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Aromatase Inhibitors: New Drug of Choice for Induction of Ovulation

M SIDDIQUI[a], N MAHMUD[b], MR BEGUM[c], T A CHOWDHURY[d]

Summary:

Anovulation accounts for around 20% cases of infertility even when other fertility factors are normal. Clomiphene Citrate (CC), the oral anti-estrogen has long been used as the first line drug for induction of ovulation. Clomiphene is associated with a high ovulation (60-80%) but relatively poor pregnancy rate (30-40%). CC leads to long lasting estrogen receptor depletion. Because of its long half-life (2 weeks), CC possibly exerts a negative feedback effect on the cervical mucous and endometrial development with subsequent implantation failure. The aromatase inhibitor letrozole (originally approved for use in postmenopausal women with breast cancer to suppress estrogen production) is now increasingly being used by fertility specialists worldwide for ovulation induction. With a half-life of around 45 hours, letrozole possibly avoids the adverse effects of CC on endometrium. Preliminary trials have shown impressive prospects of aromatase inhibitor letrozole for induction of ovulation (even in CC resistant cases) with satisfactory pregnancy rates. Letrozole is now being marketed by our local pharmaceutical companies. Though large scale randomized controlled trials are not yet available, letrozole holds a very promising chance of replacing CC in near future.

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Introduction:

Infertility is thought to affect 10 to 15% of couples but this percentage may be an underestimate[1,2]. The inability to conceive carries a hidden stigma of shame and secrecy for some couples, whereas others are never enumerated because they cannot afford to seek medical treatment[3]. Failure to seek management, investigation and treatment compounds the tragedy of infertility because simple, inexpensive therapeutic options may be appropriate for anovulatory infertility or even in expectant management of unexplained infertility. In a study on rural population of Bangladesh, 3.2% of married women of reproductive age have primary infertility and 3% have secondary infertility[4]. Majority of infertile women (40%) believed this to be their fate and 33% accused themselves for infertility[4].

In a review, Homberg and Insler[5] concluded that taking into account efficacy, complication rates and cost of infertility treatment, women with hypogonadotrophic hypogonadism or polycystic ovary syndrome(PCOS) should be offered acceptable methods of ovulation induction and that couples with 'unexplained' or 'multifactorial subfertility' should be exposed to controlled ovarian hyperstimulation with intrauterine insemination and only after the failure of these therapies should be offered in vitro fertilization(IVF).

Ovulatory dysfunction is one of the most common causes for reproductive difficulty in otherwise fertile couples. Once successful ovulation is achieved, fertility is often restored. Ovarian stimulation during infertility treatment is used either alone or in conjunction with intrauterine insemination and assisted reproductive technologies. At present, the two main medications used for induction of ovulation include an oral antiestrogen, such as clomiphene citrate (CC), and an injectable gonadotropins,

a. Dr.Maruf Siddiqui, FCPS, Junior Consultant (Obstetrics & Gynaecology), OSD, DGHS, Deputed to MS, BIRDEM

b. Dr.Nusrat Mahmud, MSc(Singapore), Junior Consultant (Infertility), Centre for Assisted Reproduction (CARE), BIRDEM

c. Dr.Mosammat Rashida Begum, FCPS, MS, MSc(ART,UK), Assistant Professor of Obstetrics & Gynaecology, DMCH

d. Professor T A Chowdhury, FRCS, FRCOG, FRCP, FCPS(B), FCPS(P), Professor & Head of the Department of Obstetrics & Gynaecology, BIRDEM

Address of Correspondence: Dr.Maruf Siddiqui, Junior Consultant (OBGYN), OSD, DGHS, Deputed to MS, BIRDEM, Apt # A1, Oriental Tower-1, 1/G/1, Paribagh, Dhaka-1000, Tel: 9675555, Cell: 01711 593978, E-mail: drmaruf2000@yahoo.com

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predominantly recombinant follicle stimulating hormone (FSH)[6-9]. In specific situations, there are other less frequently used treatments to induce or restore ovulation, such as pulsatile administration of gonadotropin-releasing hormone (GnRH) for women with hypothalamic anovulation[10], dopaminargic agonists for women with hyperprolactinemic anovulation[11,12] and insulin sensitizers for women with PCOS[13].

Both clomiphene citrate(CC) and gonadotropins are associated with various disadvantages that include risk of life threatening ovarian hyperstimulation syndrome, high order multiple pregnancy, lower pregnancy rate despite high ovulatory rate (especially for clomiphene citrate) and high expenses with parenteral administration requiring intensive monitoring (FSH treatment)[14].

Clomiphene citrate (CC) is the most commonly used drug for the induction and augmentation of ovulation. However 20-25% women are resistant to clomiphene citrate[14]. In addition, clinical data reveal a discrepancy between ovulation and conception rates between CC treatment, and a higher than expected incidence of miscarriage in conception cycles. These observations have been attributed to the peripheral anti-estrogenic mechanism of action of CC that involves long lasting estrogen receptor depletion in the endometrium and cervix[14].

In spite of high ovulation rate, clomiphene is associated with low pregnancy rate with resistance to 20-25% 0f women. In CC failures, expensive gonadotropin injections are the next treatment option but, especially in polycystic ovary syndrome, are associated with increased risk of ovarian hyperstimulation requiring intensive monitoring. So, obviously a cheap oral agent is preferred that can induce ovulation in resistant cases without extensive monitoring and having less side effects on the endometrium.

Letrozole : The aromatase inhibitor

Mode of Action

Letrozole belongs to a new group of very potent, non-steroidal, selective reversible third generation aromatase inhibitor developed for postmenopausal breast cancer therapy[14]. Letrozole inhibits the conversion of adrenally generated androstenedione to estrone or estradiol by aromatase enzyme in peripheral tissues. It acts by competitive binding to the haem of cytochrome P450 subunit of the aromatase enzyme and interrupts the metabolism of estrogen resulting in a decrease level of estrogen in the body. As a negative feedback mechanism, the pituitary gland produces follicle stimulating hormone (FSH) leading to ovulation or superovulation. Therefore, letrozole generally mimics the action of CC without depletion of estrogen receptors when administered early in the menstrual cycle[14]. Because of the much shorter life span (2 days) and absence of estrogen receptor binding, it possibly avoids the antiestrogenic effects associated with CC[14].

Metabolism and side effects

Letrozole has no significant active metabolites. It is completely absorbed after oral administration and has a mean terminal half-life of 45 hours (range 30-60 hours). It is cleared from the systemic circulation mainly by the liver.

Letrozole generally is well tolerated; the most common treatment-related adverse effects are hot flushes, nausea, and hair thinning. In the trial of extended adjuvant therapy, adverse events reported more frequently with letrozole than placebo were hot flushes, arthralgia, myalgia and arthritis, but cessation of letrozole was no more frequent than placebo in this double-blind trial. A greater number of new diagnosis of osteoporosis occurred among women receiving letrozole, but the long term effects on bone mineral density or lipid metabolism are yet to be determined.

Is it teratogenic?

Over the recent years, letrozole has been studied at the University of Toronto as a fertility drug with satisfying results[15]. Their studies found that the drug appears to be completely eliminated from the body within a few days of the last tablet. So far there is no evidence that this drug has any harmful effects on the developing fetus. It therefore appears to be safe as a fertility drug.

In 2005, some concern was raised as a result of an abstract of a study that compared 150 babies born to women who had used letrozole with 36,005 babies

born to low-risk pregnant women[16]. The results of this study, which had several gross methodological drawbacks, suggested that letrozole might increase the risk of cardiac and bone anomalies[16]. Since that initial report, however, several full-length studies have not shown an increased risk for congenital malformations following the use of letrozole to induce ovulation. A study published in 2006 examined 514 babies born to mother who had used letrozole to conceive, and compared them with 397 babies born to mothers who had conceived using clomiphene citrate[17]. There were no increased rates of major and minor malformations beyond what would be expected in the general population (1-3%)[17]. Additionally, the number of cardiac anomalies in the letrozole group (0.2%) was slightly lower than that of the general population[17].

Letrozole is approved by the United States Food and Drug Administration (FDA) for the treatment of local or metastatic breast cancer that is hormone receptor positive in postmenopausal women. Infertility specialists have been using this drug for ovulation induction since 2001. However, like many other drugs (eg.misoprostol), induction of ovulation by letrozole is an 'off-label' indication because it is not marketed for use as a fertility drug[15].

Recent Studies on letrozole

Over the last few years, several published studies, both controlled and noncontrolled, compared clomiphene citrate and letrozole, either alone or in combination with gonadotropins, for ovulation induction or augmentation[18].These studies found letrozole as effective as clomiphene in inducing ovulation, with the major advantage of absence of any anti-estrogenic adverse effects. Patients treated with letrozole demonstrated low estrogen production per developing follicle resulting in more physiological estrogen levels around the time of ovulation and good pregnancy rates with a lower incidence of multiple pregnancies than with clomiphene[18]. When combined with gonadotropins, letrozole reduces the dose of gonadotropins required for optimal follicular recruirment and improve the response to gonadotropin stimulation in poor responders[19]. However, a recent study involving 438 PCOS patients did not show any advantage of letrozole over CC as a first line treatment for induction of ovulation in PCOS patients[20]. A group of Turkish researchers concluded that letrozole and CC have comparable effectiveness in ovulatory patients with unexplained infertility[21]. A small study involving 22 patients from the University of Toronto showed the supremacy of letrozole in ovulation induction in patients with an inadequate response to Clomiphene citrate[22]. This hypothesis is supported by another study in a tertiaty referral infertility clinic at Dhaka involving 35 infertile patients non responsive to CC which showed a high success rate (77.77%) for follicular development using letrozole[23]. Another survey also reported a successful induction (62%) in PCOS patients using letrozole previously treated with Clomiphene citrate[24]. Researchers from a university hospital in Greece concluded that ovulation induction with letrozole is associated with acceptable success rate compared with gonadotropin with significant less cost, risks and patient inconvenience[25]. In patients who failed to conceive with CC, gonadotrophins have a higher pregnancy rate for ovulation induction than letrozole[26]. However, pregnancy rates were high enough with letrozole to justify its use[26]. Compared to CC in gonadotrophin combined Intrauterine Insemination (IUI) cycles, number of mature follicles and serum estradiol levels on the day of hCG were significantly lower in the letrozole group. No significant differences were found in endometrial thickness measured on the day of hCG but the pregnancy rate was higher in letrozole group[27]. Comparing the endocrinological environment, significantly lower estradiol concentrations and fewer follicles were observed in cycles stimulated with 2.5 mg letrozole compared to 100 mg of CC from day 3 to day 7 of the cycle[28]. However, the administration of 50 mg CC was found superior to 2.5 mg letrozole for superovulation induction in Asian women with normal ovulation[29]. Similar to CC, aromatase inhibition by letrozole reduces FSH dose required for controlled ovarian hyperstimulation (COH) without the undesirable antiestrogenic effects sometimes seen with CC[29]. Letrozole appears to constitute a good alternative to CC in patients with unexplained infertility undergoing gonadotrophin stimulated COH cycles combined with IUI therapy[30]. It also seems to be an acceptable alternative to CC as an ovulation

inducing agent in patients with PCOS[31]. The third generation aromatase inhibitor letrozole is as effective as or superior to CC in ovulation induction and in superovulation[32]. Unlike CC, they do not carry an antiestrogenic effect on the endometrium[32]. Letrozole blocks estrogen production, not estrogen receptors, and would therefore be expected to produce superior conception rates and less multiple pregnancies[33]. Letrozole has got better ovulation and pregnancy rate in comparison to clomiphene citrate in patients with PCOS[34]. It also seems to be an effective alternative as a low-cost IVF protocol in women with poor response to gonadotrophins[35]. Letrozole is yet to undergo further large, robust clinical trials in order to fulfill these promises as a feasible alternative to CC in this role, but some preliminary trials have shown at least equality and some superiority.

Conclusion

Clinical utilization of ovarian stimulation to facilitate the ability of a couple to conceive has not only provided a valuable therapeutic approach, but has also yielded extensive information on the physiology of ovarian follicular recruitment, endometrial receptivity and early embryo competency. For the last 40 years, the first line of treatment for induction of ovulation has been clomiphene citrate. It is a safe, cheap oral agent but is known to have relatively common antiestrogenic endometrial and cervical mucous side effects that could prevent pregnancy in the face of successful ovulation. Infertility specialists have been increasingly using letrozole for induction. Because of the recent acceptance of the concept of using aromatase inhibitors for ovulation induction, a few small controlled studies were identified, and the rest were pilot or preliminary comparisons. Based on these studies, it appears that aromatase inhibitor letrozole is as effective as clomiphene in inducing ovulation, results in lower serum estrogen concentrations, and is associated with a good pregnancy rate with a lower incidence of multiple pregnancies than clomiphene citrate. Letrozole reduces the dose of FSH required for optimal follicular recruitment and improves the response to FSH in poor responders. So, preliminary evidence is suggesting that letrozole may replace clomiphene citrate in the future because of similar efficacy with a reduced side effect profile. Although worldwide experience with letrozole for ovulation induction is increasing, at present, definitive large scale studies in the form of randomized controlled trials comparing clomiphene citrate with letrozole are lacking.

References:

1. Whiteford LM, Gonzalez L. Stigma: the hidden burden of infertility. Soc Sci Med 1995;40:27-36
2. Downey J, Yingling S, McKinney M, Husami N. Mood disorders, psychistric symptoms and distress in women presenting for infertility evaluation. Fertil Steril 1989;52:425-432
3. Schroeder P. Infertility and the world outside. Fertil Steril 1988;49:765-767
4. Bangladesh Institute of Research in Promotion of Essential and Reproductive Health & Technologies (BIRPERHT). Assessment of Reproductive Health Care and Review Services provided at the level of Thana, Union and Villages. August 1997 issue, vol-5
5. Hommburg R, Insler V. Ovulation Induction in perspective. Hum Reprod Update 2002;8:449-462
6. Melis GB, Paoletti AM, Strigini F, et al. Pharmacologic induction of Multiple follicular development improves the success rate of IUI in inexplained infertility. Fertil Steril 1987;47:441-445
7. Serhal PF, Katz M, Little V, Woronowski H. Uuexplained infertility: the value of pergonal superovulation combined with intrauterine insemination. Fertil Steril 1988;49:602-606
8. Melis GB, Strigini F, Meis V, et al. Critical reappraisal of the clinical effectiveness of different methods of assisted fertilization. J Endocrinol Invest 1990;13:263-274
9. Franks S. Polycystic ovary syndrome. N Engl J Med 1995;333:853-861
10. Gomped A, Mauvais Jervis P. Induction of ovulation with pulsatile GnRH in hypothalamic amennorhoea. Hum Reprod 1988;3:473-477
11. Lin SG, Gu CX, Xu L, et al. Experience with bromocriptine for the treatment of female infertility due to hyperprolactinemia. Chin Med J (Eng) 1991;104:679-684
12. The ESHRE Capri workshop. Female infertility: treatment options for complicated cases. Hum Reprod 1997;12:1191-1196
13. Nestler JE, Stovall D, Akhter N, et al. Strategies for the use of insulin sensitizing drug to treat infertility in women with polycystic ovary syndrome. Fertil Steril 2002;77:209-215
14. Casper RF. Aromatase inhibitors: New experiments or new value. Updates in Infertility treatment 2004 Seminar in Florida 22-24 January

15. Hudson Stephen. Infosheet: Letrozole . Victoria Fertility Centre. #207-4400 Chatterton way Victoria BC. www.victoriafertility.com

16. Biljan MM, Hemmings R, Brassand N. The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins. Fertil Steril 2005;84:S95

17. Tulandi T, Martin J, Al-Fadhli R, Kabli N, Forman R, Hitkari J, et al. Fetal safety of letrozole and clomiphene citrate for ovulation induction. J Obstet Gynaecol Can 2007;29(8):668-71

18. Mitwally MF, Casper RF. Potential of aromatase inhibitors for ovulation and superovulation induction in infertile women. Drugs 2006;66(17):2149-60

19. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril 2002 April; 77(4):776-80

20. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozol for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril 2007 Jun 18

21. Bayar U, Tanriverdi HA, Barut A, Ayoglu F, Ozcan O, Kaya E. Letrozole vs clomiphene citrate in patients with ovulatory infertility. Fertil Steril 2006 Apr; 85(4):1045-48

22. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001 Feb;75(2):305-309

23. Begum MR, Quadir E, Begum A, Begum RA, Begum M. Role of aromatase inhibitor in ovulation induction in patients with poor response to clomiphene citrate. J Obstet Gynaecol Res 2006 Oct;32(5):502-506

24. Badawy A, Mosbah A, Shady M. Anastrozole or letrozole for ovulation induction in clomiphene resistant women with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril 2007 Aug 7

25. Gregoriou O, Viahos NF, Konidaris S, Papadis K, Botsis D, Creatsas GK. Randomized controlled trial comparing superovulation with letrozole versus recombinant follicle-stimulating hormone combined to intrauterine insemination for couples with unexplained infertility who had failed clomiphene citrate stimulation and intrauterine stimulation. Fertile Steril 2007 Oct 23

26. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotrophins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertil steril 2007 Oct;88(4):879-85

27. Jee BC, Ku SY, Suh CS, Kim KC, Lee WD, Kim SH. Use of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles: a pilot study. Fertil Steril 2006 Jun;85(6):1774-7

28. Fatemi HM, Kolibianakis E, tournaye H, Camus m, Steirtegham Van AC, Devroy P. Clomiphene citrate versus letrozole for ovarian stimulation: a pilot study. Reprod Biomed Online 2003 Nov;7(5):543-546

29. Topipat C, Choktanasiri W, Jultanmas R, Weerakiet S, Wongkularb A, Rojanasakul A. A comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on superovulation in Asian women with normal ovulatory cycles. Gynecol Endocrinol 2008 Mar;24(3):145-50

30. Noriega-Portella L, Noriega-Hoces L, Delgado A, Rubio J, Gonzales GF. Effect of letrozole at 2.5mg or 5.0mg/day on ovarian stimulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril 2007 Dec 14

31. Bayar U, Basaran M, Kiran S, Coskun A, Gezwe S: Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril 2006 Nov;86(5):1447-51

32. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertil Steril 2006 Feb;85(2):277-84

33. Homburg R. Oral agents for ovulation induction-clomiphene citrate vs aromatase inhibitors. Hum Fertil (Camb) 2008 Mar;11(1): 17-22

34. Begum MR, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovary syndrome. Fertil Steril January 2008

35. Chakravarty BN, Goswami SK, Das T, Chattopadhyay R, Sawhney V, Kumar J, Chaudhury K, Kabir SN. A randomized single-blind controlled trial of letrozole as a low-cost IVF protocol in women with poor ovarian response: a preliminary report. Human Reproduction 2004 19(9):2031-35

36. Casper RF, Mitwally MF. Review: aromatase inhibitors for ovulation induction. J Clin Endocrinol Metab 2006 Mar;91(3):760-71

37. Mitwally MF, Casper RF. Aromatase inhibitors in ovulation induction. Semin Reprod Med 2004 Feb;22(1):61-78

38. Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. Fertil Steril 2004 Dec;82(6):1561-3

39. Mitwally MF, Casper RF. Aromatase inhibitors for the treatment of infertility. Expert Opin Investig Drugs 2003 Mar;12(3);353-71