

# Nationwide survey on the usage of ovulation-induction agents among obstetricians and gynecologists in China

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Ovulation-induction refers to the type of ovarian stimulation for anovulatory women aimed at restoring normal fertility by generating normal ovulatory cycles and inducing single dominant follicle selection and ovulation. In China, a great number of women with ovulatory disorders are treated by obstetricians and gynecologists (ob-gyns) who are not specialized in infertility. The aim of this study was to investigate the self-reported ob-gyns proficiency of ovulation induction and the most commonly used drug for this procedure.

This was a cross-sectional survey. The questionnaires were distributed on site to 4006 physicians attending the workshops held by the Gynecological Endocrinology Committee of the Chinese Maternal and Child Health Association from December 2017 to February 2018 in 20 provinces in China. Before the workshops began, physicians attending the workshops were invited to fill out the questionnaires voluntarily. It took approximately 3 min to complete the questionnaire and no private details were collected. The study was approved by the Ethics Committee of Peking Union Medical College Hospital. The questionnaire included questions on demographic information, self-evaluation of proficiency in ovulation induction, first choice of ovulation drugs, preferred drug concentration and duration used for clomiphene-citrate treatment, and knowledge of the side effects of clomiphene citrate [Supplementary questionnaire, <http://links.lww.com/CM9/A104>]. A Chi-square test was used to compare categorical data. We analyzed the influence of hospital type, education, title, specialty and relevant training on the first choice of ovulation drugs, correct use of clomiphene citrate, and knowledge of the side effects of clomiphene citrate by binary logistic-regression analysis. Before binary logistic-regression analyses, univariable analysis was performed for variable selection. SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA) was used for all of the statistical analyses. A value of  $P < 0.05$  was considered to be statistically significant.

A total of 4006 questionnaires were distributed, of which 3401 were returned. Inclusion criteria were as follows: (1) ob-gyns involved in infertility care; (2) forms with all the questions completed. Exclusion criteria were as follows: (1) not ob-gyns; (2) ob-gyns not involved in infertility care; (3) forms with uncompleted questions; (4) obviously unreliable responses. Ultimately, 1077 questionnaires (26.9%) were included for final analysis. Demographic characteristics of the respondents are presented in Supplementary Table 1, <http://links.lww.com/CM9/A98>. Among analyzed respondents, 24.1% were ob-gyns specialized in infertility and 75.9% were ob-gyns not specialized in infertility but who were required to provide care for infertile couples. Most analyzed respondents (76.7%) did not have any relevant training experience in infertility.

More than half of the respondents reported that they were limited (20.5%) or devoid (34.9%) in their experiences with ovulation induction. Only 10.1% of respondents reported to be proficient and 34.4% reported to be average in terms of performing ovulation induction. A significantly higher proportion of ob-gyns specialized in infertility or who had relevant training experience in infertility considered themselves to be proficient or average in ovulation induction compared to those who did not have these attributes in infertility care (24.6% *vs.* 5.5%,  $P < 0.010$ ; 24.3% *vs.* 5.8%,  $P < 0.010$ , respectively) [Supplementary Figure 1, <http://links.lww.com/CM9/A105>].

Clomiphene citrate was the first choice of ovulation drug for most of the ob-gyns. Specifically, 67.0% of ob-gyns chose clomiphene citrate and 16.6% chose letrozole, while 9.8% chose both of these drugs as their first choice of ovulation drug. A significantly higher proportion of ob-gyns specialized in infertility or who had relevant training experience chose letrozole compared to those who did not have these attributes in infertility care (41.5% *vs.* 21.7%,  $P < 0.010$ ; 37.8% *vs.* 25.0%,  $P < 0.010$ , respectively) [Supplementary Figure 2, <http://links.lww.com/CM9/A106>].

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Less than half (43.0%) of the respondents thought that clomiphene citrate should not be used for more than six cycles, whereas a higher proportion (51.1%) of respondents thought clomiphene citrate should be used for three cycles. A higher proportion of respondents specialized in infertility or who had relevant training experience chose six cycles for the preferred number of cycles using clomiphene citrate (53.1% *vs.* 39.8%,  $P < 0.010$ ; 53.0% *vs.* 40.0%,  $P < 0.010$ , respectively) [Supplementary Figure 3, <http://links.lww.com/CM9/A107>]. Next, 85.1% of respondents correctly chose 5 days as the duration of treatment for clomiphene citrate and 70.8% reported 50 mg as the initial dose of clomiphene during their clinical practice. Unexpectedly, a lower proportion of the ob-gyns who had relevant training experience chose 5 days as the usual treatment course or 50 mg as the initial dose (80.1% *vs.* 86.7%,  $P = 0.010$ ; 60.6% *vs.* 74.0%,  $P < 0.010$ , respectively); there was no significant difference in this answer in terms of specialty.

There was insufficient awareness of the side effects of clomiphene citrate. Only 50.9% knew about the anti-estrogenic effects of clomiphene citrate and only 51.1% knew that it can thin the endometrium. Additionally, only 37.0% of the respondents thought that clomiphene citrate could increase the risk of luteinized unruptured follicle syndrome (LUFs). In terms of specialty, ob-gyns specialized in infertility or who had relevant training experience had a better knowledge of the side effect of a thinned endometrium but had less knowledge about the increased risk of LUFs [Supplementary Figure 4, <http://links.lww.com/CM9/A108>].

Binary logistic-regression analyses [Supplementary Table 2, <http://links.lww.com/CM9/A98>] showed that ob-gyns who specialized in infertility or who had relevant training experience were less likely to choose clomiphene citrate as the first-line ovulation-induction drug, as compared to that of ob-gyns who did not have such attributes in infertility care (odds ratio [OR]: 0.7; 95% confidence interval [CI]: 0.5–1.0;  $P = 0.032$ ; OR: 0.5; 95% CI: 0.4–0.7;  $P < 0.010$ , respectively). Rather, ob-gyns who specialized in infertility or who had relevant training experience were more likely to choose letrozole (OR: 2.2; 95% CI: 1.6–3.0;  $P < 0.010$ ; OR: 1.5; 95% CI: 1.1–2.0;  $P = 0.024$ , respectively) and were more likely to report the correct number of cycles for clomiphene citrate (OR: 1.5; 95% CI 1.1–2.0;  $P = 0.009$ ; OR: 1.4; 95% CI: 1.1–2.0;  $P = 0.020$ , respectively). Relevant training experience was negatively correlated to the correct rate of the usual course and initial dose of clomiphene citrate (OR: 0.6; 95% CI: 0.4–0.9;  $P = 0.012$ ; OR: 0.5; 95% CI: 0.4–0.7;  $P < 0.010$ , respectively), whereas position titles had a positive correlation with this parameter. Associate chief physicians were over four times more likely to report the correct duration of treatment and initial dose of clomiphene citrate compared with that of residents. Additionally, ob-gyns who specialized in infertility were more likely to be aware of the side effects of a thinned endometrium induced by clomiphene citrate (OR: 1.6; 95% CI: 1.2–2.1;  $P = 0.003$ ), whereas associate chief physicians or chief physicians were 1.7 to 2.5 times more likely to be aware of the anti-estrogenic and endometrium-thinning side effects of

clomiphene citrate compared with that of residents. Relevant training experience was negatively correlated with knowing the risk of LUFs during clomiphene-citrate treatment (OR: 0.6; 95% CI: 0.5–0.9;  $P = 0.007$ ). The hospital type had no correlation with any of the results, and educational background only slightly affected the correct response rate of the treatment duration and initial dose of clomiphene citrate.

Anovulatory subfertility is a heterogeneous condition with various underlying causes. It can be classified as hypogonadism (I), normogonadotropic ovarian dysfunction (II), and hypergonadotropic hypogonadism (III). Other endocrinopathies, such as hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, and androgen-secreting adrenal and ovarian tumors can also lead to ovulation disorders. The most common type is normogonadotropic ovulation (II), with which polycystic ovary syndrome (PCOS) accounts for the most. Clomiphene citrate, a selective estrogen-receptor modulator, is the most applied ovulation drug for normogonadotropic anovulation worldwide since it was first introduced in 1960. Letrozole is an aromatase inhibitor. In patients with PCOS, both the ovulation and live-birth rates are higher with letrozole compared with those of clomiphene citrate.<sup>[1,2]</sup> Letrozole has been recommended as the first-line ovulation drug for patients with PCOS by guidelines.<sup>[3]</sup> There is a growing interest in the use of letrozole for ovulation induction. A survey in the United States showed that 77.9% of physicians prescribed clomiphene citrate and 14.9% physicians prescribed letrozole as the first-line ovulation therapy.<sup>[4]</sup> We found a similar result in which 16.6% of physicians used letrozole as their first-line ovulation drug and 67.0% chose clomiphene citrate as their first-line ovulation drug. The recognition of association between PCOS and insulin resistance has led to the use of insulin-sensitizing agents in ovulation induction. Metformin has been studied most extensively, but was unable to improve live-birth rates. Inositol has been shown to improve endocrine and ovulation in women with PCOS, but the study is too small and needs to be further studied.<sup>[5]</sup>

This study showed that more than half of the ob-gyns involved in infertility care considered themselves to be limited or devoid of competency in performing ovulation induction. Clomiphene citrate remained as the first choice of ovulation drug by most ob-gyns, but the standardized usages in their practice and their knowledge of the side effects were both poor overall. Physicians who were specialized in infertility did better in terms of these parameters, but the proportion of physicians specialized in infertility was low. These findings suggest that there is an unmet need for high-quality medical care for infertile women who require ovulation induction. Pragmatic basic education programs for ob-gyns involved in infertility care are in urgent need.

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### Conflicts of interest

None.

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