Influence of estrogen, progesterone and their synthetic derivatives on ovarian functions

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Abstract

Estrogen and progesterone, the main sex steroids mostly bound to plasma proteins while circulating in the bloodstream. Only unbound estrogen and progesterone are biologically active. Gonadotrophins like *Luteinizing hormone* (LH) and Follicle stimulating hormone (FSH) promote ovulation and stimulate secretion of the sex hormones-estrogen and progesterone from the ovaries. These sex steroids stimulate the target organs of the reproductive system and inhibit as well as around the time of ovulation stimulate gonadotropin secretion. Since estrogen circulating in the blood can negatively feed-back to reduce circulating levels of FSH and LH, most oral contraceptives contain a synthetic estrogen, along with a progestin. The present article overviews the role of estrogen, progesterone and their synthetic derivatives on ovarian functions.

Keyword: Estrogen, Progesterone, Progestin, Ovary

1. Introduction

A way of controlling estrus and conception in cattle would be of sensible significance to the livestock industry. By using the tool of synthetic service, the probable rate of genetic development can be greatly increased. The genetic superiority of an outstanding bull could be capitalized on many breeders, rather than selecting a few. Progesterone (pregn-4-ene-3,20-dione; abbreviated as P4) is an endogenous steroid hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species (1). Progestins are synthetic progesterones that have progestogenic effects similar to those of progesterone. Three major naturally occurring estrogens are estrone (E1), estradiol (E2), and estriol (E3). The common synthetic estrogens are Chlorotrianisene, Dienestrol, Diethylstilbestrol, Ethinyl estradiol, Fosfestrol, Mestranol and Quinestro. Synthetic progesterone (progestins) and estrogens are widely used in human and veterinary medicine, e.g., in contraceptive therapy, hormone replacement therapy and assisted reproductive technology (2). Progestins exert biological effects via binding to the progesterone receptors, but some of them also interact with other hormone receptors causing progestagenic, (anti) estrogenic, (anti) androgenic, gluco-corticogenic, or anti-mineralocorticogenic effects depending on the type of compound and tissue examined (2, 3). Estrogen regulates the expression of the gene encoding estrogen receptors (*esrs), pgr* and *ar* in a cell-specific manner (2, 4). Thus, estrogens and progestins share estrogenic, progestagenic, and androgenic signaling pathways (2). The present article overviews the role of estrogen, progesterone and their synthetic derivatives on ovarian functions.

Progesterone and its synthetic derivatives

Progestins may be classified into old progestins (norethisterone, levonorgestrel, gestodene) and new progestins (drospirenone, dienogest, trimegestone) (5). Newer progestins are designed to be less androgenic. Individual progestins, however, differ in their ability to suppress ovulation in animal models in the following declining order of potency: desogestrel > levonorgestrel > MPA >norgestimate >

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norethindrone. Drospirenone alone, and in combination with ethinyl estradiol, suppresses ovulation but does not completely suppress follicular development (5). All progesterones have a similar 4-ring steroid skeleton. It has three tetracyclic structures. Hence it can be categorized as -pregnanes (derived from the progesterone molecule), -estranes (derivatives of testosterone), and -gonanes (6). The Exogenous progestins used so far for contraception and menopausal hormone therapy are derived either from testosterone (19-nortestosterone derivatives) or from progesterone (17-OH progesterone derivatives and 19-norprogesterone derivatives) (7). Among the 19-nortestosterone derivatives, the estrane group correspond to first-generation progestogens, such as norethisterone (NET) and its metabolites. Gonane group include the second-generation progestogens, the levonorgestrel (LNG) and its derivatives. The desogestrel (DSG) and its derivative etonogestrel, gestodene (GES) and norgestimate (norelgestromin), have been referred to as third-generation progestins. Several new progestins have been synthesized in the last decade and may be considered as a fourth-generation of progestins (7). Progestins has been grouped into "generations" in the medical literature based on when they were introduced (Table 1) (8).

Dienogest is referred to as a hybrid progestin being derived from the estrane group with a 17alpha-cyanomethyl group, and drospirenone derives from spirolactone.

Table1. Different generations of progesterone (8)

Generation	Name
First Generation	Ethisterone
	Norethindron
	Norethindrone Actetate
	Norethynodrel
	Ethynodiol Diacetate
	Medroxyprogesterone Acetate
	Megestrol Acetate
Second Generation	Norgestrel
	Levonorgestre
Third Generation	Norgestimate
	Norelgestromin
	Desogestrel
	Etonogestrel
	Gestodene
Fourth Generation	Drospirenone
	Elcometrine
	Nomegestrol Acetate
	Trimegestone

These two progestins show a partial antiandrogenic effect but no androgenic effect. The later exerts anti-mineralocorticoid effects. This property leads to a decreased salt and water retention and a lowering in blood pressure in users of pills containing this progestin. The 19-norprogesterone derivatives appear more specifically progestational and do not possess any androgenic, estrogenic or glucocorticoid activity. They bind almost exclusively to the progesterone receptor (PR) and do not interfere with the other steroid receptor and hence they are called as "pure" progestational molecules. This category includes trimegestone, nomegestrol acetate and Nestorone. They are found to be inactive orally but proved to be a potent anti-ovulatory agent when given in implants, vaginal rings or percutaneous gel. Non-androgenic progestins would appear neutral on metabolic factors and on the vessels. They have the advantage of avoiding acne. Progestins with antiandrogenic properties may also be used for the treatment of women with preexisting androgen related conditions. The progestins available for therapy exhibit great differences in structure or metabolites and considering the various effects of the old and new molecules as class-effects is inappropriate (9).

Role of progesterone and its synthetic derivatives on ovarian functions

Hormonal supplementation, estrogen and progesterone decrease the incidence of an ovulation, anestrus and cystic ovarian disease (10). Numerous and variable drugs available for the treatment of Cystic ovarian disease (COD), and have changed considerably over the years (11). Administration of exogenous hormones is one of the conventional remedy for treatment of COD. GnRH, with human chorionic gonadotropins (hCG) is being normally used. GnRH at the time of insemination has been reported to improve the conception rate of repeat breeder animals and a good treatment of COD for these animals (10). LH can also be used in this case. These hormones are equally effective, because GnRH is a small synthetic peptide, and causes fewer side effects. The main aim for using these therapeutic agents is to induce luteinization of the cyst through the action of LH. The lysis of the luteal tissue will subsequently occur by natural mechanisms, usually within 20 days, or following administration of exogenous PGF2α (10) .

Progesterone influenced follicular development and ovulation. Transitional levels of progesterone slow down follicular turnover chunk the LH surge and foil ovulation, and finally results in large

dominant follicles (10). Progesterone resets the hypothalamic surge centre by reinstating the sensitivity of the hypothalamus to estradiol (10). Thus, treatment with progesterone decreased the mean LH and LH pulse frequency resulting in regression of cysts and by initiation of new follicle (10). Progesterone also has a direct, negative effect on estradiol production by granulosa cells. Cystic cows with high estrogen levels fail to generate a LH surge in response to exogenous estradiol. This indicates that, the cows with cysts have lost the ability to respond to the positive feedback effect of estradiol. Progesterone induces regression of the cyst, allows normal follicular turnover and ovulation following termination of the treatment (10).

Animals show signs of ovulation breakdown following the oestrus and have asymmetrical inter-oestrus interval and standard follicular wave pattern. The fundamental cause is the breakdown of hypothalamic reply to estradiol, or the small follicles produce inadequate Estradiol. These animals will probable react to the Ovsynch or Ovsynch plus CIDR programs (12). Many an ovulatory cows have ovulatory size follicles but lack an LH surge. The conception rate of anovulatory cows treated with the Ovsynch program averages 25-35%, with a range of 10% to 40%. Thus Ovsynch plus CIDR will yield a better response in an ovulatory cows and results in a better conception rate (12-14).The progestogen component of oral contraceptives (OC) has undergone changes since it was first recognized that their chemical structures could influence the spectrum of minor adverse and beneficial effects. The major determinants of OCs are effectiveness, cycle control and common side effects (7).

According to the finding of Shirley et al. (15), Levonorgestrel does not have an adverse effect on either fertilization or preimplantation development, but it increases the proportion of oocytes fertilized and the fraction of embryos that developed to morulae. Contraceptive effect of Levonorgestrel implants should be accredited to good effects other than diminished oocyte quality They suggests, it will not adversely affect early embryonic development and pregnancy should be initiated during its use. Since Dienogest lacks any androgenic activity, it affects the glucocorticoids to a lesser extent than mifepristone (6)

In a human endometrial epithelial cell line, Dienogest inhibits the PGE2 production via progesterone receptors. This effect was supported by the suppression of PGE2 synthase expression, which differed from those of COX inhibitors. Moreover, Dienogest also inhibited the expression of the aromatase and estrogen synthetase. Thus concluded that dienogest directly inhibit the effect on PGE2 production and aromatase expression of endometriotic tissue, which leads to the therapeutic effect of it on endometriosis and pain relief (16). Oral contraceptive progestin also induces apoptosis in the ovarian epithelium. Given the importance of the apoptosis pathway for cancer prevention, an effective chemopreventive strategy may be possible using progestins or other agents that selectively induce apoptosis in the ovarian epithelium to prevent the development of ovarian cancer (17).

Exogenous progestin directly inhibits the FSH-stimulation of granulosa cell steroidogenesis in vitro and suggests that the effect may be mediated by the progesterone (P) receptor. So possibly, progesterone could exert a direct but reversible inhibitory action on ovarian follicular development (18). Hormonal contraceptives (HCs), containing progestins suppress gonadotropins, which interrupts the normal synergism between androgens and FSH at small follicle growth stages, in turn impacting oocyte yields. Since many fertility centres routinely use OCs in preparation for IVF cycles, such a practice, even in young women with normal functional reserve, appears to have negative consequences on oocyte numbers (5). Levonorgestrel hormone releasing intrauterine system can also be used safely by the egg donors as a contraceptive device during treatment, without compromising follicular development and oocyte quality (19).

Role of estrogen and its synthetic derivatives on ovarian functions

17-α-ethinyl oestradiol (EE2), an important component of most oral birth-control pills, acts as a xeno-oestrogen after being released into the environment through urine and feces. Although this emphasizes the need for the evaluation of its toxicity, several oocyte and embryo-toxic effects have been reported (20). No immediate statistical significant effect of short-term EE2 exposure during the morulae stage in *in vitro* culture on subsequent blastocyst development and quality, additional research is necessary to find out if EE2 may affect gene-expression patterns, eventually resulting in still unknown embryo toxic effects that might turn up during later embryonic development (21). Treatment with 5 mg EV resulted in a longer and more variable interval to follicular wave emergence than treatment with 5 mg estradiol-17β, which affected preovulatory dominant follicle size following progestin removal, and may have also affected super stimulatory response in Holstein cows. Additionally, 5 mg EV

appeared to induce luteolysis in heifers, reducing the interval to ovulation following norgestomet removal. Conversely, intervals to, and synchrony of, follicular wave emergence, estrus and ovulation following treatment with 1 or 2 mg EV suggested that reduced doses of EV may be more useful for the synchronization of follicular wave emergence in progestogen-treated cattle (22).

The efficacy of estradiol cypionate (ECP) for synchronizing ovarian follicular development was determined in lactating Holstein-Friesian cattle. Mean days of wave emergence (Day 3.4; range: -2 to 7) and ovulation (Day 12.1; range: 10 to 14) indicated that ECP had limited efficacy for synchronizing follicular development and ovulation in dairy cattle when given at random stages of the estrous cycle (23). Cows in treatment groups were received either ear implant (n=9) containing norgestomet+oestradiol valerate or progesterone releasing intravaginal device (n=9) containing progesterone+oestradiol benzoate, at random stage of the oestrus cycle, for 9 days. , both protocols synchronized the oestrus cycle in follicle stimulating hormone treated cows (24). In postpartum beef cows, GnRH-induced ovulation of small dominant follicles decreased pregnancy rates and increased late embryonic/fetal mortality. ECP supplementation during the preovulatory period increased pregnancy rates in cows induced to ovulate smaller dominant follicles (25).

Outlook

Additional research is necessary to find out the effects of estrogens, progesterone, their derivatives, either singly or in combination affecting gene-expression patterns in target cells, tissue (ovarian follicles, oocytes, granulosa cells, cumulus cells, thecal cells, uterine cells, oviduct cells). Moreover their role as xenoestrogens or endocrine disruptors may also be ascertained.

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