MILD OVARIAN STIMULATION WITH CLOMIPHENE CITRATE & GONADOTROPHINS USING ANTAGONIST PROTOCOL IN POOR OVARIAN RESERVE WOMEN UNDERGOING IVF/ICSI

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ABSTRACT

Background; Poor ovarian responsiveness is a challenge met by many clinicians during COH, these patients usually have higher FSH level, lower levels of AMH and few oocyte retrieved.

Aim and objectives; to assess the efficacy& safety of mild ovarian stimulation using CC& low dose of Gn with antagonist protocol in comparison to the conventional ovarian stimulation with mid-luteal GnRH agonist protocol in women with poor ovarian reserve undergoing IVF/ICSI cycles,

Subjects and methods; This prospective clinical study was conducted in the Department of Obstetrics and Gynecology at Beni-suef University Hospital. The study included 352 who were been assigned randomly who were eligible, wasing to comply with the study protocol,

Result; Clinical pregnancy rate was 12.6% (19 from 151 cases to whom embryos were transferred) in Group A. Meanwhile; 12.4% (21 cases from 170 cases had ET) in group B. With (p = 0.95) that is as well; statistically; of no evidence of significant difference. The ongoing pregnancy rate showed no evidence of significant difference. Ongoing pregnancy rate per ET was 11.3% in Group A Meanwhile; 10.6% in group B. With (p = 0.85).

Conclusion; The "mild" CC/Gn/GnRH-an stimulation protocol is a valid alternative to the long protocol with high Gn dose as it obtains a comparable success rate and requires significantly less medications, with an obvious economic advantages.

Keywords: ovarian stimulation; clomiphene citrate; gonadotrophins; antagonist protocol; Controlled ovarian hyperstimulation.

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Introduction

Controlled ovarian hyperstimulation (COH) is established as a prerequisite in assisted reproduction technology (ART), as it induces coordinated multi-follicular development, leading to a higher yield of oocytes and consequently higher number of embryos to select from, in order to select those with the highest implantation dynamics to increase the chance for a positive outcome in terms of clinical pregnancy **(1)**

Difficulties in clinical management arise initially from the complexity surrounding the definition of this group of patients; in this context, in 2011 Ferraretti et al. presented the Bologna criteria in order to characterize this group and adapt its management accordingly. Among the various strategies and modified COH protocols employed over the years towards optimization of management of subfertility, there is no concrete evidence on the advantage of any one stimulation protocol over another (**2**).

A recent comparison among the GnRH-agonist protocols, through a subgroup analysis, including four trials with poor responders, revealed a superiority of long duration GnRH-agonist compared to the short duration (mild) GnRH-agonist protocol with regards to clinical pregnancy rates, number of oocytes retrieved, and cancellation rates (**3**).

Mild COH protocols using low doses of gonadotrophins have been implemented in clinical practice, demonstrating significant advantages, including cost effectiveness (**3**), although the expected number of retrieved oocytes is low, usually ranging from two to seven (**4**). Clomiphene citrate is one of the main adjuncts used in mild regimes for the ovarian stimulation of poor responders, the definition of whom varies widely **(1)**

The main aim of this study was to assess the efficacy& safety of mild ovarian stimulation using

CC& low dose of Gn with antagonist protocol in comparison to the conventional ovarian stimulation with mid-luteal GnRH agonist protocol in women with poor ovarian reserve undergoing IVF/ICSI cycles.

Patients & methods

This randomized controlled trial was be conducted in Beni-Suef university hospital from March 2018 to march 2021, where 352 patients was be randomly assigned into two groups after approval from the ethical committee & informed consent from every patient about the possible benefits or drawbacks during conduct of the trial.

The sample size was determined using **G*Power Version 3.1.9.2** [computer software] (Franz Faul, Kiel, Germany),Power analysis for a t- test was conducted in G-POWER based on number of Mп oocytes to determine a sufficient sample size using an alpha error of probability of 0.05, power of 0.8, a medium effect size (w = 0.3) and 1 degree of freedom. Based on the aforementioned assumptions, the desired sample size is 352 in both groups (176 patients in each group).

They were classified into 2 groups: **Group A** (involve 176 patients) was receive clomiphene citrate 100mg daily from day 2 of menstrual cycle for 5 consecutive days , then 150 FSH/HMG was be given starting from day 7 of the cycle till reaching appropriate response (leading follicle 18 – 22 mm). GnRH antagonist (cetrotide0.25 mg SC daily) was be given when the leading follicle reaches 12 – 14 mm. **Group B** (involve 176 patients) was receive mid luteal GnRH agonist (Decapeptyl) &the conventional dose of Gn 450 IU FSH/HMG daily starting from day 2.

Monitoring of follicular growth was be done by TVS & serum E2 level.

Triggering of ovulation with Bhcg 5000 – 10000 IU was be given when a desired ovarian response is reached (≥2 follicles more than 18 – 22 mm).

Primary outcome of this trial is the mean number of retrieved M2 follicles, while secondary outcomes include fertilization rate, ongoing pregnancy rate & endometrial thickness.

Inclusion criteria: Day 3 FSH ≥ 12 on at least 2 occasions, previous poor response < 3 oocytes with standard protocol in a previous IVF cycle, previous weak E2 rise ≤ 500 after mean FSH 4750 IU per cycle, age ≥ 38 yrs, expected poor response irrespective of the patients age, day 3 FSH ≥ 10 IU/ml, E2 level ≥ 80 pg/ml, AMH 0.14 – 1 ng/ml and AFC 4 -10

Exclusion criteria: PCO patients, severe endometriosis, hypothalamic amenorrhea, severe male factor (patients with testicular biopsy or those with azoospermia), associated uterine factor and IVF/ ICSI for sex selection.

Results

This study was conducted at the Department of Obstetrics and Gynecology at Beni-suef University Hospitalfrom march 2018 to march 2021. The study included 352 which were been assigned randomly who were eligible, wasing to comply with the study protocol.

Table (1): Summarizes the relevant patients' baseline characteristics of the patients (Group A- Mild stimulation Group) and (group B- Long protocol Group).

Groups / Variables	Group A (Mild stimulation Group) Mean (SD) or Frequency (%)	Group B (long protocol Group) Mean (SD) Or Frequency (%)	P-value
Age	36.2(3.6)	36.7 (3.8)	0.09
BMI	28.8 (2.8)	28.6 (2.1)	0.18
Period of infertility (year)	6.3 (3.7)	5.6 (3.2)	0.06
Type of infertility	Primary 73(41.5%) Secondary 103 (58.5%)	Primary 67(38.1%) Secondary 109(61.9%)	0.59
* P value: Probability value: non-significant.			

These data shows that there was no statistical significant difference between the 2 groups regarding baseline characteristics.

Test of significance: Independent-samples Mann-Whitney U test, Chi square (χ^2) test $\chi 2(1, N= 352) = 0.45$

Statistical analysis of the basal hormonal profile detected no evidence of statistically significant difference between the two groups as the mean of Basal FSH was 10.3 ± 2.2 in Group A (Mild stimulation group) and 10.6 ± 2.3 in group B (Long protocol group), with (P = 0.19). While the mean of Basal LH was 7.2 ± 1.5 in Group A and 7.4 ± 1.3 in group B, with (P = 0.15). The mean of Basal E_2 was 48.9 ± 7.1 in Group A and 49.9 ± 6.2 in group B with (P= 0.08).

Table (2): Comparison between group A (Mild stimulation Group) and group B (Long protocol Group) according baseline investigations

Hormonal Profile	Group A (Mild stimulation Group) Mean (SD)	Group B (long protocol Group) Mean (SD)	P-value
Basal FSH	10.3(2.2)	10.6(2.3)	0.19
Basal LH	7.2 (1.5)	7.4(1.3)	0.15
Basal Estradiol E2	49(7.1)	50(6.2)	0.08
AMH	0.5(0.26)	0.6(0.24)	0.19
PRL	12.9(4.3)	13.1(4.2)	0.76
TSH	2.01(1)	2.09(1.03)	0.48
AFC by Ultrasound	4.1(1.7)	4.3(1.5)	0.4
*** P value: Probability value: non-significant. Test of significance: Independent-samples Mann-Whitney U test.**			

Table (3): Days of stimulation in both groups

	Group A (Mild stimulation Group) Mean (SD)	Group B (Long protocol Group) Mean (SD)	P-value
Days of stimulation	12.2(1.5)	13.3(1.4)	0.0001
*** P value: Probability value: Significant. Test of significance: Independent-samples Mann-Whitney U test.**			

There is statistically significant difference between the two groups was detected in number of days of stimulation. As the mean of days of stimulation 12.2 ± 1.5 in Group A (Mild stimulation group) and group B(long protocol) 13.3 ± 1.4 in group B, with (P = 0.0001).

Table (4): Units of gonadotropins in both groups

	Group A (Mild stimulation Group) Mean (SD)	Group B (Long protocol Group) Mean (SD)	P-value
Total Units of gonadotropins (IU)	2814(577)	4187(1183)	0.0001
*** P value: Probability value: Significant. Test of significance: Independent-samples Mann-Whitney U test.**			

As well, There was marked statistically significant difference between the two groups regarding the amount of exogenous gonadotropins used for ovarian stimulation; the mean in Group A (Mild stimulation group) was 2814 ± 577 and 4187 ± 1183 in group B **(**Long protocol Group**)**, with (P = 0.0001).

Table (5): Peak level of E2 in both groups

	Group A (Mild stimulation Group) Mean (SD)	Group B (Long protocol Group) Mean (SD)	P-value
Peak level of E2 (ng/ml)	1294(305)	1365(333)	0.034
*** P value: Probability value: Significant. Test of significance: Independent-samples Mann-Whitney U test.**			

There was statistically significant difference between the two groups regarding the peak level of E2; the mean in Group A (Mild stimulation group) was 1294 ± 305 and 1365 ± 333 in group B **(**Long protocol Group**)**, with (P = 0.034).

Table (6): Endometrial thickness at OPU in both groups

	Group A (Mild stimulation Group) Mean (SD)	**Group B (Long protocol Group) Mean (SD)**	**P-value**
Endometrial thickness at OPU (mm)	8(1.5)	10.9(1.4)	0.0001
*** P value: Probability value: Significant. Test of significance: Independent-samples Mann-Whitney U test, Chi square (χ2) test χ2(1, N= 352) = 0.45**			

There was obvious statistically significant difference between the two groups regarding the Endometrial thickness at OPU; the mean in Group A (Mild stimulation group) was 8 ± 1.5 and 10.9 ± 1.4 in group B **(**Long protocol Group**)**, with (P = 0.0001).

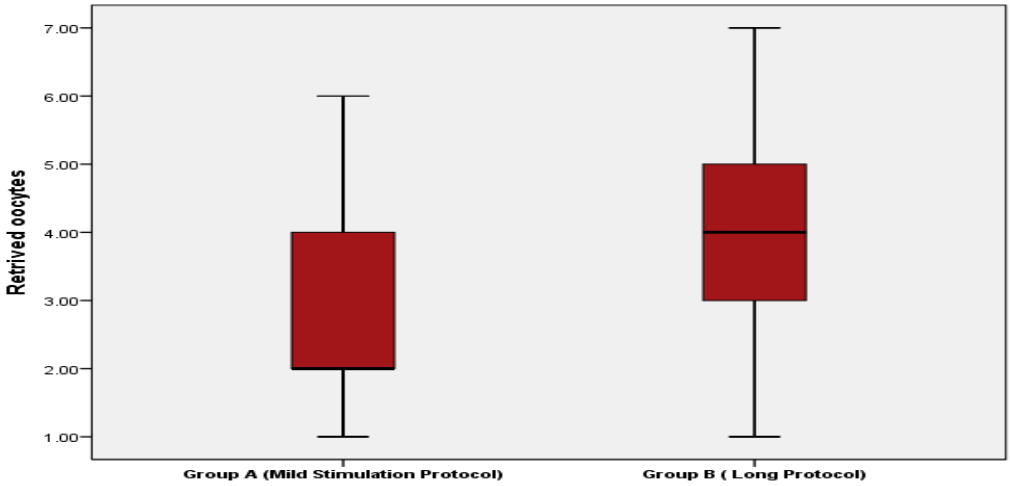

Fig. (1) : Total Number of oocytes among both groups.

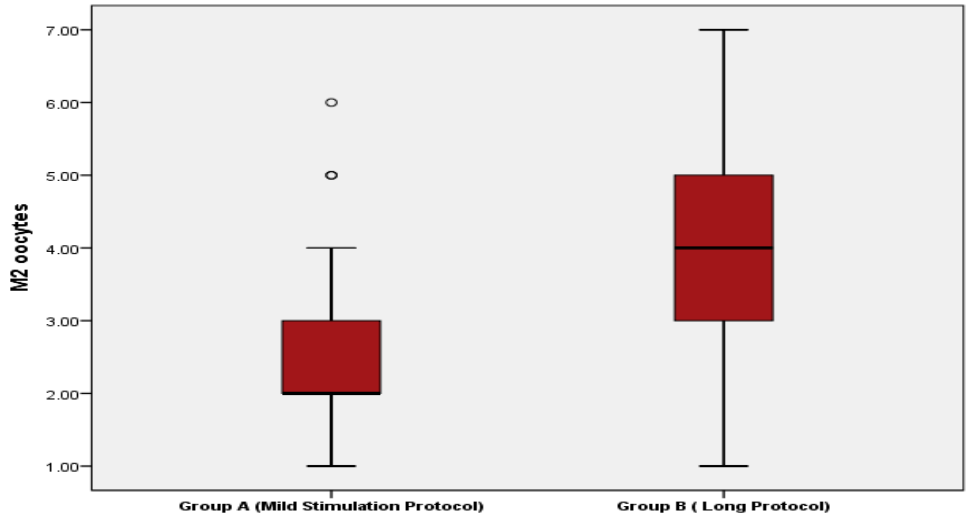

Fig.(2): Number of M II oocytes among both groups.

B-Embryos Transfer: Statistically; there was significant difference regarding the patients who had embryo

transfer 151from 162 patient who completed the ICSI cycle (93.2%) and 170 from 173cycles (98.3%) in group A and B respectively, with (P = 0.027).

Table (7): Comparison between group A (Mild stimulation Group) and group B (long protocol Group) according to embryos transfer

	Group A (Mild stimulation Group)		Group B (long protocol Group)		P value
	No.	%	No.	%	
No Transfer	11	6.8%	3	1.7%	**0.02**
ET	151	93.2%	170	98.3%	

Regarding the day of embryo transfer, most patients had their embryo transfer on day 5 in both groups, thus 145 patients (96%) of Group A (Mild stimulation group) versus 152 (89.4%) of group B had a day 5 transfer. While 6 (4%) of Group A versus 16 (9.4%) of group B had their embryo transfer carried out on day 3, on the other hand, no patients Group A and only 2 patients (1.2%) of Group B had embryo transfer D6. The P-value = 0.06, which of no evidence of statistically significant difference.

Table (8): Comparison between group A **(Mild stimulation Group)** and group B (long protocol Group) according to number of embryos transferred per cycle.

	Group A (Mild stimulation Group)		Group B (long protocol Group)		P value
	No.	%	No.	%	
No ET	11	6.8%	3	1.7%	
1 Embryo	12	7.4%	14	8.1%	
2 Embryos	124	76.5%	131	75.7%	0.07
3 Embryos	15	9.3%	25	14.5%	
*** P value: Probability value: non-significant.** **Test of Significance: Chi square (χ2) test χ2(3, N= 335) = 7**					

Regarding Pregnancy test, only 21 women (13.9%) were β- HCG positive from 151 women who had embryo transfer in Group A (Mild stimulation group), then again 130 women (86.1%) were β- HCG negative. While in group B, only 22 women (12.9 %) were β- HCG positive, nevertheless 148 women (87.1%) were β- HCG negative and. Thus (p = 0.8) which statistically has no significant difference.

As regards Clinical pregnancy rate was 12.6% (19 from 151 cases to whom embryos were transferred) in Group A. Meanwhile; 12.4% (21 cases from 170 cases had ET) in group B. With (p = 0.95) that is as well; statistically; of no evidence of significant difference.

Table (9): Comparison between group A (Mild stimulation Group) and group B (long protocol Group) according to **Serum β- HCG , CPR and ongoing pregnancy rate /ET** .

	Group A (Mild stimulation Group) No. (%)	Group B (long protocol Group) No (%)	P-value
Chemical pregnancy Rate / ET (+ve serum B-HCG)	21(13.9%)	22(12.9%)	0.87
Clinical pregnancy Rate (CPR)/ ET	19 (12.6%)	21(12.4%)	0.95
Ongoing pregnancy Rate ≥12 weeks	17(11.3%)	18(10.6%)	0.85
*** P value: Probability value: non-significant.** **Test of significance: Chi square (χ^2) test**			

Table (10): Miscarriage rate between group A (Mild stimulation Group) and group B (long protocol Group)

	Group A (Mild stimulation Group)		**Group B (long protocol Group)**		**P value**
	No.	**%**	**No.**	**%**	
Miscarriage	4	19%	4	18.2%	
Continued Pregnancy	17	81%	18	81.8.%	0.9
*** P value: Probability value: non-significant.** **Test of Significance: Chi square (χ2) test χ2(1, N= 43) = 0.005**					

Regarding, cycle cancellation: as Fourteen cases was cancelled in Group A (mild stimulation group) (8%), opposing 3 cases were cancelled in group B (1.7%), with P = 0.01; statistically; Significant difference was obtained.

Table (15): cycle cancellation between both groups

Cycle Cancellation	**Group A (mild stimulation Group)**		**Group B (long protocol Group)**		**P value**
	No.	**%**	**No.**	**%**	
Cancelled	14	8%	3	1.7%	
Completed cycles	162	92%	173	98.3.%	0.011
*** P value: Probability value: Significant.** **Test of Significance: Chi square (χ2) test χ2(1, N= 352) = 7.5**					

DISCUSSION

Evidence, to date, indicates that the most efficient approach in managing subfertile poor responders is the individualization of the treatment protocols, based on antral follicle count (AFC) and anti-Mullerian hormone (AMH) values prior to the IVF cycle (**5)**, although the success rate remains low.

Some preliminary results demonstrated superiority of the flare-up over the letrozole/antagonist protocols (**6)**, although both gonadotropin-releasing hormone (GnRH)-agonist and -antagonist protocols have similar cycle cancellation and clinical pregnancy rates **(7)**.

The main aim of this study was to assess the efficacy& safety of mild ovarian stimulation using CC& low dose of Gn with antagonist protocol in comparison to the conventional ovarian stimulation with mid-luteal GnRH agonist protocol in women with poor ovarian reserve undergoing IVF/ICSI cycles.

This prospective clinical study was conducted in the Department of Obstetrics and Gynecology at Beni-suef University Hospital. The study included 352 who were been assigned randomly who were eligible, wasing to comply with the study protocol, participants were randomized into 2 groups: Group (A) – Mild stimulation protocol: 176 Women. Group (B) –Long Agonist Protocol: 176 Women.

Regarding the baseline characteristics of the patients (Group A- Mild stimulation Group) and (group B- Long protocol Group), our results showed that there was no statistically significant difference between the 2 groups regarding age, BMI, period of infertility and type of infertility.

Also, in line with the current study **Ali et al., (8),** aimed to compare between mild and conventional protocol in ovarian stimulation for poor responders undergoing Intracytoplasmic sperm injection procedure (ICSI). The study enrolled 120 cases divided randomly into two groups: (Group 1): included 60 patients received soft ovarian stimulation protocol, (Group 2): included 60 patients received conventional ovarian stimulation protocol. There were no significant differences between groups in consideration to Age, BMI, duration, type and cause of infertility.

In the current study, Statistical analysis of the basal hormonal profile detected no evidence of statistically significant difference between the two groups as the mean of Basal FSH was 10.3 ± 2.2 in Group A (Mild stimulation group) and 10.6 ± 2.3 in group B (Long protocol group), with (P = 0.19). While the mean of Basal LH was 7.2 ± 1.5 in Group A and 7.4 ± 1.3 in group B, with (P = 0.15).

In agreement with our findings **Revelli et al., (9),** reported that there were no statistically significant

differences between the studied groups in as regard Basal FSH, AMH and Antral Follicle Count (AFC). Also, the study by **Siristatidis et al., (1),** reported that Both groups were matched in terms of basal FSH,AMH, and AFC values (p >0.05).

In agreement with our findings **Ali et al., (8),** reported that there were no statistically significant differences between the studied groups in as regard basal AMH, AFC and E2.

Youssef et al., (10), also reported that that there were no statistically significant differences between the studied groups in as regard AFC, Basal FSH, Basal estradiol and AMH.

As well **Pilehvari et al., (11),** reported that there were no statistically significant differences between the studied groups in as regard Basal FSH, LH and AMH.

Similarly, **Liu et al., (12),** reported that there were no statistically significant differences between the studied groups in as regard AMH, Antral follicle count, Basal FSH, Basal LH and Basal E2.

Regarding days of stimulation among the studied groups, we found that there is statistically significant difference between the two groups was detected in number of days of stimulation. As the mean of days of stimulation 12.2 ± 1.5 in Group A (Mild stimulation group) and group B (long protocol) 13.3 ± 1.4 in group B, with (P = 0.0001).

In agreement with our results **Revelli et al., (9),** reported that there was statistically significant difference between the studied groups as regard duration of stimulation.

As well, **Youssef et al., (10),** revealed that the duration of ovarian stimulation was significantly lower in the mild ovarian stimulation strategy (8.42 ± 2.89) compared with the conventional ovarian stimulation strategy (9.67 ± 3.10).

Also, in agreement with our results **Liu et al., (12),** reported that there was statistically significant difference between the studied groups as regard duration of stimulation.

Regarding the used Units of gonadotropins among the studied groups, we found that there was marked statistically significant difference between the two groups regarding the number of exogenous gonadotropins used for ovarian stimulation; the mean in Group A (Mild stimulation group) was 2814 ± 577 and 4187 ± 1183 in group B (Long protocol Group), with (P = 0.0001).

In agreement with our results **Revelli et al., (9),** reported that there was statistically significant difference between the studied groups as regard Total amount of Gn.

This was in line with **Siristatidis et al., 2017,** who reported that there was statistically significant difference between the studied groups as regard Dose of gonadotropins.

Also, **Ali et al., (8),** reported that there was a statistically significant difference between the studied groups as regard dose of gonadotropins

As well, **Youssef et al., (10),** revealed that a significantly lower amount of gonadotropins was used in the mild ovarian simulation strategy, with a mean difference of −3135 IU (95% CI: −3331 to −2940).

Similarly, **Pilehvari et al., (11),** reported that that there was statistically significant difference between the studied groups as regard Total dose of gonadotropin.

Also, in agreement with our results **Liu et al., (12),** reported that there was statistically significant difference between the studied groups as regard Total gonadotropin/cycle.

Regarding Peak level of E2 among the studied groups, we found that there was statistically significant difference between the two groups regarding the peak level of E2; the mean in Group A (Mild stimulation group) was 1294 ± 305 and 1365 ± 333 in group B (Long protocol Group), with (P = 0.034).

In agreement with our results **Revelli et al., (9),** reported that there was statistically significant difference between the studied groups as regard Peak E2 level.

However, **Pilehvari et al., (11),** reported that there were no statistically significant differences between two groups regarding number of oocytes retrieved (2.20 ± 1.71 vs. 2.79 ± 1.96).

Regarding embryos transfer among the studied groups, our results showed that there was significant difference regarding the patients who had embryo transfer 151from 162 patient who completed the ICSI cycle (93.2%) and 170 from 173cycles (98.3%) in group A and B respectively, with (P = 0.027).

Regarding the day of embryo transfer, most patients had their embryo transfer on day 5 in both groups, thus 145 patients (96%) of Group A (Mild stimulation group) versus 152 (89.4%) of group B had a day 5 transfer. While 6 (4%) of Group A versus 16 (9.4%) of group B had their embryo transfer carried out on day 3, on the other hand, no patients Group A and only 2 patients (1.2%) of Group B had embryo transfer D6. The P-value = 0.06, which of no evidence of statistically significant difference.

In agreement with our results, **Revelli et al., (9),** reported that there was statistically significant difference between the studied groups as regard embryos transfer.

In addition, **Liu et al., (12),** reported that a higher number of transferrable embryos (P = 0.029) was obtained in conventional controlled ovarian stimulation group.

As well, **Youssef et al., (10),** reported that the mild ovarian stimulation strategy resulted in significantly fewer embryos (mean: 2.0, 95% CI: 1.8–2.5 vs 2.7, 95% CI: 2.3–3) but the number of good quality embryos (mean: 0.8, 95% CI: 0.6–1.0 vs 0.8, 95% CI: –0.6 to 1.1) and embryos transferred (mean: 0.8,

95% CI: 0.6–1.0 vs 0.8, 95% CI: 0.6–0.9) were similar.

Regarding Pregnancy test, only 21 women (13.9%) were β- HCG positive from 151 women who had embryo transfer in Group A (Mild stimulation group), then again 130 women (86.1%) were β-HCG negative. While in group B, only 22 women (12.9 %) were β- HCG positive, nevertheless 148 women (87.1%) were β- HCG negative and. Thus (p = 0.8) which statistically has no significant difference.

Four women (19%) had miscarriage in group A and also 4 (18.2%) women of pregnant women group B experienced miscarriage, with P-value=0.1. which statistically; of no significant difference.

In agreement with our results, **Revelli et al., (9),** reported that the clinical pregnancy rate per completed treatment (CPR/ET) was 23.2 % and 19.9 % for the "mild" and "long" groups, respectively, with no significant differences between the two stimulation regimens. Also the implantation rate was similar in the two groups (15.2 % in the "mild" group vs. 12.3 % in the "long" group). Similarly, the abortion rate did not significantly differ among groups, and finally the ongoing pregnancy rate/ET at 12 weeks was comparable with either stimulation regimen (17.8 vs 16.8 % in the "mild" and "long" groups, respectively)

Also, **Ali et al., (8), reported** that that there was no statistically significant difference between the studied groups as regard Chemical and Clinical pregnancy.

Also, **Pilehvari et al., (11),** reported that pregnancy rates were similar between two groups (4% vs.5.6 %; p > 0.05). Fertilization rate did not differ significantly in both group (66.6 ± 37.7 vs.62.3 ± 34.4; p > 0.05).

In addition, **Liu et al., (12),** reported that the cumulative live birth rates (OR 1.103; 95% CI 0.53 to 2.28; P= 0.791) were comparable between the two groups.

Regarding OHSS, there were no reported cases of OHSS in both groups. Regarding, cycle cancellation there were 14 cases was cancelled in Group A (mild stimulation group) (8%) mainly due to failed retrieval of COCs, opposing 3 cases were cancelled in group B (1.7%), with P = 0.01; statistically; Significant difference was obtained.

In agreement with our results **Siristatidis et al., (1),** reported that the cancellation rates were significantly higher [36.4% (95% CI=19-53.7) vs. 12% (95% CI=1.7- 25.7), p=0.036]. All cancellations occurred due to the failed retrieval of COCs during OR for both groups, although there was at least a leading follicle of over 16mm at triggering in all cases. There were no cases of failed fertilization.

However, the study by **Siristatidis et al., (1)** reported that the rates of cancelation were similar between groups. No incidence of OHSS was observed in any of the groups studied.

Also, **Ali et al., (8), Pilehvari et al., (11),** reported that that there was no statistically significant difference between the studied groups as regard the rates of cancelation.

As well, **Youssef et al., (10),** reported that in the mild ovarian stimulation strategy, 52 (26%) cycles were canceled and 37 (18%) cycles in the conventional ovarian stimulation strategy (RR 1.5; 95% CI: 0.96–2.5).

CONCLUSION

The "mild" CC/Gn/GnRH-an stimulation protocol is a valid alternative to the long protocol with high Gn dose as it obtains a comparable success rate and requires significantly less medications, with an obvious economical advantage.

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