 7.33 ± 4.00                 | 2.526  | 0.082     |
| AFC                    | 27.74 ± 9.47                | 26.87 ± 9.17                     | 27.03 ± 10.39               | 0.322  | 0.725     |
| Initiation dose of Gn (U) | 131.46 ± 36.78         | 137.83 ± 41.00                   | 143.49 ± 50.00              | 2.050  | 0.130     |
| Total dosage of Gn (U) | 1897.39 ± 674.13            | 1872.56 ± 772.03                 | 2008.90 ± 940.95            | 0.581  | 0.560     |
| Days of Gn             | 12.44 ± 3.12                | 12.52 ± 4.58                     | 12.91 ± 4.15                | 0.314  | 0.731     |
| E2 on HCG day (pg/mL)  | 3421.53 ± 1282.95           | 3245.60 ± 1281.52                | 3169.09 ± 1443.26           | 0.961  | 0.384     |
| P on HCG day (ng/L)    | 0.76 ± 1.28                 | 1.01 ± 0.51                      | 0.97 ± 0.51                 | 0.245  | 0.783     |

Data were presented as mean ± standard deviation. *P < 0.05 vs. Group A. AFC: Antral follicle count; AMH: Anti-Mullerian hormone; BMI: Body mass index; E2: Estradiol; FSH: Follicle stimulation hormone; Gn: Gonadotropin; HCG: Human chorionic gonadotropin; LH: Luteinizing hormone; P: Progesterone; PDF: Proportion of dominant follicles; T: Testosterone.

two-sided level of 0.05. Analysis was performed using SPSS version 19.0 (IBM® SPSS® Statistics, International Business Machines Corp, Chicago, IL, USA).

Results

Comparison of baseline data of patients

In GnRH agonist long protocol and GnRH antagonist protocol, the basic clinical data such as age, body mass index, basal FSH, LH, testosterone, and AFC were compared between the three groups. There were no statistical differences in these basic characteristics and serum hormones on the HCG day among the three groups of different PDFs. Only in GnRH antagonist protocol, serum E2 on the HCG day in low PDF group was statistically significantly higher than the other groups [Tables 1 and 2].

Comparison of embryo culture and outcome measurements

In GnRH agonist long protocol, the rate of normally fertilized oocytes was highest in group A (59.74 ± 31.21 vs. 49.70 ± 37.95, 49.67 ± 36.62; F = 3.743, P = 0.025). There was no significant difference in the rate of top-quality embryos, the clinical pregnancy rate among the groups. The clinical pregnancy rate was similar in three groups (63.6%, 62.3%, 67.5%, $\chi^2 = 0.989$, P = 0.911). While the implantation rate was comparable in the three groups, the implantation rate in Group C was lower than those in other two groups (35.8% vs. 47.7%, 46.7%, $\chi^2 = 3.600$, P = 0.015). The moderate and severe OHSS rate increased statistically significantly with an increase in PDF, which was highest in group C [Table 3].

In GnRH antagonist protocol, there was no significant difference in the rate of top-quality embryos, the rate of
Table 3: Analysis of outcomes of patients in GnRH agonist long protocol.

| Items                                      | Group A (PDF ≤ 20%) (n = 150) | Group B (20% ≤ PDF ≤ 40%) (n = 161) | Group C (PDF > 40%) (n = 60) | F or H | P     |
|--------------------------------------------|---------------------------------|---------------------------------------|--------------------------------|--------|-------|
| Number of ≥18 mm follicles on HCG day      | 2.00 (1.00–3.00)                | 4 (3–6)                               | 7.00 (4.24–9.00)               | 179.42 | <0.001|
| Proportion of ≥18/≥210 mm follicles        | 0.11 (0.06–0.15)                | 0.28 (0.25–0.33)                      | 0.51 (0.44–0.62)               | 313.11 | <0.001|
| Rate of ET cancelled because of no available embryos | 0.7                             | 0                                     | 0                              | 1.477  | 0.478 |
| Number of oocytes retrieved                | 16.0 (12.0–22.0)                | 13.0 (8.5–16.0)                       | 10.0 (7.2–75.0)                | 44.12  | <0.001|
| Rate of matured oocytes                    | 0.87 ± 0.12                     | 0.87 ± 0.13                           | 0.93 ± 0.10                   | 4.360  | 0.013 |
| Rate of top quality embryos                | 0.27 ± 0.22                     | 0.26 ± 0.22                           | 0.23 ± 0.24                   | 0.466  | 0.628 |
| Rate of available embryos                  | 0.49 ± 0.27                     | 0.46 ± 0.29                           | 0.46 ± 0.28                   | 0.396  | 0.674 |
| Rate of normally fertilized oocytes        | 0.71 (0.46–0.82)                | 0.61 (0–0.80)                         | 0.66 (0–0.83)                 | 4.765  | 0.092 |
| Clinical pregnancy rate, % (n/N)           | 63.6 (6/99)                     | 62.5 (8/128)                          | 67.5 (27/40)                  | 0.898  | 0.911 |
| Implantation rate, % (n/N)                 | 47.7 (2/193)                    | 46.7 (122/261)                        | 35.8 (29/81)                  | 3.600  | 0.165 |
| OHSS (moderate and severe), % (n/N)        | 1.4 (2/150)                     | 3.1 (5/161)                           | 6.7 (4/60)                    | 12.014 | 0.017 |

Table 4: Analysis outcomes of patients in GnRH antagonist protocol.

| Items                                      | Group A (PDF ≤ 20%) (n = 148) | Group B (20% ≤ PDF ≤ 40%) (n = 141) | Group C (PDF > 40%) (n = 58) | F or H | P     |
|--------------------------------------------|---------------------------------|---------------------------------------|--------------------------------|--------|-------|
| Number of ≥18 mm follicles on HCG day      | 2.00 (1.00–3.00)                | 4.00 (3.00–5.00)                      | 5.00 (3.76–5.00)              | 112.779 | <0.001|
| Proportion of ≥18/≥210 mm follicles        | 0.11 (0.06–0.16)                | 0.27 (0.23–0.33)                      | 0.50 (0.44–0.60)              | 294.536 | <0.001|
| Number of oocytes retrieved                | 17.5 (11.3–22.0)               | 12.0 (8.0–16.0)                       | 8.0 (6.0–10.0)                | 83.331  | <0.001|
| Rate of matured oocytes                    | 0.85 ± 0.14                     | 0.89 ± 0.11*                          | 0.90 ± 0.13*                  | 5.858   | 0.003 |
| Rate of available embryos                  | 0.56 ± 0.24                     | 0.55 ± 0.26                           | 0.60 ± 0.28                   | 0.615   | 0.541 |
| Rate of normally fertilized oocytes        | 0.64 ± 0.24                     | 0.63 ± 0.29                           | 0.61 ± 0.32                   | 0.194   | 0.824 |
| Clinical pregnancy rate, % (n/N)           | 46.6 (41/88)                    | 55.2 (58/105)                         | 57.9 (22/38)                  | 10.850  | 0.093 |
| Implantation rate, % (n/N)                 | 33.7 (57/169)                   | 37.3 (78/209)                         | 38.4 (28/73)                  | 0.708   | 0.702 |
| OHSS (moderate and severe), % (n/N)        | 2.7 (4/148)                     | 2.1 (3/141)                           | 3.4 (2/58)                    | 7.351   | 0.118 |

Table 3 was presented by mean ± standard deviation for ANOVA, by percentage for Chi-square test, non-normal distribution data were presented by median (Q1–Q3). *P < 0.05 vs. Group A; †P < 0.05 vs. Group B. OHSS: Ovarian hyperstimulation syndrome; PDF: Proportion of dominant follicles.

normally fertilized oocytes, the clinical pregnancy rate, the implantation rate, and moderate and severe OHSS rate between groups. The clinical pregnancy rate in Group C was higher than that in Group A (57.9% vs. 46.6%, χ² = 10.850, P = 0.093) [Table 4].

Logistic regression analysis of factors associated with clinical pregnancy rate

In the GnRH agonist long protocol, only the total dose of the HCG trigger and AFC were associated with the clinical pregnancy rate, but it was not statistically significantly [Table 5].

In the GnRH antagonist protocol, the number of available embryos was associated with the clinical pregnancy rate (odds ratio = 1.320) [Table 6].

Discussion

In the ovulation cycle, HCG was administered to induce ovulation when the follicles had reached 18 to 22 mm in diameter; the administration time was based on the follicle diameter to determine the oocyte maturity. The timing of the administration of HCG plays a vital part in in vitro fertilization/intra-cytoplasmic sperm injection cycles. Premature administration can lead to follicular atresia, delayed administration can cause follicular aging and a decrease in endometrial receptivity, and it may increase the rate of OHSS. Patients with PCOS were characterized by a high ovarian reserve and a good ovarian response to FSH. In COH of patients with PCOS, a large cohort of medium size follicles are easily seen on HCG day, if the trigger time is postponed and PDF increases, the serum E2 level and size follicles are easily seen on HCG day, if the trigger time is postponed and PDF increases, the serum E2 level and
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increase the rate of mature oocytes, but early progesterone elevation may appear, and endometrial receptivity is affected. The appropriate PDF on the HCG day, can make the appropriate number of oocytes, synchronized maturation of the cytoplasm and the nucleus, the number of high-quality embryos to ensure the outcome of pregnancy. Previously, some scholars have proposed the concept of follicle output rate. In our view, the number and quality of follicles on HCG day is the key factor that affects the outcome of the ART. At present, the relevant research is very rare, how to seize the specific population such as PCOS, the optimum PDF on the HCG day to ensure the prognosis of patients is one of the purposes of this study.

We clearly know the limitations of this study. It was a retrospective study, so some confounding bias may exist. The PDF was based on the measurements by ultrasound, which may be affected by different operators. A large size, multi-center and strictly designed randomized study is needed.

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Conflicts of interest

None.

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