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Short Communication

Utilization of Letrozole and Clomiphene Citrate for Better Optimization of Ovulation Induction Rates in PCOS Patients

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Short Communication

One of the commonest causes of anovulatory infertility is PCOS in reproductive aged women [1]. Clomiphene Citrate (CC) is one of the most commonly used drugs for achieving ovulation induction, followed by pregnancy in women having PCOS. Its mechanism of action is that it is a selective estrogen (E2) receptor modulator which it does by competitive binding nuclear E2 receptors. On negative feedback, reduction of E2=>increased gonadotropin secretion, that induces ovarian follicular growth. Further CC possesses antiestrogenic activity on endometrial development along with cervical mucus production that has been suggested to=>lower pregnancy rate in spite of a high ovulation rate [2,3].

Besides CC another ovulation induction agent is letrozole whose mechanism of action is markedly different from that of CC. It acts as an aromatase inhibitor, thereby preventing E2 to Androgen conversion. One of the mechanisms hypothesized is suppression of E2 =>reduced negative feedback on hypothalamus and thus resulting in increased FSH secretion. Further another mechanism that is given for the reason why greater ovulatory rates are there with letrozole is >sensitivity of follicles to FSH that results secondary to temporarily raised androgens in the ovary [4]. Moreover another benefit given by letrozole over CC regarding ovulation induction is in view of it not blocking E2 receptors both centrally along with in peripheral target tissues, with normal central feedbacks remaining intact. Hence optimizing ovulation induction will help in restricting the side effects to the least, reduce risks of multiple gestation, birth defects, and side effects and be most cost effective.

Based on various RCT's optimal 1st line drugs got evolved with results that gave a surprise. Initially based on early work regarding value of metformin in ovulation induction in PCOS, Legro et al. [5] conducted a Randomized Controlled Trial (RCT) of extended release, CC or both for testing this probability that metformin would give higher live birth rates than CC, and that combining the 2 would give even more superior result. Although earlier non RCT's pointed to higher ovulatory rates of metformin alone or in combination with CC, they did not find either of the 2 was superior to CC alone in their RCT. Resistance to CC (25%), inability to achieve live birth (78% over 6 cycles), risk of multiple gestations (3% to 8%) along with side effects provoked interest in letrozole. It was postulated that letrozole would give better pregnancy rates, along with lower rate of multiple pregnancies via mono follicular recruitment and lower periconceptional exposure. Thus a RCT of letrozole or CC was finished for checking the postulate that letrozole would be superior to CC's get live births and add to better safety profiles [6]. Cumulative ovulation (62% *vs.* 48%) and live births (28% *vs.* 19%) rates were significantly more possibility following treatment with letrozole than with CC. Though the rate of twin pregnancies was lesser with letrozole in comparison with CC (3.4% *vs.* 7.4%) this was not statistically significant, limitations of this study was it was under powered for finding outcomes between treatment outcomes. Standard of earlier ovulation induction in PCOS was laid down using the combination of these 2 RCT's that emphasize how important well designed RCT's are to challenge the results from non RCT's.

Though letrozole has now come out to be the 1st line drugs regarding ovulation induction in women presenting with PCOS [7], still there are lot of patients who are non responders. For optimizing ovulation induction in women having PCOS, Meija et al. [8] proposed a novel protocol which combined both CC and letrozole. A pilot study RCT involving letrozole or combination of CC was fashioned by them where letrozole or combination of CC and letrozole for testing this proposition that combination therapy would give even better ovulation rate in contrast to letrozole alone, in view of synergistic actions of the 2 drugs [8]. 70 patients were randomized to letrozole alone or in combination with CC and stratified these patients by age and BMI. Chances of ovulation were significantly higher following single treatment with combination treatment as compared to letrozole alone; 77% *vs.* 4.3%; p=0.007; rate ratio 1.8,95% CI 1.28-2.75. Though live birth was similar between 2 groups. Mega et al. [8] thought of powering his first study with the idea of comparing rates of ovulation, rather than the live birth rates in view of absence of prospective randomization results on combination therapy. They found no twin pregnancies or any serious side effects in their treatment protocol

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patients. Only 1 patient refused to repeat combination therapy in view of mood instability.

This study gave initial data that confirmed their novel hypothesis regarding use of combination therapy in ovulation induction being better than single agent alone. It gives a possibility of usage of other therapies in comparison to using gonadotropins that are costly and constitute a riskier therapy. Still different factors are required to be noticed. One being this was not a trial that involved observing live birth but only a single ovulation attempt. It is still not clear whether repeated ovulations can be sustained for obtaining greater pregnancy rates. Earlier metformin results were very positive regarding ovulation, but there was no improvement in live birth in the properly powered large RCT, hence one need to move forward with being careful with this treatment. Further individuals from this study were permitted to continue the metformin therapy that they were already using, that though equally distributed across groups, might have altered the baseline sensitivity regarding which population will respond to treatments postulated in PCOS is not clear. A Systematic review and network analysis by Wang et al. showed that CC and metformin combined had greater ovulation rates [9]. Moreover they did not compare increased dose of single agent Screw a Screw multidrug regimens for showing if this approach has greater value rather than just raising the dose of a single drug.

Thus a valuable study has been conducted by Meija et al. [8] with the idea of development of a low cost ovulation induction protocol for optimizing ovulation rates in obese PCOS women and fashioning such a novel protocol for this pilot study. Further full randomized trial of this combination therapy and letrozole alone which is powered for live birth and adds to the safety data regarding birth defects and side effects. Prior to Meija et al. [8], only Hagshava et al. [10], conducted a prospective cohort study where they only used this protocol on 100 patients who were resistant to CC alone (6 cycles) and letrozole alone (4 cycles) and showed a follicular development rate of 82.9% (213/257 cycles) on the basis of development of a Dominant Follicle (DF) using 5 mg letrozole +100 mg CC/day × 5 days from day 3 to 5, in contrast to 2.5 mg letrozole and 50 mg CC used in this study. Further they additionally gave an FSH injection on day 11 once a DF was present and then administered HCG trigger once DF was >=18 mm, that was followed by Intrauterine Insemination (IUI), 36 h to 38 h later. That study although gave interesting findings it had its own limitations, where only DF size was used instead of serum progesterone >3 ng/ml in this study of Maya et al. [8] and their study was limited to CC and letrozole resistant patients only while this study included all general PCOS patients [10]. Subsequent step might establish this concept of combining therapy of letrozole with CC as 1st line treatment for PCOS general patients.

References

1. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007;370(9558):685-97.
2. Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of Clomiphene citrate on endometrial growth. Hum Reprod. 1990;5(6):670-4.
3. Randall JM, Templeton A. Cervical mucus score and in vitro sperm mucus interaction in spontaneous and Clomiphene citrate cycles. Fertil Steril. 1991;56(3):465-8.
4. Casper RF. Aromatase inhibitors in ovarian stimulation. The J Steroid Biochem Mol Biol. 2007;106(1-5):71-5.
5. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Cooperative multicentre Reproductive Medicine Network. Clomiphene, metformin or both for infertility in polycystic ovary syndrome. N Engl J Med. 2007;356(6):551-66.
6. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole vs clomiphene for infertility in polycystic ovary syndrome. N Engl J Med. 2014;371:119-29.
7. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. International PCOS Network recommendation from the international evidence based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2018;110(3):364-79.
8. Meija RB, Summers KM, Kresowik JD, Van Voorhis BJ. A randomized trial of combination letrozole and Clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome. Fertil Steril. 2019;111(3):571-8.
9. Hajshahifa M, Dehghan M, Kiarang N, Sadegh-Asadi M, Shayegh SN, Ghasemi-Rad M. Combined letrozole and Clomiphene citrate versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug Des Devel. 2013;7:1427-31.
10. Wang R, Kim BV, Van Wely M, Johnson MP, Costello MF, Zheng H, et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. BMJ 2017;356:j138.