Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;371:119-29. DOI: 10.1056/NEJMoa1313517

Supplemental Appendix:

Legro et al., **Letrozole versus Clomiphene for Infertility in Polycystic Ovary Syndrome**

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SUPPLEMENTAL TEXT

Teratogenicity of Letrozole

Following a published abstract suggesting an increased risk of birth defects (cardiac and locomotor) in women who conceived on letrozole,[1] Novartis, the manufacturer of letrozole, issued a global statement to health providers advising against the use of letrozole for ovulation induction in pre-menopausal women in 2005, which was echoed by the U.S. Food and Drug Administration, Health Canada, and the European Medicines Agency.[2] A subsequent case-control study suggested comparable or lesser anomaly rates in pregnancies conceived with letrozole compared to clomiphene.[3]

Interpretation of Midluteal Progesterone levels

A progesterone level in the ovulatory range (i.e. serum progesterone ≥ 3 ng/mL) could be considered low by an investigator's interpretation. A cutoff was not defined in the protocol for a "low" progesterone level. Rather we left it to individual investigators to integrate the assumed midluteal serum level, the findings on midluteal ultrasound, and the date of the subsequent menses (all patients had a baseline visit with menses) to determine if the progesterone level was "low" and increase the dose for the next cycle. This mirrors our previous study of clomiphene and metformin[4] where investigators integrated serum progesterone levels obtained in the luteal phase with the date of the subsequent menses to determine if the level was "low", also with no specified cutoff (there was no midluteal ultrasound in this study). Because the luteal phase is relatively fixed at 14 days, serum progesterone peaks at midluteal phase or roughly 7 days before expected menses and generally is > 10 ng/mL, so knowing the date of the subsequent menses and the level of progesterone prior to it allows the investigator to make a clinical estimate if the progesterone was "low" and increase the dose. For example if the patient came in for a midluteal visit and had a progesterone level of 6 ng/mL, and experienced menses a week later, the investigator had the option to determine this was a "low" progesterone level and increase the dose of study medication by one tablet a day in the next ovulation induction cycle (up to 3 tablets a day for five days or 150 mg of clomiphene or 7.5 mg of letrozole). This happened rarely as noted in the main text of the paper (i.e. 2% of cycles). If a patient had an adequate ovulation based on the information collected, the patient was maintained on the same study medication dose for the next cycle. Further information about the management of our patients based on data obtained during the midluteal visit can be found in our complete protocol included in the supplementary materials.

Effects of a Progestin-Induced Withdrawal Bleed after an Anovulatory Cycle on Live Birth in the Next Cycle

Whether to give progestin or not after an anovulatory cycle is uncertain, both in this protocol and in our previous study.[4] Many clinicians have rejected the time and expense of inducing a withdrawal bleed and opted to immediately escalate the ovulation induction medication dose after documented anovulation and lack of follicular development during a "midluteal" ultrasound.[5] Therefore, exactly as in the previous study, we left it to the discretion of the individual site investigators whether to give it in this protocol and what type of progestin to prescribe. While this study was underway, we completed a post hoc analysis of progestin use in the previous study which suggested that a progestin-induced bleed was associated with lower pregnancy rates in the subsequent ovulation induction cycle.[6] This likely exerted little effect on investigator use in this study as recruitment was wrapping up when we published

the article in 2012. The rate of progestin administration was reduced in this study [given after 34% of anovulatory cycles 551/1624 in the previous study[6] versus 24.6% of cycles in this study (309/1255)]. Unlike in our previous study,[6] we detected no effects of progestin administration on the live birth rate. With clomiphene, the live birth rate after an anovulatory cycle with progestin-induced bleed was 4.0% (N = 9 live births) versus 3.0% without progestin (N = 11 live births)(P = NS). With letrozole, the live birth rate after a progestin-induced bleed was 5.8% (N = 5 live births) versus 6.6% (N = 22 live births) (P = NS). Obviously we have limited statistical power as there were small numbers of anovulatory cycles given progestin and even smaller pregnancy numbers. Finally this is a post hoc analysis. We conclude that progestin use had little impact on our final outcomes or conclusions.

Figure S1. Flow Chart: Enrollment and outcomes of the trial

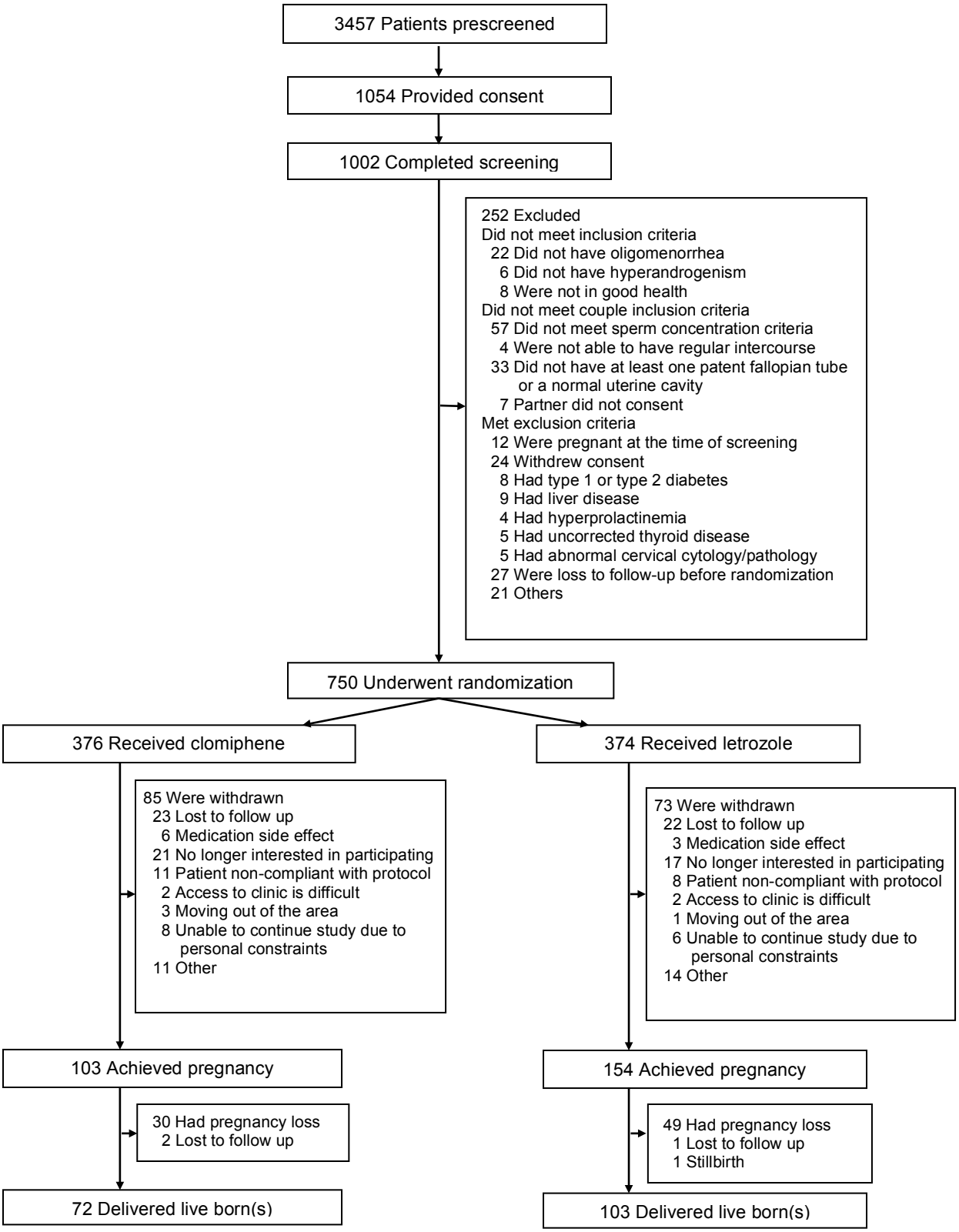

Table S1: Drop out or study exclusion reasons by study timepoint.

Drop out reasons	Treatment	After randomization and before baseline visit	Between baseline visit and monthly visit 1	Between monthly visit 1 and visit 2	Between monthly visit 2and visit 3	Between monthly visit 3 and visit 4	Between monthly visit 4 and visit 5	After monthly visit 5	Total
Lost to follow up	Clomiphene	2	2	2	4	6	4	3	**23**
	Letrozole	2		3	5	4	2	6	**22**
Medication side effect	Clomiphene		1	2	1	2			**6**
	Letrozole			1	1	1			**3**
No longer interested in participating	Clomiphene	3		2	3	4	7	2	**21**
	Letrozole	3		2		5	6	1	**17**
Patient non-compliant with protocol	Clomiphene	1	1	1	1	2	5		**11**
	Letrozole			2	2	1	3		**8**
Access to clinic is difficult	Clomiphene			1			1		**2**
	Letrozole				1	1			**2**
Moving out of the area	Clomiphene			1	1	1			**3**
	Letrozole	1							**1**

Drop out reasons	Treatment	After randomization and before baseline visit	Between baseline visit and monthly visit 1	Between monthly visit 1 and visit 2	Between monthly visit 2and visit 3	Between monthly visit 3 and visit 4	Between monthly visit 4 and visit 5	After monthly visit 5	Total
Unable to continue study due to personal constraints	Clomiphene	1	1	1	2		3		**8**
	Letrozole		1			2	3		**6**
Other	Clomiphene		1	1	2	2	5		**11**
	Letrozole	2	1	2	2	2	4	1	**14**
Total		**15**	**8**	**21**	**25**	**33**	**43**	**13**	**158**

Table S2: Live birth, pregnancy, conception, and ovulation rates per cycle*.

Outcome	Clomiphene group (N=376)	Letrozole group (N=374)	Absolute difference between Letrozole and Clomiphene	Rate ratio with letrozole (95% CI)	p value†
	no./total no. (%)		*% (95% CI)*		
Live birth per treatment cycle					
Pre- treatment cycle 1	7/376 (1.9)	1/374 (0.3)	-1.6 (-3.1 to -0.1)	0.14 (0.02 to 1.16)	0.07
Treatment cycle 1	14/369 (3.8)	23/373 (6.2)	2.4 (-0.8 to 5.5)	1.63 (0.85 to 3.11)	0.14
Treatment cycle 2	16/355 (4.5)	26/350 (7.4)	2.9 (-0.6 to 6.4)	1.65 (0.90 to 3.02)	0.10
Treatment cycle 3	15/339 (4.4)	23/324 (7.1)	2.7 (-0.9 to 6.2)	1.60 (0.85 to 3.03)	0.14
Treatment cycle 4	9/324 (2.8)	16/301 (5.3)	2.5 (-0.6 to 5.6)	1.91 (0.86 to 4.27)	0.11
Treatment cycle 5	11/315 (3.5)	14/285 (4.9)	1.4 (-1.8 to 4.7)	1.41 (0.65 to 3.05)	0.39
Pregnancy per treatment cycle					
Pre- treatment cycle 1	7/376 (1.9)	2/374 (0.5)	-1.3 (-2.9 to 0.2)	0.29 (0.06 to 1.37)	0.18
Treatment cycle 1	17/369 (4.6)	25/372 (6.7)	2.1 (-1.2 to 5.4)	1.46 (0.80 to 2.66)	0.21
Treatment cycle 2	19/352 (5.4)	29/347 (8.4)	3.0 (-0.8 to 6.7)	1.55 (0.89 to 2.71)	0.12
Treatment cycle 3	17/333 (5.1)	28/318 (8.8)	3.7 (-0.2 to 7.6)	1.73 (0.96 to 3.09)	0.06

Treatment cycle 4	10/316 (3.2)	16/290 (5.5)	2.4 (-0.9 to 5.6)	1.74 (0.80 to 3.78)	0.15
Treatment cycle 5	11/306 (3.6)	17/274 (6.2)	2.6 (-0.9 to 6.2)	1.73 (0.82 to 3.62)	0.14
Conception per treatment cycle					
Pre- treatment cycle 1	9/376 (2.4)	4/374 (1.1)	-1.3 (-3.2 to 0.5)	0.45 (0.14 to 1.44)	0.26
Treatment cycle 1	23/367 (6.3)	32/370 (8.7)	2.4 (-1.4 to 6.2)	1.38 (0.82 to 2.31)	0.22
Treatment cycle 2	24/344 (7.0)	38/338 (11.2)	4.3 (-0.1 to 8.6)	1.61 (0.99 to 2.63)	0.05
Treatment cycle 3	22/320 (6.9)	37/300 (12.3)	5.5 (0.8 to 10.1)	1.79 (1.08 to 2.97)	0.02
Treatment cycle 4	13/298 (4.4)	21/263 (8.0)	3.6 (-0.4 to 7.6)	1.83 (0.93 to 3.58)	0.07
Treatment cycle 5	12/285 (4.2)	22/242 (9.1)	4.9 (0.6 to 9.2)	2.16 (1.09 to 4.27)	0.02
Ovulation per treatment cycle					
Pre- treatment cycle 1	9/22 (40.9)	4/14 (28.6)	-12.3 (-43.7 to 19.0)	0.70 (0.27 to 1.84)	0.50
Treatment cycle 1	151/354 (42.7)	178/360 (49.4)	6.8 (-0.5 to 14.1)	1.16 (0.99 to 1.36)	0.07
Treatment cycle 2	168/320 (52.5)	204/318 (64.2)	11.7 (4.1 to 19.3)	1.22 (1.07 to 1.40)	0.003
Treatment cycle 3	141/282 (50.0)	179/268 (66.8)	16.8 (8.7 to 24.9)	1.34 (1.16 to 1.54)	<0.001
Treatment cycle 4	111/243 (45.7)	149/216 (69.0)	23.3 (14.5 to 32.1)	1.51 (1.28 to 1.78)	<0.001
Treatment cycle 5	108/204 (52.9)	120/176 (68.2)	15.2 (5.5 to 25.0)	1.29 (1.09 to 1.52)	0.003

*Live birth was defined by the delivery of a live-born infant. Conception was defined by a serum level of human chorionic gonadotropin of more than 10 mIU per milliliter. Pregnancy was defined by observation of fetal heart motion on ultrasonography. Ovulation was defined by a progesterone level of more than 3 ng per milliliter (10 nmol per liter).
†Chi-square or Fisher's exact test was used.

Table S3: Additional Data on Pregnancy and Pregnancy Loss*

Outcome	Clomiphene group (N=376)	Letrozole group (N=374)	Absolute difference between Letrozole and Clomiphene	Rate ratio with letrozole (95% CI)	p value†
	no./total no. (%)		*% (95% CI)*		
Pregnancy					
Conception	103/376 (27.4)	154/374 (41.2)	13.8 (7.1 to 20.5)	1.50 (1.23 to 1.84)	<0.001
Pregnancy	81/376 (21.5)	117/374 (31.3)	9.7 (3.5 to 16.0)	1.45 (1.14 to 1.85)	0.003
Singleton pregnancy	75/81 (92.6)	113/117 (96.6)	4.0 (-2.6 to 10.6)	1.04 (0.97 to 1.12)	0.32
Twin pregnancy	6/81 (7.4)	4/117 (3.4)	-4.0 (-10.6 to 2.6)	0.46 (0.13 to 1.58)	0.32
Triplet pregnancy	0	0	0		1.00
Time to pregnancy (days) ‡	85.9 ± 48.8 (90)	90.4 ± 44.4 (145)	4.5 (-8.0 to 17.0)		0.27
Pregnancy Loss					
Pregnancy loss among patients who conceived	30/103 (29.1)	49/154 (31.8)	2.7 (-8.7 to 14.1)	1.09 (0.75 to 1.60)	0.65
Loss in first trimester	29/103 (28.2)	45/154 (29.2)	1.1 (-10.2 to 12.3)	1.04 (0.70 to 1.54)	0.85
Biochemical factor or no fetal heart motion	18/103 (17.5)	29/154 (18.8)	1.4 (-8.2 to 10.9)	1.08 (0.63 to 1.84)	0.78
Ectopic pregnancy	4/103 (3.9)	4/154 (2.6)	-1.3 (-5.8 to 3.2)	0.67 (0.17 to 2.61)	0.72

Outcome	Clomiphene group (N=376)	Letrozole group (N=374)	Absolute difference between Letrozole and Clomiphene	Rate ratio with letrozole (95% CI)	p value†
Treated pregnancy of unknown location	1/103 (1.0)	1/154 (0.7)	-0.3 (-2.6 to 2.0)	0.67 (0.04 to 10.6)	1.00
Loss after observed heart motion	6/103 (5.8)	11/154 (7.1)	1.3 (-4.8 to 7.4)	1.22 (0.47 to 3.21)	0.68
Loss in second or third trimester	1/103 (1.0)	4/154 (2.6)	1.6 (-1.5 to 4.8)	2.67 (0.30 to 23.6)	0.65

* Conception was defined by a serum level of human chorionic gonadotropin of more than 10 mIU per milliliter. Pregnancy was defined by observation of fetal heart motion on ultrasonography.
†Chi-square or Fisher's exact for categorical data and Wilcoxon rank sum test for continuous data.
‡ Days between the first day the patients took medicine and the first day of positive pregnancy test recorded.

Table S4: Serious Adverse Events (all) and Adverse Events (with more than 2% of patients experiencing them) between the Treatment Groups

Event	Clomiphene Group	Letrozole Group
	No. of women /total no. (%)	
Before conception in female patients who received a study drug		
Serious adverse event		
Cholecystectomy	1/355 (0.3)	0/359
Ovarian torsion	1/355 (0.3)	0/359
Ruptured corpus luteum cyst	0/355	1/359 (0.3)
Stage 3 carcinoma of the skin	1/355 (0.3)	0/359
Hospitalization*	1/355 (0.3)	2/359 (0.6)
Other adverse event		
Headache	170/355 (47.9)	167/359 (46.5)
Abdominal/pelvic pain	138/355 (38.9)	146/359 (40.7)
Nausea	91/355 (25.6)	110/359 (30.6)
Hot flashes†	117/355 (33)	73/359 (20.3)
Breast pain	76/355 (21.4)	76/359 (21.2)
Fatigue‡	53/355 (14.9)	78/359 (21.7)
Dysmenorrhea	64/355 (18)	60/359 (16.7)
Back pain	55/355 (15.5)	64/359 (17.8)
Dyspepsia	62/355 (17.5)	45/359 (12.5)
Abdominal bloating	42/355 (11.8)	49/359 (13.6)
Agitation	37/355 (10.4)	43/359 (12)
Dizziness‡	27/355 (7.6)	44/359 (12.3)
Upper respiratory infection	31/355 (8.7)	38/359 (10.6)
Irritability	33/355 (9.3)	33/359 (9.2)
Joint/limb pain	26/355 (7.3)	33/359 (9.2)

Event	Clomiphene Group	Letrozole Group
Flu like symptoms	18/355 (5.1)	29/359 (8.1)
Diarrhea	18/355 (5.1)	24/359 (6.7)
Vomiting	20/355 (5.6)	21/359 (5.8)
Acne/oily skin	24/355 (6.8)	16/359 (4.5)
Constipation	20/355 (5.6)	17/359 (4.7)
Abnormal vaginal bleeding	9/355 (2.5)	18/359 (5)
Insomnia	14/355 (3.9)	12/359 (3.3)
Vaginal infection	16/355 (4.5)	8/359 (2.2)
Allergic rhinitis	12/355 (3.4)	10/359 (2.8)
Fever	9/355 (2.5)	13/359 (3.6)
Urinary tract infection	10/355 (2.8)	12/359 (3.3)
Myalgia	9/355 (2.5)	10/359 (2.8)
Depression	10/355 (2.8)	6/359 (1.7)
Urinary frequency	8/355 (2.3)	7/359 (1.9)
Vaginal discharge	4/355 (1.1)	9/359 (2.5)
Blurred vision	4/355 (1.1)	8/359 (2.2)
Chills	8/355 (2.3)	4/359 (1.1)
Sinus complaints	4/355 (1.1)	8/359 (2.2)
After conception in female patients who discontinued study drug		
Serious adverse event - mother		
First Trimester		
Ectopic pregnancy	3/94(3.2)	4/149(2.7)
Heterotopic pregnancy	1/94 (1.1)	0/149
Pregnancy of Unknown Location (PUL)	1/94 (1.1)	1/149 (0.7)
Hospitalization during first trimester§	2/94 (2.1)	3/149 (2.0)
Appendectomy	0/94	1/149 (0.7)

Event	Clomiphene Group	Letrozole Group
Second and Third Trimester		
Cholecystis/Cholecystectomy	0/94	2/149 (1.3)
Right mid ureteral stone	0/94	1/149 (0.7)
Umbilical hernia repair	0/94	1/149 (0.7)
Hospitalization and premature labor	0/94	2/149 (1.3)
Hospitalization for other reasons¶	2/94 (2.1)	3/149 (2.0)
Delivery and Postpartum		
Anemia requiring transfusion after delivery	0/94	1/149 (0.7)
Other adverse event - mother		
First Trimester		
Headache	3/94 (3.2)	2/149 (1.3)
Nausea	3/94 (3.2)	4/149 (2.7)
Abdominal/pelvic pain	2/94 (2.1)	3/149 (2)
Fatigue	1/94 (1.1)	3/149 (2)
Vaginal infection	2/94 (2.1)	0/149
Other complication during pregnancy	8/94 (8.5)	15/149 (10.1)
Second and Third Trimester		
Hyperemesis	5/94 (5.3)	8/149 (5.4)
Gestational diabetes	13/94 (13.8)	27/149 (18.1)
Pre-eclampsia/eclampsia	13/94 (13.8)	18/149 (12.1)
Preterm labor	12/94 (12.8)	14/149 (9.4)
Premature rupture of membrane	7/94 (7.4)	8/149 (5.4)
Incompetent cervix	6/94 (6.4)	8/149 (5.4)
Placental abnormalities	4/94 (4.3)	5/149 (3.4)
Delivery and Postpartum		
Post-partum hemorrhage	3/94 (3.2)	8/149 (5.4)
Post-partum infection	2/94 (2.1)	7/149 (4.7)

Event	Clomiphene Group	Letrozole Group
Post-partum depression	1/94 (1.1)	4/149 (2.7)
Other post-partum complication ‖	3/94 (3.2)	3/149 (2.0)
After 20 weeks pregnancy in fetus through neonatal period in infant		
Serious adverse event - fetus/infant		
Congenital anomaly**	1/66 (1.5)	4/102 (3.9)
Fetal demise	1/66 (1.5)	1/102 (1)
Neonatal death	2/66 (3)	1/102 (1)
Other adverse event - fetus/infant		
Neonatal jaundice	17/66 (25.8)	27/102 (26.5)
Neonatal respiratory distress syndrome	2/66 (3)	7/102 (6.9)
Neonatal hospitalization > 3 days	4/66 (6.1)	4/102 (3.9)
Intrauterine growth restriction	1/66 (1.5)	5/102 (4.9)
Neonatal infection	2/66 (3)	2/102 (2)
Minor birth defect††	0/66	1/102 (1)
Other complication of infant after delivery‡‡	4/66 (6.1)	5/102 (4.9)

*For clomiphene this was due to a reported malignancy, for letrozole, one was due to non-compliance with ER treatment plan, and one for drainage and removal of an ovarian cyst.
†$p<0.01$
‡$p<0.05$
§Included Clomiphene: 1) cervical cerclage, 2) vaginal bleeding and for Letrozole: 1) constipation, 2) viral meningitis, 3) chest pain
¶For clomiphene these included 1) Bell's Palsy associated with preeclampsia and subsequent diagnosis of multiple sclerosis, 2) hypertension, for letrozole these included 1) back pain, 2) MSRA abscess, 3) pre-eclampsia
‖For letrozole these included 1) right arm superficial vein thrombophlebitis, 2) pelvic misalignment after delivery, 3) high blood pressure, for letrozole these included 1) possible coccyx fracture, 2) gall stones, 3) HBP not related to pre-eclampsia treated with Procardia & 2 transfusions related to low hgb & hct

**For letrozole these included 1) cerebral palsy with arrested hydrocephalus with polycythemia and neutropenia, 2) imperforate anus with perineal fistula and spina bifida with a tethered spinal cord, 3) right hemimegalencephaly, and dysgenesis of the left frontal and temporal lobes but no hydrocephalus, and 4) large cardiac ventricular septal defect requiring surgical repair, and for clomiphene there was one atrial/ventricular septal cardiac defect with pulmonary stenosis.

††One minor birth defect (ankyloglossia on letrozole) was detected on neonatal exam.

‡‡For clomiphene these included 1) slow weight gain, 2) baby was floppy due to high levels of magnesium in her system from medicine given to mom for pre-eclampsia, 3) left ear folded; taped for a few weeks and has resolved, 4) GERD diagnosed at 6 weeks treated with medicine #2; congenital torticollis, for letrozole these included 1) GERD, 2) blood sugar-24 hours, 3) baby treated with antibiotics prophylactically as mom being treated for possible chorioamnionitis, 4) polycythemia, 5) admitted to NICU for respirations due to grunting /nasal flaring

Table S5: Complete Details of Major Congenital Anomalies in the Trial

Anomaly Case Number	Letrozole	Clomiphene
1	The infant was born with a birth defect of an imperforate anus with perineal fistula. Surgery was performed for a transplant anoplasty. The infant also had a birth defect of spina bifida with a tethered cord with a presumed dermal sinus tract. Infant had a lumbosacral laminectomy for resection of intradural lesion and intraoperative microscopic dissection. Infant tolerated the procedure well and was discharged to home. Post operative examination was normal and infant is healing well.	
2	At approximately 20 weeks gestation, a fetal ultrasound showed a brain malformation consistent with Dandy-Walker Malformation. Delivery occurred via caesarean section, the infant was admitted to the NICU for further evaluation. After MRI of the brain, Dandy-Walker malformation was ruled out and the MRI showed right hemimegancephaly, and dysgenesis of the left frontal and temporal lobes without hydrocephalus. EEG was normal for age and showed no seizure activity. Infant was discharged to home with parents. Multiple follow-up appointments were scheduled for ophthalmology, genetics, neurology, NICU high risk clinic and feeding clinic. The outcome of the infant at this time is unknown but will require early intervention services.	
3	When the patient was contacted to participate in our Pregnancy Registry she stated that "her son has been ill since birth with various ailments". 1) Neutropenia:; 2) Asthma: 3) Arrested hydrocephalus 4) Mild Cerebral Palsy: 5) Polycythemia	
4	Male infant was delivered vaginally at 36.3 weeks due to preterm labor and possibly maternal hypothyroidism. On the day of birth, the baby was transferred to the NICU because he was grunting. That same day he had several apnea spells. He remained in the NICU for three weeks as the heart problem was diagnosed and child was treated for lack of weight gain. He was hospitalized later for successful open heart surgery to repair the VSD.	
5		Patient delivered a 37 week baby girl . At birth baby was diagnosed with an atrial septal defect ,, a ventricular septal defect , and pulmonary stenosis. At birth, the baby was also hospitalized for neonatal jaundice. The patient was advised that the low birth weight and heart problems could be attributed to her smoking throughout her entire pregnancy. The baby is being followed by a specialist for her heart condition.

Table S6: Absolute Changes in Key Measures from Baseline to Last Midluteal-Phase Visit.*

Measure	Clomiphene	Letrozole	P Value†
Biometric measures			
Body mass index			
No. of women	352	357	
Mean change- kg/m^2	0.4±1.4	0.3±1.7	
Median change (IQR)- kg/m^2	0.4 (-0.4 to 1.1)	0.4 (-0.3 to 1.0)	0.98
Systolic blood pressure			
No. of women	351	356	
Mean change- mm Hg	-0.9±12.7	-0.6±12.1	
Median change (IQR)- mm Hg	-1.0 (-8.0 to 7.0)	-1.0 (-9.0 to 8.0)	0.81
Diastolic blood pressure (mm Hg)			
No. of women	351	356	
Mean change	-1.0±8.4	-0.1±9.9	
Median change (IQR)	-1.0 (-7.0 to 5.0)	0 (-7.0 to 6.0)	0.35
Sebum			
No. of women	337	340	
Mean change- mcg/cm2	-11.5±57.4	-3.7±56.0	
Median change (IQR)- mcg/cm2	-6.0 (-47.0 to 22.0)	-1.5 (-36.0 to 28.5)	0.06
F-G score			
No. of women	287	289	
Mean change	-0.3±5.4	-0.4±5.1	
Median change (IQR)	0.0 (-3.0 to 3.0)	0.0 (-3.0 to 3.0)	0.98
Ultrasonographic findings			
Number of measured follicles/cysts			
(>10 mm diameter)			
No. of women	352	357	

Measure	Clomiphene	Letrozole	P Value†
Mean change	0.7±1.1	0.7±0.9	
Median change (IQR)	0.0 (0.0 to 1.0)	1.0 (0.0 to 1.0)	0.45
Antral follicle count (both ovaries)			
No. of women	321	325	
Mean change	-2.8±22.9	-5.2±21.9	
Median change (IQR)	-1.0 (-12.0 to 8.0)	-4.0 (-16.0 to 5.0)	0.04
Ovarian volume (both ovaries)			
No. of women	335	346	
Mean change- mm^3	14.2±35.0	9.3±17.9	
Median change (IQR)- mm^3	7.5 (1.0 to 17.5)	7.1 (0.2 to 14.5)	0.24
Endometrial thickness in the sagittal			
plane	351	352	
No. of women	3.4±3.7	2.4±3.8	
Mean change- mm	3.0 (1.0 to 6.0)	2.0 (0.0 to 5.0)	<0.001
Median change (IQR)- mm			
Fasting serum biochemical values			
Total testosterone			
No. of women	351	355	
Mean change- ng/dL	4.1±34.8	4.1±26.3	
Median change (IQR)- ng/dL	0.0 (-14.0 to 18.4)	2.5 (-11.8 to 17.5)	0.43
SHBG			
No. of women	350	354	
Mean change- nmol/L	13.7±19.5	-1.5±15.5	
Median change (IQR)- nmol/L	9.9 (3.3 to 20.7)	-1.2 (-5.1 to 3.1)	<0.001

Measure	Clomiphene	Letrozole	P Value†
Free Androgen Index			
No. of women	350	354	
Mean change	-1.9±4.7	1.7±6.4	
Median change (IQR)	-1.5 (-4.0 to 0.2)	0.4 (-1.2 to 3.2)	<0.001
Estradiol			
No. of women	351	355	
Mean change- pg/mL	52.9±107.7	9.2±59.5	
Median change (IQR)- pg/mL	22.5 (-2.0 to 92.2)	-0.8 (-21.4 to 32.6)	<0.001
Progesterone			
No. of women	351	355	
Mean change- ng/dL	11.0±21.5	13.2±21.0	
Median change (IQR)- ng/dL	0.2 (-0.1 to 14.8)	2.7 (0.1 to 18.2)	<0.001
LH			
No. of women	349	354	
Mean change- mIU/mL	-1.9±9.1	-2.4±9.7	
Median change (IQR)- mIU/mL	-1.4 (-5.1 to 1.6)	-2.0 (-5.7 to 1.9)	0.50
FSH			
No. of women	349	354	
Mean change- mIU/mL	-1.6±2.6	-1.5±2.7	
Median change (IQR)- mIU/mL	-1.3 (-3.3 to 0.0)	-1.3 (-3.0 to 0.1)	0.72
AMH			
No. of women	350	355	
Mean change- ng/mL	0.1±5.1	-0.5±4.8	
Median change (IQR)- ng/mL	0.1 (-1.1 to 1.9)	-0.2 (-2.0 to 1.1)	0.02
Fasting glucose			
No. of women	351	355	

Measure	Clomiphene	Letrozole	P Value†
Mean change- mg/dL	3.3±16.7	3.3±15.0	
Median change (IQR)- mg/dL	1.0 (-5.3 to 8.3)	2.2 (-4.8 to 9.2)	0.64
Insulin			
No. of women	349	354	
Mean change- µU/mL	6.8±29.5	6.3±27.1	
Median change (IQR)- µU/mL	3.6 (-1.7 to 9.7)	4.1 (0 to 9.3)	0.25
Proinsulin			
No. of women	351	355	
Mean change- pmol/L	9.9±23.5	12.9±45.5	
Median change (IQR)- pmol/L	3.2 (-1.4 to 12.2)	4.1 (-0.7 to 13.4)	0.32
Quality-of-life measures			
PCOSQ total score			
No. of women	272	271	
Mean change	0.3±0.8	0.3±1.0	
Median change (IQR)	0.2 (-0.2 to 0.7)	0.3 (-0.2 to 0.8)	0.86
Emotion			
No. of women	272	271	
Mean change	0.1±1.0	0.2±1.1	
Median change (IQR)	0.1 (-0.4 to 0.8)	0.1 (-0.5 to 0.8)	0.99
Body hair			
No. of women	272	271	
Mean change	0.4±1.0	0.2±1.1	
Median change (IQR)	0.3 (-0.2 to 1.0)	0.2 (-0.4 to 0.8)	0.03
Weight			
No. of women	272	271	
Mean change	0.3±1.2	0.4±1.3	

Measure	Clomiphene	Letrozole	P Value†
Median change (IQR)	0.2 (-0.4 to 1.2)	0.2 (-0.4 to 1.2)	0.77
Infertility			
No. of women	272	271	
Mean change	0.4±1.5	0.6±1.6	
Median change (IQR)	0.3 (-0.5 to1.0)	0.5 (-0.5 to 1.5)	0.18
Menstrual problems‡			
No. of women	270	271	
Mean change	0.3±1.1	0.4±1.2	
Median change (IQR)	0.3 (-0.3 to 1.0)	0.3 (-0.5 to 1.3)	0.53
SF-36 score			
Physical component			
No. of women	266	269	
Mean change	-0.9±7.4	-1.5±7.4	
Median change (IQR)	-0.2 (-4.0 to 2.7)	-1.0 (-5.8 to 3.1)	0.24
Mental component			
No. of women	266	269	
Mean change	-3.4±10.9	-1.9±10.4	
Median change (IQR)	-2.6 (-8.5 to 2.1)	-1.2 (-6.9 to 3.6)	0.07

* If conception occurred to the last visit was the one before pregnancy was documented. Plus–minus values are means ± SD. IQR denotes interquartile range.
† Wilcoxon's rank-sum test was used to compare the difference in change from baseline between the two treatment groups.
‡ Headaches, irregular menstrual periods, abdominal bloating, and menstrual cramps

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