Ovulation induction with letrozole in women with polycystic ovary syndrome

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Abstract

Study question: What is the effectiveness of first-line letrozole treatment in anovulatory women with polycystic ovary syndrome (PCOS) and what ovulation induction protocols are followed in Dutch fertility clinics?

Background: Current guidelines on ovulation induction in women with PCOS recommend letrozole as first-line treatment for six ovulatory cycles before switching to gonadotrophins. Since ovulation induction with gonadotrophins leads to higher costs and is less sustainable, continuing letrozole over 12 ovulatory cycles may be a preferable alternative. To determine the feasibility of a randomised trial we need to know what first and second-line treatments are provided in practice in the Netherlands, and whether clinics are inclined to participate in a trial. Furthermore, in order to estimate the potential population size, we need to know the percentage of women ovulating but not getting pregnant on letrozole as these women will be eligible for further treatment after six cycles of letrozole.

Methods: We developed a questionnaire for a national survey among all 66 fertility clinics in the Netherlands. Furthermore, we collected the databases from all studies that had compared letrozole and clomiphene citrate in randomised controlled trials, and evaluated the individual participant database (IPD) for the outcomes ovulation rate per cycle and live birth rate, while accounting for cycle number. Data was analysed with study as fixed variable using general linear models with a Poisson as distribution and Log as link function to calculate relative risks with 95% CI.

Results: The survey was returned by 39 fertility clinics (59.1%). Of these, 36 (92.3%) used letrozole as first-line treatment, the other three clinics used clomiphene citrate. Letrozole was provided for six ovulatory cycles by 17 clinics (47.2%), eight clinics (22.2%) always provided 12 cycles. Injections with gonadotrophins was the most used second-line treatment with 34 clinics (94.4%) providing this after anovulation on letrozole, and 30 clinics (83.3%) providing this in case of ovulation but no pregnancy. Other multiple used second-line treatment options were LOD, CC, letrozole + metformin, and IVF.
We were able to obtain the full databases of six trials including 1230 women. The analysis of the pooled IPD showed a relative risk of 1.202 (95% CI 1.082-1.335) in ovulation rates, favouring letrozole. We found a negative interaction between BMI and treatment effects on ovulation rate, at disadvantage of CC (p=0.035). In the ovulating group, we found live birth rates of 51% for letrozole and 38% for CC after six treatment cycles, with a hazard ratio of 1.45 (95% CI 1.106-1.813).

Interpretation: In women with polycystic ovary syndrome, letrozole is more effective than clomiphene citrate in terms of both ovulation rates and live birth rates among ovulating women. With about half of the ovulating women achieving live birth on first-line letrozole treatment and given the willingness of Dutch clinics to participate in a trial, we consider a randomised controlled trial comparing letrozole versus gonadotrophins as second-line treatment after ovulation on a first-line letrozole treatment in the Netherlands to be relevant and feasible.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive women[1], with a heterogeneous clinical presentation. At least two of the three key features oligo-anovulation, hyperandrogenism, and polycystic ovaries are needed for diagnosing PCOS[2]. PCOS is the leading cause of anovulatory infertility[3], therefore ovulation induction plays a major role in the management of PCOS in women pursuing pregnancy.
In the past, clomiphene citrate (CC) has been first-line treatment for ovulation induction[4] with ovulation rates around 75%[5]. With only about half of these women conceiving, initial CC treatment fails in the majority of cases when it comes to inducing pregnancy[5].
For this group, multiple options for second-line treatment have been evaluated, with Weiss et al. describing live birth rates of 41% after prolonged CC treatment versus 52% after switching to gonadotrophins[6].
Since 2001, letrozole has been in use for ovulation induction. Recent guidelines recommend letrozole as first-line treatment because of higher ovulation and live birth rates compared to clomiphene citrate[7]. Meta-analyses found that ovulation induction with letrozole over six cycles may result in over 10% higher live birth rates[8,9]. Women who do not conceive will usually switch to ovulation induction with gonadotrophins on which about half of the women will have a conception leading to a live birth[6,7]. Compared to letrozole, ovulation induction with gonadotrophins is more burdensome for patients given the daily injections, has a higher risk of overstimulation and multiple pregnancies, and is relatively expensive[10–12]. Furthermore, the use of plastic ampoules and syringes as well as the requirement for more intense monitoring, make its use less sustainable. Alternatively, women that ovulate on letrozole may continue to use letrozole for another six cycles. It would be interesting to evaluate in a randomised controlled trial the effectiveness of continuing letrozole treatment compared to a treatment switch to gonadotrophins.
To determine the feasibility of such a randomised trial, we need to know what first and second-line treatments are provided in practice in the Netherlands, and whether clinics are inclined to participate in a trial. Furthermore, in order to estimate the potential population size, we need to know the percentage of women ovulating but not getting pregnant on letrozole as these women will be eligible for further treatment after six cycles of letrozole.

Methods

IPD analysis

We conducted a retrospective study using the individual participant database (IPD) used in the meta-analysis of Wang et al.[13] and collected the data from all studies that had compared letrozole and clomiphene citrate in randomised controlled trials.
The main outcome measures were ovulation rates per treatment cycle and cumulative live birth rates. For ovulation rates, we assumed that above 4 to 5 cycles, anovulatory women would have switched to a second-line treatment. Therefore, we used a cut-off at cycle number 5.
Per patient data was transformed into data per treatment cycle. We compared treatment with letrozole versus treatment with clomiphene citrate and calculated ovulation rates and relative risk with 95% confidence intervals (CIs) using general linear models with a Poisson as distribution and Log as link function. We explored the treatment-covariate interaction for BMI and age within these models and visualised the interaction in spline curves prepared in STATA 15.1 (StataCorp, Texas, USA).
To estimate cumulative live birth rates, Kaplan Meier curves were used, the hazard ratio was calculated and significance was determined using a log-rank test. SPSS software (version 28.0; IBM Corp, USA) was used for statistical analysis.

Questionnaire

We developed an online questionnaire for a national survey among all 66 fertility clinics in the Netherlands. Clinicians were asked to fill in questions about the first and second-line treatment options they provide for ovulation induction, including details about dose, duration and use of intra-uterine insemination (IUI). The questionnaire was prepared in Castor EDC (Version 2022.5.3)[14]. Data was extracted and percentages were obtained using SPSS software (version 28.0; IBM Corp, USA).

Results

Study and patient characteristics

Data from six studies assessing letrozole versus clomiphene citrate was included (Amer et al.[15], Bayar et al.[16], Kar et al.[17], Legro et al.[18], Liu et al.[19], and Nazik et al.[20]). This included data of 1230 patients. Mean age and BMI were similar in both treatment groups, but differed between studies, with a remarkably high mean BMI population in the study of Legro et al. (Table I).

Table I Characteristics of included studies

	Sample size		Age (years)		BMI (kg/m^2)	
Study	**LE**	**CC**	**LE**	**CC**	**LE**	**CC**
Amer et al., 2015[15]	78	77	28.3 ± 4.4	28.1 ± 4.3	27.5 ± 4.8	27.6 ± 4.9
Bayar et al., 2006[16]	38	36	32.2 ± 3.9	30.6 ± 4.0		
Kar et al., 2012[17]	52	51			25.9 ± 3.6	26.0 ± 3.3
Legro et al., 2014[18]	360	354	28.9 ± 4.5	28.7 ± 4.0	35.0 ± 9.5	35.2 ± 9.0
Liu et al., 2015[19]	62	63	26.9 ± 2.7	27.1 ± 3.1	20.9 ± 2.4	21.5 ± 2.8
Nazik et al., 2012[20]	31	33	25.7 ± 4.8	27.9 ± 6.0	24.5 ± 3.7	25.6 ± 4.9
Total	621	614	28.6 ± 4.5	28.6 ± 4.1	31.2 ± 9.4	31.4 ± 9.0

Data presented as n, or mean ± SD
LE = letrozole, CC = clomiphene citrate

A total of 3873 treatment cycles (1891 with letrozole, 1982 with CC) were analysed (Table II). There was a wide spreading in total treatment cycles between the studies, due to differences in study protocol and study size. In Kar et al.[17] for instance, all patients received only one treatment cycle, whereas Amer et al.[15] treated up to seven cycles (Supplementary Table I). Besides this, study protocols differed in dosing strategy for both letrozole and CC. Some studies started with letrozole 2.5mg/day for 5 days[15,16,18,20], while the others started with 5mg/day for 5 days[17,19]. Only two studies increased dose after one anovulatory cycle, with a maximum dose of 5mg/day[15] or 7.5mg/day[18]. For CC, some studies started with 100mg[16,17,20], where others started with 50mg and increased dose up to 100mg[15] or 150mg[18,19] daily (Supplementary Table I).

Table II Included treatment cycles

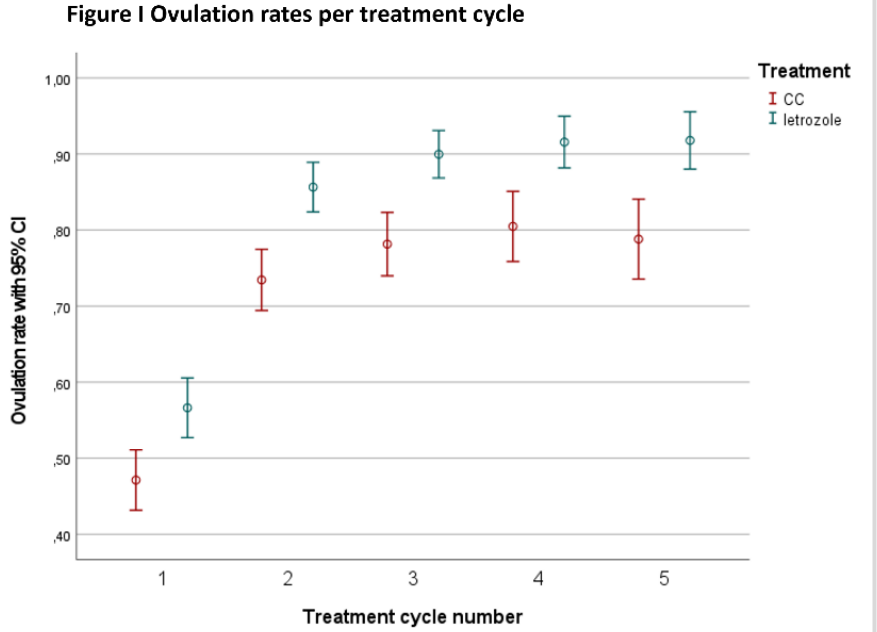
		Number of treatment cycles (total 3872)
Treatment	Letrozole	1891 (48.8%)
	CC	1982 (51.2%)
Study	Amer et al., 2015[15]	488 (12.6%)
	Bayar et al., 2006[16]	173 (4.5%)
	Kar et al., 2012[17]	103 (2.7%)
	Legro et al., 2014[18]	2741 (70.8%)
	Liu et al., 2015[19]	304 (7.8%)
	Nazik et al., 2012[20]	64 (1.7%)
Treatment cycle number	1	1230 (31.8%)
	2	913 (23.6%)
	3	739 (19.1%)
	4	548 (14.1%)
	5	443 (11.4%)

CC = clomiphene citrate

Ovulation and live birth

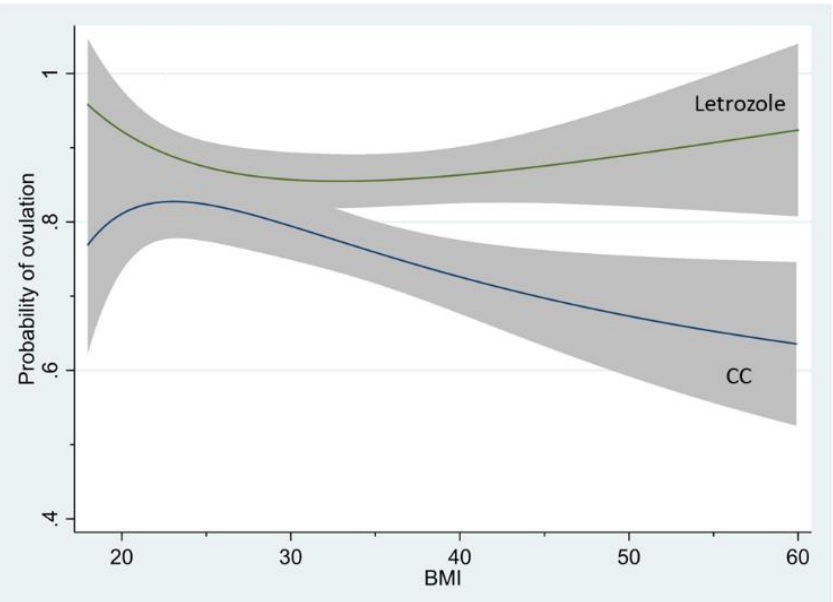
Treatment with letrozole showed a statistically significant higher ovulation rate when compared to CC (RR 1.202, 95% CI 1.082-1.335).
Ovulation rates per treatment cycle increased from 56.6% (95% CI 52.7-60.6) for letrozole and 47.1% (95% CI 43.1-51.1) for CC in the first cycle to respectively 91.8% (95% CI 88.0-95.6) and 78.8% (95% CI 73.6-84.1) after five treatment cycles (Figure I)
In all treatment cycles, the ovulation rate showed an about ten percent higher ovulation rate for letrozole compared to CC. Both treatment groups showed a rapid rise in ovulation rate from the first to the second cycle. As of the third cycle, this rise stagnated with even a small decrease in the CC group.

Figure I Ovulation rates per treatment cycle

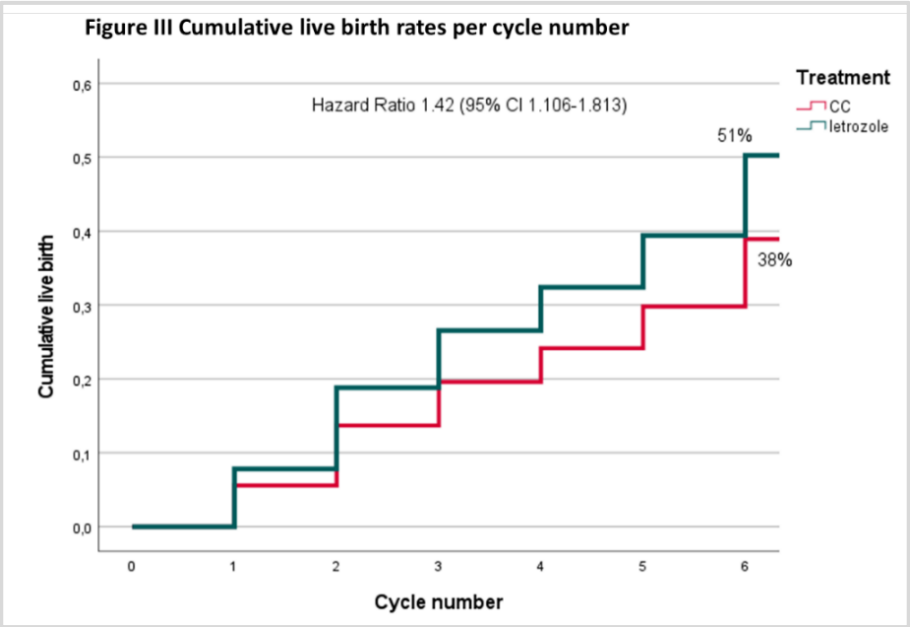


We did not find an interaction between age and treatment. For BMI, we found an interaction with treatment effects on ovulation rate, at disadvantage of CC (p=0.035). As indicated in Figure II, BMI was not associated with ovulation in women receiving letrozole, while in women taking CC BMI was negatively associated with chance to ovulate. The overall interaction effect of BMI on chance to ovulate following letrozole versus CC suggests that per unit increase in BMI letrozole had a 0% to 1.4% higher ovulation rate compared to CC (RR 1.007, 95% CI 1.000-1.014).

Figure II Interaction effect of BMI and treatment



Within the group of ovulating women, cumulative live birth rates after six treatment cycles were 51% for letrozole and 38% for CC (log-rank p <0.004), with a hazard ratio of 1.45 (95% CI 1.106-1.813) (Figure III).



Ovulation induction in the Netherlands

The online questionnaire was sent to 66 fertility clinics in the Netherlands, of which 39 responded (59%). Of these, 36 fertility clinics (92%) used letrozole as first-line treatment, the other three clinics used clomiphene citrate, of which one sometimes added metformin (Figure IV). Of the 36 fertility clinics that used letrozole as first-line treatment, all started with a 2.5mg daily dose of letrozole except for one that used a starting dose of 5mg daily. In all clinics the dose was increased with 2.5mg after one anovulatory cycle, up to a maximum dose of 7.5mg daily. 17 clinics prescribed letrozole for six ovulatory cycles (47%), 11 clinics prescribed letrozole for at least 6 ovulatory cycles (31%) and eight clinics (22%) prescribed letrozole for 12 cycles (Supplementary Table II). Of these clinics, 11 (31%) always used intra-uterine insemination and 18 (50%) never used IUI. The three fertility clinics that used CC as first-line treatment did not concurrently use IUI (Figure IV).

If ovulation failed to occur on letrozole, the fertility clinics offered multiple second-line treatment options. Almost all clinics providing injections with gonadotrophins (94%). Other commonly used options were laparoscopic ovarian drilling (28%), CC (17%), and letrozole + metformin (11%).
In case of ovulation but no pregnancy, treatment with gonadotrophins was again the most used second-line treatment with 30 clinics (83.3%) providing this. Used alternatives were IVF (5.6%), CC (2.8%), and other non-specified alternatives (19.4%) (Figure V).
The three fertility clinics that used CC as first-line treatment all applied gonadotrophins as second-line treatment option, with one clinic (33.3%) also providing CC + metformin and LOD as alternative. In case of ovulation but no pregnancy, all clinics used injections with gonadotrophins (Supplementary Table II).

Figure IV First-line treatment in Dutch fertility clinics

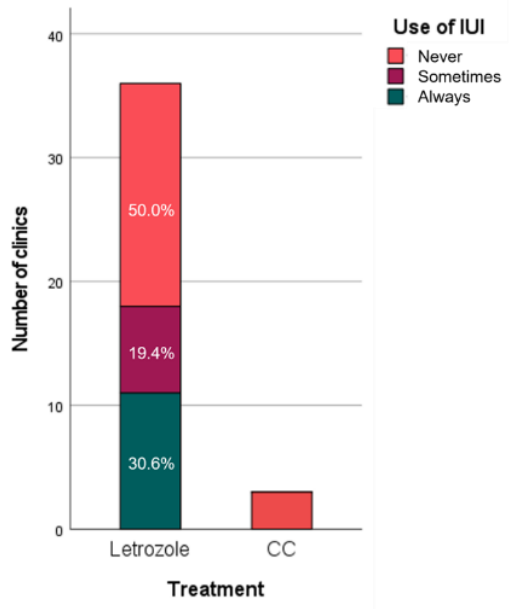
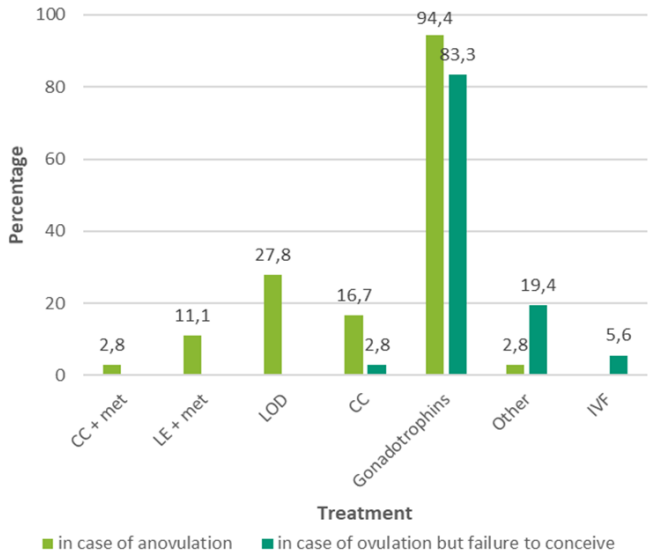


Figure V Second-line treatment options provided after first-line treatment with letrozole in Dutch fertility clinics



CC = clomiphene citrate, met = metformine, LE = letrozole, LOD = laparoscopic ovarian drilling

Discussion

In this study, we analysed ovulation rates per treatment cycle and live birth rates per ovulating patient while accounting for cycle number in women with PCOS. Furthermore, we evaluated the feasibility of an RCT comparing letrozole and gonadotrophins as second-line treatment options in the Netherlands.

Summary of evidence and interpretation

Our study showed that letrozole is more effective in ovulation induction compared to clomiphene citrate with an over ten percent higher ovulation rate (91.8% vs 78.8%), which is consistent with the Cochrane systematic review of Franik et al.[9].
A recent meta-analysis reported a similar ovulation rate per cycle for letrozole around 90%[8].
Looking at the evolution of ovulation rates over the treatment cycles, the favour of letrozole was comparable in all treatment cycles. From the third cycle, ovulation rates stagnated and even dropped in the CC treatment group.
BMI appeared to negatively affect ovulation rates in the CC group compared to the letrozole group. Since the data of the last two treatment cycles mainly consisted of the high BMI population of Legro et al., this may have resulted in both a greater negative effect on ovulation rates in the last few cycles compared to the first cycles, and in the CC group compared to the letrozole group.

In the ovulating group, we found letrozole to be more effective in terms of live birth compared to CC with a statistically significant difference. Although most studies report a slightly different outcome by analysing live birth among the whole treatment group (not only ovulating women), recent meta-analyses are conclusive on the benefit of letrozole in terms of live birth[8,11,21].
For analysing live births, we used the number of treatment cycles in which pregnancy was achieved as a measure of time. However, data on the course of ovulation, the exact number of ovulating cycles prior to pregnancy, and the dosage on which pregnancy was achieved is lacking.
In our study, the percentage of ovulating women failing to have a live birth after six treatment cycles with letrozole was 49%. Assuming that in the Netherlands there are 10.000 women with PCOS and a child wish undergoing ovulation induction each year, this implies that 9000 women will ovulate on letrozole of which 4500 will conceive, leaving 4500 women eligible for further treatment on a yearly basis.

According to the questionnaire, almost all Dutch fertility clinics that responded are following the international guidelines on ovulation induction by using letrozole as first-line treatment[7]. 22-53% of the clinics used letrozole for more than six cycles, showing their willingness to continue letrozole treatment if pregnancy fails to occur. Besides this, the majority of the clinics provided gonadotrophins as second-line treatment option. This, along with the fact that the majority of clinics have indicated their willingness to participate in a trial, implies that a trial comparing those two second-line options would be feasible.

Strengths and limitations

Our study has several strengths. First, we did our analysis using individual participant data (IPD). By analysing the raw data of the trials, we were not depending on the analyses and reports of the original trials. Second, we looked from a new perspective by analysing ovulation and live birth rates per cycle number, which allowed us to show the gradient of ovulation and live birth rates within the multiple-cycle treatments. Besides that, by using the outcome of live birth rates in only ovulating women, we were able to show the effect of letrozole on live birth independent of its effect on ovulation rates.
Third, with evaluating the feasibility of a future trial in the Netherlands, we showed some previously unknown information by providing an indication of which protocols are followed in Dutch fertility clinics.

This study also has several limitations. First, differences in study protocol (dosing strategy, number of treatment cycles, crossing over strategy) between the included studies make it difficult to compare the individual study results and interpret the gradient rates over the treatment cycles. However, since all studies are RCTs, we think that some conclusions can be drawn from the pooled data. Second, as mentioned above, detailed data on treatment dose per cycle and ovulation course before achieving pregnancy are lacking and therefore, we cannot say anything about the exact number of ovulating cycles before achieving pregnancy leading to live birth.
Third, with only 59% of the Dutch fertility clinics responding to our questionnaire, a complete summary of the provided treatments in the Netherlands cannot be given. However, we think that with these results, we got a good indication of provided treatments in the Netherlands and showed enough feasibility for a future trial.

Conclusion

In conclusion, this study showed a double benefit of letrozole compared to CC by both reaching higher ovulation rates and higher live birth rates within the ovulating group. We found a percentage of 49% of the women failing to have a live birth while ovulating on letrozole, and therefore being eligible for second-line treatment. This potential population size along with the willingness of Dutch clinics to participate in a trial, lead us to the conclusion that a randomised controlled trial comparing letrozole versus gonadotrophins as second-line treatment after ovulation on a first-line letrozole treatment in women with PCOS in the Netherlands will be both relevant and feasible.

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Supplementary material

Supplementary table I Study characteristics

Study	Sample size		Number of treatment cycles *mean (range)*	Letrozole dose	CC dose
	LE	CC			
Amer et al., 2015	78	77	3.3 (0-7)	2.5mg - 5mg	50mg - 100mg
Bayar et al., 2006	38	36	2.6 (1-4)	2.5mg	100mg
Kar et al., 2012	52	51	1	5mg	100mg
Legro et al., 2014	360	354	3.6 (0-5)	2.5mg - 5 mg - 7.5mg	50mg - 100mg - 150mg
Liu et al., 2015	62	63	2.1 (0-3)	5 mg	50mg - 100mg - 150mg
Nazik et al., 2012	31	33	1.3	2.5mg	100mg

LE = letrozole, CC = clomiphene citrate

Supplementary Table II Questionnaire data

First-line treatment		
LETROZOLE	**36 (92.3%)**	
	Starting dose	
	2.5mg	35 (97.2%)
	5mg	1 (2.8%)
	Timing of treatment in menstrual cycle	
	Day 3-7	34 (94.4%)
	Day 4-8	1 (2.8%)
	Day 5-9	4 (11.1%)
	Use of IUI	
	Always	11 (30.6%)
	Sometimes	7 (19.4%)
	Never	18 (50.0%)
	Duration of first-line treatment if ovulation is reached	
	6 cycles	17 (47.2%)
	6-12 cycles	11 (30.6%)
	12 cycles	8 (22.2%)
	Second-line treatment if ovulation fails to occur	
	LE + metformin	4 (11.1%)
	CC	6 (16.7%)
	CC + metformin	1 (2.8%)
	Gonadotrophins	34 (94.4%)
	LOD	10 (27.8%)
	Other	1 (2.8%)
	Second-line treatment after ovulation but no pregnancy	
	CC	1 (2.8%)
	Gonadotrophins	30 (83.3%)
	IVF	2 (5.6%)
	Other	7 (19.4%)
CC	**3 (7.7%)***	
	Use of IUI	
	Never	3 (100%)
	Duration of first-line treatment if ovulation is reached	
	6 cycles	1 (33.3%)
	6-12 cycles	1 (33.3%)
	12 cycles	1 (33.3%)
	Second-line treatment if ovulation fails to occur	
	CC + metformin	1 (33.3%)
	Gonadotrophins	3 (100%)
	LOD	1 (33.3%)
	Second-line treatment after ovulation but no pregnancy	
	Gonadotrophins	3 (100%)

*one clinic also used CC + metformin as first-line treatment

IUI = intra-uterine insemination, LE = letrozole, CC = clomiphene citrate, LOD = laparoscopic ovarian drilling