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ORIGINAL ARTICLE *Reproductive endocrinology*

Emulating a target trial of the comparative effectiveness of clomiphene citrate and letrozole for ovulation induction

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STUDY QUESTION: What are the comparative pregnancy outcomes in women who receive up to six consecutive cycles of ovulation induction with letrozole versus clomiphene citrate?

SUMMARY ANSWER: The risks of pregnancy, livebirth, multiple gestation, preterm birth, neonatal intensive care unit (NICU) admission and congenital malformations were higher for letrozole compared with clomiphene in participants with polycystic ovarian syndrome (PCOS), though no treatment differences were observed in those with unexplained infertility.

WHAT IS KNOWN ALREADY: Randomized trials have reported higher pregnancy and livebirth rates for letrozole versus clomiphene among individuals with PCOS, but no differences among those with unexplained infertility. None of these trials were designed to study maternal or neonatal complications.

STUDY DESIGN, SIZE, DURATION: We emulated a hypothetical trial of the comparative effectiveness of letrozole versus clomiphene citrate for ovulation induction among all women, then stratified by PCOS and unexplained infertility status. We used real-world data from a large healthcare claims database in the USA (2011–2015).

PARTICIPANTS/MATERIALS, SETTING, METHODS: We analyzed data from 18 120 women who initiated letrozole and 49 647 women who initiated clomiphene during 2011–2014, and who were aged 18–45 years with no history of diabetes, thyroid disease, liver disease or breast cancer and had no fertility treatments for 3 months before trial initiation. The treatment strategies were clomiphene citrate or letrozole for six consecutive cycles. The outcomes were pregnancy, livebirth, multiple gestation, preterm birth, small for gestational age (SGA), NICU admission and major congenital malformations. We estimated the probability of each outcome under each strategy via pooled logistic regression and used standardization to adjust for confounding and selection bias due to loss to follow-up.

MAIN RESULTS AND THE ROLE OF CHANCE: The estimated probabilities of pregnancy, livebirth and neonatal outcomes were similar under each strategy, both overall and among individuals with unexplained infertility. Among women with PCOS, the probability of pregnancy was 43% for letrozole vs 37% for clomiphene (risk difference [RD] = 6.0%; 95% CI: 4.4, 7.7) in the intention-to-treat analyses. The corresponding probability of livebirth was 32% vs 29% (RD = 3.1%; 95% CI: 1.5, 4.8). In per protocol analyses, the risk of multiple gestation was 19% vs 9%, the risk of preterm birth was 20% vs 15%, the risk of SGA was 5% vs 3%, the risk of NICU admission was 22% vs 16% and the risk of congenital malformation was 8% vs 2% among those with a livebirth.

LIMITATIONS, REASONS FOR CAUTION: We cannot completely rule out the possibility of residual confounding by body mass index or duration of infertility. However, we adjusted for proxies identified in administrative data and results did not change.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings suggest that for women with unexplained infertility, the two treatments result in comparable probabilities of a livebirth. For women with PCOS, letrozole appears slightly more effective for attaining a livebirth.

Neonatal outcomes were similar for the two treatments among women with unexplained infertility; we did not confirm the hypothesized higher risk of adverse neonatal outcomes for clomiphene versus letrozole. The risks of adverse neonatal outcomes were slightly greater among women with PCOS who were treated with letrozole versus clomiphene. It is likely that these effects are partially mediated through an increased risk of multiple gestation among women who received letrozole.

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Key words: clomiphene citrate / letrozole / ovulation induction / infertility / polycystic ovarian syndrome

Introduction

Infertility affects up to 15% of couples trying to conceive (Louis *et al.*, 2013; Thoma *et al.*, 2013), and ~25% of infertility is attributable to ovulatory dysfunction (American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology, 2002; National Collaborating Centre for Women's and Children's Health (UK), 2004). Two commonly used oral agents for inducing ovulation are clomiphene, an older drug, and the newer letrozole. Clomiphene citrate is a nonsteroidal antiestrogen which has been used as a first line ovulation induction agent since its approval in 1967 (US Food and Drug Administration, 1967). The ovulation rate in women treated with clomiphene is 50–75% and the clinical pregnancy rate is 30–40% over the course of six cycles of treatment (Gorlitsky *et al.*, 1978; Imani *et al.*, 2002; Homburg, 2005; Legro *et al.*, 2007; Diamond *et al.*, 2015).

Treatment with clomiphene has several limitations. First, the anti-estrogenic effects of clomiphene on the endometrium may reduce the probability of pregnancy after ovulation and also result in side effects including mood changes, hot flashes, nausea and dizziness (Legro *et al.*, 2014). Second, clomiphene supports multiple follicle development and thus results in a high rate of multiple births (8–13%) compared with spontaneously conceived pregnancies (2%) (Wallach and Scialli, 1986; Homburg, 2005; Diamond *et al.*, 2015). Finally, clomiphene might increase the risk of congenital malformations, including certain neural tube defects, septal heart defects and hypospadias (Greenland and Ackerman, 1995; Meijer *et al.*, 2006; Wu *et al.*, 2006; Reefhuis *et al.*, 2010; Auffret *et al.*, 2019), though the evidence is inconclusive (Greenland and Ackerman, 1995; Sørensen *et al.*, 2005).

Recently, the aromatase inhibitor letrozole has become a common alternative to clomiphene. Unlike clomiphene, letrozole does not exert anti-estrogenic effects on the endometrium (Baruah *et al.*, 2009; Samani *et al.*, 2009; Jirge and Patil, 2010), typically results in single monofollicular ovulation (Mitwally *et al.*, 2005) and has a shorter half-life than clomiphene, which reduces the risk of periconceptional exposure and thus potentially of congenital malformations (Casper and Mitwally, 2006).

Randomized trials of letrozole versus clomiphene in women with polycystic ovarian syndrome (PCOS) found increased ovulation, pregnancy and livebirth rates among those treated with letrozole (Banerjee Ray *et al.*, 2012; Roy *et al.*, 2012; Legro *et al.*, 2014; Amer *et al.*, 2017; Liu *et al.*, 2017; Franik *et al.*, 2018; Wang *et al.*, 2019). In contrast, randomized trials in couples with unexplained infertility found similar outcomes for the two treatments (Diamond *et al.*, 2015; Eskew *et al.*, 2019). These trials had sample sizes too small to study neonatal outcomes. We therefore used a large, observational dataset to compare neonatal outcomes of pregnancies conceived with letrozole versus clomiphene citrate. We did so by emulating a (hypothetical) target trial (Hernán and Robins, 2016) using real-world data.

Materials and methods

A target trial is the pragmatic randomized trial that we would like to conduct to answer the causal question of interest. Explicitly designing and emulating a target trial facilitates careful specification of a causal question and addresses common sources of bias in observational studies (Hernán *et al.*, 2016; Hernán and Robins, 2016). In this section, we first describe the protocol of a target trial to assess the comparative effectiveness and safety of clomiphene and letrozole, and then describe our procedures to emulate the target trial as closely as possible.

Target trial specification

Table I outlines the key elements of the protocol of the target trial: eligibility criteria, treatment strategies, treatment assignment, outcomes of interest, follow-up period, causal contrasts of interest and statistical analysis.

Eligibility criteria

Women aged 18–45 years; with at least one ovary, patent fallopian tube and uterus; with no history of fertility treatments, diabetes, thyroid disease, liver disease or breast cancer; and with continuous enrollment in MarketScan with prescription benefits for at least 3 months before trial initiation.

Table I Protocol for the target trial and emulation.

Protocol component	Target trial	Emulation
Eligibility criteria	• Non-pregnant women aged 18–45 years who seek fertility treatments between July 2011 and December 2014. • At least one ovary, patent fallopian tube and uterus. • Continuous enrollment in MarketScan with prescription benefits for at least 3 months. • No history of fertility treatment. • No pre-existing diabetes, thyroid disease, liver disease or breast cancer. Not using sex steroids, thyroid replacement, other infertility drugs or insulin sensitizers.	We assumed that women who received treatment had at least one ovary, patent fallopian tube and uterus. We defined no history of fertility treatment as having no claims for ovulation induction agents, IUI or ARTs in the 3 months before treatment. Pre-existing diabetes, thyroid disease, liver disease or breast cancer; and use of sex steroids, thyroid replacement, other infertility drugs or insulin sensitizers were identified using claims in the 3 months before treatment.
Treatment strategies	1. Initiate one cycle of clomiphene citrate for 5 days per menstrual cycle immediately and for 5 additional consecutive menstrual cycles, unless the patient becomes pregnant via the assigned treatment (6 total consecutive treatment cycles). 2. Initiate one cycle of letrozole for 5 days per menstrual cycle immediately and for 5 additional consecutive menstrual cycles, unless the patient becomes pregnant via the assigned treatment (6 total consecutive treatment cycles). Treatment may continue for up to 10 months. Dosing and monitoring are left to physician's discretion. Use of either timed intercourse or intrauterine insemination is permitted. Switching between clomiphene citrate and letrozole is not permitted under the protocol. Discontinuing treatment before becoming pregnant or before completing six failed treatment cycles is not permitted under the protocol.	Same. We assumed that one dispensation of medication was equal to one treatment cycle and allowed up to 60 days between dispensations to be considered consecutive treatment cycles.
Assignment procedures	Individuals are randomly assigned to one of the two treatment strategies and are aware of their assignment.	Individuals are assigned to the strategy compatible with their observed treatment dispensation. We assumed that women were randomly assigned with levels of baseline covariates: maternal age at first dispensation, year at first dispensation, geographic region, overweight/obesity, tobacco, alcohol or drug use or dependence, hypertension, epilepsy, anticonvulsant use, antidepressant use, antibiotic use, use of teratogenic medications, diagnosis of infertility, diagnosis of PCOS and dispensations of prescription prenatal vitamins or folate supplements.
Follow-up period	Starts at treatment assignment. Participants have up to 10 months to complete six treatment cycles (60 days per cycle for 6 cycles). Participants who become pregnant are followed until 90 days after birth, pregnancy loss or loss to follow-up, whichever occurred earliest.	Same.
Outcome	Pregnancy (regardless of pregnancy outcome), livebirth, adverse neonatal outcomes: multiple gestation, preterm birth, small for gestational age (SGA), neonatal intensive care unit (NICU) admission and major congenital malformations.	Same. Pregnancies are identified based on claims associated with the end of pregnancy (e.g. delivery).
Causal contrasts of interest	Intention-to-treat effect Per-protocol effect	Observational analog to intention-to-treat effect Observational analog to per-protocol effect
Statistical analysis	Pregnancy and livebirth are reported as marginal risks. Neonatal outcomes are reported both as joint and conditional risks. Risks and RDs are estimated using pooled logistic regression and standardizing the model-derived estimates standardized to the distribution of the baseline covariates. 95% CIs are estimated using percentile-based bootstrapping with 500 samples.	Same, except that the observational analogs of the intention-to-treat and per-protocol analyses require additional adjustment for confounding.

Treatment strategies and assignment

Eligible participants would be randomized to one of two treatment strategies and would be aware of the treatment they are receiving: (i) clomiphene citrate for 5 days per menstrual cycle for six consecutive menstrual cycles, unless the patient becomes pregnant via the assigned treatment; (ii) letrozole for 5 days per menstrual cycle for six consecutive menstrual cycles, unless the patient becomes pregnant via the assigned treatment. For both strategies, dosage and pregnancy monitoring are left to the physician's discretion and IUI may be used as clinically indicated. Concurrent treatment with gonadotropins or metformin is not permitted. In addition, neither switching between clomiphene citrate and letrozole nor discontinuing treatment before becoming pregnant or completing six failed treatment cycles is permitted under the protocol. A variation of this target trial might allow discontinuation after adverse reactions or lack of ovulation, but these events would be difficult to identify based on claims.

Follow-up period

Follow-up would start at randomization and end at livebirth, 10 months after randomization, loss of insurance eligibility or administrative end of follow-up on 1 October 2015. Participants who become pregnant are followed until 90 days after birth, pregnancy loss or loss to follow-up, whichever occurred earliest.

Outcomes

The outcomes are pregnancy, livebirth, multiple gestation, preterm birth, delivery small for gestational age (SGA), neonatal intensive care unit (NICU) admission and major congenital malformations (a structural abnormality with surgical, medical or cosmetic importance, excluding chromosomal or Mendelian-inherited anomalies).

Causal contrasts of interest

The causal contrasts are the intention-to-treat effect (the effect of treatment assignment, regardless of whether individuals adhered to the protocol) and the per-protocol effect (the effect if everybody had adhered to the protocol). We would estimate the intention-to-treat effect for only pregnancy and livebirth, but the per-protocol effect for all outcomes, because the per-protocol effect reflects the periconceptional exposure for the index fetus and is more clinically relevant.

Statistical analysis

The intention-to-treat analysis estimates the risks of each outcome in each treatment group according to the assigned strategy, and their risk differences (RDs). In the presence of loss to follow-up with potential selection bias due to informative censoring, the probability of pregnancy would be estimated by fitting a pooled logistic model with indicators of treatment assignment, treatment cycle, and their product terms; and the baseline covariates maternal age at first dispensation, year of first dispensation, geographic region, overweight/obesity, tobacco, alcohol or drug use or dependence, hypertension, epilepsy, anticonvulsant use, antidepressant use, antibiotic use, use of teratogenic medications, diagnosis of infertility, diagnosis of PCOS and dispensations of prescription prenatal vitamins or folate supplements. Among those with pregnancy, a logistic regression model with the same covariates would be fit separately for each neonatal outcome. The model-derived estimates would be standardized to the distribution of the baseline covariates to obtain absolute risks and RDs. For comparison with previous studies, we would also calculate the conditional risk of neonatal outcomes among liveborn infants (the probability of congenital malformations as calculated above would be interpreted as becoming pregnant and having a liveborn infant with a congenital malformation among those that initiate that treatment strategy, whereas the conditional probability described here would be interpreted as the probability that a liveborn infant would have a congenital malformation).

The per-protocol analysis would be the same as the intention-to-treat analysis with baseline covariates, except that individuals would be censored if/when they switch treatments after a cycle failure or if they prematurely discontinue treatment (i.e. violate the protocol). All analyses would be repeated among the subgroup of women with evidence of PCOS. Nonparametric bootstrapping with 500 samples would be used to construct a percentile-based 95% CI.

Several analyses would be conducted under modified eligibility criteria. First, we would estimate the probability of livebirth among overweight women with PCOS to compare our findings most directly with those of the Reproductive Medicine Network's Pregnancy in Polycystic Ovarian Syndrome II (PPCOS II) trial, which enrolled a high proportion of obese women (Legro *et al.*, 2014). Second, we would estimate the probabilities of pregnancy and livebirth among women with idiopathic infertility origin to facilitate comparison with previous trials conducted among couples with unexplained infertility. Third, we would stratify our analyses by age at treatment initiation, because age-related changes in the endometrial environment may impact the efficacy of treatment. For example, previous studies indicate that pregnancy rates are very low (<5%) for women older than 40 years of age treated with clomiphene (Armstrong and Akande, 2013). Age categories are based on clinical guidelines by the American Society for Reproductive Medicine, which divide patient age into the following groups: <35, 35–37, 38–40, 41–42 and ≥43 years (Centers for Disease Control and Prevention, 2020). Lastly, we would restrict the analyses to women who received clomiphene or letrozole without IUI because outcomes may differ between cycles with timed intercourse versus IUI.

Target trial emulation

We emulated the target trial using data from the IBM MarketScan Commercial Claims and Encounters Database for 2011–2015, which contains de-identified reimbursed claims for commercially insured people in the USA. MarketScan includes inpatient and outpatient medical claims for clinical diagnoses and procedures (e.g. International Classification of Disease [ICD]-9 codes, Current Procedural Terminology [CPT] codes), pharmacy claims (i.e. medication dispensations), and demographic information (e.g. age, sex, geographic region, employment industry). Pharmacy claims recorded in the database can be linked to the Red Book, a resource for drug pricing and packaging information, to provide data including labeling, route of administration, dosage and days' supply. We specified and operationalized the trial emulation protocol as follows (Table I).

Eligibility criteria

We used ICD-9 codes in claims to identify pre-existing diabetes, thyroid disease, liver disease or breast cancer; and use of levothyroxine, sex steroids, other infertility drugs or insulin sensitizers in the 3 months before treatment (Supplementary Table SI). We assumed that

individuals with no claims for ovulation induction agents, IUI or ARTs in the 3 months before treatment had no history of fertility treatment.

Treatment strategies

We identified pharmacy dispensations for oral letrozole or clomiphene. We assumed that one dispensation of medication was equal to one treatment cycle and allowed up to 60 days between dispensations to be considered consecutive treatment cycles. Individuals with more than 60 days without evidence of treatment or pregnancy were classified as having discontinued. Some women had several dispensations for clomiphene or letrozole on the same day or within a few days. To limit potential misclassification, we required at least 7 days between dispensations to be considered a unique treatment cycle. Individuals were assigned to the strategy compatible with their first observed treatment dispensation.

Treatment assignment

We assumed randomization of treatment within levels of the baseline covariates maternal age at first dispensation, year of first dispensation, geographic region, overweight/obesity, tobacco, alcohol or drug use or dependence, hypertension, epilepsy, anticonvulsant use, antidepressant use, antibiotic use, use of teratogenic medications, diagnosis of infertility, diagnosis of PCOS and dispensations of prescription prenatal vitamins or folate supplements. Covariate data were ascertained using claims recorded in the 3 months prior to the first treatment cycle (Supplementary Table SI).

Follow-up period

Treatment was monitored for 10 months after the first treatment dispensation (i.e. 60 days per cycle for 6 cycles). Participants were followed for at least 60 days after the last treatment cycle to observe a pregnancy in the database. Thus, women who did not become pregnant were followed for 1 year (10 months of treatment plus 2 months of additional follow-up). Those who became pregnant were followed until 90 days after birth, pregnancy loss or loss to follow-up, whichever occurred earliest.

Outcomes

We estimated the timing of pregnancy using a validated algorithm based on claims associated with the end of pregnancy (Li *et al.*, 2013; Margulis *et al.*, 2013). To account for some misclassification of gestational duration, we allowed the estimated date of the last menstrual period (LMP) to fall up to 60 days before treatment initiation (i.e. we established a window around the *actual* LMP during which to identify the *estimated* LMP). A participant was classified as having a pregnancy if they had pregnancy-related claims with an estimated LMP date between 60 days before treatment initiation (to allow for some misclassification of estimated LMP) and 365 days after treatment initiation (reflecting initiation of pregnancy within follow-up). Linkage between treatment and pregnancy was established when the date of LMP fell within 60 days of the last treatment dispensation.

For evaluation of neonatal outcomes, we required maternal-infant linkage, as well as maternal and infant insurance enrollment for 90 days after delivery (Fig. 1). The procedure for linking pregnancies to infants in healthcare claims databases has been previously described (Palmsten *et al.*, 2013; MacDonald *et al.*, 2018). We identified neonatal outcomes based on previously validated algorithms using ICD-9 and CPT codes, with high positive predictive values (Supplementary Table SI) (Cooper *et al.*, 2008; Palmsten *et al.*, 2014; Phiri *et al.*, 2015).

Causal contrast of interest

The causal contrasts of interest were the observational analog of the intention-to-treat effect (the effect of treatment initiation) and the per-protocol effect.

Statistical analysis

The analytic approach was the same as in the target trial except that the observational analog of the intention-to-treat analysis required adjustment for confounding. In the analysis restricting to women with idiopathic infertility, we ascertained 'unspecified' origin of infertility as a proxy for idiopathic: participants were classified as having infertility of unspecified origin if they had associated claims (ICD-9 628.9) and no other claims for infertility diagnoses or related disorders. PCOS was identified using ICD-9 diagnosis code 256.4. In age stratified analyses, we implemented the following categories: <35, 35–37, 38–40, ≥ 41 years overall; <35, 35–37, ≥ 38 years for women with PCOS (data were sparse among older participants). We conducted an additional sensitivity analysis restricted to women with no evidence of endometriosis to reduce the possibility of exposure misclassification, as aromatase inhibitors may be used to treat endometriosis-related pain. Finally, we used a period of 180, rather than 90, days to establish that participants had no history of fertility treatment. All statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA).

Results

Of 67 767 eligible participants, 18 120 initiated letrozole and 49 647 initiated clomiphene (Fig. 1). Of 4898 individuals with PCOS, 1675 initiated letrozole and 3223 clomiphene. The average age of participants at baseline was approximately 33 years for both treatment groups. The baseline characteristics of the two treatment groups are presented in Table II. Compared with women in the clomiphene group, women in the letrozole group were more likely to reside in the Southern USA and less likely to reside in the northeast, and slightly more likely to have diagnoses of PCOS (9.2% versus 6.5%) and endometriosis (6.8% versus 2.4%).

Discontinuation, switching and pregnancy outcomes were similar for the two treatment groups in each treatment cycle (Fig. 2). Approximately 13–15% of women became pregnant in each treatment cycle for both letrozole and clomiphene, whether they continued their initial treatments or switched. During up to 6 cycles of treatment, 5% of women who initiated letrozole switched to clomiphene, and 12% of women who initiated clomiphene switched to letrozole. On average, women who switched treatments did so after 2 failed cycles (mean $= 2.0$ for letrozole initiators; mean $= 2.3$ for clomiphene initiators). Approximately 63% of women who initiated letrozole discontinued treatment for more than 60 days during the study period, compared with 57% of women who initiated clomiphene.

Intention-to-treat analyses

The estimated probability of pregnancy was 37.4% in the letrozole group and 37.6% in the clomiphene group (RD $= -0.27\%$; 95% CI: -0.70, 0.21), and the probability of livebirth was 28.4% for letrozole

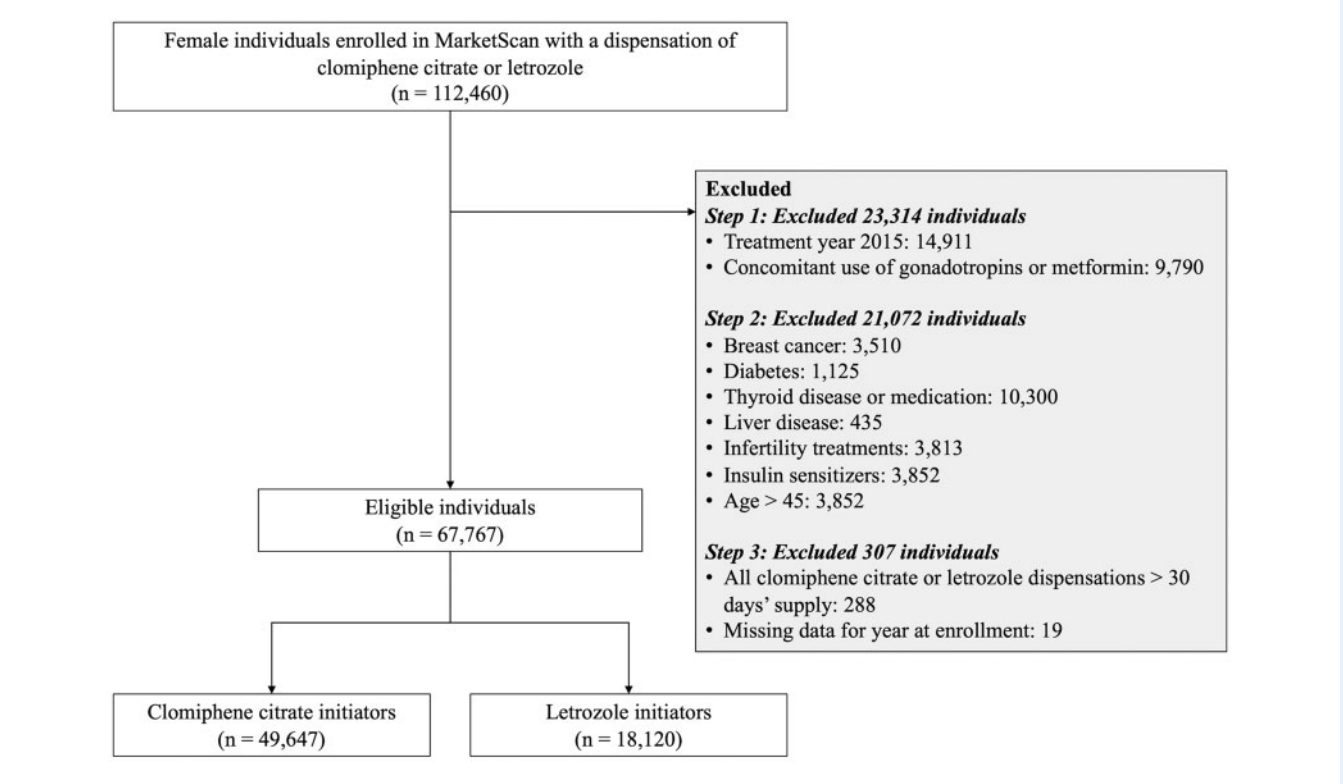

Figure 1. Enrollment flowchart, IBM MarketScan Commercial Claims and Encounters Database 2011–2014. Exclusion criteria are applied before initiation of treatment. 'Concomitant use of gonadotropins or metformin' refers to evidence of use simultaneously with the first cycle of letrozole or clomiphene citrate. This is distinct from baseline use of insulin sensitizers without concomitant use of letrozole or clomiphene.

and 28.6% for clomiphene (RD = −0.16%; 95% CI: −0.58, 0.31). Among women with PCOS, the probability of pregnancy was 43.2% for letrozole and 37.2% for clomiphene (RD = 6.02%; 95% CI: 4.44, 7.70), and the probability of livebirth was 32.4% for letrozole and 29.3% for clomiphene (RD = 3.13%; 95% CI: 1.49, 4.75).

Per protocol analyses

The estimated probability of pregnancy was 36.7% in the letrozole group and 35.9% in the clomiphene group (RD = 0.77%; 95% CI: 0.27, 1.28) (Table III), and the probability of livebirth was 27.9% for letrozole and 27.6% for clomiphene (RD = 0.32%; 95% CI: −0.15, 0.82). In general, the RDs were small for neonatal outcomes (Table III). Frequencies of specific congenital malformations by treatment group are presented in Supplementary Table SII.

Among women with PCOS, the RDs for pregnancy and livebirth were similar to the corresponding intention-to-treat results (Table IV). The RDs for neonatal outcomes conditional on livebirth, comparing letrozole versus clomiphene, were 9.46% (95% CI: 5.75, 13.79) for multiple gestation, 4.69% (95% CI: 0.77, 9.47) for preterm birth, 2.80% (95% CI: 0.53, 5.86) for SGA, 6.50% (95% CI: 1.58, 11.31) for NICU admission and 6.55% (95% CI: 4.25, 9.92) for major congenital malformations. We observed the largest differences in risk of genital malformations, particularly hypospadias.

Among women with claims for unspecified origin of infertility and no other infertility diagnoses (N = 16 540), the probabilities for pregnancy were 40.5% and 38.6% (RD = 1.99%; 95% CI: 0.95, 2.96), and the probabilities for livebirth were 30.2% and 28.8% (RD = 1.42%; 95% CI: 0.41, 2.45) for letrozole and clomiphene, respectively, in the observational intention-to-treat analysis. In the per-protocol analysis, the probabilities of pregnancy were 39.2% and 35.1% (RD = 4.08%; 95% CI: 2.98, 5.14), and the probabilities of livebirth were 30.3% and 27.1% (RD = 3.21%; 95% CI: 2.14, 4.26) for letrozole and clomiphene, respectively.

The probabilities of pregnancy and livebirth were inversely related to age for both treatment groups (Fig. 3). In all age groups, the probability of pregnancy was similar or slightly greater for letrozole compared with clomiphene (the difference was greatest for women older than 40 years). Among women with PCOS, the probability of pregnancy was greater for letrozole than clomiphene for all age groups, and the difference was greatest for women aged >37 years (RD = 19.42%; 95% CI: 11.22, 25.41). However, the probabilities of livebirth in this group were 10.0% and 19.4% for letrozole and clomiphene, respectively (RD = −9.41%; 95% CI: −11.30, 5.34). These results are based on only 133 participants in the letrozole group and 198 in the clomiphene group who were aged >37 years. The unadjusted percent of pregnancies that resulted in a spontaneous abortion (SAB) in this age group was 56.7% among women who received letrozole (17 SABs out of 30 pregnancies), compared with 4.0% among women who received clomiphene (1 SAB out of 25 pregnancies).

Table II Baseline characteristics of eligible individuals by treatment group, IBM MarketScan Commercial Claims and Encounters Database 2011–2014.

Characteristic	Clomiphene citrate (n = 49 647)	Letrozole (n = 18 120)
Demographics and lifestyle		
Age (years)		
Mean	32.8	33.2
Median (interquartile range)	33 (29, 36)	33 (30, 37)
(Minimum, Maximum)	(18, 45)	(18, 45)
Region of residence, %		
Northeast	25.7	11.3
North Central	23.4	19.6
South	31.6	54.2
West	19.3	14.9
Year of treatment initiation, %		
2011	25.4	22.3
2012	30.2	28.6
2013	23.0	21.2
2014	21.4	27.9
Obesity or overweight, %	1.8	2.0
Substance abuse/ dependence, %	0.9	1.0
Medication dispensations, %		
Potential teratogens	6.6	7.4
Antidepressants	6.9	8.8
Anticonvulsants	1.3	1.7
Antibiotics	19.9	21.0
Prenatal vitamins†	8.0	7.2
Diagnoses, %		
Hypertension	1.8	2.0
Epilepsy	0.2	0.2
Polycystic ovarian syndrome	6.5	9.2
Endometriosis	2.4	6.8
Female Infertility‡	38.5	36.9
Associated with anovulation	19.9	22.3
Of pituitary-hypothalamic origin	0.2	0.4
Of tubal origin	4.8	4.6
Of uterine origin	0.6	0.6
Of cervical or vaginal origin	0.2	0.3
Of other specified origin	11.3	13.5
Of unspecified origin	80.0	76.3

†The percent of participants who received prenatal vitamins is low because these frequencies apply only to prescribed medications.
‡The percent of participants with diagnosis codes for each sub-category of female infertility was calculated among women with an infertility diagnosis, by group. The subcategories are not mutually exclusive.

Among women with both PCOS and overweight/obesity (N = 231), the 'intention-to-treat' probability of pregnancy was 31.9% in the letrozole group and 27.8% in the clomiphene group. The corresponding probabilities for livebirth were 18.4% for letrozole and 19.3% for clomiphene. When we excluded patients with claims for IUI or endometriosis, our findings were generally consistent with the primary analyses (Supplementary Tables SIII, SIV, SV). When we expanded the period to establish that participants had no history of fertility treatment before study entry from 90 to 180 days, an additional 487 individuals were excluded (<1%). The results for this cohort were consistent with the main analysis.

Discussion

We emulated a target trial of the comparative effectiveness and safety of letrozole versus clomiphene citrate for ovulation induction during up to six menstrual cycles, using healthcare claims data from 67 767 women. While most previously published randomized trials could not precisely evaluate outcomes beyond livebirth, this large cohort enabled us to consider both additional outcomes and clinically relevant patient subgroups. Our findings suggest that letrozole is more effective than clomiphene for achieving pregnancy only among women with PCOS. However, the probability of livebirth was similar among individuals with PCOS who received letrozole compared with clomiphene, and the risks of multiple gestation, preterm birth, NICU admission, and congenital malformations were higher.

Our findings are consistent with previous randomized trials, which identified a treatment advantage for pregnancy with letrozole among women with PCOS (Kamath *et al.*, 2010; Legro *et al.*, 2014; Amer *et al.*, 2017). We identified a 45% probability of pregnancy for the letrozole group and 39% for the clomiphene group in per protocol analyses; the probabilities of livebirth were 34% and 32%, respectively. A trial conducted in the UK randomized 159 women with PCOS to letrozole or clomiphene for up to six ovulatory cycles and reported livebirth rates of 49% in the letrozole group and 35% in the clomiphene group (Amer *et al.*, 2017). The PPCOS II study randomized 750 women with PCOS to receive either clomiphene or letrozole for up to five cycles and reported pregnancy rates of 31% in the letrozole group and 22% in the clomiphene group; the probabilities of livebirth were 28% and 19%, respectively (Legro *et al.*, 2014). The lower rates of pregnancy and livebirth observed in PPCOS II relative to the UK trial may be due in part to the higher mean BMI of participants in PPCOS II (35 kg/m^2 vs 28 kg/m^2). Indeed, the PPCOS II study reported decreasing livebirth rates with increasing BMI. We also investigated this relationship and found probabilities of livebirth lower in women with claims for overweight/obesity (18% for letrozole, 19% for clomiphene) than in women without those claims. The relationships among BMI, medication dosing and reproductive outcomes are complex, as body fat influences both endogenous estrogen levels and medication pharmacodynamics. The balance of body composition and dosage may influence the effectiveness of clomiphene and letrozole and contribute to the heterogeneity of findings in these trials.

In the present study, among women with PCOS, the risk of multiple gestations in the letrozole group was approximately double that in the clomiphene group (19% vs 9%). This could explain the higher rate of preterm birth, NICU admission and congenital malformations in the letrozole group. The risk of multiple gestations was also substantially higher for both groups than among spontaneously conceived pregnancies in the IBM MarketScan cohort (~4%; note, these pregnancies were not included in the present study). This finding was unexpected. While clomiphene suppresses normal feedback mechanisms to

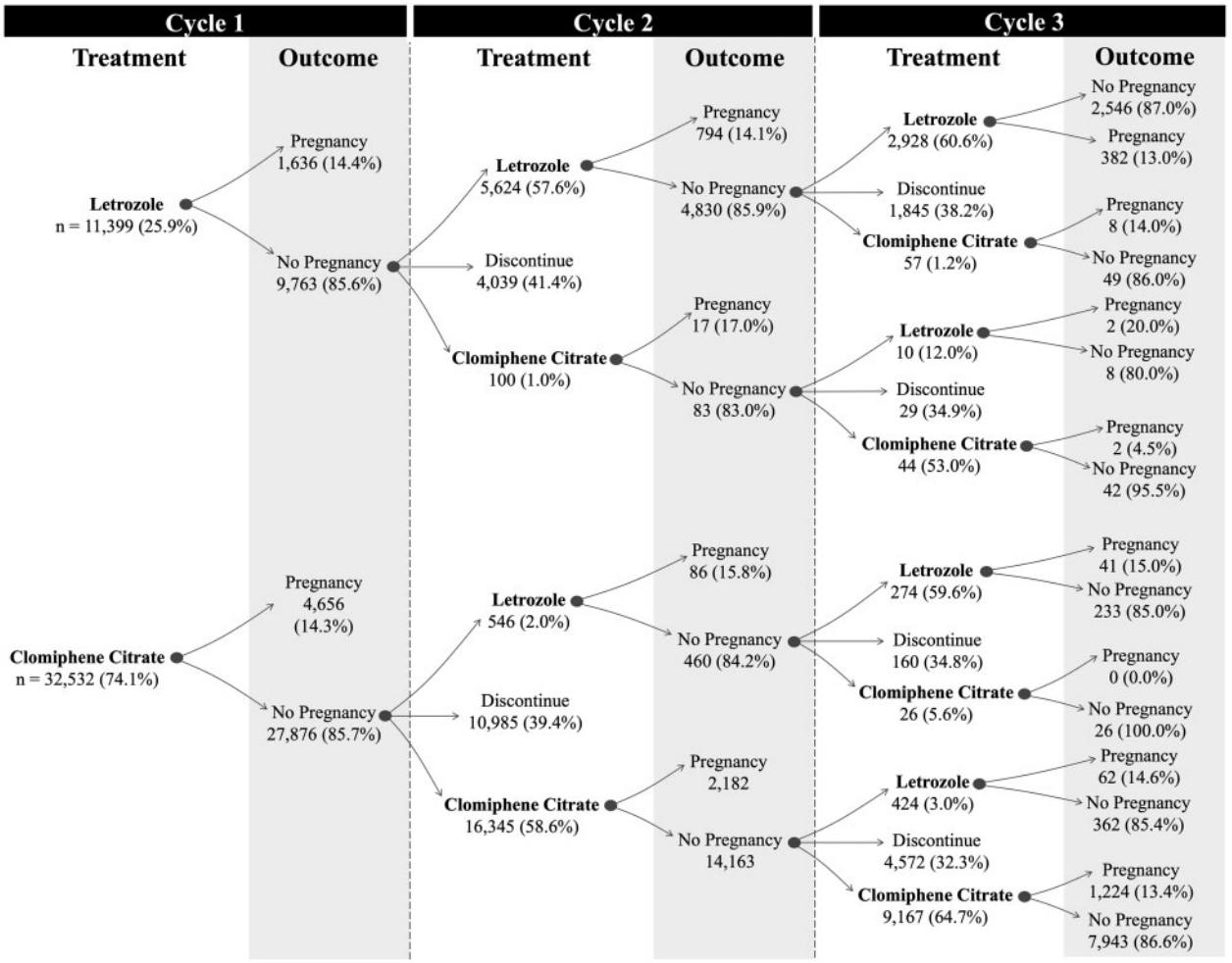

Figure 2. Treatment trajectories and outcomes for the first three consecutive cycles, IBM MarketScan Commercial Claims and Encounters Database 2011–2014. Results presented among participants who were enrolled for a complete year after treatment (N = 43 931) (i.e. long enough to ascertain a full-term pregnancy). The percentages presented in this figure are unadjusted; percentages were calculated using the previous node as the denominator.

promote development of several dominant follicles (Randall and Templeton, 1991), letrozole typically induces monofollicular ovulation because normal feedback mechanisms remain active during treatment. Furthermore, the PPCOS II study reported a lower frequency of twin livebirth in the letrozole group (3.9%) compared with the clomiphene group (6.9%). The lower rate of multiple gestation in the PPCOS II study relative to our findings may be related to the effect of BMI on dosage and probability of conception. Other trials were too small to evaluate multiple gestation (Kamath *et al.*, 2010; Amer *et al.*, 2017).

The PPCOS II study reported four infants with a major congenital malformation in the letrozole group (3.9%) and one in the clomiphene group (1.4%). Among women with PCOS in the present study, the risk of malformations was greater in the letrozole group (standardized risk = 8.1%; 95% CI: 6.2, 11.5) than in the clomiphene group (standardized risk = 1.6%; 95% CI: 0.8, 3.2), based on 17 major malformations total. The frequency of major congenital malformations is approximately 4% in the IBM MarketScan pregnancy cohort overall (among 1 039 163 linked liveborn infants conceived spontaneously or with any infertility treatment). We observed no definitive patterns in type of malformation. Treatment with clomiphene was previously associated with cardiac malformations (compared with couples who did not receive any fertility treatments) in the National Birth Defects Prevention Study (Reefhuis *et al.*, 2010). Furthermore, an early abstract presented to the American Society for Reproductive Medicine suggested an increased risk of cardiac malformations associated with letrozole (Biljan *et al.*, 2005). We did not observe an apparent difference in cardiac malformations between the two treatments. Other observational studies of congenital malformations after treatment with letrozole versus clomiphene have been small, yielding mixed results (Sharma *et al.*, 2014; Akbari Sene *et al.*, 2018; Yun *et al.*, 2018).

Our findings are also consistent with previous trials conducted among women with unexplained infertility, which found no appreciable differences between treatment with letrozole and clomiphene (Badawy *et al.*, 2009; Diamond *et al.*, 2015; Huang *et al.*, 2018). Badawy *et al.*

Table III Per-protocol analysis for the effectiveness of letrozole versus clomiphene, IBM MarketScan Commercial Claims and Encounters Database (N = 67 767; 2011–2014).

	Standardized risks, % (95%CI)†		Risk difference % (95%CI)
	Clomiphene citrate	Letrozole	Letrozole vs clomiphene
Pregnancy	35.9 (35.6, 36.1)	36.7 (36.2, 37.1)	0.77 (0.27, 1.28)
Livebirth	27.6 (27.4, 27.9)	27.9 (27.6, 28.4)	0.32 (-0.15, 0.82)
All women (marginal risks, N = 67 767)			
Multiple gestation	2.7 (2.6, 2.9)	3.2 (3.0, 3.4)	0.45 (0.16, 0.74)
Preterm birth	4.6 (4.4, 4.8)	5.2 (4.9, 5.5)	0.66 (0.31, 1.04)
Small for gestational age	2.2 (2.1, 2.3)	1.6 (1.5, 1.8)	−0.57 (−0.75, −0.36)
NICU admission	4.0 (3.8, 4.2)	4.8 (4.5, 5.1)	0.79 (0.48, 1.12)
Major congenital malformation	1.5 (1.4, 1.6)	1.6 (1.4, 1.7)	0.09 (−0.12, 0.30)
Genital malformation	0.24 (0.20, 0.28)	0.13 (0.08, 0.21)	−0.11 (−0.18, −0.03)
Hypospadias‡	0.08 (0.05, 0.11)	0.12 (0.06, 0.19)	0.04 (−0.02, 0.12)
Livebirths only (conditional risks, N = 11 203)			
Multiple gestation	9.8 (9.2, 10.4)	11.3 (10.5, 12.2)	1.49 (0.53, 2.50)
Preterm birth	16.7 (15.9, 17.6)	18.9 (17.8, 20.0)	2.21 (0.98, 3.54)
Small for gestational age	8.0 (7.4, 8.6)	5.9 (5.3, 6.6)	−2.15 (−2.80, −1.39)
NICU admission	14.6 (13.9, 15.4)	17.3 (16.3, 18.3)	2.70 (1.57, 3.84)
Major congenital malformation	5.5 (5.0, 6.0)	5.7 (5.1, 6.4)	0.26 (−0.44, 1.00)
Genital malformation	0.89 (0.73, 1.07)	0.49 (0.29, 0.74)	−0.39 (−0.68, 0.11)
Hypospadias‡	0.30 (0.18, 0.43)	0.44 (0.25, 0.68)	0.15 (0.10, 0.40)

The unit of observation for all analyses is woman/pregnancy, not fetus/infant and the data were analyzed per cycle.
†All analyses were adjusted for cycle, maternal age at first dispensation, year at first dispensation, geographic region, overweight/obesity, tobacco, alcohol or drug use or dependence, hypertension, epilepsy, anticonvulsant use, antidepressant use, antibiotic use, use of teratogenic medications, infertility, PCOS and dispensations of prescription prenatal vitamins or folate supplements. 95% CI obtained using the bootstrapping percentile method with 500 samples.
‡Models for genital malformations and hypospadias were adjusted for maternal age at first dispensation, year at first dispensation and geographic region.
NICU, neonatal intensive care unit.

Table IV Per-protocol analysis for the effectiveness of letrozole versus clomiphene among women with polycystic ovarian syndrome, IBM MarketScan Commercial Claims and Encounters Database (N = 4898; 2011–2014).

	Standardized risks, % (95% CI)†		Risk difference % (95% CI)
	Clomiphene citrate	Letrozole	Letrozole vs clomiphene
Pregnancy	39.2 (38.1, 40.1)	45.0 (43.4, 46.3)	5.72 (3.97, 7.52)
Livebirth	31.6 (30.5, 32.6)	33.8 (32.3, 35.4)	2.19 (0.27, 3.98)
All women (marginal risks, N = 4898)			
Multiple gestation	2.9 (2.4, 3.5)	6.4 (5.3, 7.7)	3.45 (2.19, 4.96)
Preterm birth	4.4 (3.8, 5.3)	6.3 (5.2, 7.8)	1.87 (0.58, 3.47)
Small for gestational age	0.7 (0.5, 1.2)	1.7 (1.1 2.7)	0.96 (0.22, 2.02)
NICU admission	4.5 (3.9, 5.2)	6.9 (5.7, 8.3)	2.44 (0.88, 3.96)
Major congenital malformation	0.4 (0.2, 0.7)	2.5 (1.8, 3.7)	2.13 (1.34, 3.33)
Livebirths only (conditional risks, N = 877)			
Multiple gestation	9.1 (7.5, 11.3)	18.6 (15.4, 22.4)	9.46 (5.75, 13.79)
Preterm birth	15.0 (12.9, 17.6)	19.7 (16.6, 23.8)	4.69 (0.77, 9.47)
Small for gestational age	2.5 (1.6, 4.1)	5.3 (3.7, 8.1)	2.80 (0.53, 5.86)
NICU admission	15.5 (13.2, 18.0)	22.0 (18.1, 26.6)	6.50 (1.58, 11.31)
Major congenital malformation	1.6 (0.8, 3.2)	8.1 (6.2, 11.5)	6.55 (4.25, 9.92)

The unit of observation for all analyses is woman/pregnancy, not fetus/infant and the data were analyzed per cycle. Results are not presented for genital malformations and hypospadias (these analyses were based on <11 events).
†All analyses were adjusted for cycle, maternal age at first dispensation, year at first dispensation, geographic region, overweight/obesity, tobacco, alcohol or drug use or dependence, hypertension, epilepsy, anticonvulsant use, antidepressant use, antibiotic use, use of teratogenic medications, infertility and dispensations of prescription prenatal vitamins or folate supplements. 95% CI obtained using the bootstrapping percentile method with 500 samples.
NICU, neonatal intensive care unit.

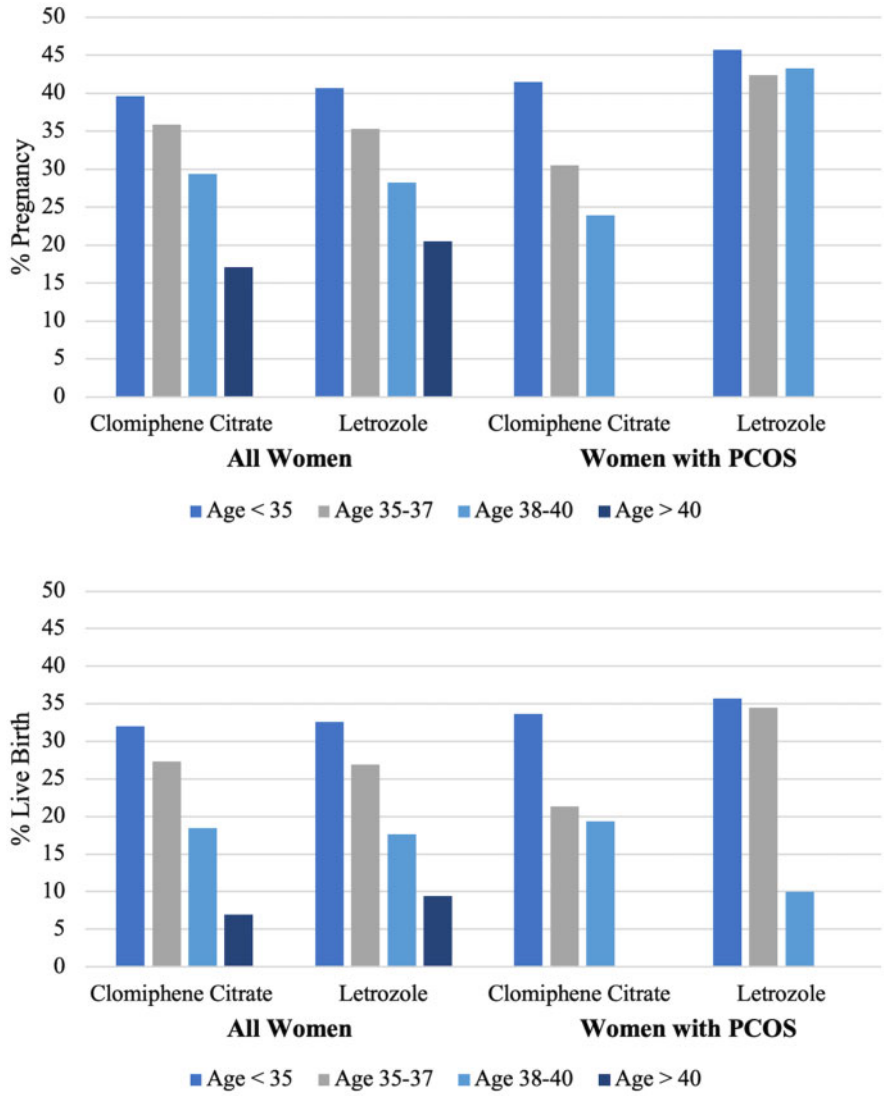

Figure 3. Age stratified standardized probabilities of pregnancy and livebirth from the per-protocol analysis of letrozole versus clomiphene citrate, overall and among women with polycystic ovarian syndrome (PCOS), IBM MarketScan 2011–2014. Age categories 38–40 and >40 years were collapsed in the PCOS group due to sample size. Overall, there were 42 552 participants aged <35 years, 11 634 participants aged 35–37 years, 7838 participants aged 38–40 years and 5743 participants aged >40 years. Among women with PCOS, there were 3944 participants aged <35 years, 623 participants aged 35–37 years and 331 participants aged >37 years.

(2009) reported similar clinical pregnancy and multiple gestation rates for letrozole (N = 269) and clomiphene (N = 420). In the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) Study (Diamond *et al.*, 2015), the clinical pregnancy rates were 28% for the clomiphene group (N = 300) and 22% for the letrozole group (N = 299), following intrauterine insemination. The respective livebirth rates were 23% and 19%. Interestingly, the authors reported higher rates of multiple gestation among livebirths in the letrozole group (14%) compared with the clomiphene group (6%) (Diamond *et al.*, 2015). There were three infants with a congenital anomaly in the clomiphene group (4.3%) and two infants in the letrozole group (3.6%) in the AMIGOS study. In the present study, we observed 333 infants with congenital anomalies and a similar overall risk of malformations for the two treatment groups with no clear pattern of malformation type. Overall, these findings suggest no notable differences in pregnancy and livebirth rates, or neonatal outcomes, between letrozole and clomiphene for treating women with unexplained infertility. This is consistent with the most recent treatment guidelines of the American Society for Reproductive Medicine (2020).

In this study, we demonstrated the application of the target trial framework to research on real-world pregnancy outcomes. By explicitly emulating a target trial, we were able to specify clear eligibility criteria, specific treatment strategies, active comparators and explicit follow-up, thus avoiding common biases in observational studies (Hernán *et al.*, 2016; Hernán and Robins, 2016). While previous randomized trials were too small to evaluate neonatal outcomes, utilization of a large

administrative healthcare database enabled us to study endpoints beyond livebirth, including teratogenic risks. Furthermore, we were able to evaluate these outcomes within several subgroups of interest, thereby increasing the specificity of the clinical question for a given patient.

However, this study has several limitations. First, we identified treatment cycles based on claims for drug dispensations, which do not perfectly reflect utilization. However, we do not expect much misclassification of treatment cycles in women undergoing infertility treatments, because it is very likely that they used their dispensation. We may have erroneously linked some spontaneously conceived pregnancies to a treatment cycle if LMP was misclassified, though this would only impact the per-protocol analyses. Furthermore, very few pregnancies are expected to have misclassification of LMP of more than 4 weeks (Margulis *et al.*, 2013). Conversely, we may have failed to identify some pregnancies, particularly those resulting in early miscarriage, because we can only identify pregnancy losses for which medical care was sought. However, women in this study population are likely to be more closely monitored compared with the general population, and the pregnancy rate in this study is relatively high compared with previous trials. Overall, we expect these sources of misclassification to be nondifferential with respect to the treatment, and we do not expect substantial bias. We cannot rule out residual confounding of treatment assignment (i.e. treatment assignment may not be random within levels of the measured covariates) or adherence, either by unmeasured variables or by misclassification of measured covariates (e.g. overweight/obesity). Potentially important variables that are not feasibly identified in administrative data include BMI and duration of infertility; parity is also challenging to ascertain. However, we attempted to mitigate residual confounding by adjusting for proxies identified in administrative data (e.g. claims for overweight/obesity). In addition, participants who became pregnant or continued for six failed cycles may not be representative of all those who initiated treatment. Thus, we may have overestimated of the probability of success had the entire cohort adhered to the assigned treatment strategy. There may have also been some misclassification of PCOS. Given the imperfect sensitivity of codes to identify PCOS, it is likely that the prevalence is higher than estimated, but those identified as PCOS in the subgroup analysis are most likely to have PCOS. Another limitation of this study was that even with nearly 68 000 women in the study population, we were unable to evaluate most specific congenital malformations, due to the rarity of the outcome. However, we observed many more malformations than in previous studies, substantially increasing the available evidence.

Conclusions

Our findings indicate that the pregnancy and neonatal outcomes are similar after six cycles of letrozole or clomiphene among women with unexplained infertility. We did not confirm the previously suggested elevated risk of congenital malformations with clomiphene. These findings should be considered in the context of the differential side effect profiles and costs of the two medications. Both medications cause mood changes, hot flashes, nausea and dizziness (Legro *et al.*, 2014). However, side effects may be worse for clomiphene due to its longer half-life, and they can become intolerable over the course of numerous treatment cycles. While the rate of pregnancy may be improved for women with PCOS who are treated with letrozole versus clomiphene, the risks of genital malformations, preterm birth and NICU admission may also be increased among infants conceived via letrozole. It is likely that these effects are partially mediated through an increased risk of multiple gestation among women who receive letrozole.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

We do not own and cannot share disaggregated MarketScan data per data use agreement. MarketScan data are available by commercial license from IBM.

Authors' roles

J.J.Y. was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript writing, revision and finalization. M.A.H. was responsible for study design, statistical oversight, results interpretation, manuscript revision and finalization. Y.-H.C. was responsible for formulation of the study design, results interpretation, manuscript revision and finalization. P.R. was responsible for results interpretation, manuscript revision and finalization. J.H. was responsible for results interpretation, manuscript revision and finalization. S.H.-D. was responsible for formulation of the study hypotheses and study design, statistical analyses, results interpretation, manuscript writing, revision and finalization.

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Conflict of interest

Y.-H.C. reports grants from the American Heart Association (834106) and NIH (R01HD097778). P.R. reports grants from the National Institutes of Health. J.H. reports grants from the National Institutes of Health, the Agency for Healthcare Research and Quality and the California Health Care Foundation during the conduct of the study; and consulting for several health care delivery organizations including Cambridge Health Alliance, Columbia University, University of Southern California, Community Servings and the Delta Health Alliance. S.H.-D. reports grants from the National Institutes of Health and the US Food and Drug Administration during the conduct of the study; grants to her institution from Takeda outside the submitted work; consulting for UCB (biopharmaceutical company) and Roche; and being an adviser for the Antipsychotics Pregnancy Registry and epidemiologist for the North American Antiepileptics Pregnancy Registry, both at Massachusetts General Hospital. M.A.H. reports grants from the National Institutes of Health and the U.S. Veterans Administration during the conduct of the study; being a consultant for Cytel; and being an adviser for ProPublica.

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