

Cumulative live birth rate and cost-effectiveness analysis between GnRH-antagonist protocol and multiple minimal ovarian stimulation in poor responder

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Research

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Abstract

Background

The overall cumulative live birth rate (CLBR) of poor ovary responders (POR) is extremely low. Minimal ovarian stimulation (MOS) suggested a relative realistic solution in ART for POR. Our study aimed to investigate whether multiple MOS strategy results in higher CLBR compared to GnRH antagonist protocol and the cost-effectiveness analysis in POR.

Methods

This retrospective study involved 699 patients (1058 cycles) who fulfilled the Bologna criteria in one center performed from 2010–2018. Specifically, 325 women (325 cycles) were treated with one time conventional GnRH antagonist ovarian stimulation (GnRH-antagonist). Another 374 patients (733 cycles) were treated with multiple minimal ovarian stimulations (MOS) including natural cycles. CLBR and cost-effectiveness analysis were performed comparing these two groups of women.

Results

GnRH- antagonist leads to more oocytes retrieved, more fertilized oocytes and more viable embryos compared to first MOS ($p < 0.001$) and the cumulative corresponding ones in multiple MOS ($p < 0.001$). For the first IVF cycle, GnRH- antagonist results in higher CLBR than MOS (12.92% versus 4.54%, Adjusted OR 2.606; 95%CI 1.386, 4.899, $p = 0.003$). However, GnRH-antagonist induces comparable CLBR with multiple MOS (12.92% versus 7.92%, Adjusted OR 1.702; 95%CI 0.971, 2.982, $p = 0.063$), but absolutely shorter time to live birth (9 (8, 10.75) months versus 11 (9, 14) months, $p = 0.014$) and similar financial expenditure compared to repeated MOS (20838 (17953, 23422) ¥ versus 21261.5 (15892.5, 35140.25) ¥, $p = 0.13$).

Conclusion

Both MOS and GnRH-antagonist provide low chance of live birth for poor responders. GnRH antagonist protocol is a sound choice for POR with comparable CLBR, shorter time to live birth and similar financial expenditure.

Background

About 20% of all women under assisted reproductive technology (ART) treatment demonstrate a poor ovarian response with very few oocytes retrieved or low-quality oocytes. Most of these patients are with poor ovarian reserve[1]. Some patients are retrospectively found after some conventional ovarian stimulation. Patients with advanced age or abnormal ovarian reserve test are more appropriately defined

as expected poor responder. Bologna criteria has been validated to represent a homogenous population with uniform poor prognosis and similar clinical outcomes. According to ESHRE consensus Bologna criteria on the definition of “poor response” to ovarian stimulation for IVF, two of the following three features must be present: (1) age \geq 40 years or any other risk factor for POR, (2) previously \leq 3 oocytes retrieved with conventional stimulation, (3) AFC $<$ 5–7 follicles or AMH $<$ 0.5 ng/ml[2].

These patients represent a conundrum in modern IVF. Studies of ART didn't offer a solid evidence for preferred strategy and sound solution for parenthood in these patients considering the limited supply of oocytes, poor quality of embryo, high frequency of canceled cycles. The pregnancy rate per cycle of POR varies from 7.6 to 17.5% compared to 25.9–36.7% in normal responders[3]. The drop-out rate for this population of women is as high as 25% around the world. The live birth rate is extremely low and varies between different POSEIDON groups which are majorly attributed to maternal age and ovarian response. Adjuvant treatments like growth hormone (GH), Dehydro-epiandrosterone(DHEA), CoQ10 have been claimed to be co-treatment of choice in controlled ovarian stimulation(COS) for these patients and showed somewhat better clinical results in some studies in term of achieving pregnancy[4–6]. But the overall cumulative live birth rate (CLBR) of POR is still extremely low. It is utmost important to provide effective and patient-friendly treatment alternative options via the couple's genetic material.

Several ovarian stimulation protocols have been investigated either gonadotrophin-releasing hormone (GnRH) agonists or antagonists, however no consistent and conclusive results was concluded[7–10]. Recently DuoStim strategy which means luteal-phase stimulation (LPS) and follicular-phase stimulation (FPS) in one single ovarian cycle has been reported promising to avoid discontinuation after failed attempt and slightly increase CLBR per intention to treat (ITT)[11]. However, the cost-benefit analysis and more RCTs are needed to verify the effectiveness and safety issues. Previous data on minimal ovarian stimulation (MOS) or modified nature cycles in POR is limited but suggested a relative realistic solution for parenthood for POR, compared to conventional high dose stimulation. Minimal ovarian stimulation showed relatively higher implantation rate, acceptable live birth rate and preferred cost-effectiveness, though with fewer oocytes retrieved[12–18]. Increased starting dose in predicted poor responders for IVF/ICSI has been proved not to raise live birth rate but is more highly priced[19, 20]. However, no study evaluated the CLBR per person for multiple modified nature cycle, since CLBR has been better indicator of quality and success of IVF in its totality, as cryopreservation has become an integral aspect of IVF[21]. It is still unclear whether poor responder could actually benefit from minimal ovarian stimulation. No data exists comparing the CLBR and cost-effectiveness analysis between multiple modified nature cycle and high-dose GnRH antagonist protocol in POR.

The aim of this study was to evaluate CLBR and cost-effective difference between GnRH-antagonist and multiple minimal ovarian stimulation protocols in poor responders who fulfill the Bologna criteria. GnRH-antagonist includes the utilization of a GnRH antagonist in conventional treatments with additional FSH or hMG. GnRH antagonist requires a higher starting dose of gonadotropins aiming for retrieving more than 8 oocytes in one cycle. Minimal ovarian stimulation indicates that oral compounds (anti-estrogens or aromatase inhibitors) are used, either alone or in combination with gonadotropins, with anticipation of

fewer oocytes retrieved in one cycle. This study would help clinicians to personalize and select relative superior COS strategy for these difficult patients.

Methods

Study design and patient population

This retrospective study analyzed 325 poor responders who underwent 325 GnRH-antagonist cycles and another 374 poor responders who underwent 733 minimal ovarian stimulation cycles between Jan 2010 and Jun 2018 at one assisted reproduction center. All patients fulfilled the Bologna criteria for the definition of poor responders. Specifically, poor responders whose first stimulations cycle was GnRH-antagonist protocol were included. Only the first stimulation cycles and the corresponding FET cycles were exclusively included for these patients. The other group of poor responders included those whose stimulation cycles were only minimal ovarian stimulation(MOS) and natural cycles and the patients who have ever underwent other protocols were excluded (Fig. 1). All poor responders were informed that the clinical pregnancy rate is frustratingly low and the choice of GnRH-antagonist protocol or multiple minimal ovarian stimulation was discussed with patients.

GnRH antagonist and minimal ovarian stimulation protocol

In flexible GnRH antagonist protocol, at least 300 IU/day recombinant FSH and/or HMG were initiated on Day 2 or 3 of period and continued daily afterwards until the day of hCG administration. The dose was adjusted according to ovarian response. 0.25 mg of Cetrorelix was started flexibly when a follicle reaches the size of mean diameter of 14 mm from ultrasound, and continued daily afterwards until the day of hCG administration. HCG 6000–10000 IU was administered for final oocyte maturation when at least 2 follicles reach diameter of 17 mm.

In minimal ovarian stimulation, Clomiphene 25–100 mg was started from Day2 or 3 of cycles and continues for 5 days or lasts until trigger day. 75–150 IU Gonadotropin was selectively initiated from Day3 or Day5. HCG 6000–10000 IU was selectively used as trigger for final oocyte maturation when 1–2 follicles reach diameter of 17 mm. Mono-follicular development was advocated to proceed the oocyte retrieval.

Oocyte retrieval, laboratory procedures and luteal phase support

Oocyte retrieval was performed 35–36 hours after trigger under guidance of ultrasound. IVF or ICSI was selectively used for fertilization. Embryos were either freshly transferred after oocyte retrieval or frozen-thawed transferred in consecutive FET cycles. All embryos were cultured in incubator at 37°C, under 6% CO₂ and 5% O₂. Embryo development was evaluated according to morphological criteria. Day2 or Day3 cleavage-stage embryos with at least three or six blastomeres respectively and less than 20% fragmentation were eligible for transfer and cryopreservation. For blastocysts, fully expanded to hatched blastocysts with inner cell mass and trophectoderm B quality (from 4BC upwards) were eligible. Luteal

phase supplement was applied differently according to fresh embryo transfer or different endometrium preparation methods in FET cycles.

Outcome measures

Primary outcome is cumulative live birth rate (CLBR) per aspiration for women with GnRH-antagonist protocol, defined as at least one delivery of live infant resulting from an ART aspiration cycle including fresh and FET cycles within 24 months, and CLBR per person for women with MOS, defined as at least one delivery of live infant resulting from all ART cycles within 24 months[21]. Number of oocytes retrieved, number of oocytes fertilized, number of viable embryos, financial expenditure, time to first live birth were secondary outcomes. Cycles where no oocytes were retrieved and no viable embryos generated were also included in this study. Women whom the follow-up were not completed because of loss of contact and who have remained frozen embryos un-transferred within 24 months were considered “not having live birth”.

Statistical analysis

Analyses were performed according to intention to treat principle. Comparisons between GnRH-A and MOS were performed by Student’s t-test, Wilcoxon rank sum tests and chi-square, as appropriate. Univariate regression and multivariate logistic regression were applied to identify candidate factors that predict the CLBR. The candidates were age, BMI, basal FSH, basal E2, infertility years and primary infertility (vs secondary infertility). All independent variables were concomitantly entered into the logistic regression model. The likelihood of CLBR is presented as an OR and 95% confidence interval (CI). All analyses were conducted with spss statistics. P value < 0.05 was considered statistically significant. The economic analysis included costs for pharmacological compounds and IVF procedures up to pregnancy test day. Economic evaluation was performed focused on direct medical costs, not including the cost of examinations before IVF treatment or any commute fees. Costs were based on Shanghai General Hospital prices and were expressed in RMB.

Results

This study included 325 women (325 cycles) who underwent GnRH antagonist ovarian stimulation and 374 patients (733 cycles) who underwent multiple minimal ovarian stimulation (MOS) including natural cycles. Baseline demographic and clinical characteristics were similar between GnRH-antagonist and MOS groups, though basal FSH in MOS group is higher than in GnRH-antagonist ($p < 0.001$), as shown in Table 1. GnRH-antagonist cycles were characterized by significant longer duration of gonadotropin(Gn) stimulation days, more total dose of Gn, higher peak E2, higher P level, lower LH level and thicker endometrium at trigger day, compared to MOS cycle (Table 2). GnRH-antagonist resulted in more oocytes retrieved, more fertilized oocytes and more viable embryos than both first MOS and the cumulative ones of multiple MOS. ($p < 0.001$) (Table 2).

Table 1
Baseline demographic and clinical characteristics according to different protocols

	GnRH-antagonist	Minimal ovarian stimulation	P
Maternal age (y)	38.46 ± 4.64	38.83 ± 4.75	0.328
BMI	23.57 ± 2.9	23.78 ± 3.1	0.056
Primary infertility	143	154	0.451
Infertility years	5 (2,8)	4 (2,7)	0.134
Primary cause of infertility			
Male	117	129	0.677
Tubal	209	231	0.487
Poor ovary response	6	25	0.002
Endometriosis	14	21	0.429
Anovulatory	10	4	0.105
Unexplained	12	4	0.039
Other causes	8	15	0.252
Basal E2 level (pmol/L)	145(95.5, 211.5) (N = 315)	134(88.59 211)(N = 355)	0.220
Basal FSH level (mIU/ml)	9(7.2, 15.1) (N = 315)	11.7(8.6, 17.725) (N = 354)	< 0.001

Table 2
Cycle characteristics according to different protocols

	First GnRH-antagonist (325 cycles)	Minimal ovarian stimulation		p ^a	p ^b
		First (374 cycles)	Multiple (733 cycles)		
Duration of Gn stimulation(days)	9 (8, 10)	6 (4, 8)	/	< 0.001	/
Total dose of Gn(IU)	2400(1800,2925)	900(600,1256.25)	/	< 0.001	/
Peak E2 level at trigger day (pmol/L)	7585(4213.5, 11666) (N = 320)	2707(1630, 4815) (N = 365)	/	< 0.001	/
P level at trigger day (nmol/L)	2.64(1.623, 3.683) (N = 68)	1.36(1.032, 3.105) (N = 96)	/	0.005	/
LH level at trigger day(U/L)	3.14(2.205, 5.21) (N = 67)	7.96(5.318, 13.858) (N = 96)	/	< 0.001	/
Endometrial thickness at trigger day(mm)	9(8.5, 10.4)	6(5, 8.2)	/	< 0.001	/
ICSI/IVF	100/225	104/270	/	0.390	/
No. of oocytes retrieved	7(4, 10)	2(1, 4)	4 (2, 7)	< 0.001	< 0.001
No. of fertilized oocytes	5(3, 7)	2(1, 3)	3 (1, 5)	< 0.001	< 0.001
No. of viable embryos	2(1, 4)	1(0, 2)	2 (1,3)	< 0.001	< 0.001
a : First GnRH-antagonist vs First minimal ovarian stimulation					
b : First GnRH-antagonist vs Multiple minimal ovarian stimulation					

As for clinical result (Table 3), the CLBR for both groups of patients was generally low. For the first IVF cycle, GnRH-antagonist demonstrated higher CLBR per aspiration than first MOS from both univariate analysis (12.92% versus 4.54%, Crude OR 3.117; 95%CI 1.737, 5.592, p < 0.001) and multivariate analysis after adjusting for female age, BMI, basal FSH, basal E2, infertility years and primary infertility (vs secondary infertility) (Adjusted OR 2.606; 95%CI 1.386, 4.899, p = 0.003). Female age and basal FSH and infertility years were also independent factors negatively associated with likelihood of CLBR per aspiration (Supplemental Fig. 1). In the MOS group, clustering of multiple treatment cycles per woman has to be considered. So we also measured the CLBR per person in this group of patients. GnRH-

antagonist displayed higher CLBR per aspiration than the CLBR per person of multiple MOS from univariate analysis (12.92% versus 7.22%, Crude OR 1.907; 95%CI 1.147, 3.171, $p < 0.001$), while the type of treatment (GnRH-antagonist vs MOS) was not associated with CLBR in multivariate logistic regression after adjusting the same factors as above (Adjusted OR 1.702; 95%CI 0.971, 2.982, $p = 0.063$). Female age and basal FSH were only independent factors negatively associated with likelihood of CLBR per person (Supplemental Fig. 2).

Table 3
Clinical outcomes according to different protocols

	First GnRH-antagonist (325 cycles, 325 persons) (per aspiration)	First minimal ovarian stimulation (374 cycles, 374 persons) (per aspiration)	Multiple minimal ovarian stimulation (733cycles, 374 persons) (per ITT)	p^a	p^b	Adjusted OR (95%CI) ^a	Adjusted OR (95%CI) ^b
						p^a	p^b
CLBR	42 (12.92%)	17 (4.54%)	27 (7.22%)	< 0.001	0.012	2.606 (1.386, 4.899) 0.003	1.702 (0.971, 2.982) 0.063
Cost	20838 (17953, 23422)	12254 (9612.5, 14875.5)	21261.5 (15892.5, 35140.25)	< 0.001	0.13	/	/
Time to First Live Birth	9(8, 10.75)	/	11 (9, 14)	/	0.014	/	/
^a : First GnRH-antagonist vs First minimal ovarian stimulation							
^b : First GnRH-antagonist vs Multiple minimal ovarian stimulation							
Adjusted OR: Adjusting for age, BMI, basal FSH, basal E2, infertility years, primary infertility (vs secondary infertility).							

In the economy-effectiveness analysis, when considering only the first cycle of ovarian stimulation, the cost of GnRH-antagonist was higher than MOS (20838 (17953, 23422) ¥ versus 12254 (9612.5, 14875.5) ¥, $p < 0.001$). But the cumulative financial expenditure was statistically similar between one time GnRH-antagonist and multiple MOS (20838 (17953, 23422) ¥ versus 21261.5 (15892.5, 35140.25) ¥, $p = 0.13$). When it comes to the time to first live birth, GnRH-antagonist showed obviously shorter time than repeated modified natural cycles (9 (8, 10.75) months versus 11(9, 14) months, $p = 0.014$).

Discussion

In the present retrospective study of POR, patients undergoing COS with conventional GnRH-antagonist protocol resulted in a significantly higher numbers of oocytes retrieved, viable embryos and statistically similar CLBR but sooner time to live birth with similar financial expenditure, compared to multiple minimal ovarian stimulation. GnRH-antagonist protocol is a sound choice when making COS strategy plan for poor responders.

We evaluated whether poor responders benefit from GnRH-antagonist protocol compared to minimal ovarian stimulation, as it is unclear from current literature what policy should be recommended for these patients. We think controlled ovarian hyperstimulation with high daily gonadotropin doses in GnRH-antagonist protocol should be commonly offered to poor responders. Our observations are in accordance with researches that raising FSH levels during stimulation by high-dose FSH reduced cancelations and improved clinical successful results[22]. In the context of laboratory performance, the need for a large number of oocytes via ovarian stimulation is an integral part of successful IVF treatment, since the number of oocytes and viable embryos are independent factors that increase CLBR[23]. The increasing likelihood of CLBR per aspiration is associated with large oocytes fields across female age. Pregnancy rate reduces when fewer oocytes were retrieved for poor responders. The maximum CLBR was observed when around 9 oocytes were retrieved in women more than 45 years of age[3, 24] Adding any additional one oocyte retrieved means possible improvement of CLBR to these challenging population of POR.

Reports indicated that higher dose of gonadotropins resulted in increasing rate of aneuploidy in embryos and granulosa cells[25]. But there are some controversies about that. Earlier research suggested that higher proportion of good morphologic quality embryos was observed in mild stimulation compared to conventional stimulation, and embryo development was adversely affected in COS dose-dependent manner[26]. However, recent studies demonstrated that aggressive stimulation does not increase the rate of embryo aneuploidy rate in preimplantational genetic screening (PGS) cycles in both infertile patients and oocyte donors[27]. The higher number of euploid blastocysts was correlated to higher cumulative pregnancy rate. So-called “detrimental effect” of high dose stimulation is not evident when natural and stimulated IVF cycles are compared. The benefits of higher number of oocytes retrieved cannot be mitigated by the age-related embryo aneuploidy rate, and can justify why high stimulation results in similar reproductive outcomes.

Minimal stimulation was thought to less disturb the ovarian and uterine physiology. Higher dose of gonadotropins tends to infect endometrial development during luteal phase. But the freeze-all policy and more frequency of frozen-thawed embryo transfer (FET) just alleviate the possible negative influence of conventional high dose stimulation to endometrial receptivity. Trifon G et.al suggested that live birth is significantly higher in modified natural cycles than high-dose FSH stimulation GnRH-antagonist in poor responders in a retrospective analysis[12]. But they only accounted for the live birth rate in fresh transfer cycles, didn't consider the other FET transfers which represent the whole picture of these patients

situation. Tilborg et. al also indicated that increased dose of FSH resulted statistically similar CLBR compared to standard dose regimen, but with collateral increasing financial cost[19].

The financial factor plays an important role when considering the number of IVF cycles patient is about to attempt, since there is no insurance coverage of IVF treatment in China. The modified natural cycle was considered patient friendly ovarian stimulation protocol. Some research showed that performing multiple repeated minimal ovarian stimulation or modified natural cycles offers a reasonable long-term success rate with less financial cost. However, report suggested that modified natural cycle is of no benefit with less than 1% live birth rate for genuine poor responders who yielded up to 3 oocytes with conventional COH[28]. The lower ongoing pregnancy rate resulted from mild stimulation was especially due to a high cancellation rate[29]. In our analysis, the whole financial expenditure per person of repeated minimal ovarian stimulation turns to be similar with GnRH-antagonist protocol. From our experience, in the multiple MOS strategy, the cost of repeated oocyte retrieval and embryo transfers procedures makes up the most cumulative financial cost, while the pharmacological expense for COS is far less. In our study repeated MOS showed longer time to live birth than GnRH-antagonist protocol. Thus repeated minimal ovarian stimulation is not as beneficial as presumed.

In the minimal ovarian stimulation group, clustering of multiple treatment cycles per woman has to be considered. One strength in our study is that we measured the CLBR for multiple modified natural cycles which included not only live birth rate from one single cycle, but also the consecutive cycles within 2 years of follow-up. This research is limited by its retrospective design. Patients were allocated to two stimulation protocols based on the physician's discretion and patients consultation. The selection bias is possible. There are potential confounders that can not be accounted for. Poor responders are not a homogeneous group of patients and the prognosis varies greatly depending on age or actual number of oocytes obtained. The predicted and proven poor responders are both included in our analysis. The heterogeneous population might have different prognosis which hinders our conclusion to make.

Conclusions

Current study provides evidence that GnRH-antagonist is not worse than multiple minimal ovarian stimulation both in successful rate and cost-effective analysis. When making COS strategy plans for predicted POR, this analysis improves the counseling of IVF treatment for this poor responders and assists clinical doctors in determining the best candidate for COS strategy. GnRH-antagonist protocol could be reasonable alternative for this difficult-to-treat group of patients.

Declarations

Availability of data and materials

Data will be available from the corresponding author on request.

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Author contribution

YW conceived the idea, designed the study and edited the manuscript. YL retrieved and analyzed the data, and wrote the manuscript.

Ethics declarations

The study was approved by Shanghai General Hospital Institution review board.

Consent for publication

Not applicable.

Competing interests

The authors have nothing to declare.

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Figures

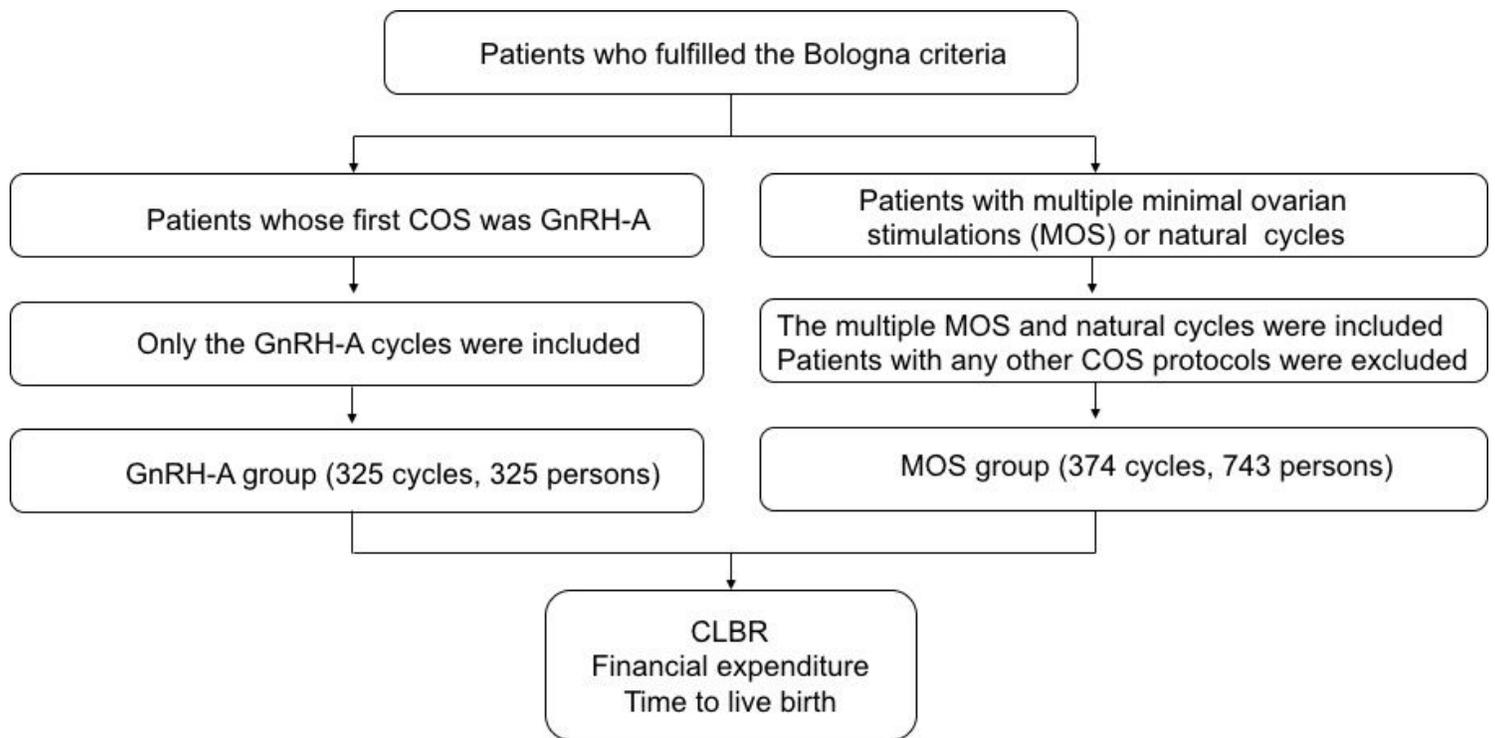


Figure 1

Flow diagram of patient inclusion.

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