Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/7438
DOI URL: http://dx.doi.org/10.21474/IJAR01/7438
ISSN NO. 2320-5407

RESEARCH ARTICLE

TWO DAYS MINIMAL STIMULATION PROTOCOL WITH INTRAUTERINE INSEMINATION IN THE TREATMENT OF UNEXPLAINED INFERTILITY.

Mostafa Abdulla Elsayed Mahmoud.
Prof Doctor, Assistant professor of obstetrics and gynecology, Benha university hospital, Qalubia district – Egypt.

Manuscript Info

Manuscript History

Received: 19 May 2018
Final Accepted: 21 June 2018
Published: July 2018

Keywords:-
unexplained infertility, IUI, gonadotropin stimulation, minimal stimulation protocol, pregnancy rate**.**

Abstract

Objective: To determine whether minimal stimulation with clomiphene and one injection of 150 IU of human menopausal gonadotrophin (hMG) provides pregnancy rates comparable with those in a conventional full hMG stimulation protocol for unexplained infertile patients undergoing intrauterine insemination (IUI).

Methods: A prospective study was carried out at the Infertility Clinic of Elshorok hospital Benha Egypt. Two hundred couples with either unexplained infertility or ovulatory dysfunction cases who ovulated with clomiphene citrate (CC) but failed to conceive were offered ovarian stimulation with CC and hMG along with IUI for 200 cycles.

Patients divided into two groups according to the stimulation protocol in **group one** patients given clomiphene citrate 50mg from day 3 to 7 two tablets per day with hMG (merional)75 unit injection on day 5 and 7 .in **group two** (full stimulation regimen clomiphene citrate given with hMG injection from day 5 to 9 daily then dose adjusted according to finding on trans-vaginal ultrasound scan of follicles .

Pregnancy rate, medication and monitoring cost were compared between minimal and conventional stimulation protocols.

Results: Number of ampoules of hMG and monitoring costs were significantly higher in the full hMG stimulation cases whereas pregnancy rate was comparable in both protocols.

Conclusion: Minimal stimulation appears to be an effective protocol in cases of unexplained infertility undergoing intrauterine insemination.

Introduction:-

Unexplained infertility means a couple fails to conceive and no definite cause for infertility can be diagnosed after a complete check-up. The prevalence of unexplained infertility ranges from 6% to 60% with an average of 20%.**1**

Controlled ovarian stimulation (COS) with human menopausal gonadotrophin (hMG) along with intrauterine insemination (IUI) has been used with success in couples with unexplained infertility.**2**

For anovulatory infertile cases failing to conceive after four to six ovulatory cycles with clomiphene citrate (CC), switching to COS with hMG and IUI offers an alternative before offering assisted reproductive techniques (ART).**3**
Drawbacks of hMG include cost of a treatment, the necessity of increased monitoring by hormone assays and ultrasound measurements, frequent injections, time and emotional stress on patients.

Corresponding Author:-Mostafa Abdulla Elsayed Mahmoud.
Address:-Assistant professor of obstetrics and gynecology, Benha university hospital, Qalubia district – Egypt.

A combination of CC and hMG have been devised to decrease costs by reducing the amount of hMG necessary in an ovarian stimulation cycle, without sacrificing effectiveness.**3–5**

Corfman et al. developed a novel ovarian stimulation protocol of CC and hMG termed 'minimal stimulation' which is less expensive, requires minimal monitoring, minimizes patient discomfort and is easy to administer.**6**

It was used in cases undergoing in vitro fertilization procedures. This protocol produced pregnancy rates comparable to conventional hMG stimulation at a much lower expense.

This prospective study planned to compare the two ovarian stimulation protocols of CC and hMG combination in couples with unexplained infertility and CC failures in whom IUI is planned. But with 2 alternate day regimen instead of one shot

Materials and Methods:-

The present study was conducted in the infertility clinic Elshorok infertility Hospital Benha city Qalubia district Egypt, from January 2017 to January 2018.

Two hundred women with unexplained infertility or ovulatory dysfunction cases who ovulated with clomiphene but failed to conceive were booked in to the study (Table 1) and were offered COS with clomiphene and hMG along with IUI.

After recruitment in the study the cases were divided into two groups according to random table before starting the first cycle of ovarian stimulation. A total of 200 ovarian stimulation cycles, minimal stimulation (100) and full conventional stimulation (100), were included in the analysis.

Inclusion criteria of patients:-

Infertility of at least 2 years
Normal history and physical examination
Adequate coital frequency
Normal semen analysis
Regular ovulatory menstrual cycles
Adequate cervical mucus and a normal postcoital test
Normal FSH, LH, PRL and TSH levels
Normal hysterosalpingography and/or laparoscopy
Criteria for clomiphene (CC) failures
A-Anovulatory women who ovulate with CC but fail to conceive in 3 cycles
Women with unexplained infertility who have been given CC empirically

Conventional stimulation protocol:-

Patients assigned for CC/hMG standard protocol received 100 mg of CC daily on days 3–7, and 75–150 IU of hMG was given intramuscularly, daily on days 5–9. Further hMG dosage was adjusted according to follicular monitoring by transvaginal sonography (TVS) and serum estradiol (E2) results done for the first time on day 10, and then afterwards TVS was done on alternate days or daily.

When the leading follicle was of diameter > 18 mm, 5000 IU of hCG was given to trigger ovulation. An E2 sample was taken prior to administration of hCG. Intrauterine insemination of husband's semen was performed 36 hours after hCG injection.

Minimal stimulation protocol:-

One hundred milligrams of CC was administered during cycle days 3–7; on day 5, 7, a single injection of 75 IU of hMG (total of 2ampoules) was given. On day10, TVS was performed to assess follicle development and growth. 5000 IU of Hcg (choriomon: IBSA) was given accordingly and IUI was done 36 after hCG injection.

Semen preparation and insemination technique:-

Couples were advised abstinence for 3–4 days. Semen collected in sterile containers after masturbation was allowed to liquefy at 37°C and then prepared by wash and swim-up technique using Ham's F-10 culture medium. 21-22

0.3 mL sample was injected into the uterine cavity with an IUI cannula, the rest of the sample was injected at the external os of the cervix. The patient asked to remain supine with buttocks elevated for 10 to 15 min.

Monitoring of outcome:-
Pregnancy was tested by pregnancy urine test (babycheck) 4–5 days after the missed periods followed by ultrasound (USG) examination 2 weeks later for detection of gestational sac and cardiac activity.

Multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) was assessed. It was considered mild to moderate when there was ovarian enlargement with abdominal discomfort and weight gain.

Severe OHSS was diagnosed when there was massive ovarian enlargement, ascites, hemoconcentration, hypo-volemia, oliguria, hypercoagulability and electrolyte imbalance. Cost of CC, hMG and hCG were assessed according to the current market rate of drugs. Monitoring cost was assessed according to number of USG examinations and serum hormones.

Statistical analysis:-
The data statistically analyzed and compared by applying 'test of proportion' and correlation coefficient (Pearson's r) where applicable by smith statistical package. Life table analysis was applied to calculate cumulative PRs by treatment. $P < 0.05$ defined the level of significance.

Results:-

A total of 200 couples completed 200 ovarian stimulation cycles along with IUI. There was no difference between the two stimulation protocols regarding mean age, years of infertility, type of infertility or the indication for treatment (Table 2).

Among the 100 subjects who received minimal stimulation for 100 cycles, mean number of dominant follicles (DF) per cycle was 1.8 ± 0.51 and the mean number of DF in the 100 treatment cycles of full hMG stimulation given to the other 100 women was 3.2 ± 1.50. The difference was not statistically significant.

There was a significant correlation between E2 level and maximum number of follicles developed.

Maximum number of DF and pregnancies were observed when the E2 levels were between 500 and 1500 pg/mL.

Table 1:-epidemiological data

	Minimal stimulation	Full stimulation
Age (years)	28.45 ± 4.23	30.03 ± 4.62
Duration of infertility	6.06 ± 2.80	6.92 ± 2.86
Primary infertility (%)	76	80
Unexplained infertility (%)	69	65
Clomiphene failure (%)	40	42

The number of ampoules of hMG used in the two treatment groups was significantly different, two for minimal stimulation (1 amp of 75 IU of hMG on day 5 and 7) and 12 ± 5.4 for full hMG stimulation.

Follicle monitoring in minimal stimulation required a one visit for trans-vaginal ultrasound while three to four visits were required in subjects receiving conventional stimulation protocol.

The pregnancy rate per couple as well as per cycle did not differ significantly in the two stimulation protocols.

Table 2:-Analytical clinical data

item	Minimal stimulation	Full stimulation	P value
No. of cases	100	100	
treatment cycles	100	100	
dominant follicles	1.8± 0.5	3.2± 1.5	0.6(non significant)

visits for monitoring	1	3.1±1.2	0.3(non significant)
ampoules of hMG	2	12±5.3	0.0005 (high sigificance)
Pregnancy rate per couple	37	40	0.6
Abortion	5	15	0.01
Multiple gestation	1	5	0.09
Hyperstimulation	0	2	0.1
Cost	282.8	1206.8±462	In Egyptian pound

Though the luteal phase support was the same in both the protocols, miscarriage rate was higher in women who conceived on full stimulation. One patient in minimal stimulation had multiple gestation and no cases of ovarian hyperstimulation.

Discussion:-

Anovulation in women desiring fertility is the most common indication for use of ovulation induction therapy. Ovarian stimulation is also quite often recommended for women who apparently have spontaneous ovulation.**9**

Clomiphene citrate is the most commonly used drug because of its relative economy and ease of administration. **7**

Women who remain anovulatory on CC or who have not conceived after five or six ovulatory cycles with CC are considered appropriate candidates for controlled ovarian hyperstimulation with hMG.(**9-12)**

Controlled ovarian hyperstimulation (COH) with hMG has been used along with IUI in couples with unexplained infertility. However, the cost of superovulation regimens is high.

Sequential regimens using a combination of CC and hMG have been devised to decrease costs by reducing the total amount of hMG necessary in an ovarian stimulation cycle, without sacrificing effectiveness.**3–5**

Corfman et al.6 described ovarian stimulation protocol termed ‘minimal stimulation’ which is less expensive, requires minimal monitoring, minimizes patient discomfort and is easy to administer. This protocol produced a clinical pregnancy rate comparable to conventional hMG stimulation at a lower expense.**6**

In the present study, minimal stimulation protocol was compared with the standard conventional protocol for ovarian stimulation, along with IUI in couples with unexplained infertility and CC failures. The pregnancy rate achieved per couple was 37% and the with minimal stimulation regimen while in conventional stimulation protocol cases these rates were 40%.

Pregnancy rates with COH with CC plus hMG as well as IUI in couples with unexplained infertility have been reported to range from 12.4% to 34%, and the per cycle pregnancy rate from 8.6% to 26.4%.10–13 The pregnancy rates achieved in the present study were 23.07% and 29.41% with minimal and conventional regimens; in cases of unexplained infertility, they were 14.63% and 18.75% per cycle, respectively. **7**, **8**

A single USG visit sufficed for minimal stimulation group while patients in conventional group required an average of 3.16 ± 1.50 visits per cycle. The total number of ampoules of hMG required in a cycle differed significantly (2.0 for minimal stimulation vs 12 ± 5.4 for conventional stimulation). Cost of minimal protocol was even less than one-fourth of that of the conventional protocol.

In the present prospective study all pregnancies in minimal stimulation and 95% in the conventional stimulation protocol were singleton. Pregnancy wastage in minimal stimulation group was 5% only and it was 15% in the conventional stimulation group in this study. With the conventional stimulation with multiple hMG injections, premature leutinizing hormone surge plays a significant adverse role. **9**

Patients who undergo full stimulation will have post-hCG E2 levels in excess compared to minimal stimulation; hence the altered E2 and progesterone balance may affect embryonic implantation.

None of the patients in our study had ectopic pregnancy. The incidence of OHSS was 2% in conventional stimulation cycles while none of the cases had OHSS among minimal stimulation group.

The minimal stimulation protocol for COH in our study showed comparable pregnancy rates. It was easy to administer, required less intensive monitoring, fewer medications, lower pregnancy wastage and virtually eliminated the risk of OHSS. **(15-20)**

The savings in cost and no morbidity suggests minimal stimulation as a viable alternative to conventional stimulation. Minimal stimulation should be offered to unexplained and CC failure cases and it is a good alternative before doing ICSI.**10**

References:-

1. Sagnella F, Moro F, Lanzone A, Tropea A, Martinez D, Capalbo A, et al. A prospective randomized noninferiority study comparing recombinant FSH and highly purified menotropin in intrauterine insemination cycles in couples with unexplained infertility and/or mild-moderate male factor. Fertil Steril. 2011;95:689–694.
2. Wolff EF, Vahidi N, Alford C, Richter K, Widra E. Influences on endometrial development during intrauterine insemination: clinical experience of 2,929 patients with unexplained infertility. Fertil Steril. 2013;100:194–199.
3. Reindollar RH, Goldman MB. Gonadotropin therapy: a 20th century relic. Fertil Steril. 2012;97:813–818.
4. Azargoon A, Bahrami M, Alavy Toussy J. Comparing clomiphen citrate plus HMG with clomiphen citrate plus rFSH in IUI cycles in couples with unexplained or male factor infertility: A prospective randomized study. Iran J Reprod Med. 2013;11(3):243–248.
5. Merviel P, Heraud MH, Grenier N, Lourdel E, Sanguinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. Fertil Steril. 2010;93:79–88.
6. Corfman RS, Ory SJ, Milad MP, Erickson LD, Bellevance TL, Ball GD. A novel ovarian stimulation protocol for use with assisted reproductive technologies. Fertil Steril 1993; 60: 864–870.
7. Goverde AJ, McDonnell J, Vermeiden JPW, Schats R, Rutten FFH, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopatic subfertility and male subfertility: a randomised trial and cost effectiveness analysis. Lancet. 2000;355:13–18.
8. Wolff EF, Vahidi N, Alford C, Richter K, Widra E. Influences on endometrial development during intrauterine insemination: clinical experience of 2,929 patients with unexplained infertility. Fertil Steril. 2013;100:194–199.
9. Coulam CB1374–1381., Moore SB, O'Fallon W. Investigating unexplained infertility. Am J Obstet Gynecol 1988; 158.
10. Hughes E, Collins J, Vandekerckhove P. Clomiphene citrate for unexplained subfertility in Women. Cochrane database Syst Rev. 2010;(1):CD000057. 31, 1588–1609.
11. Gatimel N, Moreau J, Parinaud J & Leandri RD. (2017a) Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. Andrology 5, 845–862.
12. Gatimel N, Mansoux L, Moreau J, Parinaud J & Leandri RD. (2017b) Continued existence of significant disparities in the technical practices of sperm morphology assessment and the clinical implications: results of a French questionnaire. Fertil Steril 107, 365–372. e363
13. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST, Vogel DL & Canfield RE. (1999) Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. N Engl J Med 340, 177–183.
14. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, Carson SA, Cisneros P, Steinkampf MP, Hill JA, Xu D, Vogel DL & National Cooperative Reproductive Medicine N. (2001) Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 345, 1388–1393.
15. Haagen EC, Nelen WL, Grol RP, Braat DD, Hermens RP & Kremer JA. (2010) Variation in guideline adherence in intrauterine insemination care. Reprod Biomed Online 20, 533–542.
16. Guideline adherence is worth the effort: a cost-effectiveness analysis in intrauterine insemination care (2013). Hum Reprod 28, 357–366.
17. Helmerhorst FM, Oei SG, Bloemenkamp KW & Keirse MJ. (1995) Consistency and variation in fertility investigations in Europe. Hum Reprod 10, 2027–2030.
18. Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL & te Velde ER. (2004) Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. Hum Reprod 19, 2019–2026.

19. Jedrzejczak P, Taszarek-Hauke G, Hauke J, Pawelczyk L & Duleba AJ. (2008) Prediction of spontaneous conception based on semen parameters. Int J Androl 31, 499–507.
20. Keel BA, Stembridge TW, Pineda G & Serafy NT. (2002) Lack of standardization in performance of the semen analysis among laboratories in the United States. Fertil Steril 78, 603–608.
21. Lemmens L, Kos S, Beijer C, Brinkman JW, van der Horst FA, van den Hoven L, Kieslinger DC, van Trooyen-van Vrouwerff NJ, Wolthuis A, Hendriks JC, Wetzels AM & Semen Section of the Dutch Foundation for Quality Assessment in Medical L (2016) Predictive value of sperm morphology and progressively motile sperm count for pregnancy outcomes in intrauterine insemination.Fertil Steril 105, 1462–1468.
22. Lemmens L, Kos S, Beijer C, Braat DDM, Nelen W, Wetzels AMM & Dutch Foundation for Quality Assessment in Medical L. (2017) Techniques used for IUI: is it time for a change? Hum Reprod 32, 1835–1845.