Letrozole, Gonadotropin or Clomiphene for Unexplained Infertility

A Case Study

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Objectives for today's session

- Define Letrozole, Gonadotropins, and Clomiphene Citrate to compare their effectiveness in treating unexplained infertility
- Identify the risk of multiple gestations associated with each treatment option to support clinical awareness
- Describe the live-birth outcomes among treatment groups for application in reproductive sonography practice

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Standard Treatment for Unexplained Infertility

- Gonadotropin
- Clomiphene Citrate (Clomid)
- Letrozole

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Gonadotropins

- Peptide hormones
- Regulate ovarian and testicular function
- Essential for normal growth, sexual development and reproduction
- Human gonadotropins include:
  - FSH (follicle stimulating hormone)
  - LH (luteinizing hormone)
  - Chorionic gonadotropin (hCG)

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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What is GnRH?

- Gonadotropin releasing hormone
- Decapeptide
- Produced in the hypothalamus
- Highly purified formulations of gonadotropins have been developed and used to treat hypogonadism and infertility

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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What is FSH?

- Follicle stimulating hormone
- Pituitary hormone that regulates growth, sexual development and reproduction
- Regulated in part by gonadotropin releasing hormone
- Interacts with receptors on ovarian follicles
- Mid menstrual cycle surge
- Essential for sexual maturation and reproduction in both men and women

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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What is LH?

- Luteinizing hormone
- Promotes maturation of ovarian follicles
- LH surge triggers ovulation
- Stimulates production of testosterone by the testes in males

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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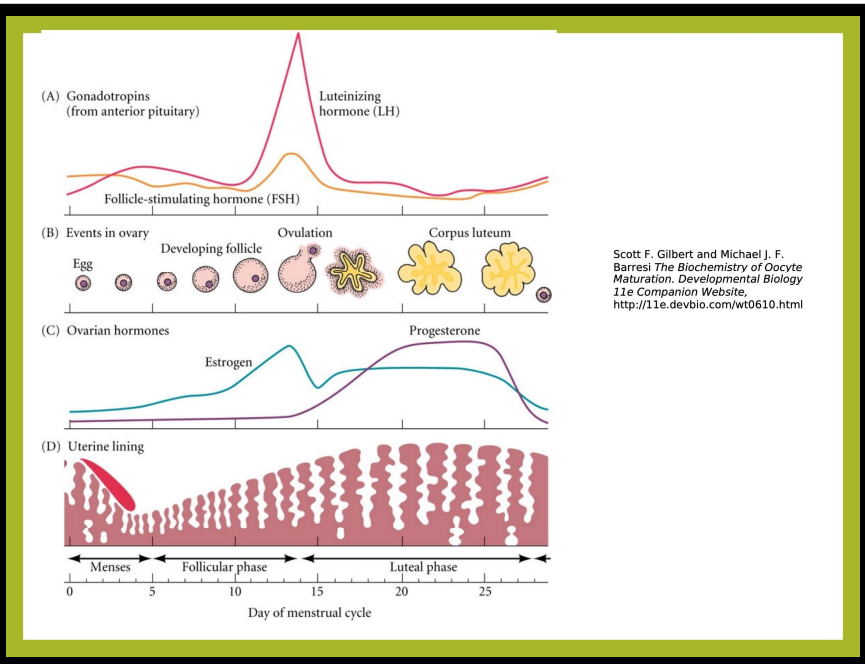

Scott F. Gilbert and Michael J. F. Barresi *The Biochemistry of Oocyte Maturation. Developmental Biology 11e Companion Website,* http://11e.devbio.com/wt0610.html

Scott F. Gilbert and Michael J. F. Barresi *The Biochemistry of Oocyte Maturation. Developmental Biology 11e Companion Website,* http://11e.devbio.com/wt0610.html

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What is hCG?

- Polypeptide
- Produced by the placenta after implantation of the fertilized egg
- Injections of hCG are used in the therapy of female infertility

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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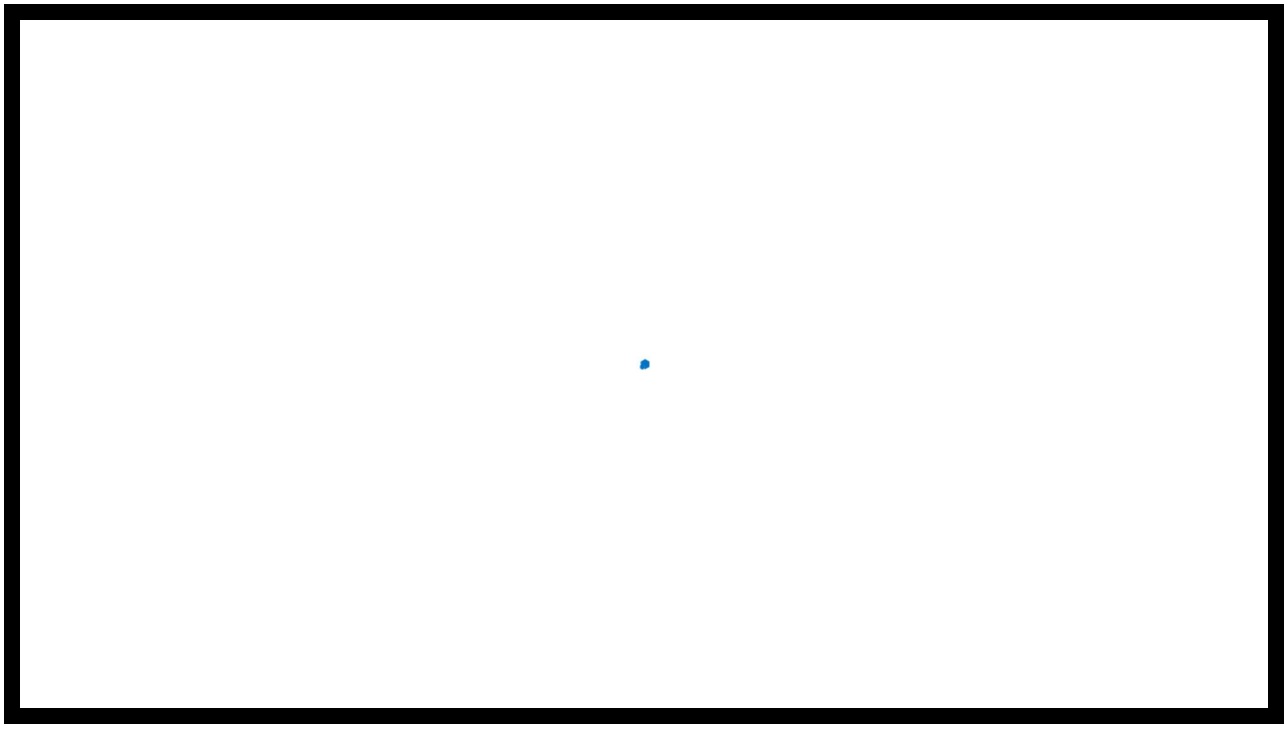

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Medications

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Gonadotropin-Menopur

- Ovarian stimulation medication
- Combines FSH and LH to:
  - Stimulate the growth of multiple eggs
  - Mature eggs
- Common side effects:
  - Stomach cramps
  - Fullness or pain
  - Headache
  - Injection site swelling



Why IVF With MENOPUR (menotropins for injection) [Internet] Year: 2026 Container: MENOPUR (menotropins for injection) https://www.menopur.com/why-ivf-with-menopur

Gonadotropins. PubMed. 2012. Accessed September 4, 2026. https://www.ncbi.nlm.nih.gov/books/NBK548856/

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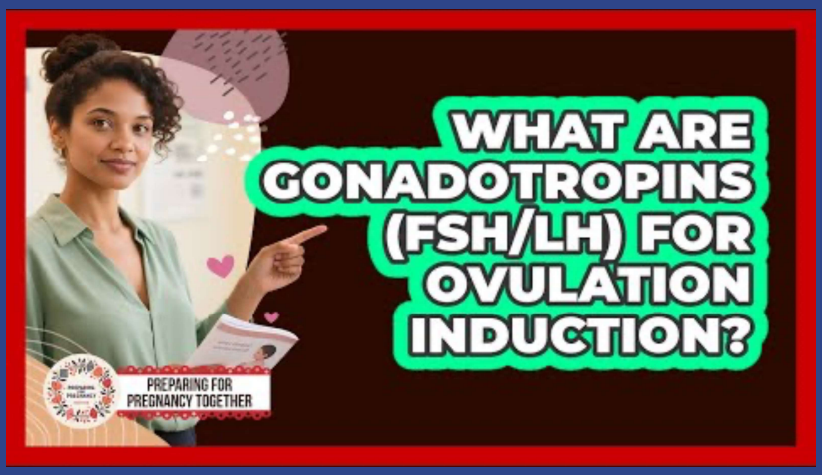
Gonadotropins



Preparing for Pregnancy Together. *What Are Gonadotropins (FSH/LH) For Ovulation Induction? - Preparing for Pregnancy Together*. YouTube; 2025. Accessed September 3, 2026. https://www.youtube.com/watch?v=kPjpUtiHo7k

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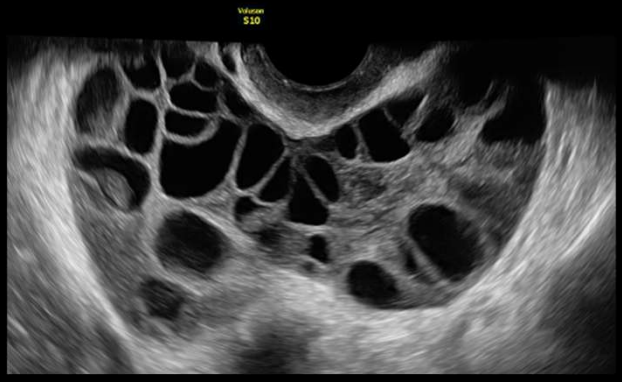
Ovarian Hyperstimulation Syndrome (OHSS)

- Risk Factors
  - Young age
  - History of elevated response to gonadotropins
  - Previous OHSS
  - Polycystic ovarian syndrome
    - Now known as Polyendocrine Metabolic Ovarian Syndrome (PMOS)



From personal files of Candace Summerskill (University of Michigan) (on file with author)

Kumar P, Sait S, Sharma A, Kumar M. Ovarian hyperstimulation syndrome. *Journal of Human Reproductive Sciences*. 2011;4(2):70. doi:10.4103/0974-1208.86080
Joseph G Whelan, Nikos F Vlahos, The ovarian hyperstimulation syndrome, Fertility and Sterility, Volume 73, Issue 5, 2000, ISSN 0015-0282, https://doi.org/10.1016/S0015-0282(00)00491-X.

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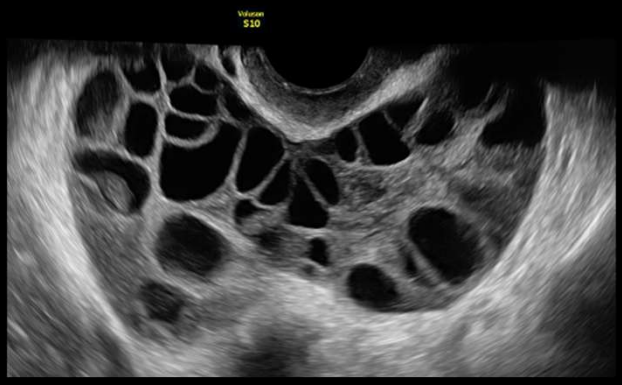
Varying Degrees of Ovarian Hyperstimulation Syndrome (OHSS)

- Mild
  - Grade 1: Abdominal distention/discomfort
  - Grade 2: Features grade 1 symptoms plus nausea/vomiting and/or diarrhea
  - Ovaries enlarged to 5-12 cm
- Moderate
  - Grade 3: Features of mild OHSS plus ultrasound evidence of ascites
- Severe
  - Grade 4: Features of moderate OHSS plus clinical evidence of ascites and/or difficulty breathing
  - Grade 5: The above listed symptoms, plus a change in blood volume and diminished renal perfusion and function



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Joseph G Whelan, Nikos F Vlahos, The ovarian hyperstimulation syndrome, Fertility and Sterility, Volume 73, Issue 5, 2000, ISSN 0015-0282, https://doi.org/10.1016/S0015-0282(00)00491-X.

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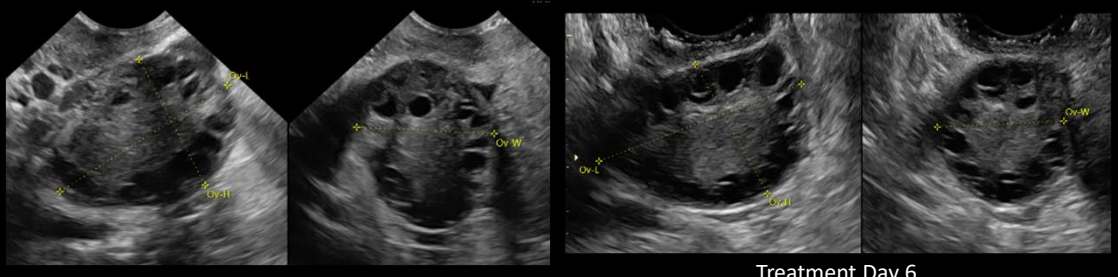
Ovarian Hyperstimulation Syndrome (OHSS)



Treatment Day 4

Treatment Day 6

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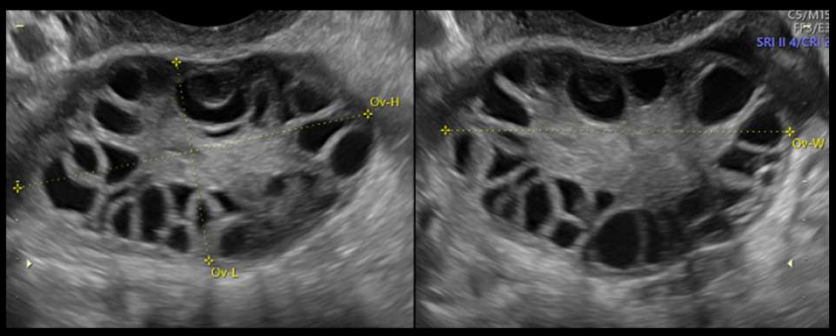
Ovarian Hyperstimulation Syndrome (OHSS)



Treatment Day 8

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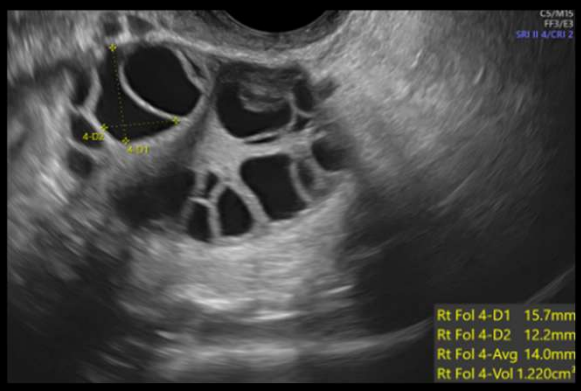
Ovarian Hyperstimulation Syndrome (OHSS)



Treatment Day 10

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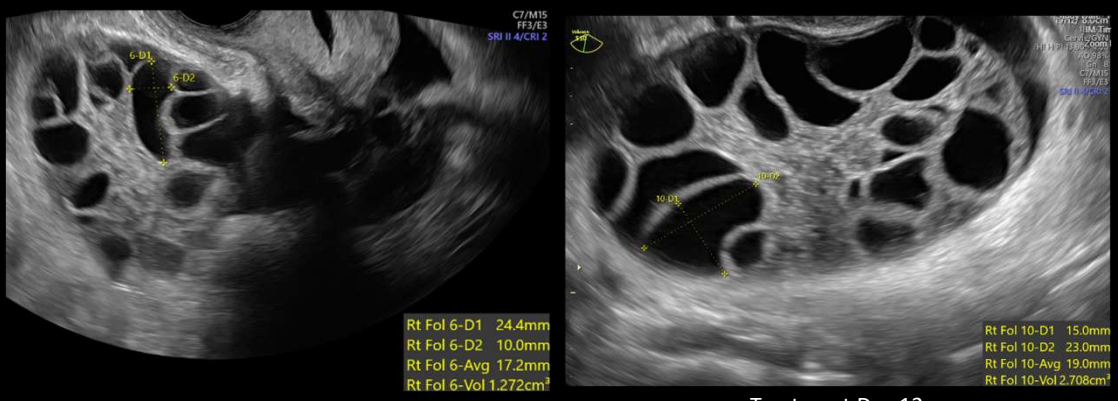
Ovarian Hyperstimulation Syndrome (OHSS)



Treatment Day 11

Treatment Day 12

From personal files of Candace Summerskill (University of Michigan) (on file with author)

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OHSS



Sports Med Review. *Pelvic Ultrasound: Ovarian Hyperstimulation Syndrome*. YouTube; 2022. Accessed September 3, 2026. https://www.youtube.com/watch?v=cMdPuLsJEWo

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Clomiphene Citrate

- Also known as Clomid
- FDA-approved selective estrogen receptor modulator (SERM)
  - Anovulatory or oligo-ovulatory infertility (Ovulation induction)
  - Male infertility (spermatogenesis induction)

Mbi Feh MK, Wadhwa R. Clomiphene. PubMed. 2020. Accessed September 3, 2026. https://www.ncbi.nlm.nih.gov/books/NBK559292/

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Clomiphene Citrate

- Available as a 50 mg oral tablet
- Dosages vary on personal ovulation induction protocols



CD DA. Clomid (Clomiphene): Uses, Dosage, Side Effects & Safety. iMedix: Independent Drug & Health Platform. March 13, 2024. Accessed September 3, 2026. https://www.imedix.com/drugs/clomid/

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Clomid



CCRM Fertility. *Conceiving with Clomid*. YouTube; 2023. Accessed September 3, 2026. https://www.youtube.com/watch?v=FxrmU63Evx8

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Letrozole

- A non-steroidal, highly selective oral aromatase inhibitor
- Inhibits the conversion of testosterone to estradiol
- Down regulated estrogen increases the secretion of pituitary follicle stimulating hormone (FSH) to stimulate ovulation
- Used extensively to induce ovulation in patients with anovulatory infertility patients and to augment follicles for ovulatory patients

Yang AM, Cui N, Sun YF, Hao GM. Letrozole for Female Infertility. *Frontiers in Endocrinology*. 2021;12(676133). doi:10.3389/fendo.2021.676133

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Letrozole

- Is used as an adjunct for IUI and IVF
- Utilized in fertility preservation cycles in women with estrogen-sensitive cancers
- Can be effective in preparing the endometrium for a FET



https://www.indiamart.com/proddetail/letoz-2-5mg-tablets-2857372336112.html

Yang AM, Cui N, Sun YF, Hao GM. Letrozole for Female Infertility. *Frontiers in Endocrinology*. 2021;12(676133). doi:10.3389/fendo.2021.676133

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Letrozole



Fertility Support Channel. *How Is Letrozole Used For Ovulation Induction? - Fertility Support Channel*. YouTube; 2025. Accessed September 3, 2026. https://www.youtube.com/watch?v=23ON70HgGWU

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The Case Study

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Baseline Characteristics

- Prescreened:
  - 3,730 couples
- Couples with unexplained infertility:
  - 1,220 couples
- 900 randomly assigned to treatment groups:
  - Gonadotropin
  - Clomiphene Citrate (Clomid)
  - Letrozole
- 746 couples completed the study

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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320 Excluded:
Did not meet inclusion criteria
1 Was not 18 to 39 years of age
1 With less than 1 year infertility
8 Did not have regularly ovulating (less than 9 menses per year)
43 Did not have one open fallopian tube or a normal uterine cavity
16 No evidence of ovarian function/reserve
6 Abnormal thyroid function within one year of study initiation
9 Abnormal prolactin level within one year of study initiation
9 Were not in good health
53 Did not meet sperm concentration criteria
Met exclusion criteria
38 Currently pregnant or pregnancies within 12 months of initiating participation
2 Undiagnosed abnormal uterine bleeding
3 Suspicious ovarian mass
2 Known significant anemia
2 Known or suspected adrenal or ovarian androgen secreting tumors
2 Allergy or contraindication to the treatment medications
7 Known moderate or severe endometriosis
2 Known polycystic ovarian syndrome
2 Couples in which either partner is legally married to someone else
10 Medical conditions that are contraindications to pregnancy
10 Withdrew consent prior to randomization
46 Patient lost to follow-up before randomization
21 Study closed
21 Others
Unknown 6

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Baseline Characteristics

- Dropouts among study groups:
  - Gonadotropin Group: 17.3%
  - Clomid Group: 16.3%
  - Letrozole Group: 17.7%
- Treatment-cycle cancellation rates:
  - Gonadotropin Group: 6.9%
  - Clomid Group: 3.3%
  - Letrozole Group: 3.7%

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Reasons for cycle cancellation	Gonadotropin Group	Clomiphene Group	Letrozole Group	Total
1. Leading follicle does not reach a mean diameter of 18 mm after 18 days of treatment	3	4	12	19
2. Endogenous LH surge happens with a mean diameter of the leading follicle <16 mm	5	4	10	19
3. Increased risk for OHSS and/or high-order multiple gestational pregnancy exists when more than 4 growing follicles develop (mean diameter >18 mm)	16	5	0	21
4. The serum E2 exceeds 3000 pg/m around the day of expected hCG administration	11	0	0	11
5. Patient or partner related reasons (withdrawal, unable to complete the cycle, no show, patient request, family reasons, etc.	12	14	3	29
6. Already ovulated	3	2	3	8
7. Others (Physician discretion, irregularly shaped follicle, fluctuating E2 levels, patient pregnant, etc.)	8	1	7	16
Total	**58**	**30**	**35**	**123**

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 1. Baseline Characteristics of the Women Enrolled in the Study.*

Characteristic	Gonadotropin (N=301)	Clomiphene (N=300)	Letrozole (N=299)
Biometric features			
Age — yr	32.3±4.1	32.0±4.6	32.2±4.3
Body-mass index†	26.8±6.7	26.7±6.4	27.3±6.5
Race or ethnic group — no. (%)‡			
White	238 (79.1)	241 (80.3)	243 (81.3)
Black	23 (7.6)	31 (10.3)	30 (10.0)
Asian	28 (9.3)	17 (5.7)	14 (4.7)
Mixed race	9 (3.0)	7 (2.3)	9 (3.0)
Hispanic or Latino	29 (9.6)	30 (10.0)	35 (11.7)
Fertility history			
Length of time attempting conception — mo	34.8±26.2	34.2±24.1	35.2±26.8
Previous live birth — no. (%)	64 (21.3)	67 (22.3)	52 (17.4)
Ultrasonographic findings			
Antral follicle count, both ovaries	20.6±12.6	20.3±11.3	21.2±11.2
Endometrial thickness, sagittal plane — mm	6.4±3.1	7.0±3.3	6.7±3.1
Fasting serum biochemical values			
Estradiol — pg/ml	33.7±40.4	32.4±21.5	32.7±28.0
Antimüllerian hormone — ng/ml	2.6±2.1	2.6±2.1	2.6±1.9
Follicle-stimulating hormone — mIU/ml	6.9±2.4	7.2±2.8	7.0±2.9

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Case Study Background

- Unexplained infertility standard therapy:
  - Gonadotropin
  - Clomid
- Using Letrozole in ovarian stimulation has been proposed to:
  - Reduce multiple gestations while maintaining live birth rates

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Details

- Couples with unexplained infertility
- Multicenter, randomized trial
- Ovulatory women
  - Ages 18-40 years of age
  - Normal uterine cavity
  - At least one patent fallopian tube
  - Male partner with at least 5 million sperm per milliliter

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Ovarian Stimulation Groups

- Gonadotropins
  - 301 women
- Clomiphene Citrate (Clomid)
  - 300 women
- Letrozole
  - 299 women

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Ovarian Stimulation Groups

- Medications initiated on cycle days 3, 4, or 5
  - 18-34 years old
  - 35-40 years old
- Ovarian stimulation
  - Up to 4 cycles
  - Intrauterine Insemination (IUI)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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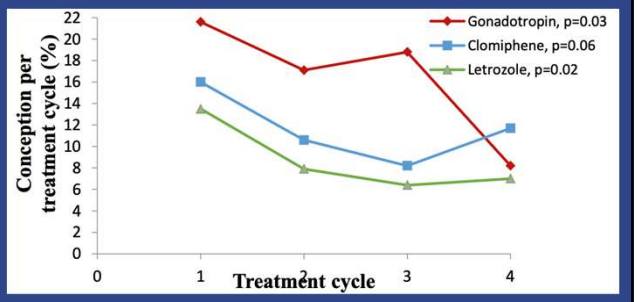
Conception per treatment cycle

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)
Pre- treatment cycle 1	2/301(0.7)	0/300(0)	2/299(0.7)
Treatment cycle 1	63/292(21.6)	47/294(16.0)	39/288(13.5)
Treatment cycle 2	37/217(17.1)	25/235(10.6)	19/242(7.9)
Treatment cycle 3	30/160(18.8)	16/195(8.2)	13/204(6.4)
Treatment cycle 4	9/110(8.2)	19/163(11.7)	12/172(7.0)



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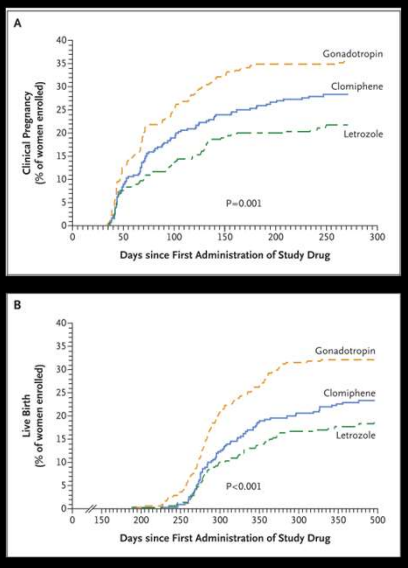
Pregnancy Outcomes

- Clinical pregnancies
  - Gonadotropin 35.5%
  - Clomid 28.3%
  - Letrozole 22.4%
- Live births
  - Gonadotropin 32.2%
  - Clomid 23.3%
  - Letrozole 18.7%



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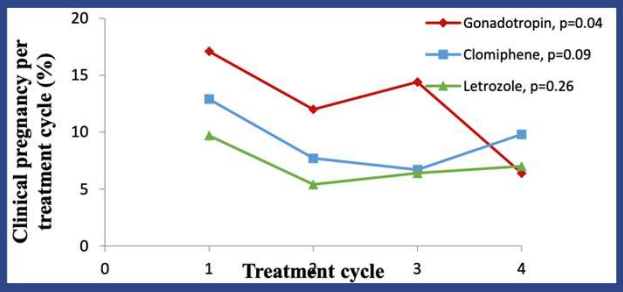
Clinical pregnancy per treatment cycle

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)
Pre- treatment cycle 1	1/301(0.3)	0/300(0)	1/299(0.3)
Treatment cycle 1	50/292(17.1)	38/294(12.9)	28/288(9.7)
Treatment cycle 2	26/217(12.0)	18/235(7.7)	13/242(5.4)
Treatment cycle 3	23/160(14.4)	13/195(6.7)	13/204(6.4)
Treatment cycle 4	7/110(6.4)	16/163(9.8)	12/172(7.0)



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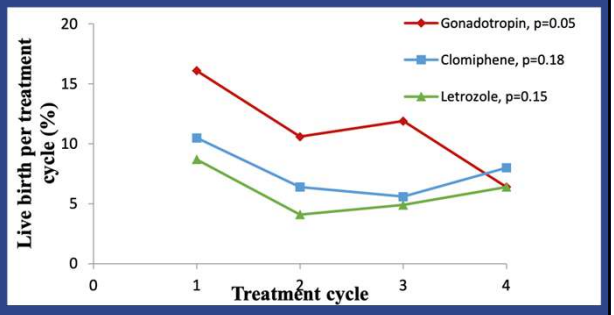
Live birth per treatment cycle

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)
		no./total no. (%)	
Live birth per treatment cycle			
Pre- treatment cycle 1	1/301(0.3)	0/300(0)	0/299(0)
Treatment cycle 1	47/292(16.1)	31/294(10.5)	25/288(8.7)
Treatment cycle 2	23/217(10.6)	15/235(6.4)	10/242(4.1)
Treatment cycle 3	19/160(11.9)	11/195(5.6)	10/204(4.9)
Treatment cycle 4	7/110(6.4)	13/163(8.0)	11/172(6.4)



Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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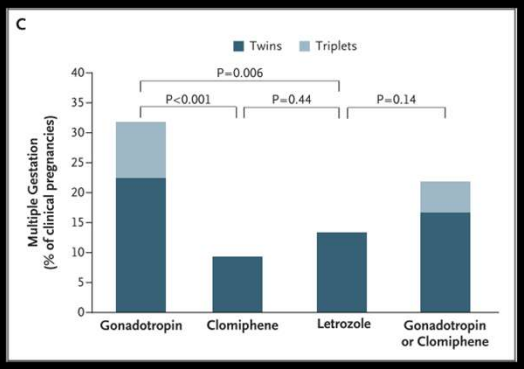
Multiple Gestation Rates

- Multiple gestation rates
  - Gonadotropins
    - 34 of 107 pregnancies (31.8%)
  - Clomid
    - 8 of 85 pregnancies (9.4%)
  - Letrozole
    - 9 of 67 pregnancies (13.4%)
  - Gonadotropin OR Clomid
    - 42 of 192 pregnancies (21.9%)



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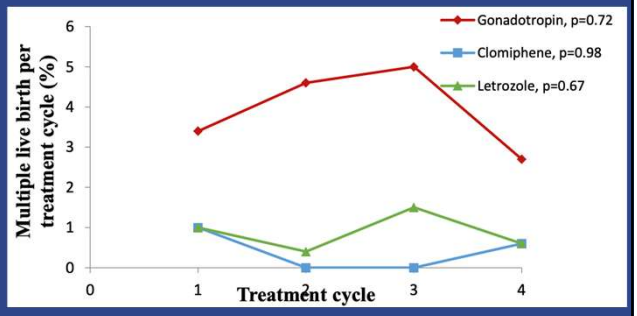
Multiple live birth per treatment cycle

Variable	Gonadotropin group (N=301)	Clomiphene group (N=300)	Letrozole group (N=299)
Multiple live birth per treatment cycle			
Pre- treatment cycle 1	0/301(0.0%)	0/300(0.0%)	0/299(0.0%)
Treatment cycle 1	10/292(3.4%)	3/294(1.0%)	3/288(1.0%)
Treatment cycle 2	10/217(4.6%)	0/235(0.0%)	1/242(0.4%)
Treatment cycle 3	8/160(5.0%)	0/195(0.0%)	3/204(1.5%)
Treatment cycle 4	3/110(2.7%)	1/163(0.6%)	1/172(0.6%)



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Multiple Gestations

- Clomid and Letrozole group:
  - All twin gestations
- Gonadotropin group:
  - 24 twin gestations
  - 10 triplet gestations

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Pregnancy Loss

- Gonadotropin
  - 36.4%
- Clomid
  - 29.2%
- Letrozole
  - 30.6%

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Pregnancy Loss

- No identified fetal heart motion
  - Approximately half of first trimester loss
- Ectopic pregnancy
  - 21 pregnancies
- Pregnancies of unknown location
  - 3 pregnancies

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Pregnancy Loss

- Loss in first trimester
  - Gonadotropins 34%
  - Clomid 26%
  - Letrozole 29%
- Loss in second or third trimester
  - Gonadotropins 2%
  - Clomid 3%
  - Letrozole 1%

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 2. Rates of Clinical Pregnancy, Live Birth, and Pregnancy Loss.*

Variable	Gonadotropin (N=301)	Clomiphene (N=300)	Letrozole (N=299)	Gonadotropin or Clomiphene (N=601)	Absolute Difference			
					Clomiphene vs. Gonadotropin	Letrozole vs. Gonadotropin	Clomiphene vs. Letrozole	Gonadotropin or Clomiphene vs. Letrozole
	number/total number (percent)				*percent (95% confidence interval)*			
Clinical pregnancy among all women enrolled	107/301 (35.5)	85/300 (28.3)	67/299 (22.4)	192/601 (31.9)	−7.2 (−14.7 to 0.2)	−13.1 (−20.3 to −6.0)¶	5.9 (−1.0 to 12.9)	9.5 (3.5 to 15.6)§
Multiple gestations among clinical pregnancies	34/107 (31.8)	8/85 (9.4)	9/67 (13.4)	42/192 (21.9)	−22.4 (−33.2 to −11.6)¶	−18.3 (−30.4 to −6.3)§	−4.0 (−14.3 to 6.2)	8.4 (−1.6 to 18.5)
Live birth among all women enrolled†	97/301 (32.2)	70/300 (23.3)	56/299 (18.7)	167/601 (27.8)	−8.9 (−16.0 to −1.8)	−13.5 (−20.4 to −6.6)¶	4.6 (−1.9 to 11.1)	9.1 (3.4 to 14.8)§
Singleton live birth among all women enrolled	66/301 (21.9)	66/300 (22.0)	48/299 (16.1)	132/601 (22.0)	0.1 (−6.5 to 6.7)	−5.9 (−12.1 to 0.4)	6.0 (−0.3 to 12.2)	5.9 (0.6 to 11.2)
Twin live birth among all women enrolled	25/301 (8.3)	4/300 (1.3)	8/299 (2.7)	29/601 (4.8)	−7.0 (−10.4 to −3.6)¶	−5.6 (−9.2 to −2.0)§	−1.3 (−3.6 to 0.9)	2.2 (−0.4 to 4.7)
Triplet live birth among all women enrolled	6/301 (2.0)	0	0	6/601 (1.0)	−2.0 (−3.6 to −0.4)	−2.0 (−3.6 to −0.4)	0	1.0 (−0.1 to 2.0)
Multiple gestations among live births‡	31/97 (32.0)	4/70 (5.7)	8/56 (14.3)	35/167 (21.0)	−26.2 (−37.0 to −15.5)¶	−17.7 (−30.7 to −4.6)	−8.6 (−19.2 to 2.1)	6.7 (−4.4 to 17.7)
Gestations with ≥1 loss	51/140 (36.4)	31/106 (29.3)	26/85 (30.6)	82/246 (33.3)	−7.2 (−19.9 to 4.6)	−5.8 (−18.5 to 6.8)	−1.3 (−14.4 to 11.7)	2.8 (−8.7 to 14.2)
Loss in first trimester	48/140 (34.3)	28/106 (26.4)	25/85 (29.4)	76/246 (30.9)	−7.9 (−19.4 to 3.6)	−4.9 (−17.4 to 7.6)	−3.0 (−15.8 to 9.8)	1.5 (−9.8 to 12.8)
Loss in second or third trimester	3/140 (2.1)	3/106 (2.8)	1/85 (1.2)	6/246 (2.4)	0.7 (−3.3 to 4.7)	−1.0 (−4.3 to 2.4)	1.7 (−2.3 to 5.6)	1.3 (−1.7 to 4.3)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 2. Rates of Clinical Pregnancy, Live Birth, and Pregnancy Loss.*

Variable	Gonadotropin (N=301)	Clomiphene (N=300)	Letrozole (N=299)	Gonadotropin or Clomiphene (N=601)	Absolute Difference			
					Clomiphene vs. Gonadotropin	Letrozole vs. Gonadotropin	Clomiphene vs. Letrozole	Gonadotropin or Clomiphene vs. Letrozole
	number/total number (percent)				*percent (95% confidence interval)*			
Clinical pregnancy among all women enrolled	107/301 (35.5)	85/300 (28.3)	67/299 (22.4)	192/601 (31.9)	−7.2 (−14.7 to 0.2)	−13.1 (−20.3 to −6.0)¶	5.9 (−1.0 to 12.9)	9.5 (3.5 to 15.6)§
Multiple gestations among clinical pregnancies	34/107 (31.8)	8/85 (9.4)	9/67 (13.4)	42/192 (21.9)	−22.4 (−33.2 to −11.6)¶	−18.3 (−30.4 to −6.3)§	−4.0 (−14.3 to 6.2)	8.4 (−1.6 to 18.5)
Live birth among all women enrolled†	97/301 (32.2)	70/300 (23.3)	56/299 (18.7)	167/601 (27.8)	−8.9 (−16.0 to −1.8)	−13.5 (−20.4 to −6.6)¶	4.6 (−1.9 to 11.1)	9.1 (3.4 to 14.8)§
Singleton live birth among all women enrolled	66/301 (21.9)	66/300 (22.0)	48/299 (16.1)	132/601 (22.0)	0.1 (−6.5 to 6.7)	−5.9 (−12.1 to 0.4)	6.0 (−0.3 to 12.2)	5.9 (0.6 to 11.2)
Twin live birth among all women enrolled	25/301 (8.3)	4/300 (1.3)	8/299 (2.7)	29/601 (4.8)	−7.0 (−10.4 to −3.6)¶	−5.6 (−9.2 to −2.0)§	−1.3 (−3.6 to 0.9)	2.2 (−0.4 to 4.7)
Triplet live birth among all women enrolled	6/301 (2.0)	0	0	6/601 (1.0)	−2.0 (−3.6 to −0.4)	−2.0 (−3.6 to −0.4)	0	1.0 (−0.1 to 2.0)
Multiple gestations among live births‡	31/97 (32.0)	4/70 (5.7)	8/56 (14.3)	35/167 (21.0)	−26.2 (−37.0 to −15.5)¶	−17.7 (−30.7 to −4.6)	−8.6 (−19.2 to 2.1)	6.7 (−4.4 to 17.7)
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Loss in first trimester	48/140 (34.3)	28/106 (26.4)	25/85 (29.4)	76/246 (30.9)	−7.9 (−19.4 to 3.6)	−4.9 (−17.4 to 7.6)	−3.0 (−15.8 to 9.8)	1.5 (−9.8 to 12.8)
Loss in second or third trimester	3/140 (2.1)	3/106 (2.8)	1/85 (1.2)	6/246 (2.4)	0.7 (−3.3 to 4.7)	−1.0 (−4.3 to 2.4)	1.7 (−2.3 to 5.6)	1.3 (−1.7 to 4.3)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Neonatal Outcomes

- Total of 272 infants born
- 9 infants with congenital anomalies
  - 4 from Gonadotropin group
  - 3 from Clomid group
  - 2 from Letrozole group
- 1 neonatal death
  - Letrozole group
  - Preterm labor and delivery
  - 23 weeks gestation

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Congenital Anomalies

Table S6. Congenital anomaly

Case number	Treatment group	Brief description of congenital anomaly
1	Clomiphene	Aortic arch hypoplasia
2	Clomiphene	Congenital hypothyroidism
3	Clomiphene	Renal duplicated right collecting system and ureterocele
4	Letrozole	Hypospadias
5	Letrozole	Right facial hemangioma; Biventricular hypertrophy; Bifid uvula; Small cataracts bilaterally; Widening of the corneal horizontal diameter
6	Gonadatropin	Right club foot
7	Gonadatropin	Transposition of genes on chromosome 19*
8	Gonadatropin	Multiple VSDs
9	Gonadatropin	Twin A VSD Twin B VSD

*Pregnancy loss at 16 weeks, not included in Table 4.
VSD = Ventricular Septal Defect

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Placental Abnormalities

Table S9. Placental Abnormality

Case number	Treatment group	Brief description of placental abnormality
1	Clomiphene	Placenta with succenturiate lobe
2	Clomiphene	Placental disc infarction
3	Clomiphene	Acute chorioamnionitis and umbilical cord with acute funisitis
4	Clomiphene	Marginal cord insertion
6	Gonadatropin	Calcifications
7	Gonadatropin	Acute chorioamnionitis
8	Gonadatropin	Velamentous cord insertion
9	Gonadatropin	Velamentous cord insertion
10	Gonadatropin	Velamentous cord insertion
11	Gonadatropin	Velamentous cord insertion

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Neonatal Outcomes

- Most common neonatal complications:
  - Jaundice
  - Respiratory distress syndrome
  - Intrauterine growth restriction

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 3. Neonatal Outcomes According to Treatment Group and Number of Fetuses.*

Outcome	Gonadotropin				Clomiphene			Letrozole		
	Singleton	Twin	Triplet	Total	Singleton	Twin	Total	Singleton	Twin	Total
Live delivery by mother — no.	66†	25‡	6‡	97	66	4	70	48	8	56
Estimated gestational age at delivery — wk	38.6±1.5	35.0±3.2	34.2±1.6	37.4±2.7§	38.6±1.7	37.3±1.5	38.5±1.7	38.5±3.3	35.0±1.6	37.7±4.0
Birth weight — g¶	3211±540	2271±602	1847±245	2891±726§	3215±529	2693±605	3184±543	3267±805	2256±439	3138±837
Male infants, including twins and triplets — no./total no. (%)	32/66 (48)	23/50 (46)	10/18 (56)	65/134 (49)	30/66 (46)	4/8 (50)	34/74 (46)	25/48 (52)	8/16 (50)	33/64 (52)
NICU admission — no./total no. (%)	5/66 (8)	10/25 (40)‖	6/6 (100)‖	21/97 (22)	7/66 (11)	0/4§	7/70 (10)	5/48 (10)	6/8 (75)	11/56 (20)
Length of neonatal hospitalization — days**	8.0±3.6	39.4±23.0	17.6±4.8	24.3±19.9	17.5±3.9	NA	17.5±3.9	23.5±15.5	17.8±8.1	21.1±12.3
Neonatal complications — no./total no. (%)	15/66 (23)	11/25 (44)	4/6 (67)	30/97 (31)	12/66 (18)	1/4 (25)	13/70 (19)	12/48 (25)	3/8 (38)	15/56 (27)
Congenital malformations — no./total no. (%)	1/66 (2)	2/25 (8)††	0/6	3/97 (3)	3/66 (5)	0/4	3/70 (4)	2/48 (4)	0/8	2/56 (4)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 3. Neonatal Outcomes According to Treatment Group and Number of Fetuses.*

Outcome	Gonadotropin				Clomiphene			Letrozole		
	Singleton	Twin	Triplet	Total	Singleton	Twin	Total	Singleton	Twin	Total
Live delivery by mother — no.	66†	25‡	6‡	97	66	4	70	48	8	56
Estimated gestational age at delivery — wk	38.6±1.5	35.0±3.2	34.2±1.6	37.4±2.7§	38.6±1.7	37.3±1.5	38.5±1.7	38.5±3.3	35.0±1.6	37.7±4.0
Birth weight — LBS / g¶	7.0 / 1.2 3211±540	5.0 / 1.3 2271±602	4.0 / 0.5 1847±245	6.3 / 1.6 2891±726§	7.1 / 1.1 3215±529	5.9 / 1.3 2693±605	7.0 / 1.2 3184±543	7.2 / 1.7 3267±805	4.9 / 0.9 2256±439	6.9 / 1.8 3138±837
Male infants, including twins and triplets — no./total no. (%)	32/66 (48)	23/50 (46)	10/18 (56)	65/134 (49)	30/66 (46)	4/8 (50)	34/74 (46)	25/48 (52)	8/16 (50)	33/64 (52)
NICU admission — no./total no. (%)	5/66 (8)	10/25 (40)‖	6/6 (100)‖	21/97 (22)	7/66 (11)	0/4§	7/70 (10)	5/48 (10)	6/8 (75)	11/56 (20)
Length of neonatal hospitalization — days**	8.0±3.6	39.4±23.0	17.6±4.8	24.3±19.9	17.5±3.9	NA	17.5±3.9	23.5±15.5	17.8±8.1	21.1±12.3
Neonatal complications — no./total no. (%)	15/66 (23)	11/25 (44)	4/6 (67)	30/97 (31)	12/66 (18)	1/4 (25)	13/70 (19)	12/48 (25)	3/8 (38)	15/56 (27)
Congenital malformations — no./total no. (%)	1/66 (2)	2/25 (8)††	0/6	3/97 (3)	3/66 (5)	0/4	3/70 (4)	2/48 (4)	0/8	2/56 (4)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Outcome	Gonadotropin				Clomiphene			Letrozole		
	Singleton	Twin	Triplet	Total	Singleton	Twin	Total	Singleton	Twin	Total
Live delivery by mother — no.	66†	25‡	6‡	97	66	4	70	48	8	56
Estimated gestational age at delivery — wk	38.6±1.5	35.0±3.2	34.2±1.6	37.4±2.7§	38.6±1.7	37.3±1.5	38.5±1.7	38.5±3.3	35.0±1.6	37.7±4.0
Birth weight — g¶	3211±540	2271±602	1847±245	2891±726§	3215±529	2693±605	3184±543	3267±805	2256±439	3138±837
Male infants, including twins and triplets — no./total no. (%)	32/66 (48)	23/50 (46)	10/18 (56)	65/134 (49)	30/66 (46)	4/8 (50)	34/74 (46)	25/48 (52)	8/16 (50)	33/64 (52)
NICU admission — no./total no. (%)	5/66 (8)	10/25 (40)‖	6/6 (100)‖	21/97 (22)	7/66 (11)	0/4§	7/70 (10)	5/48 (10)	6/8 (75)	11/56 (20)
Length of neonatal hospitalization — days**	8.0±3.6	39.4±23.0	17.6±4.8	24.3±19.9	17.5±3.9	NA	17.5±3.9	23.5±15.5	17.8±8.1	21.1±12.3
Neonatal complications — no./total no. (%)	15/66 (23)	11/25 (44)	4/6 (67)	30/97 (31)	12/66 (18)	1/4 (25)	13/70 (19)	12/48 (25)	3/8 (38)	15/56 (27)
Congenital malformations — no./total no. (%)	1/66 (2)	2/25 (8)††	0/6	3/97 (3)	3/66 (5)	0/4	3/70 (4)	2/48 (4)	0/8	2/56 (4)

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Safety

Table 4. Adverse Events and Serious Adverse Events According to Treatment Group.*

Event	Gonadotropin	Clomiphene	Letrozole	P Value†
		no./total no. (%)		
Overall adverse events				
≥1 Serious adverse event	21/297 (7.1)	8/298 (2.7)	8/291 (2.7)	0.009
≥1 Adverse event	208/297 (70.0)	212/298 (71.1)	214/291 (73.5)	0.63
Adverse events before conception				
Serious adverse events				
Presumed pyelonephritis	1/297 (0.3)	0/298	0/291	0.66
Pyosalpinx after intrauterine insemination	1/297 (0.3)	0/298	0/291	0.66
Other adverse events				
Abdominal bloating	81/297 (27.3)	50/298 (16.8)	54/291 (18.6)	0.003
Breast pain	65/297 (21.9)	19/298 (6.4)	21/291 (7.2)	<0.001
Constipation	6/297 (2.0)	28/298 (9.4)	8/291 (2.7)	<0.001
Headache	89/297 (30.0)	104/298 (34.9)	122/291 (41.9)	0.01
Hot flashes	25/297 (8.4)	92/298 (30.9)	49/291 (16.8)	<0.001
Injection-site reaction	32/297 (10.8)	6/298 (2.0)	9/291 (3.1)	<0.001
Joint or limb pain	5/297 (1.7)	8/298 (2.7)	17/291 (5.8)	0.02
Adverse events after conception				
Serious adverse events				
First trimester				
Cholecystitis	1/139 (0.7)	0/107	0/83	1.00
Ectopic pregnancy	11/139 (7.9)	5/107 (4.7)	5/83 (6.0)	0.58
Ovarian hyperstimulation syndrome	1/139 (0.7)	0/107	0/83	1.00
Pain due to ovarian enlargement	1/139 (0.7)	0/107	0/83	1.00
Pregnancy of unknown location	1/139 (0.7)	2/107 (1.9)	0/83	0.48
After first trimester				
Hemorrhagic hematoma	0/139	0/107	1/83 (1.2)	0.25
Hospitalization	1/139 (0.7)‡	0/107	1/83 (1.2)§	0.72
Hyperemesis	2/139 (1.4)	0/107	0	0.51
Hypertension	0/139	1/107 (0.9)	1/83 (1.2)	0.33
Severe preeclampsia	0/139	1/107 (0.9)	0/83	0.58
Emergency cesarean section	1/139 (0.7)	0/107	0/83	1.00
Other adverse events				
Breast pain, first trimester	0/139	0/107	5/83 (6.0)	0.001
Serious adverse events after 20 wk of gestation				
Congenital anomaly¶	3/96 (3.1)	3/70 (4.3)	2/56 (3.6)	0.90
Neonatal death	0/96	0/70	1/56 (1.8)	0.25

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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Table 4. Adverse Events and Serious Adverse Events According to Treatment Group.*

Event	Gonadotropin	Clomiphene	Letrozole	P Value†
		no./total no. (%)		
Overall adverse events				
≥1 Serious adverse event	21/297 (7.1)	8/298 (2.7)	8/291 (2.7)	0.009
≥1 Adverse event	208/297 (70.0)	212/298 (71.1)	214/291 (73.5)	0.63
Adverse events before conception				
Serious adverse events				
Presumed pyelonephritis	1/297 (0.3)	0/298	0/291	0.66
Pyosalpinx after intrauterine insemination	1/297 (0.3)	0/298	0/291	0.66
Other adverse events				
Abdominal bloating	81/297 (27.3)	50/298 (16.8)	54/291 (18.6)	0.003
Breast pain	65/297 (21.9)	19/298 (6.4)	21/291 (7.2)	<0.001
Constipation	6/297 (2.0)	28/298 (9.4)	8/291 (2.7)	<0.001
Headache	89/297 (30.0)	104/298 (34.9)	122/291 (41.9)	0.01
Hot flashes	25/297 (8.4)	92/298 (30.9)	49/291 (16.8)	<0.001
Injection-site reaction	32/297 (10.8)	6/298 (2.0)	9/291 (3.1)	<0.001
Joint or limb pain	5/297 (1.7)	8/298 (2.7)	17/291 (5.8)	0.02
Adverse events after conception				
Serious adverse events				
First trimester				
Cholecystitis	1/139 (0.7)	0/107	0/83	1.00
Ectopic pregnancy	11/139 (7.9)	5/107 (4.7)	5/83 (6.0)	0.58
Ovarian hyperstimulation syndrome	1/139 (0.7)	0/107	0/83	1.00
Pain due to ovarian enlargement	1/139 (0.7)	0/107	0/83	1.00
Pregnancy of unknown location	1/139 (0.7)	2/107 (1.9)	0/83	0.48
After first trimester				
Hemorrhagic hematoma	0/139	0/107	1/83 (1.2)	0.25
Hospitalization	1/139 (0.7)‡	0/107	1/83 (1.2)§	0.72
Hyperemesis	2/139 (1.4)	0/107	0	0.51
Hypertension	0/139	1/107 (0.9)	1/83 (1.2)	0.33
Severe preeclampsia	0/139	1/107 (0.9)	0/83	0.58
Emergency cesarean section	1/139 (0.7)	0/107	0/83	1.00
Other adverse events				
Breast pain, first trimester	0/139	0/107	5/83 (6.0)	0.001
Serious adverse events after 20 wk of gestation				
Congenital anomaly¶	3/96 (3.1)	3/70 (4.3)	2/56 (3.6)	0.90
Neonatal death	0/96	0/70	1/56 (1.8)	0.25

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Serious adverse events				
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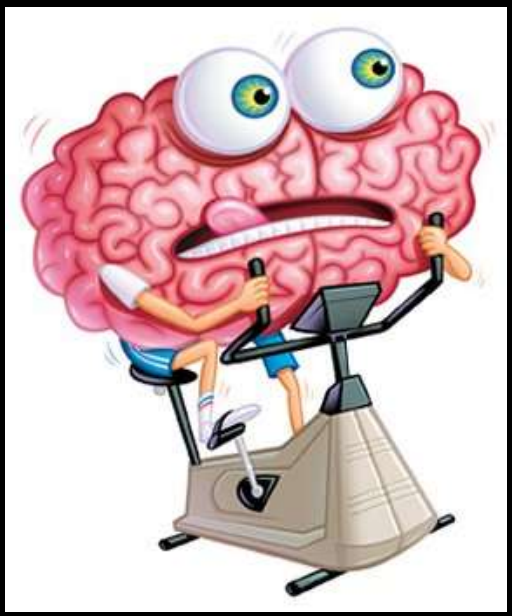

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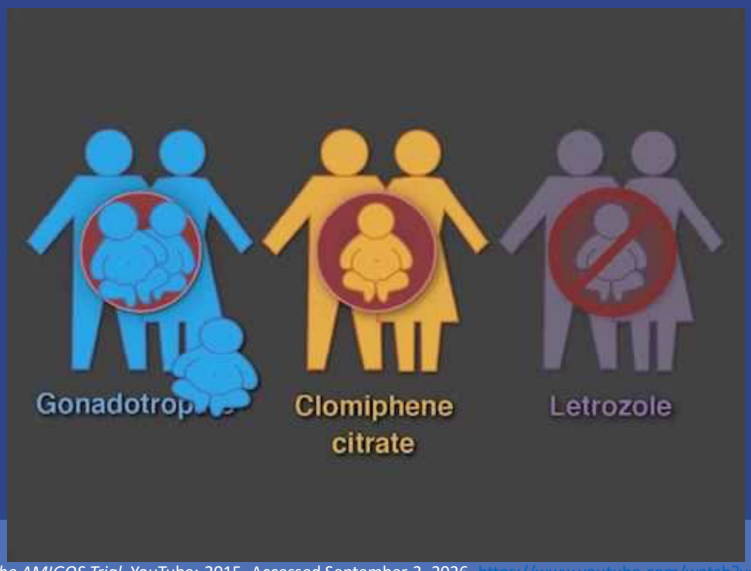
AMIGOS Trial Summary



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Conclusions

- Letrozole resulted in:
  - Lower frequency of multiple gestations
  - Lower frequency of live births
- Clomid, when used with IUI, remains the first line therapy for couples experiencing unexplained infertility

Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility. *The New England Journal of Medicine*. 2015;373(13):1230-1240. doi:10.1056/NEJMoa1414827

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THANK YOU!



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