Behandling med letrozol

Hvad er letrozol?

Letrozol er et medicinsk præparat, der hæmmer dannelsen af det kvindelige kønshormon østradiol.

Hvordan virker letrozol?

I fertilitetsbehandling udnyttes, at letrozol nedsætter mængden af østradiol. Et lavere niveau af østradiol i blodet resulterer i, at der dannes mere af hormonet FSH (follikel stimulerende hormon). FSH stimulerer æggestokkene til at modne ægblærer.

Hvem behandles med letrozol?

Letrozol i forbindelse med inseminationsbehandling

- Kvinder med uregelmæssig menstruationscyklus, som ikke udvikler et modent æg hver måned, kan bruge letrozol til at stimulere FSH-produktionen og normalisere væksten af ægblærer. Her vil målet være 1(-2) modne ægblærer før insemination.
- Kvinder med regelmæssig menstruationscyklus, som har prøvet at opnå graviditet hjemme med en partner, kan bruge letrozol til at udvikle 2(-3) modne ægblærer for at øge graviditetschancen ved insemination.

Letrozol til fertilitetsbehandling med nedfrosne æg

- Kvinder med uregelmæssig menstruationscyklus, som ikke udvikler et modent æg hver måned, kan bruge letrozol til at stimulere FSH-produktionen og normalisere væksten af ægblærer. Derved kan cyklus blive normaliseret og slimhinden i livmoderen forberedes til at modtage det optøede befrugtede æg.

Letrozol til fertilitetsbehandling ved reagensglasbefrugtning

- Til kvinder med meget lav ægreserve eller til særlige patientgrupper, kan lægen ordinere letrozol som supplement til stimulationen med FSH-indsprøjtninger.
- Til kvinder med aktuel eller tidligere brystkræft eller øget risiko for brystkræft, kan lægen ordinere letrozol som supplement til stimulationen med FSH-indsprøjtninger.

Hvor længe gives behandlingen?

Letrozol tages i 5 dage fra 3.-7. cyklusdag og kan evt. suppleres med FSH-indsprøjtninger.

Ved reagensglasbefrugtning benyttes letrozol i særlige tilfælde. Du vil blive vejledt af din behandlende læge om, hvor længe du skal fortsætte med medicinen.

Hvordan tages letrozol?

Letrozol er filmovertrukne tabletter, der indeholder 2,5 mg letrozol. Nogle kvinder skal tage 1 tablet, andre 2 tabletter dagligt. Tabletterne tages uafhængigt af måltider og på ca. samme tidspunkt hver dag. Glemt dosis skal tages straks. Kontakt din behandler ved tvivl.

Dansk Fertilitetsselskab

Bivirkninger

I indlægssedlen står der beskrevet mange bivirkninger, men disse er forbundet med længere tids brug, som ved behandling af brystkræft.

I forbindelse med fertilitetsbehandling bruges letrozol over en kortere periode, hvorfor der ikke ses de samme bivirkninger. De fleste kvinder vil kun opleve få eller ingen bivirkninger.

De bivirkninger, der er beskrevet i forbindelse med fertilitetsbehandling, er hyppigst hovedpine, hedeture, smerter i muskler og led samt kvalme, diarré og mavesmerter. Disse gener forsvinder, når du ophører med at tage letrozol.

Letrozol kan evt. tages til natten for at mindske eventuelle bivirkninger.

Letrozol er et "Off-label" præparat

Letrozol er et såkaldt "Off-label" præparat, når det bruges i forbindelse med fertilitetsbehandling. Dette betyder, at letrozol oprindelig er godkendt til behandling af brystkræftformer, der er følsomme for østradiol, og ikke til fertilitetsbehandling. Gennem mere end 20 år har letrozol været anvendt til fertilitetsbehandling og er internationalt anbefalet.

Der er ikke fundet øget forekomst af misdannelser eller graviditetstab efter behandling med letrozol i forhold til andre fertilitetsbehandlinger.

Forholdsregler når du er i behandling med letrozol

Ved nedsat nyre- eller leverfunktion – kontakt din behandlende læge.

Indeholder laktose.

Amning: Letrozol bør ikke anvendes ved amning, det er ukendt om letrozol udskilles i modermælk.

Bloddonor: Der er karantæne i 10 dage efter endt behandling.

Anvendelse af letrozol medfører udelukkelse/diskvalifikation fra sportsstævner.

Hvordan opbevares letrozol?

Letrozol opbevares i stuetemperatur, i den originale emballage.

Yderligere spørgsmål?

Ved tvivl eller spørgsmål, er det altid en god ide at kontakte dit behandlingssted.

Derudover henvises til indlægssedlen i pakken med medicin.

Tabel 1 , PICO 1a. Letrozol vs Clomifen til anovulatoriske patienter

LBR (timed intercourse)						
Studie	**n**	**Sammenligning**	**Ovulationsrate (%)**	**Fund LZ vs CC LBR**	**Lutealfase støtte**	**Metaananalyse**
Amer (2017)	159	LZ 2.5 mg vs CC 50 mg CD 2-4	84 vs 80 (NS)	OR 1,73 (0,92-3,27)	Ingen	1,2
Bayar (2016)	74	LZ 5 mg vs CC 100 mg CD 3-7	66 vs 75 (NS)	OR 1,18 (0,38; 3,63)	Ingen	1,2
Begum (2009)	64	LZ 7,5 mg vs CC 150 mg (CC resistent) CD 3-7	63 vs 38 (S)	OR 2,6 (0,93; 8,13)	Ingen	1
Dehbashi (2009)	100	LZ 5 mg vs CC 100 mg CD 3-7	60 vs 32 (S)	OR 1,83 (0,61;5,50) (	Ingen	1
Legro (2014)	750	LZ 2,5-7,5 mg vs CC 50-150 mg CD 3-5	62 vs 48 (S)	OR 1,60 (1,14;2,26)	Ingen	1,2
Liu (2017)	268	LZ 5 mg vs CC 50-150 mg CD 3-7	?	OR 1,73 (0,79;3,78)	?	1,2
Ray (2012)	147	LZ 2,5 -5 mg vs CC 50-100 mg	?	OR 2,04 (0,93;4,50)	?	1
Roy (2012)	204	LZ 2,5 -5 mg vs CC 50-100 mg CD 3-7	67 vs 68 (NS)	OR 2,49 (1,34;4,62)	Ingen	1
Sohrabvand (2006)	59	LZ 2,5 mg+metformin vs CC 100 mg+metformin CD3-7	91 vs 80 (NS)	OR 4,5 (1,09; 18,5)	Ingen	1
Fohroozanfard (2011)		LZ 5 mg+FSH 150 IU vs CC 100 mg+FSH 150 IU CD 3-7+CD 5-8	?	OR 1,18 (0,53;2,61)	?	1

Tabel 1 , PICO 1a. Letrozol vs Clomifen til anovulatoriske patienter

Seyedoshohadaei (2016)	100	LZ 5 mg vs CC 100 mg+ estradiol 4 mg CD 3-7 + 8-14	Ikke opgivet	OR 1,48 (0,54;4,06)	Ingen	1
CPR (IUI)						
Kar (2012)	103	LZ 5 mg vs CC 100 mg CD 2-6	73 vs61 (NS)	3,15 (0,93;10,66)	Duphastone 10 mg	1,2
Ganesh (2009)	1041	LZ 2.5 mg vs CC 10 mg + FSH 75 IU CD 3+8 CD 3-7	79 vs 57 (S)	1,53 (0,55;4,24)	Utrogestan 300 mg 15 dage	1
Zeinalzadeh (2010)	107	LZ 5 mg vs CC 100 mg CD 3-7	86 vs 72	1,66 (1,23;2,22)	?	1
1: Cochrane						
2: Wang 2019 IPD						
RCT						Dominant follikel/monifollikulær
Wang (2021)	270	LZ 2,5 mg vs CC 50 mg CD 5-9	63.3 61	CPR LZ>CC	Ingen	1,2 vs 1,1
Bansal (2020)	90	LZ 2,5-7,5 mg vs CC 50-150 mg CD 2-6	86 vs 85 (3 cycles)	CPR LZ>CC	Ingen	68 vs 45 %
Rezk (2018)	202	LZ 2,5 mg vs CC 100 mg+ metformin 500 mg	82 vs 43	CPR LZ>CC	?	?

Tabel 2. PICO 1b. Letrozol vs FSH til anovulatoriske patienter

Author, Year, Country	**Study design, cohort**	**LTZ IUI**	**CC IUI**	**FSH IUI**	**Outcomes**	**Adjustments/characteristics/ Other treatment characteristics**	**Conclusion/bias/grade**
Ganesh 2009 *Indien*	**Design:** RCT **Study period:** ? **Population:** **PCOS women with resistance to CC** **Grp A: 372 women – letrozol** **Grp B: 669 women – CC +FSH** **Grp C: 346 women - FSH**	**Start LTZ:** CD: 3 Dose: 2,5 mg x 2 Days of LTZ: 5 **Ovulation induction:** 1 follicle ≥ 17mm Scan CD8 **Luteal phase support** Utrogestan 300 mg	**Start CC+FSH:** CD: 3 Dose: 100 mg 75 or 100 ie FSH at CD 3 and 8 **Ovulation induction:** 1 follicle ≥ 17mm Scan CD8 **Luteal phase support** Utrogestan 300 mg	**Start FSH:** CD: 3 Dose: 75/100 ie **Ovulation induction:** 1 follicle ≥ 17mm Scan CD8 **Luteal phase support** Utrogestan 300 mg	**CPR** Group A: 87 (372) – 23.39% Group B: 96 (669) -14.35% Group C: 62 (346) – 17.92% ab<0.0001 bc NS ca NS **Miscarriage rate** Group A: 12 (372) – 13.80% Group B: 16 (669) -16.67% Group C: 9 (346) – 14.52% ab NS bc NS ca NS **Ovulation rate** Group A: 295 (372) – 79.3% Group B: 381 (669) -56.9% Group C: 311 (346) – 89.89% ab<0.0001 bc<0.0001 ca <0.001 **Cancellation rate** Group A: 77 (372) – 20.7% Group B: 288 (669) - 43.05.% Group C: 35 (346) – 10.11 % ab<0.0001 bc<0.0001 ca <0.001		Same CPR between letrozole and FSH But higher ovulation rate and lower cancellationrate among FSH stimulated compared to letrozol
Hassan 2017 ***Ægypten*** **(From Cochrane – Franik et al 2018)**	**Design:** RCT **Study period:** 2013-2015 **Population:** **PCOS women with resistance to CC** **Grp A: 70 women – letrozol**	**Start LTZ:** CD: 3 Dose: 2,5 mg x 2 Days of LTZ: 5 **Ovulation induction:** 1 follicle ≥ 17mm Scan CD10		**Start FSH:** CD: 3 Dose: 75 ie – step up protocol. Increase with 37,5 ie if no response **Ovulation induction:** 1 follicle ≥ 17mm Scan CD10 **Luteal phase support**	**CPR** Intervention: 21 (70) Control group: 24 /(70) OR 0.82[0.4,1.67] **Miscarriage rate** Intervention: 2/70 Control group: 3/70 OR 0.66[0.11,4.06]		Same CPR, miscarriage and multiple pregnancy rate

Tabel 2. PICO 1b. Letrozol vs FSH til anovulatoriske patienter

Author, Year, Country	**Study design, cohort**	**LTZ IUI**	**CC IUI**	**FSH IUI**	**Outcomes**	**Adjustments/characteristics/ Other treatment characteristics**	**Conclusion/bias/grade**
	Grp B: 70 women – FSH 75ie - step up protocol	**Luteal phase support** None		None	**Multiple pregnancy rate** Intervention: 0/70 Control group: 2/70 OR: 0.19[0.01,4.12]		
Shi 2019 ***Kina***	**Design:** RCT **Study period:** 2015-2018 **Population:** **PCOS women with resistance to CC** **Grp A: 48 women – letrozole (125 cycles)** **Grp B: 48 women – FSH 75ie - step up protocol (119 cycles)**	**Start LTZ:** CD: 3 Dose: 2,5 mg x 2 Days of LTZ: 5 **Ovulation induction:** 1 follicle ≥ 18mm Scan CD10 **Luteal phase support** None		**Start HMG:** CD: 3 Dose: 75 ie – step up protocol. Increase with 37,5 ie if no response **Ovulation induction:** 1 follicle ≥ 17mm Scan CD10 **Luteal phase support** None	**CPR** Intervention: 11 (48) Control group: 13 (48) 22.9% vs 27.1% P>.05 **Miscarriage rate** Intervention: 3 (48) Control group: 5 (48) 6.2% vs 10.4% P>.05 **Multiple pregnancy rate** Intervention: 1 (48) Control group: 8 (48) 4.2% vs 8.3% P<.05 **OHSS** Intervention: 2 (48) Control group: 6 (48) 4.2% vs 12.5% P<.05	Small sample size No Confidence intervals	Same CPR and miscarriage rate Significantly more women in the HMG group with multiple pregnancy rate and OHSS

TABEL 3. STUDY CHARACTERISTICS AND RESULTS
DFS guideline: Letrozole stimulated ovulation induction in ovulatory patients

Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
Al-Fozan 2004 **Canada** **Fra Cochrane + Danhof + Qin + Eskew**	**Design:** RCT **Study period:** 2002-2003 **Population:** Unexplained LTZ: 74pt (115 cycle) CC: 80 pt (123 cycle)	**Start LTZ: N**=74 (115 cycles) CD: Dose: 7,5mg Days of LTZ: ? **Ovulation induction:** 1 follicle ≥ 18mm Scan CD10	**Start CC: N**=80 (123 cycles) CD: Dose: 100mg Days of CC: ? **Ovulation induction:** 1 follicle ≥ 18mm Scan CD10		**CPR week (no)** Intervention: 13 (74) Control group: 15/(80) CI: NS /? **Miscarriage rate (no)** Intervention: 0 (74) Control group: 4 (80) CI:? **Multiple pregnancy rate (no)** Intervention:0 (74) Control group:1(80) CI:?	Higher number of follicles>14 mm in the letrozole group (2.0 vs 1.7, p<0,05	Same CPR, lower miscarriage rate
Fouda 2011 **Egypt** **Fra Cochrane + Danhof + Qin + Gunn + Eskew**	**Design:** RCT **Study period:** 2008-2010 **Population:** 214 Unexplained LTZ: 107 (210 cycle) CC: 107 (210 cycle)	**Start LTZ: N**=107 (210 cycle) CD: 1-9 Dose: 2,5mg Days of LTZ: **Ovulation induction:** 1 follicle ≥ 18mm	**Start CC: N**=107 (210 cycle) CD: 3-7 Dose: 100mg Days of CC: **Ovulation induction:** 1 follicle ≥ 18mm		**CPR week (no)** Intervention: 40 (107) Control group: 24(10/) 1.81 (1.05:3.13) **Miscarriage rate (no)** Intervention: 5(107) Control group:4(107) 0.71 (0.71,2.97) **Multiple pregnancy rate (no)** Intervention:4 Control group:3 P-value: **OHSS rate** Intervention: 0 Control group: 0 P-value:		
Diamond 2015 **Multicentre US** **Fra Cochrane + Zolton + Danhof + Gunn + Eskew**	**Design:** RCT **Study period:** **Population:** LTZ 300 CC 299 FSH 301	**Start LTZ: N=300** CD: 3 Dose: 5mg Days of LTZ: 5 **Ovulation induction:** When follicles 1>20mm or 2 > 18 mm	**Start CC: N=299** CD: 3 Dose: 100mg Days of CC: 5 **Ovulation induction:** When follicles 1>20mm or 2 > 18 mm	**Start FSH: N=301** CD: 3 Dose: 150 Days of FSH: step down from CD7 **Ovulation induction:** When follicles 1>20mm or 2 > 18 mm	**LBR (no)** Intervention:56 Control CC: 70 (ns) Contol FSH: 97 (sig) **CPR week (no)** Intervention: 67 Control CC: 85 Contol FSH:107 Lower than FSH, not NS than CC	**Cancellation with >4 follicles**	Letrozole has lower CPR than FSH but NS than CC

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Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
		Luteal phase support No luteal support was given	**Luteal phase support** No luteal support was given	**Luteal phase support** **No**	**Miscarriage rate (no)** Intervention:25 Control CC:28 Contol FSH: 48 **Multiple pregnancy rate (no)** Intervention:9 Control CC: 8 Contol FSH:34 (triplets) **OHSS rate** Intervention: 0 Control CC: 0 Control FSH 1		
Gregoriou 2008 **Greece** **From Cochrane + Danhof + Gunn**	**Design:** RCT **Study period:** May 2004 – June 2006 **Population:** Unexplained infertility who had failed 3 x CC + IUI 50 couples Group A: rFSH: 25 (64 cycles) Group B: LTZ: 25 (67 cycles)	**Start LTZ: N=25 (67 cycles)** CD: 3-7 Dose: 5 mg daily Days of LTZ: **Ovulation induction:** When: 1 follicle ≥ 18mm **Luteal phase support** 100 mg vaginal micronized P (Utrogestan) every night. Start on night after insemination.		**Start rFSH: N= 25 (n=64 cycles)** CD: 3 Dose: 150 IU every 2 days, modified according to response (also based on s-E2 levels) Days of rFSH: ? **Ovulation induction:** When: 1 follicle ≥ 18mm **Luteal phase support** 100 mg vaginal micronized P (Utrogestan) every night. Start on night after insemination.	**LBR (no)** Intervention: 20% (5/25) Control group: 28% (7/25) P-value: >0.05 **PR per initiated cycle (no)** Intervention: 8,9% (6/67) Control group: 14% (9/64) P-value: >0.05 **Miscarriage rate (no)** Intervention: Control group: 2 P-value: **Multiple pregnancy rate (no)** Intervention: 0 Control: 0 **Cancellation rate** Intervention: 7/67 Control group: 2/64 P-value: **OHSS rate** Intervention: Control group: 1 P-value: **Cumulative pregnancy rate (per couple)** Intervention: 6/25 (24%) Control group: 9/25 (36%) P-value: >0.05	November 2005: Recruitment was interrupted, because the manufacturing company of the drug issued a statement that LTZ should not be used for ovulation induction in premenopausal women.	No significant differences in pregnancy rate per cycle, cumulative pregnancy rate (per couple) or take-home baby rate when comparing LTZ with rFSH.

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Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
Akbari 2012 **Iran** Tertiary infertility care unit and a university hospital, in Tehran, Iran. From Cochrane	**Design:** RCT **Study period:** **Population:** Women <40 years, patent fallopian tubes and infertility (both ovulatory and anovulatory or PCOS groups) Group A (LTZ): 80 Group B (CC): 80	**Start LTZ: N=80** CD: 3-7 Dose: 5 mg Days of LTZ: 5 **Start gonodotropin:** When: hMG 150 IU daily from CD8 until hCG administration **Ovulation induction:** When: ≥ 1 follicle > 18mm **Luteal phase support** No luteal support was given	**Start CC: N=80** CD: 3 Dose: 100 mg Days of CC: 5 **Start gonodotropin:** When: hMG 150 IU daily from CD8 until hCG administration **Ovulation induction:** When: ≥ 1 follicle > 18mm **Luteal phase support** No luteal support was given		**Full term pregnancy (no)** Intervention: 17 (21,3%) Control group: 9 (11,3%) P-value: 0.062 **CPR week (no)** Intervention: 17 (21,3%) Control group: 11 (13,8%) P-value: 0.146 **Miscarriage rate (no)** Intervention: 0 (0%) Control group: 2 (2,5%) P-value: 0.454 **Multiple pregnancy rate (no)** Intervention: 0 Control group: 1 (twin) P-value:		No significant differences in full term pregnancy, CPR or miscarriage rate between LTZ+hMG vs. CC+hMG
Haqnawaz 2013 **Pakistan** Performed at fertility care center in Pakistan. Fra Cochrane	**Design:** Prospective cohort study (pilot study) **Study period:** March 2008-March 2010 **Population:** 500 women (< 40 years) with unexplained infertility, PCOS, early stage endometriosis, and borderline male factor infertility. Infertility > 2 years, normal FSH, LH, Prolactin & Testosterone. Tubal patency. Patients with stage I or II endometriosis and normal semen analysis were categorized as early stage endometriosis patients. **Group A (n=300): LTZ** **Group B (n=200): CC**	**Start LTZ: N=300** CD: ? Dose: 5 mg Days of LTZ: 5 **Start gonodotropin:** When: 75 IU hMG daily for 3−5 days **Ovulation induction:** When: ≥ 1 follicle ≥ 18 mm and an endometrial thickness of >7 mm was noted.	**Start CC: N=200** CD: Dose: 50 mg Days of CC: 5 **Start gonodotropin:** When: 75 IU hMG for 3−5 days based on follicular response on ultrasound at day 8 of the cycle. **Ovulation induction:** When: ≥ 1 follicle ≥ 18 mm and an endometrial thickness of >7 mm was noted.		**LBR (no)** Intervention: 22/26 (84.6%) Control group: 28/35 (80%) P-value: 0.32 **Pregnancy rate (no)** Intervention: 26/200 (11%) Control group: 35/300 (12%) P-value: 0.9 **Miscarriage rate (no)** Intervention: 4/200 Control group: 7/300 P-value: 0.32 **Multiple pregnancy rate (no)** Intervention: 2/200 Control group: 6/300 P-value: 0.56 **OHSS rate** Intervention: 0 Control group: 0 P-value:	The median age in group A was relatively higher i.e. 35 years *vs.* 31 years (p=0.01). One of the findings in our study was that better ovulation and pregnancy rates in women > 35 years are achieved with the use of Letrozole and it revealed less need for gonadotrophins (tror ikke der menes sammenlignet med CC). The patients were assigned to either group A or B by random sampling technique. Not a blinded study and quasi- randomization.	No significant differences in LBR, pregnancy rate, miscarriage rate or multiple pregnancy rate between LTZ+hMG and CC+hMG. Usikkerhed vedr. statistik. I tabellen står der n=200 i gruppe A og n=300 i gruppe B. Uoverensstemmelse mellem study aim og bl.a. conclusion samt mellem teksten og tabellerne (bl.a. duration of infertility).

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Pourali 2017 **Iran** **1 infertility clinic, Iran** **From Cochrane**	**Design:** Prospective randomized trial **Study period:** April 2010 – March 2011 **Population:** 170 infertile women (< 38 years), eligible for superovulation and IUI for the first time. Inclusion criteria: unexplained infertility + resistance to 3 cycles of clomiphene therapy who were candidate for IUI. CC group: 87 (51.2%) LTZ group: 83 (48.8%)	**Start LTZ: N=83** CD: 3 Dose: 2.5 mg x 2 dgl. Days of LTZ: 5 **Start gonodotropin:** When: 75 IU hMG x 1 dgl. From CD6 to hCG adm. **Ovulation induction:** When: ≥ 1 follicles > 16mm Ifølge abstract: 2 follicles ≥ 16 mm	**Start CC: N=87** CD: 3 Dose: 50 mg x 2 dgl. Days of CC: 5 **Start gonodotropin:** When: 75 IU hMG x 1 dgl. From CD6 to hCG adm. **Ovulation induction:** When: ≥ 1 follicles > 16mm Ifølge abstract: 2 follicles ≥ 16 mm		**CPR week (no)** Intervention: 22 (26.51%) Control group: 11 (12.64%). P-value: 0.022 **Miscarriage rate (no)** Intervention: 4 (4.8%) Control group: 5 (5.7%) P-value: 0.80 **Multiple pregnancy rate (no)** Intervention: 0 Control group: 0 P-value: **Cancellation rate (pga. OHSS)** Intervention: 0% Control group: 5 (5.7%) P-value: 0.027 **Cancellation rate (non-formation of at least 2 follicles ≥ 16 mm)** Intervention: 5 (6%) Control group: 7 (8%) P-value: 0.607 **OHSS rate (also cancelled cycles)** Intervention: 0 (0%) Control group: 5 (5.7%) P-value: 0.03	OHSS: If > 15 follicles in each ovary it is considered as ovarian hyperstimulation, so the cycle was cancelled and participant was excluded. Rates of pos. hCG: CC: 16 (18.4%) vs. LTZ: 26 (31.3%), p=0.059	Significantly higher CPR in LTZ group. No significant differences in miscarriage rates. Significantly higher OHSS rate in CC group, and thereby cancellation rate due to this reason. No significant difference between groups in regards to cancellation due to lacking follicles, but significantly more cancelled cycles due to OHSS in the CC-group. Der er nogle uoverensstemmelser mellem teksten og tabellen. Jeg har noteret hvad der står i tabellen.
Zadehmohares 2012 **Iran** **1 infertility clinic** **From Cochrane**	**Design: Randomized clinical trial** **Study period:** **Population:** 106 infertile couples eligible for stim. IUI for first time were recruited. Inclusion: female age <36 years, tubal patency, mild oligoasthenospermia, unexplained infertility. LTZ group: 53 CC group: 53	**Start LTZ: N=53** CD: 3-7 Dose: 5 mg Days of LTZ: 5 **Start gonodotropin:** When: recombinant FSH (Fostimon) 75 IU was administrated the following two days. **Ovulation induction:** When: 2-3	**Start CC: N=53** CD: 3 Dose: 100 mg Days of CC: 5 **Start gonodotropin:** When: recombinant FSH (Fostimon) 75 IU was administrated the following two days. **Ovulation induction:** When: 2-3		**Pregnancy rate (no)** Intervention: 20.8% Control group: 22.6% P-value: 0.501 (i abstract står der p=0.814) **Miscarriage rate (no)** Intervention: 2/11 (18.2%) Control group: 4/12 (33.3%). P-value: "no difference" (ifølge abstract, ingen p-værdi) **Multiple pregnancy rate (no)** Intervention: 1 (triplet) Control group: 1 (twin) P-value: **OHSS rate** Intervention: 1	β-hCG was positive in 11 (20.8%) in LTZ and 12 (22.6%) in CC groups (*P*=0.814).	No significant difference in pregnancy rate, multiple pregnancy rate and OHSS rate. Probably no significant difference in miscarriage rate.

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Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
		follicles ≥ 16-18 mm **Luteal phase support** Progesterone (suppository or injection) was administrated.	follicles ≥ 16-18 mm **Luteal phase support** Progesterone (suppository or injection) was administrated.		Control group: 1 P-value:		
Barroso 2006 **Mexico/Virginia** **Academic tertiary institute** **From Eskew**	**Design:** RCT **Study period:** December 2003 to September 2004 **Population:** 41 ovulatory patients (<36 years and/or with a basal cycle serum day 3 FSH level <10 mIU/mL) with unexplained infertility undergoing IUI. Patients with previous IUI attempts were excluded from the study and only one treatment cycle was studied for each patient. LTZ group: 21 CC group: 20	**Start LTZ: N=21** CD: 3-7 Dose: 2.5 mg/d Days of LTZ: **Start gonodotropin:** When: 75 IU/d rFSH from day 7 of stimulation until the day of hCG administration. **Ovulation induction:** When: ≥ 1 follicle ≥ 18mm **Luteal phase support** Vaginal micronized progesterone (600 mg/d Utrogestan)	**Start CC: N=20** CD: 3-7 Dose: 100 mg/d Days of CC: **Start gonodotropin:** When: 75 IU/d rFSH from day 7 of stimulation until the day of hCG administration. **Ovulation induction:** When: ≥ 1 follicle ≥ 18mm **Luteal phase support** Vaginal micronized progesterone (600 mg/d Utrogestan)		**Pregnancy rate (no)** Intervention: 23.8% Control group: 20% P-value: NS There was no difference in the miscarriage rate or proportion of multiple pregnancies for LTZ and CC groups (data not shown).	Randomization: sealed envelopes for the first case and then alternating patients in a consecutive fashion. Patients were blinded. All physicians and laboratory personnel were blinded to allocation.	No significant difference in pregnancy rate. There was no difference in the miscarriage rate or proportion of multiple pregnancies for LTZ and CC groups (data not shown).
Bayar 2006 **Turkey** **University infertility clinic**	**Design:** Prospective quasi-randomized trial.	**Start LTZ: N=21 (52 cycles)** CD: 3-7 Dose: 2.5 mg/dag Days of LTZ:	**Start CC: N=25 (67 cycles)** CD: 3-7 Dose: 100 mg/dag Days of CC:		**LBR (no)** Intervention: 5 Control group: 7 P-value:	IUI was performed in patients with borderline male factor infertility both in the letrozole (n:27) and CC (n:36) groups. Timed intercourse was	No significant difference in pregnancy rate per cycle.

TABEL 3. STUDY CHARACTERISTICS AND RESULTS
DFS guideline: Letrozole stimulated ovulation induction in ovulatory patients

Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
From Danhof	**Study period:** January 2002 – January 2003 **Population:** 46 patients with unexplained infertility, early stage endometriosis, and borderline male factor infertility. LTZ: 21 patients (52 cycles) CC: 25 patients (67 cycles)	**Ovulation induction:** When: ≥ 1 follicles > 18mm	**Ovulation induction:** When: ≥ 1 follicles > 18mm		**Pregnancy rate per cycle (no)** Intervention: 5/52 (10%) Control group: 8/67 (12%) P-value: 0.9 **Miscarriage rate (no)** Intervention: 0 Control group: 1 P-value: **Multiple pregnancy rate (no)** Intervention: 0 Control group: 0 P-value:	recommended in the remaining patients in both groups. Double IUI was performed 24 and 48 hours after administration of hCG. A quasi-randomization method was used. Based on the attendance order, patients with odd numbers were prescribed LTZ and those with even numbers were given CC. Neither the patients nor the physicians were blinded in any of the groups.	
Ibrahim 2012 Egypt **1 university hospital and 1 other hospital** **From Danhof**	**Design:** RCT **Study period:** February 2010 - May 2011 **Population:** 270 women (19-38 years) with unexplained infertility. LTZ group: 130 CC group: 131	**Start LTZ: N=130** CD: 3-7 Dose: 2.5 mg/day Days of LTZ: **Ovulation induction:** When: ≥ 1 follicles ≥ 18mm	**Start CC: N=131** CD: 3-7 Dose: 100 mg/day Days of CC: **Ovulation induction:** When: ≥ 1 follicles ≥ 18mm		**CPR week (no)** Intervention: 30/130 (23.07%) Control group: 14/131 (10.68%) P-value: <0.001 **Miscarriage rate (until end of 8th week) (no)** Intervention: 2/30 (6.66%) Control group: 5/14 (35.71%) P-value: <0.001 **Multiple pregnancy rate (no)** Intervention: 1/30 (3.33%) Control group: 3/14 (21.42%) P-value: <0.001 **OHSS rate** Intervention: 0 Control group: 0 P-value:		Significantly higher CPR in LTZ group. Significantly higher miscarriage rate and multiple pregnancy rate in CC group.
Davar 2006 Iran **From Cochrane** 1 Research and Clinical Center for Infertility and 1 Hospital.	**Design:** Prospective randomized trial **Study period:** October 2004 - September 2005 **Population:** 115 patients (<40 years) with unexplained and mild male factor infertility LTZ: 60 patients (60 cycles) CC: 55 patients (55 cycles)	**Start LTZ: N=**60 (60 cycles) CD: 3-7 Dose: 5 mg daily Days of LTZ: **Start gonodotropin:** When: FSH, 150 IU/day (starting dose), start CD8	**Start CC: N=**55 (55 cycles) CD: 3-7 Dose: 100 mg daily Days of CC: **Start gonodotropin:** When: FSH, 150 IU/day (starting dose), start CD8		**CPR week (per cycle) (no)** Intervention: 4 (6.6%) Control group: 1 (1.8%) P-value: 0.6 **Miscarriage rate (no)** Intervention: 1 Control group: 2 P-value: NS **Multiple pregnancy rate (no)** Intervention: 1 Control group: 0 P-value:	Chemical pregnancy rate per cycle was 8.3% (n=5) in the LTZ group and 5.5% (n=3) in the CC group (p=NS).	No significant differences in CPR, miscarriage rate or chemical pregnancy rate.

TABEL 3. STUDY CHARACTERISTICS AND RESULTS
DFS guideline: Letrozole stimulated ovulation induction in ovulatory patients

Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
		Ovulation induction: When: ≥ 1 follicles ≥ 18mm	**Ovulation induction:** When: ≥ 1 follicles ≥ 18mm		**OHSS rate** Intervention: 0 Control group: 0 P-value:		
Baysoy 2006 **Turkey** **From Cochrane + Zolton + Danhof**	**Design:** Pilot study, randomized controlled trial **Study period:** **Population:** 80 women (20-35 years) with unexplained primary infertility for at least 2 years. All women had previously undergone at least one ovulation induction treatment cycle combined with intercourse but this was their first IUI cycle. Group A (LTZ): 40 Group B (hMG): 40	**Start LTZ: N=40** CD: 3-7 Dose: 5 mg/day Days of LTZ: **Ovulation induction:** When: ≥ 1 follicles ≥ 17mm **Luteal phase support** No luteal support was given		**Start FSH (hMG): N=40** CD: 3 Dose: 75 IU for women < 30 years and 150 IU for women ≥ 30 years Days of FSH (hMG): 5 days of starting dose. After this, the dose and duration of hMG was adjusted while monitoring the follicular development according to the patient's response including the no. of growing follicles and oestradiol concentrations. **Ovulation induction:** When: ≥ 1 follicles ≥ 17mm **Luteal phase support** No luteal support was given	**CPR week (no)** Intervention: 7/38 (18.42%) Control group: 6/38 (15.78%) P-value: NS **Multiple pregnancy rate (no)** Intervention: 1 (triplets) Control group: 1 (twins) P-value: NS **OHSS rate** Intervention: 0 Control group: 1 P-value: NS	There were 4 premature luteinizations (2 in each group, p=NS). A single IUI was performed 34–36 h after HCG administration if no endogenous LH surge occurred. When LH surge occurred, insemination was performed on the following day, but that cycle was not taken into consideration. Only the specialist who had performed the IUI was blinded to group assignment. Patients were aware of the treatment allocation.	No significant differences in CPR, multiple pregnancy rate, OHSS rate.
Badawy 2010 Egypt Fertility Outpatient Clinic, Mansoura University Hospital, and a private practice setting. **From Eskew**	**Design:** RCT **Study period:** January 2004 - December 2007 **Population:** 280 women (<40 years) with unexplained infertility or mild male factor. CC: 141 patients (219 cycles) LTZ: 139 patients (215 cycles)	**Start LTZ: N**=139 (215 cycles) CD: 3 Dose: 5 mg daily Days of LTZ: 5 **Start gonodotropin:** When: hMG 75 IU/day for 5 days from CD5.	**Start CC: N**=141 (219 cycles) CD: 3 Dose: 50 mg x 2 dgl. Days of CC: 5 **Start gonodotropin:** When: hMG 75 IU/day for 5 days from CD5.		**Pregnancy/cycle (s-hCG 2 weeks after hCG injection in the absence of menstruation)** Intervention: 33/215 (15.3%) Control group: 37/219 (16.8%) P-value: 0.68 **Pregnancy/patient (s-hCG 2 weeks after hCG injection in the absence of menstruation)** Intervention: 33/139 (23.7%) Control group: 37/141 (26.2%)		No significant difference in pregnancy/cycle, pregnancy/patient or miscarriage rate/patient.

TABEL 3. STUDY CHARACTERISTICS AND RESULTS
DFS guideline: Letrozole stimulated ovulation induction in ovulatory patients

Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
		Ovulation induction: When: ≥ 1 follicles ≥ 18mm **Luteal phase support** 30 mg/day of dydrogesterone after insemination until the day of hCG testing.	**Ovulation induction:** When: ≥ 1 follicles ≥ 18mm **Luteal phase support** 30 mg/day of dydrogesterone after insemination until the day of hCG testing.		P-value: 0.36 **Miscarriage rate/patient (no)** Intervention: 15 (10.8%) Control group: 12 (9.9%) P-value: 0.22 **Multiple pregnancy rate (no)** Intervention: 1 (twins) Control group: 2 (twins) P-value: **OHSS rate** Intervention: 0 Control group: 0 P-value:		
Fatemi 2003 **Belgium** Centre for Reproductive Medicine of the Dutch-Speaking Free University Brussels **From Danhof, Cochrane**	**Design:** Pilot study **Study period:** September 2001 - August 2002 **Population:** 15 patients (≤39 years) with primary or secondary unexplained infertility LTZ: 7 CC: 8	**Start LTZ: N=7** CD: 3-7 Dose: 2.5 mg/day Days of LTZ: **Ovulation induction:** No ovulation triggering was used. IUI was performed one day following the detection of the LH peak. **Luteal phase support** No luteal support was given	**Start CC: N=8** CD: 3-7 Dose: 100 mg/day Days of CC: **Ovulation induction:** No ovulation triggering was used. IUI was performed one day following the detection of the LH peak. **Luteal phase support** No luteal support was given		**OPR (no)** Intervention: 2/7 Control group: 3/8 P-value:		
Khanna 2013 **India** Maulana Azad Medical College, New Delhi **From Qin**	**Design:** Prospective pilot trial **Study period:** January 2009 - May 2011 **Population:** 272 (362 cycles) infertile women (<40 years) with normal hormonal profile and day 2 FSH </= 12 IU/L, at least one normal patent tube, mild to moderate male factor	**Start LTZ: N=99** CD: 3-7 Dose: 5 mg Days of LTZ: 5 **Ovulation induction:** When: ≥ 1 follicles ≥ 18mm and the endometrial thickness ≥ 6mm	**Start CC: N=115** CD: 3-7 Dose: 100 mg Days of CC: 5 **Ovulation induction:** When: ≥ 1 follicles ≥ 18mm and the endometrial thickness ≥ 6mm		**Pregnancy rate/cycle (no)** Intervention: 12/131 (9.2%) Control group: 11/136 (8.1%) P-value: 0.92 **Pregnancy rate/patient (no)** Intervention: 12/99 (12.12%) Control group: 11/115 (9.5%) P-value: 0.70 **Miscarriage or ectopic rate (no)** Intervention: 2/12 (16.6%)	IUI was canceled in patients who did not respond to drugs or had endometrial thickness <6 mm or the male partner was not able to provide semen sample on the day of IUI. (Reasons for cancellation in the 2 groups, p=0.18) Both groups had 1 case of ectopic pregnancy each. 1 case of	No difference in pregnancy rate/cycle, pregnancy rate/patient or miscarriage/ectopic pregnancy rate.

TABEL 3. STUDY CHARACTERISTICS AND RESULTS
DFS guideline: Letrozole stimulated ovulation induction in ovulatory patients

Author, Year, Country	Study design, cohort	LTZ IUI[1]	CC IUI	FSH IUI	Outcomes	Adjustments/characterisctic/ Other treatment characteristics	Conclusion/bias/grade
	infertility. Azoospermic males willing for donor insemination were also included. Various etiologies: unexplained, ovulatory, tubal, male, uterine, early stage endometriosis. LTZ: 126 patients (170 cycles). IUI performed in 99 patients (131 cycles). CC: 146 patients (192 cycles). IUI performed in 115 patients (136 cycles). The statistical analysis was done only for patients who underwent IUI.	**Luteal phase support** 400 mg/day of micronized pro-gesterone after IUI till the day of pregnancy test.	**Luteal phase support** 400 mg/day of micronized pro-gesterone after IUI till the day of pregnancy test.		Control group: 1/11 (9.1%) P-value: 0.6 **Cancellation rate** Intervention: 27 (39 cycles) Control group: 31 (56 cycles) P-value:	miscarriage was reported in LTZ group. Alternate patients were given either clomiphene or letrozole. Neither the patients nor the physicians were blinded in any of the groups.	

TABLE 4. Letrozole (LTZ) +/- hMG FET vs HRT FET. STUDY CHARACTERISTICS AND RESULTS

Author, Year, Country	**Study design, cohort**	**LTZ FET**	**HRT FET**	**Other treatment characteristics**	**Review outcomes** (Absolute values, %, OR and aOR)	**Conclusion** **LTZ FET vs HRT FET** (reference group)
OLIGO-ANOVULATION						
***Aslih N** et al.* **2021** **Israel**	**Design:** Retrospective, single centre Inclusion 2016 - 2018 **Cohort**: **Anovulatory PCOS** (A total of 634 cycles in paper stratified on ovulatory status)	**LTZ (only) FET (n=25)** LTZ cd 5-9 HCG trigger Luteal phase progesterone (oral or vaginal)	**HRT-FET (n=80)** Oral Estradiol Progesterone (oral or vaginal)	**Cryopreservation method** Vitrification **Cleavage stage vs. blastocyst transfer** Day3 (5/6?) **No. of embryos transferred:** 1	**Delivery rate**: Group LTZ: 24% (6/25) Group HRT: 5% (4/80), p=0.011 Clinical pregnancy rate: Group LTZ: 44% (11/25) Group HRT: 22.5% (18/80), p=0.044	LTZ (only) FET: Higher delivery rate Bias: Low delivery rate in HRT FET Selection bias: The LTZ group includes only letrozole responders but not women who needed additional hMG (in HRT FET these women cannot be differentiated and 'both groups' are represented)
Godiwala P et. al. **2022** **USA**	**Design:** Retrospective, single centre Inclusion 2015 - 2021 **Cohort**: **Anovulatory women**	**LTZ (only) FET (n=82)** LTZ cd 3-7 Serum LH surge (LH ≥20 IU/L) used for timing Progesterone (vaginal)	**HRT FET (n=529)** GnRHa downregulation Estradiol (oral or transdermal) Progesterone (IM)	**Cryopreservation method** Vitrification **Cleavage stage vs. blastocyst transfer** Blastocysts **No. of embryos transferred:** 1-2	**Ongoing pregnancy/Live birth rate:** (HRT group is reference group) OR: 0.95 (0.79–1.15) aOR: 0.95 (0.79–1.13) Biochemical loss OR: 1.09 (0.53–2.26) aOR: 1.09 (0.53–2.23) Clinical loss OR: 1.56 (0.88–2.75) aOR: 1.57 (0.89–2.78)	LTZ (only) FET: Similar OPR/ LBR Similar pregnancy loss rate Bias: Selection bias as mentioned above PGT and number of blastocysts transferred were not included in adjusted analyses Different baseline characteristics
***Li** S. et al.* **2014** **China**	**Design:** Retrospective, single centre Inclusion 2010 - 2012 **Cohort**: **Ovulation disorders or irregular menstruation**	**LTZ only FET (n=359)** LTZ cd 3-7 HCG/GnRH agonist trigger (or natural ovulation) Progesterone (oral, IM)	**HRT FET (n=354)** Estradiol (oral) Progesterone (IM)	**Cryopreservation method:** N/A **Cleavage stage vs. blastocyst transfer:** Day3 embryos **No. of embryos transfered:** LTZ mean 2.86 ± 0.361 HRT mean 2.89 ± 0.321	**Live birth rate:** Group LTZ: 44.6% (160/359) Group HRT: 32.5 (115/354), $p < 0.05$ **Miscarriage rate**: Group LTZ: 12.0% (23/191) Group HRT: 21.0% (33/157), $p < 0.05$	LTZ (only) FET: Higher LBR Reduced MR Bias: Selection bias as mentioned above
***Zhang** Junwei et al.* **2021** **China** *(Same Centre and inclusion period as the Zhang Wenjuan et al. 2022 paper below)*	**Design:** Retrospective, single centre Inclusion 2016 - 2020 **Cohort;** **Abnormal ovulation**	**LTZ (+/-hMG) FET (n=502)** LTZ for 5 days from 3rd-5th day of menstruation. If follicular development was poor, hMG was added. HCG trigger Progesterone (oral and vaginal)	**HRT FET (n=2280)** Estradiol (oral) Progesterone (oral and vaginal)	**Cryopreservation method:** N/A **No. of embryos transfered:** Single blastocyst transfer	**Live birth rate:** Group LTZ: 49.6 % Group HRT: 41.7 %, p = 0.001 **aOR (95% CI): 1.30 (1.06-1.58)** **Miscarriage rate:** Group LTZ: 14.3 % HRT FET: 21.7 %, p = 0.005 **aOR (95% CI): 0.63 (0.44-0.90)**	LTZ (+/-hMG) FET: Higher LBR Lower MR Bias: In Table 1 other diagnosis than abnormal ovulation?

TABLE 4. Letrozole (LTZ) +/- hMG FET vs HRT FET. STUDY CHARACTERISTICS AND RESULTS

Author, Year, Country	**Study design, cohort**	**LTZ FET**	**HRT FET**	**Other treatment characteristics**	**Review outcomes** (Absolute values, %, OR and aOR)	**Conclusion** **LTZ FET vs HRT FET** (reference group)
Zhang *Wenjuan et al.* **2022** **China**	**Design:** Retrospective, single centre Propensity score matching (PSM) Inclusion 2016 - 2020 **Cohort:** **Abnormal ovulation**	**LTZ (+/-hMG) FET (n=1461)** LTZ for 5 days from 3rd-5th day of menstruation. If follicular development was poor, hMG was added. HCG trigger Progesterone (oral and vaginal)	**HRT FET (n=1461)** Estradiol (oral) Progesterone (oral and vaginal)	**Cryopreservation method:** N/A **Cleavage stage vs. blastocyst transfer:** Day 3 or Day 5/6 **No. of embryos transferred:** 1-2	**Live birth rate:** Group LTZ: 38.0 % Group HRT: 35.4 %, p = 0.379 aOR (95% CI): 0.951 (0.808-1.120) **Miscarriage rate:** *(Denominator clinical pregnancies)* Group LTZ: 137/716 (19.1 %) HRT FET: 160/733 (21.8 %)	No significant difference in LBR Bias: Perhaps ovulatory women are also included? Embryo developmental stage and number of embryos transferred were NOT included in PMS
PCOS						
Guan *Lu et al.,* **2022** **China**	**Design:** Retrospective, single centre Inclusion 2018 - 2020 **Cohort**: **PCOS**	**LTZ (+hMG) FET (n=173)** LTZ cd 3-7 followed by hMG HCG trigger Progesterone (IM)	**HRT FET (n=507)** Estradiol (oral) Progesterone (IM)	**Cryopreservation method:** Vitrification **Cleavage stage vs. blastocyst transfer:** Day 3 or blastocysts **No. of embryos transfered:** 1-2	**Live birth rate:** Group LTZ: 49.7 % Group HRT: 41.0 %, p = 0.046 OR (95% CI): 1.39 (0.99–1.97) **aOR (95% CI): 1.46 (1.03-2.08)** **Miscarriage rate**: Group LTZ: 6.4 % Group HRT: 23.0 %, p < 0.001 OR: 0.24 (0.10–0.57) **aOR: 0.24 (0.10-0.56)**	LTZ (+/-hMG) FET: Higher LBR Lower MR Bias PCOS defined according to the Rotterdam criteria with no stratification on ovulatory status.
Hosseini-Najarkolaei *Azadeh et al.* **2020** **Iran**	**Design: RCT**, Single centre Inclusion 2018 – 2020 **Relevant Cohort**: **PCOS**	**LTZ (+hMG) FET (n=57)** LTZ cd 3-5, hMG daily from cd 5th-9th and until hCG trigger. Progesterone (IM)	**HRT FET (n=59)** Estradiol (oral) Progesterone (IM)	**Cryopreservation method:** Vitrification **Cleavage stage vs. blastocyst transfer:** Day 3 embryos **No. of embryos transfered:** 1-2	**Ongoing pregnancy rate:** Group LTZ: 35.0 % (20/57) Group HRT: 32.2 % (19/59), p = 0.74 **Miscarriage rate:** *Own calculation: denominator chemical pregnancies* *Group LTZ: 8/28 (28.6 %)* *HRT FET: 6/25 (24 %)*	LTZ (+hMG) FET: No significant difference in OPR, CPR or MR in compared to HRT FET Bias PCOS defined according to the Rotterdam criteria with no stratification on ovulatory status.
Hu *Yan-Jun et al.* **2014** **China**	**Design:** Retrospective, single centre **Inclusion:** 2011 - 2012 **Relevant Cohort** **PCOS**	**LTZ (+/-hMG) FET (n=40)** LTZ cd 3-7 If follicular development was poor, hMG was added. HCG trigger Progesterone (IM)	**HRT-FET (n=76)** Estradiol (oral) Progesterone (IM)	**Cryopreservation method:** N/A **Cleavage stage vs. blastocyst transfer:** Day 2 and 3 embryos **No. of embryos transfered:** LTZ 2.4 +/- 0.4 HRT 2.4 +/- 0.6	Live birth rate: Not reported **Ongoing pregnancy rate**: Group LTZ: 60.0% (24/40) Group HRT: 36.8% (28/76), p = 0.017 Miscarriage rate: Not reported	LTZ-FET (+/-hMG): Higher OPR and CPR Bias: VERY HIGH ongoing pregnancy rate in LTZ FET, low numbers

TABLE 4. Letrozole (LTZ) +/- hMG FET vs HRT FET. STUDY CHARACTERISTICS AND RESULTS

Author, Year, Country	**Study design, cohort**	**LTZ FET**	**HRT FET**	**Other treatment characteristics**	**Review outcomes** (Absolute values, %, OR and aOR)	**Conclusion** **LTZ FET vs HRT FET** (reference group)
Niu Y et al. **2022** **China**	**Design:** Retrospective, single centre **Inclusion:** 2012 - 2020 **Cohort** **PCOS**	**LTZ (+/-hMG) FET (n=175)** LTZ cd 3-7 If follicular development was poor, hMG was added. HCG trigger Progesterone (oral)	**HRT FET (n=3540)**	**Cryopreservation method:** Vitrification **Cleavage stage vs. blastocyst transfer:** D5/6/7 blastocysts **No. of embryos transfered:** Single blastocyst transfer	**Live birth rate:** Group LTZ: 58.9% (103/175) Group HRT: 49.6 (1756/3540) P-value: 0.051 **aOR: 1.42; 95% CI: 1.04-1.93** Total pregnancy loss rate: Group LTZ: 16.9% (21/124) Group HRT: 30.3% (765/2521) P-value: 0.003 **aOR: 0.48; 95% CI: 0.30-0.78**	Higher LBR (in adjusted analysis only) Lower total pregnancy loss rate Bias PCOS defined according to the Rotterdam criteria with no stratification on ovulatory status.
***Zhang** Jie et al.* **2019** *Fertil Steril* **China**	**Design:** Retrospective, single centre **Inclusion:** 2011 - 2016 **Cohort**: **PCOS**	**LTZ (+/-hMG) FET (n=1236)** LTZ cd 3-7 If follicular development was poor, hMG was added. HCG trigger Progesterone (vaginal)	**HRT FET (n=850)** Estradiol (oral) Progesterone (vaginal)	**Cryopreservation method:** Vitrification **Cleavage stage vs. blastocyst transfer:** Day3 (>90%) Day5 blastocysts **No. of embryos transfered:** 1-2 (approximately 90% double embryo transfer)	**Live birth rate:** LTZ-FET: 54.4% HRT-FET 50.7%, (p=0.100) OR: 1.16 (0.97-1.38) **aOR: 1.33 (1.09-1.61)** **Miscarriage rate** (defined as a loss of clinical pregnancy)**:** LTZ-FET: 9.1% HRT-FET 17%, (p<0.001) OR: 0.49 (0.35-0.69**)** **aOR: 0.51 (0.35–0.74)**	LTZ (+/-hMG) FET: Higher LBR (in adjusted analysis only). Lower MR Bias: PCOS defined according to the Rotterdam criteria with no stratification on ovulatory status. In HRT FET, a relatively low progesterone dose was used.

LTZ - letrozole; HRT – hormone replacement therapy, OR - odds ratio; aOR – adjusted odd ratio, IM – intramuscular, LBR – live births rate, OPR – ongoing pregnancy rate, MR – miscarriage rate