Fetal congenital malformations associated with letrozole use for anovulatory infertility

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ABSTRACT

There are no published case reports of letrozole (an aromatase inhibitor) induced neurological deficit with skeletal congenital malformations in a newborn born to mother taking letrozole for primary anovulatory infertility, here we report such a case. Patient had taken treatment with tablet letrozole 2.5mg from 2nd day of menses for 5 days for such 3 cycles in government hospital. Before that patient was already given such 6 cycles from private hospital, but patient did not give that history initially when asked before prescribing letrozole in government hospital. Regular followups by ultrasonography (USG) were done since starting of treatment, USG report at 4 months & 10 days of completion of therapy showed congenital malformations in male fetus and so termination of pregnancy was advised. As per Naranjo’s causality assessment, it falls in a “Probable” adverse drug reaction.

Key words: Congenital malformations, infertility, letrozole

INTRODUCTION

Ovulatory dysfunction is one of the most common causes of reproductive failure in subfertile and infertile couples. First line of treatment for anovulation in infertile women has been Clomiphene citrate (CC) followed by parenteral gonadotropins but associated with more frequent and serious complications. Casper and Mitwally (2001) demonstrated Aromatase inhibitors (AI) as a promising alternative to CC for ovulation induction.[1] Letrozole inhibits an aromatase enzyme, blocks the synthesis of estrogen. Its administration in early days of menstrual cycle results in increasing gonadotropin secretion and stimulation of ovarian follicle.[2] Letrozole is approved world over for advanced/metastatic carcinoma of breast(hormone receptor positive or unknown receptor status) in postmenopausal women as first line of treatment.[3] As per package insert, an approval of letrozole as ovulation induction agent in women with anovulatory infertility was based on phase III trial on 55 patients, conducted by private practitioners in personal clinics.[3,4] The dose of letrozole for ovulation induction is 2.5 mg once a day for 5 days (day 3 to 7 of menstrual cycle); for 3 consecutive cycles or till occurrence of pregnancy whichever is earlier.[3] Original inventor and various leading regulatory agencies in world including Canadian health regulator, US FDA, the British medicines and Healthcare products Regulatory Agency (MHRA) issued a warning that letrozole should not be used for ovulation induction because of the potential for fetal toxicity and malformations.[5] This warning was based on 2005 study by Biljan and colleagues.[6] Finally, on 12th October, 2011 letrozole was banned in India by Ministry of Health and Family Welfare for manufacture, sale and distribution for its use to treat infertility in women.[7]

CASE PRESENTATION

A 25 years old female patient was diagnosed as anovulatory infertility since 3 years, for that she was prescribed tablet letrozole (Letroz, Sun Pharmaceutical Industries Limited) 2.5mg, from the 2nd day of menses for 5 days for 3 cycles in...
government hospital. Previous history of letrozole use was not revealed to practitioners of government setup by the patient. The total exposure of patient to letrozole was for 9 cycles: six cycles from private practitioner and three from practitioner of government setup. Older history was elicited only after the patient was informed about fetal malformation.

Concomitant medications were tablet Ibuprofen and tablet Ranitidine for five days (for pain in lower abdomen, 1 month after starting 1<sup>st</sup> cycle), tablet Progesterone for seven days (for pain in lower abdomen, at 1.5 months of starting 1<sup>st</sup> cycle), tablet Iron/B-complex/Calcium/Vitamin C (after completion of 3 treatment cycles).

Ultrasonography was done periodically that is at monthly interval. Initial ultrasonography did not reveal any congenital malformation but at 4 months and 10 days after completing treatment cycle, ultrasonography showed that skull vault was not seen (so biparietal diameter could not be evaluated), herniated brain parenchyma, cervical spinal deformity and left lower limb (femur) deformity were observed. So, medical termination of pregnancy by extraamniotic betadine saline with per vaginal misoprostol was advised. Male fetus showed anencephaly, cervical vertebral fusion (webbed neck), spina bifida at cervico-thoracic level & left lower limb (femur) deformity [Figure 1 and 2]. and X-ray of fetus was done to confirm the skeletal abnormalities and showed absent skull bone, overcrowding of ribs [Figure-3].

**DISCUSSION**

Letrozole was approved for anovulatory infertility only in India by Sun Pharma, but drug was also marketed by Dabur and Dr. Reddy’s for said indication. In other countries of world, it was never approved for this indication because safety data was not available.

*Animal studies:* In rats and rabbits, in reproduction studies, embryo and fetal toxicity of letrozole during organogenesis had been noted. [3, 8]

*Human studies:* Congenital malformations, chromosomal abnormalities and case of hepatocellular carcinoma, were found in fetus resulting from the use of letrozole for ovulation induction in mother. [6, 9]

**Figure 1:** Front side photograph of baby with congenital anomalies [anencephaly, cervical vertebral fusion, left leg bone (femur) deformity].

**Figure 2:** Backside photo of baby shows anencephaly (blood clot is seen), spina bifida and left leg bone (femur) deformity.

**Figure 3:** X-Ray of delivered baby (no skull vault, overcrowding of ribs, left lower limb bone (femur) deformity.

No association had been found of concomitant medications (mentioned above) with congenital malformations [3] and other causes for congenital malformations were also ruled out.

As per causality assessment by Naranjo’s scale it falls in “Probable” and As per Severity assessment by Hartwig & Seigel, it falls in “Severe” category.
**Probable mechanisms responsible for letrozole induced congenital anomalies**

1. Recent findings have revealed new roles for brain aromatase, indicating that the enzyme regulates synaptic activity, synaptic plasticity, neurogenesis etc.\(^{[10]}\)

2. Aromatase enzyme also plays a role in skeleton homeostasis.\(^{[11]}\)

3. Letrozole’s terminal half life is about 2 days and steady state plasma concentration is attained after 2-6 weeks of daily administration. As letrozole is administered for only five days per monthly cycle and drug with nonlinear kinetics would remain in circulation for longer period than thought by its linear kinetics.\(^{[8]}\)

**Controversial points regarding approval of letrozole for anovulatory infertility, when we got a case.**

1. Letrozole for an anovulatory infertility got an approval from Drug Controller General India, only based on phase III trial on 55 patients by private practitioners in private clinics. As per the Drugs and Cosmetics Rules, even an old drug, when used for a new indication, must undergo a series of safety and efficacy studies both in animals and humans before its use in general public is allowed.\(^{[12]}\) None of these studies could be found to be done for approval process.

2. Though, it was prescribed in India for infertility for 4-5 years, post marketing safety data were not available.

3. Safety data available mostly were from use of letrozole in carcinoma breast in postmenopausal women. So based on that, we cannot imply safety results of drug’s use in anovulatory infertility in reproductive age women.

4. If it was used in anovulatory infertility with first line efficacy without producing significant harm to newborn babies, then why the original inventor was not marketing it for that indication.

**CONCLUSION**

Letrozole for anovulatory infertility was banned in India since 12th October, 2011,\(^{[7]}\) but before that it was prescribed for this indication over a period of 4-5 years without any safety data in India.

India is emerging rapidly as a hub of global clinical trials and a destination for drug discovery and development. Hence, we should have a stringent regulatory check for approval process and effective and strong vigilance system to record all such suspected ADRs.

**REFERENCES**


