



Baby monkey with mother - Kenya

PIC QUESTION OF THE WEEK: 1/17/11

Q: Why would letrozole be prescribed for a woman with PCOS and no history of breast cancer?

A: Polycystic ovary syndrome (PCOS) is a fairly common endocrine disorder affecting ~ 5-10% of women. Two of the following criteria must be met for diagnosis: oligo- or anovulation, hyperandrogenism, or ultrasound evidence of polycystic ovaries. PCOS is the cause of infertility in ~20% of couples and identifying an effective agent to induce ovulation is a priority. The current first-line of therapy for infertility associated with PCOS is clomiphene citrate, a nonsteroidal compound that induces ovulation. However, 20-25% of infertile women are resistant to clomiphene (anovulation following 10 cycles of treatment). Response appears to decrease with BMI>25, amenorrhea, and increased age. Finally, the drug has a long half-life which contributes to enhanced negative anti-estrogenic effects on the endometrium and cervical mucus. Gonadotropins and analogs are used in clomiphene-resistant women and exert their effects by interrupting the hypothalamic/pituitary axis (HPA). Their use also has a number of disadvantages including expense, increased risk of multiple births, and the need to use injectable dosage forms. Non-steroidal aromatase inhibitors such as letrozole and anastrozole (commonly used to treat breast cancer) are now considered as a possible option for managing infertility associated with PCOS. This group of compounds induces ovulation by preventing HPA negative feedback, thus ultimately stimulating follicular development. There are numerous benefits in using aromatase inhibitors such as letrozole for PCOS. First and foremost, the use of these drugs is rarely associated with ectopic pregnancy. In addition, the rate of multiple pregnancies is significantly lower than with all other methods of ovarian stimulation. Unlike clomiphene, letrozole's reversibility and shorter half-life (~2 days) result in the production of estrogen similar to physiological concentrations, thus allowing for healthy development of follicles and estrogen sensitive tissues without delayed anti-estrogenic effects. It is less costly than gonadotropins and does not require close cycle monitoring or result in ovarian hyperstimulation syndrome. Dosage of letrozole in PCOS is 2.5 – 7.5 mg daily on days 3-7 of the menstrual cycle. Early reports suggested a possible increase in fetal cardiac and bone abnormalities; however, subsequent studies have not identified an enhanced risk of congenital malformations with the use of letrozole in PCOS. In patients with PCOS, letrozole produces higher ovulation and pregnancy rates than alternative therapies and also demonstrates a more positive adverse effect profile.

References

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