CHAPTER 25

DRUGS AND ENDOMETRIUM

Onder CELIK, Mustafa ULAS, Mustafa D. OZCIL

Are there any hormone, drug or prodrug affecting endometrial receptivity except sex steroids?

Except sex steroids little is known about the influence of other hormones, drugs, and prodrugs on the endometrium receptivity. The only stimulatory agent responsible for endometrial proliferation is estrogen. Nevertheless, androgens do not exert stimulatory effect on the human endometrium (1). Although postmenopausal women have relatively high but reduced serum androgen levels compared to premenopausal women endometrial atrophy is the most common finding in postmenopausal women (2). As supportive, it has been demonstrated that estrogenic impact of DHEA observed in the vaginal epithelium was not detected in the endometrium of postmenopausal women on DHEA. Actually, endometrium of women on DHEA remained atrophic after 12 months of the treatment (3). These findings are the most powerful proof for absence of stimulatory effect of DHEA on the endometrium.

Absence of any effect of androgens on endometrium thickness might be explained by the lack of aromatase enzyme which able to transform androgens to estrogens in the normal human endometrium (4,5). On the other hand, absence of endometrial aromatase enzyme does not mean absence of endometrial estrogen. To dig down deeper, all steroidogenic enzymes are expressed in many extragonadal tissues where local estrogen biosynthesis takes place from endogenous and exogenous androgens (6). Accordingly, DHEA and its potent compounds DHT, testosterone, and estrogen are distributed by the general circulation to all tissues including endometrium indiscriminately. Conversely, the sex steroids made from DHEA in peripheral tissues are essentially released outside the cells as inactive compounds. Most importantly, 95% of the active estrogens and androgens made are inactivated locally before being released into the circulation as inactive metabolites, thus avoiding inappropriate exposure of the other tissues (7).

Clomiphene citrate and endometrial thickness

Clomiphene citrate (CC) is a selective estrogen receptor modulator having both estrogen agonist and antagonist properties (8). It has been used to induce ovulation in patients with ovulatory dysfunction. Clomiphene competes with 17

ity. Treatment of rats with 100 ng estradiol per day on gestation days 1 to 5 leads to complete absence of implantation sites supporting the adverse effect of high estrogen on implantation site (30-31).

References

1. Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab 1997;82:2396–402.
2. Labrie F, Labrie C. DHEA and intracrinology at menopause, a positive choice for evolution of the human species. Climacteric. 2013;16:205–13.
3. Labrie F, Diamond P, Cusan L, Gomez JL, Bélanger A. Effect of 12-month DHEA replacement therapy on bone, vagina, and endometrium in postmenopausal women. J ClinEndocrinol Metab1997;82:3498–505.
4. Bulun SE, Lin Z, Imir G, Amin S, Demura M, Yilmaz B, et al. Regulation of aromatase expression in estrogen-responsive breast and uterine disease: from bench to treatment. Pharmacol Rev2005;57:359–83.
5. Baxendale PM, Reed MJ, James VH. Inability of human endometrium or myometrium to aromatize androstenedione. J Steroid Biochem1981;14:305–6.
6. Simpson ER, M ahendroo MS, M eans GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, et al. A romatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocr Res1994;15:342–55.
7. Labrie F. DHEA after menopause – sole source of sex steroids and potential sex steroid defi ciency treatment. MenopauseManagement2010;19:14–24.
8. Clark JH, Markaverich BM. The agonistic-antagonistic properties of clomiphene: a review. Pharmacol Ther. 1982;15:467-519.
9. Greenblatt RB, Barfield WE, Jugck EC, Ray AW. Induction of ovulation with MRL/41, preliminary report. J Am Med Assoc. 1961; 178:101-4.
10. Kerin JF, Liu JH, Phillipou G, Yen SS. Evidence for a hypothalamic site of action of clomiphene citrate in women. J Clin Endocrinol Metab. 1985; 61(2):265-8.
11. Hsueh AJW, Erickson GF, Yen SSC. Sensitisation of pituitary cells to luteinising hormone releasing hormone by clomiphene citrate in vitro. Nature. 1978; 273(5657):57-9.
12. Seyedoshohadaei F, Zandvakily F, Shahgeibi S. Comparison of the effectiveness of Clomiphenecitrate, tamoxifen and Letrozole in ovulation induction in infertility due to isolated unovulation. Iran J Reprod Med. 2012;10(6):531–36.
13. Requena A, Herrero J, Landeras J, Navarro E, Neyro J, Salvador C et al. Use (20) of letrozole in assisted reproduction: a systematic review and meta-analysis. Human Reproduction Update. 2008;14(6):571-82.
14. Bedaiwy MA, Abdelaleem MA, Hussein M, Mousa N, Brunengraber LN, Casper (21) RF. Hormonal, follicular and endometrial dynamics in Letrozole-treated versus natural cycles in patients undergoing controlled ovarian stimulation. Reprod Biol Endocrinol. 2011;9(83):1-6.
15. Kar S. Clomiphene citrate or Letrozole as first-line ovulation induction drug (5)in infertile PCOS women: A prospective randomized trial. J Hum Reprod Sci. 2012;5(3):262.
16. Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, et al. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphenecitrate in induction of ovulation in polycystic ovarian syndrome. Journal of human reproductive sciences. 2012;5(1):20.

17. Xi W, Liu S, Mao H, Yang Y, Xue X, Lu X. Use of Letrozole and Clomiphenecitrate (29) combined with gonadotropinsin clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. Drug design, development and therapy. 2015;9:6001.
18. Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. Cochrane Database Syst Rev. 2009; (4):CD002249.
19. Gupta S, Tempe A, Sahu L.Supplementation with estradiol valerate and gonadotropins in clomiphene citrate stimulated IUI cycles. International Journal of Biomedical And Advance Research. ISSN: 2229-3809 (Online) Journal DOI:10.7439/ijbar. IJBAR (2014) 05 (04)
20. Yagel S, Ben-Chetrit A, Anteby E, Zacut D, Hochner-Celnikier D, Ron M. The effect of ethinyl estradiol on endometrial thickness and uterine volume during ovulation induction by clomiphene citrate. Fertil Steril. 1992; 57(1):33-6.
21. Swasti, Khanna SB, Kaul U. Effects of Exogenous Ethinyl Estradiol on Endometrial Receptivity in Clomiphene Induced Cycles in Infertile Women with Polycystic Ovaries. JK Sci. 2005; 7(3):140-5.
22. Van Vorrhis BJ. In vitro fertilization. N Engl J Med. 2007;356:379Y386.
23. Brezinova J, Oborna I, Svobodova M, Fingerova H. Evaluation of day one embryo quality and IVF outcome: a comparison of two scoring systems. Reprod Biol Endocrinol 2009;7:9.
24. Senturk LM, Erel CT. The endometrium in assisted reproductive technology. Cur Opin Obstet Gynecol. 2008;20:221Y228.
25. Walters DE, Edwards RG, Meistrich ML. A statistical evaluation of implantation after replacing one or more human embryos. J ReprodFertil. 1985;74:557Y563.
26. Rogers PA, Milne BJ, Trounson AO. A model to show human uterine receptivity and embryo viability following ovarian stimulation for in vitro fertilization. J In Vitro Fertil Embryo Transf. 1986;3:93Y98.
27. Kuć, Paweł. Optimal Environment for the Implantation of Human Embryo. InTech, 2012.
28. Celik O, Acet M, Kucuk T, Haberal ET, Acet T, Bozkurt M, Sahin L, Verit FF, Caliskan E. Surgery for Benign Gynecological Disorders Improve Endometrium Receptivity. Reprod Sci. 2017;24(2):174-192.
29. Celik O, Acet M, Celik S, Sahin L, Koc O, Celik N. Hypothesis: Co-transfer of genuine embryos and implantation promoting compounds via artificial containers improve endometrium receptivity. Medical Hypotheses 103 (2017) 65–70.
30. Simón C, Cano F, Valbuena D, Remohí J, Pellicer A. Clinical evidence for a detrimental effect on uterine receptivity of high serum oestradiol concentrations in high and normal responder patients. Hum Reprod 1995;10:2432-7.
31. Thorpe JB, Burgess PS, Sadkowski M, deCatanzaro D. Estrogen-progesterone balance in the context of blastocyst implantation failure induced by predator stress. Psychoneuroendocrinology 2013;38:3048-56.