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Recent perspective in medication of gynaecological disorder

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Abstract
In cases where pharmacological therapy may have serious side effects, such as in the case of gynecological disorders like amenorrhea, dysmenorrhea, premenstrual syndrome, pelvic floor dysfunction, or polycystic ovary syndrome (PCOS), many women choose to use hormonal replacement therapy to treat these symptoms instead of pharmaceutical therapy. Here, we examined the management of gynecological problems, which are frequently utilized for the aforementioned indications, with an emphasis on clinical data and a safe profile. We pointed out that information is available regarding the usage of different pharmacological classes, including biguanides, aromatase inhibitors, and antiandrogens, to treat the side effects of oral contraceptives. In addition, hormone replacement therapy (HRT) for gynecological and menopausal problems uses progestin and estradiol.
A summary of the cutting-edge methods of drug delivery for gynecological disorders is also included in this paper, including liposomal iron, polymer-drug conjugates, vaginal gel with nanocarrier, etc.

Keywords: Gynecological disorders, Amenorrhea, Harmone Replacement Therapy, Polycystic ovary syndrome, Pelvic floor dysfunction.

Introduction
More than half of all Indian women who are from lower socioeconomic strata experience gynecological issues due to factors like poverty, illiteracy, and societal shame. Women worldwide are affected by a number of benign disorders, such as endometrial cancer, endometriosis, adenomyosis, leiomyoma, polycystic ovarian syndrome (PCOS), and endometrial hyperplasia with or without atypia,[1] Chronic pelvic pain,[2] low-tone pelvic floor dysfunction, hypertonic pelvic floor dysfunction, bladder pain syndrome, and interstitial cystitis are among the conditions that can cause pelvic pain.[3] Galactagogue, Emmenagogue, pain in the uterus, dysmenorrhea, primary amenorrhea, secondary amenorrhea, PMS, leucorrhoea, and premenstrual syndrome anaemia during pregnancy, Abortion threats, challenging childbirth, postpartum haemorrhage, postpartum discomfort, postpartum insufficient lactation Menstrual disorders and vaginal pain.[4] Persistent hyperandrogenism, infertility, and in some cases, death.[5]

Gynecological disorders
Amenorrhea
The absence of menstruation in women who are of reproductive age is known as amenorrhea. [6] Amenorrhea may occur suddenly, sporadically, or continuously as a result of malfunctions in the pituitary, hypothalamus, ovaries, uterus, or vagina.[7] The lack of menstruation due to a suppression of the hypothalamic-pituitary-ovarian (HPO) axis without an identifiable anatomical or organic cause is known as functional hypothalamic Amenorrhea (FHA). It may be reversible and is commonly observed in the context of excessive exercise, stress, or weight reduction. [8]

Classification
Primary and secondary Amenorrhea are two different categories of Amenorrhea. The degree to which the hypothalamus, pituitary, ovary, uterus, and vagina regulate the menstrual cycle determines the classification of Amenorrhea. [9]

1. Primary Amenorrhoea
Failure to begin menstruation by the age of 13 without secondary sexual features or by the age of 15 with typical secondary sexual traits is known as primary Amenorrhea. [6] Furthermore, primary amenorrhea is caused by deficiencies in steroidogenesis-related enzymes and anomalies in steroid receptors at the ovarian and adrenal gland levels. [10]

2. Secondary Amenorrhoea
When a woman with a regular past menstrual cycle stops having her period for six months, it is known as secondary amenorrhea. Secondary amenorrhea is the most prevalent kind, occurring three to four times a year. In contrast, the frequency for people with primary Amenorrhea is 0.3%.[6] However, in most cases of primary Amenorrhea, there is a strong reason to suspect a chromosomal or structural problem. [11]

Pathophysiology
Individuals who suffer from Functional Hypothalamic Amenorrhea (FHA) have reduced energy expenditure, body fat percentage, and energy accessibility (EA). GnRH inhibition is linked to changes in documented adipocytokines, especially elevated adiponectin, ghrelin, PYY, and downscaled leptin. Low insulin, low total T3, elevated rudimentary cortisol, and a diminished sensitivity to corticotrophin releasing hormone (CRH) injection are among the other endocrine responses observed in this low EA state. FHA suggests relative GH resistance because it is linked to increased growth hormone (GH) and low insulin-like growth factor (IGF-1). Kisspeptins are a class of polypeptides that have recently been found to influence GnRH release, which is a key factor in the regulation of the reproductive axis. Kisspeptin, neurokinin B, and dynorphine (KNDy) act on GnRH neurons and are released due to a variety of causes. [12]

Causes of Amenorrhea [13]

Table 1: Causes of Amenorrhea

Outflow tract abnormalities Acquired Cervical stenosis Intrauterine adhesions 5α-reductase deficiency Androgen insensitivity syndrome Transverse vaginal septum	**Hypothalamic or pituitary disorders** (continued): Constitutional delay of puberty Eating disorder Stress Weight loss Gonadotropin deficiency Chronic kidney disease Physiologic (pregnancy, stress, exercise) Infection (meningitis, tuberculosis) Illicit drugs (cocaine) Trauma or surgery Tumour (primary or metastatic)	**Other endocrine gland disorders:** Adrenal insufficiency Androgen-secreting tumour (ovarian or adrenal) Cushing syndrome Diabetes mellitus, PCOS Thyroid disease
Primary ovarian insufficiency: Acquired Autoimmune Chemotherapy Congenital Turner syndrome		**Amenorrhea attributed to chronic disease:** Celiac disease Inflammatory bowel disease Other chronic disease
Hypothalamic or pituitary disorders: Autoimmune disease Brain radiation		**Physiologic or induced:** Breastfeeding Contraception Menopause

Management

1. Primary amenorrhoea

The care of primary amenorrhea is dependent upon the underlying causes as well as the health, goals, and concerns of the patient. The overall goals of estrogen replacement therapy for hypogonadistic girls are to minimize the brain effects of this hormone deficiency, ensure normal growth velocity and optimal acquisition of bone mass, and initiate the development and maturation of secondary sexual characteristics and uterine growth.[14] Because there are currently no published guidelines for the kind, method, dosage, and timing of estrogen replacement therapy during puberty, the majority of the research on the subject has been based on personal experience.[15]

A short-term test using modest estrogen dosages (2–6 mg/day) for six to twelve months was suggested by several journalists. Typically, 12 to 13-year-olds begin estrogen therapy at a modest dose (about 1/10 of the adult dose), and over the next two to four years, the amount is gradually increased. Transdermal application (gel or patch) appears to be more physiological. The usual protocol is for an estrogen equivalent of 6 µg/day for six months, followed by a six-monthly dosage increase till the alternate year. Cyclic progesterone therapy is added 12–14 days per month when vaginal bleeding starts. [14]

2. Secondary amenorrhoea

In women with reversible causes of amenorrhea, treatment of the steadying cause of secondary amenorrhea is often sufficient to facilitate the restoration of a normal ovulatory menstrual cycle, but resumption of normal menstrual patterns may take many months. Patients should be informed by their doctor that, in most cases, the return of menstrual function will coincide with the return of fertility. Women with hypothalamic or pituitary causes of amenorrhea will experience ovulatory cycles when on pulsatile GnRH or gonadotropin medication. The antiestrogen clomiphene will cause an increase in FSH in the majority of PCOS-affected women; this increase in FSH is adequate to promote follicle growth. Gonadotropin therapy is useful for patients whose FSH level is non-responsive; nevertheless, in PCOS patients, this strategy carries a significant risk of multiple pregnancies. [16]

Pelvic floor dysfunction

Affected vaginal cubes can be anterior, apical, or posterior due to pelvic floor dysfunction. The two types of pelvic floor dysfunction: hypertonic pelvic floor dysfunction (HPFD) and hypotonic or low-tone pelvic floor dysfunction (LPFD). (See table 2) Numerous BPS cases also present with concomitant hypertonic pelvic bottom dysfunction (HPFD), which manifests as voiding dysfunction as well as muscle tenderness and spasms. According to estimates, between 50% and 87% of cases with BPS have HPFD frequencies. BPS symptoms are made worse by pelvic floor dysfunction, which has been linked to incidents including trauma, altered gait, and bladder irritation. [17]

Classification

Table 2: Types of Pelvic Floor Dysfunctions

Hypotonic disorders	Hypertonic disorders
Stress urinary Incontinence Pelvic organ prolapse Fecal incontinence	Overactive bladder BPS/IC Vulvodynia Overactive bowel Sexual dysfunction

Etiology

The genesis of pelvic floor muscle injury associated with vaginal delivery (VD) is similar to that of anal incontinence, which can be either neurogenic or myogenic. It is permitted to have multiple factors. Threat variables include musculoskeletal disorders, smoking, prior surgery, age, gestation, inheritable factors, hypoestrogenism, trauma, and chronic conditions. [18]

Pathophysiology

A∂-filaments mediate the supplemental mode of transmission in a normal bladder, transmitting cold wave, pressure, and pain. Instead, the C-filaments transmit sensations of burning, heat, discomfort, and itching; they are normally silent and only become active when the bladder becomes inflamed or irritated. An acral cord wind-up or a seditious complaint of the pelvic viscera, trauma, or unusual gesticulation may elicit unpleasant stimulants to the holy cord, which sets up a malfunction of the pelvic bottom muscles with holy whim-whams sharpness [3].

Endometrial cancer

The vagina, lungs, liver, bone, and brain are among the anatomical sites where endometrial melanoma has historically been linked to original, haematological or lymphatic dispersion. According to studies, 10% of patients with restricted endometrial complaints had positive pelvic lymph nodules at diagnosis, whereas 10 of individuals with endometrial melanoma have extra-uterine complaints in these locations. [19] The term "uterine cancer" refers to cancer that develops inside the corpus, or uterine body, and can originate from either the endometrium, which is the uterus's inner lining, or the myometrium, which is the uterine muscle layer. Adenocarcinomas, which originate from the endometrium, and sarcomas, which originate from the myometrium, are the two main forms of uterine cancer.

Treatment for endometrial adenocarcinomas differs from that for uterine sarcomas, accounting for 75% to 80% of uterine cancer cases. [20]

Ectopic endometrial tissue occurring outside of the endometrium is known as endometriosis. Because of the fluctuating symptoms and various locations of ectopic tissues, it is a complex condition. Based on the disease's stage and the location of ectopic glands, which can arise in the ovary, peritoneum, ovary and peritoneum, or vagina, these researchers categorized the study participants into groups. [21] The first-line medical treatments for endometriosis management recommended by a consensus panel included the use of oral contraceptives and nonsteroidal anti-inflammatory medications. If first treatments are ineffective, second-line treatments such as danazol, progestins, GnRH analogs, or surgical procedures such laparoscopic ectopic gland excision or ablation should be started. [22]

Classification

On the basis of histological features, hormone receptor expression, and grade, endometrial cancer has been generally divided into two subgroups (table 3). Low-grade, endometrioid, diploid, hormone-receptor-positive endometrial cancer is the most prevalent subtype and has a favourable prognosis. Non-endometrioid, high grade, aneuploid, TP53-mutated, hormone-receptor negative tumors with a poor prognosis and increased risk of metastasis are referred to as type II endometrial malignancies. (table 3). [23]

Table 3: Dualistic Classification of Endometrial Cancers [23]

Type I		Type II
Associated clinical features	Obesity, hyperlipidaemia, hyperglycaemia	None
Grade	Low	High
Hormone receptor expression	Positive	Negative
Histology	Endometrioid	Non-endometrioid (serous, clear-cell carcinoma)
Genomic stability	Diploid, frequent microsatellite instability (40%)	Aneuploid
Tp53 mutation	No	Yes

Etiology

According to reports, endometrial cancer is more common in young women who have ovarian tumors that produce estrogen and Stein Leventhal syndrome, which is characterized by elevated estrogen levels. Those who utilize hormonal replacement treatment during the postmenopausal period have a higher risk of developing the condition, and this risk increases over time. [24] Similarly, endometrial cancer is more common in obese women due to their high amounts of accessible peripheral estrogens. [24]

Endometriosis

The presence of endometrial tissue, stroma, and glands outside the uterine cavity is a characteristic of endometriosis, an estrogen-dependent inflammatory condition of the endometrium. It is estimated that this disorder affects up to 11% of women globally who are of reproductive age (about 200 million women), and up to 50% of women who experience pelvic pain or infertility. [25]

Classification [26]

American Society for Reproductive Medicine (ASRM)

Staging Points

Stage 1—Minimal Endometriosis 1–5

Stage 2—Mild Endometriosis 6–15

Stage 3—Moderate Endometriosis 16–40

Stage 4—Severe Endometriosis >40

Pathology

The histological characteristics of endometriosis and the glandular and stromal features at an extrauterine location differ significantly depending on the growth site. Well-differentiated glandular, pure stromal, glandular or mixed differentiation, and pure undifferentiated glandular patterns are histologic patterns linked to DIE; the latter is most commonly linked to DIE. Consequently, it is hypothesized that undifferentiated endometriotic lesions arise from the tissue's resistance to the peritoneal fluid's suppressor effects, which permit these endometrial foci to penetrate deeper. A fibromuscular component is identified with DIE in every instance. Lesions include fibrotic tissue, and progesterone receptors (PRs) are found in smooth muscle cells, fibrosis encircling the DIE lesions, glands, and stroma. Lesions preferentially invade the large bowel wall along the nerves in the particular situation of intestinal DIE, even when the nodule is not palpable; mucosa is rarely affected. Multifocality of lesions is one of DIE's main features [27].

Polycystic Ovary Syndrome (PCOS)

Hyperandrogenism and recurrent anovulation are the hallmarks of PCOS, a variety of symptoms. [28] The primary characteristics of PCOS, an ovarian dysfunction syndrome, are polycystic ovaries seen on ultrasounds and hyperandrogenism.[29] Anovulation affects most women with PCOS. This leads to issues with dysfunctional bleeding and infertility. As will be covered below, endometrial hyperplasia and possibly cancer are caused by regular unopposed estrogen. Anaemia is often the result of excessive bleeding in patients. [30]

The most prevalent endocrine condition affecting women in their reproductive years is polycystic ovarian syndrome (PCOS), which affects 5% to 15% of them depending on the specific criteria used. In the beginning, PCOS was identified by Stein and Leventhal as a syndrome characterized by polycystic ovaries and oligo-amenorrhea, completely accompanied by hirsutism, acne, and fatness. [31]

Pathophysiologic hypothesis

According to the diagnostic criteria, PCOS affects 8% to 20% of women worldwide who are of reproductive age each year. Changes in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin generation, insulin sensitivity, adipose cell activity, inflammatory variables, and sympathetic nerve function all have an impact on the pathophysiology of this illness. Barre *et al*. state that the four main factors causing pathophysiological changes in PCOS are high carbohydrate consumption, hyperinsulinemia, hyperandrogenaemia, and persistent low-grade inflammation (Figure 1). [32]

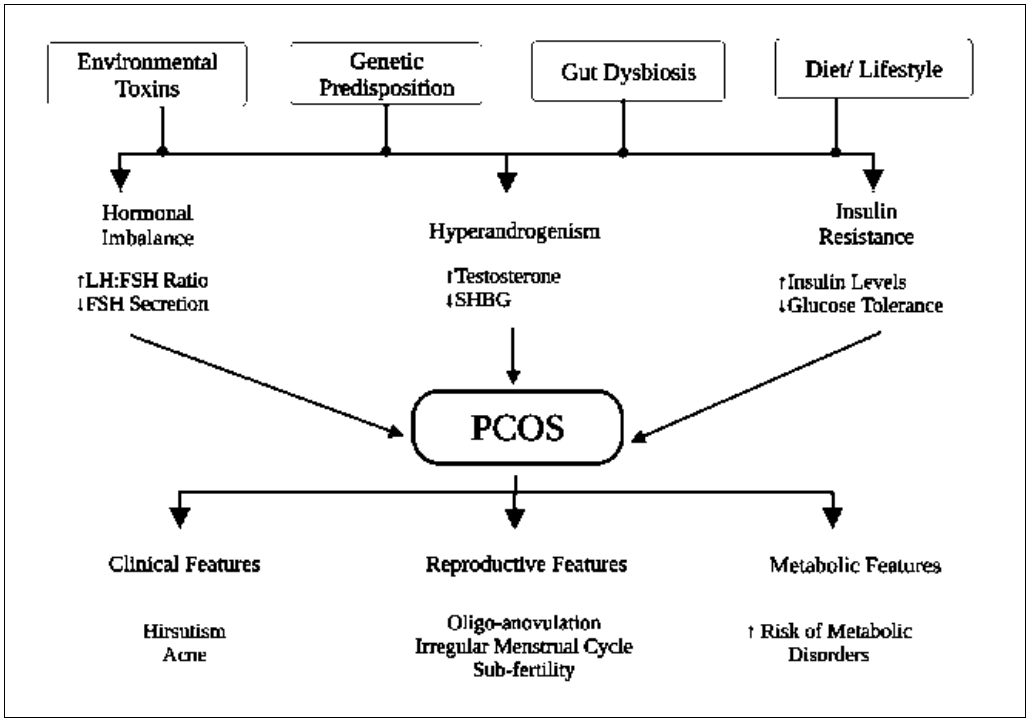

Fig 1: This schematic graphic depicts the characteristics and possible pathogenesis of PCOS.

In light of three significant laboratory findings, three main pathophysiologic theories have been put out to explain the clinical manifestations of PCOS. Three theories explain why ovarian hyperandrogenism and anovulation occur: (a) the LH hypothesis, (b) the Insulin hypothesis, (c) the Ovarian hypothesis, which is a primary defect of sex steroid synthesis or metabolism that causes exaggerated ovarian androgen secretion and anovulation. [33]

Risk factors that contribute to the pathophysiology of PCOS and the subsequent development of clinical, reproductive, and metabolic characteristics in PCOS patients include genetics, gut dysbiosis, environmental toxins, and food. FSH (follicle stimulating hormone), LH (luteinizing hormone), and SHBG (sex hormone binding globulin).[32]

Etiology of PCOS

a. Hyperandrogenism. [33, 34]
b. Environmental Pollutant. [35]
c. Obesity and PCOS. [36]

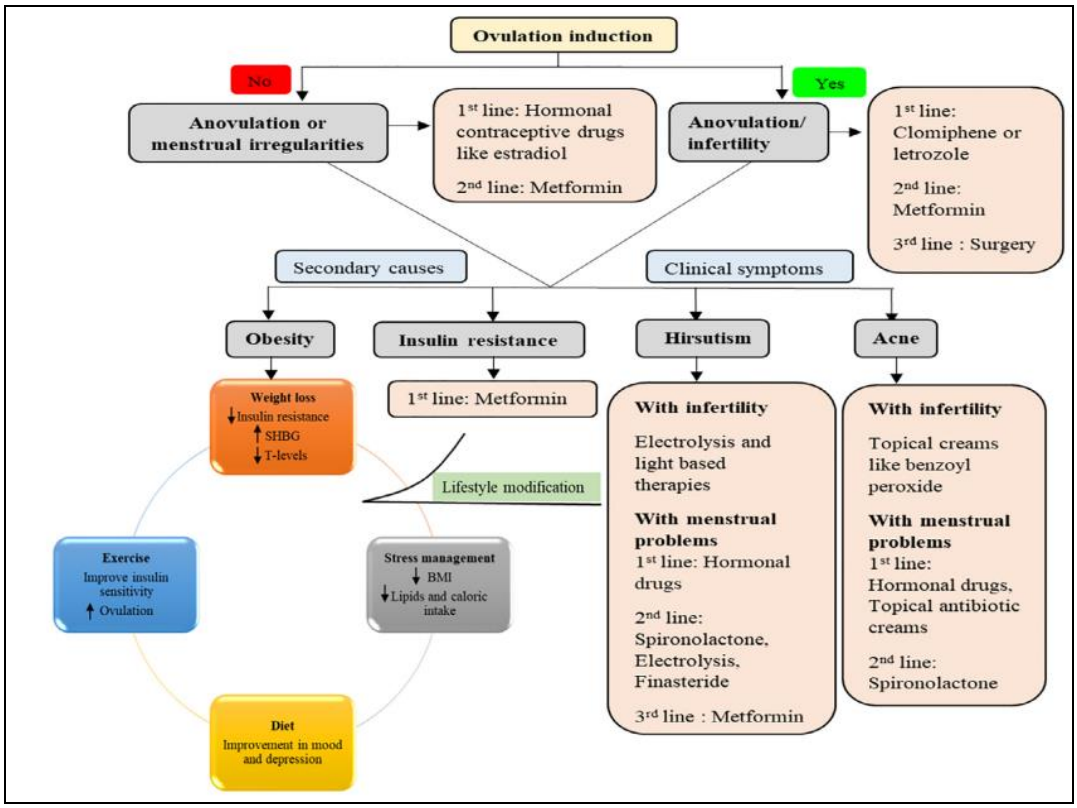

Fig 2: Procedure for managing polycystic ovarian syndrome that outlines available treatments for anovulation and infertility, along with a list of clinical signs [33]

Oral contraceptives (OCPs)

The OCPs are separated into progesterone-only and mixed pills that contain progesterone and estrogen (estradiol dosage up to 50μg). For women who experience irregular menstruation and do not want to ovulate, they are the first line of treatment.

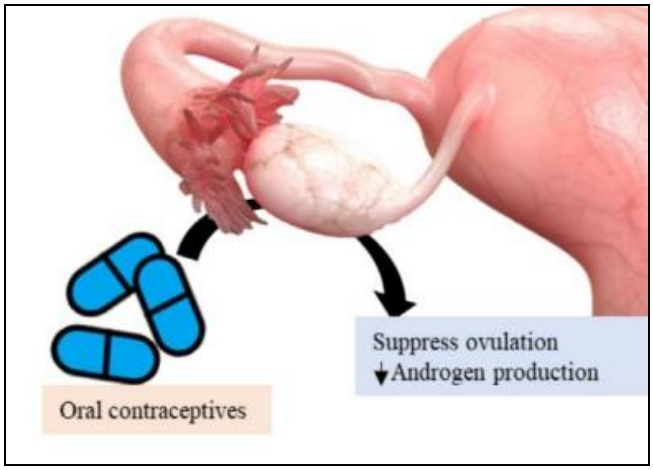

Fig 3: Mechanism of OCPs.

OCPs increase SHBG, which lowers the levels of androgens in the blood. (Fig. 3). [37] Women with PCOS are prone to cancers, but the use of OCPs diminishes the threat of ovarian cancers. The use of OCPs don't affect insulin resistance but show variability in lipid biographies which may lead to metabolic disturbances. [38] Therefore, the use of OCPs should be based on the risk grade, and if there is any contradiction, it should be halted right away.

Medicines and Treatment

Class of Drugs used in gynaecological disorders. [39]

1. Biguanides

Generic Name (Brand) - Metformin (Glucophage®).

a. Generic Name (Brand) - Levonorgestrel/Ethinyl estradiol - LD and HD.
b. Generic Name (Brand) - Desogestrel/Ethinyl estradiol (Marvelon®, Mircette®)
c. Generic Name (Brand) - Cyproterone acetate/Ethinyl estradiol (Diane 35®)
d. Generic Name (Brand) - Drospirenone/Ethinyl estradiol (Yasmin®)
e. Generic Name (Brand) - Drospirenone/Ethinyl estradiol (Yaz®)
f. Generic Name (Brand) – Dienogest / estradiol valerate (Natazia®)
g. Generic Name (Brand)- Chlormadinone acetate/ Ethinyl estradiol (Belara ®).

2. Progestins

General Name (Brand) - Medroxyprogesterone acetate (Provera ®).

3. Antiestrogen

Generic Name (Brand) - Clomiphene citrate (Clomid®)

4. Aromatase inhibitors

a. Generic Name (Brand) - Letrozole (Femara®)
b. Generic Name (Brand) - Atorvastatin (Lipitor®)

5. Antiandrogens

a. Generic Name (Brand) - Spironolactone (Aldactone ®)
b. Generic Name (Brand) - Finasteride (Propecia ®).

Hormonal Replacement Therapy

1. Progesterone [40]

Administration of progesterone – Rectal, oral, subcutaneous (SC), intramuscular (IM), and vaginal.

Dosage form – Oral capsules, sublingual tablets, vaginal capsules, tablets, gels, suppositories, and rings; rectal suppositories, [41], Pessaries, [42] etc.

Doses of progesterone – Vaginal, oral, or rectal progesterone - 600 mg/daily dose, while the centre states that the range is between 400 and 800 mg. Progesterone gel is typically taken at a dosage of 90 mg per day, while some people use more. Subcutaneous progesterone – 25mg, IM progesterone - 50 mg, and Oral progesterone – 30mg/day. [40]

Current marketed preparation and dose

Table 4: Available Forms of Progesterone [55]

Route	Form	Dose	Brand name
Oral	Capsule	100, 200, 300 mg	Prometrium
	Tablet (SR)	200, 300, 400 mg	Dubagest SR
Sublingual	Tablet	10, 25, 50, 100 mg	Luteina
Transdermal	Gel	1% (25 mg)	Progestogel
Vaginal	Capsule	100, 200 mg	Utrogestan
	Tablet	100 mg	Endometrin
	Gel	4, 8% (45, 90 mg)	Crinone
	Suppository	200, 400 mg	Cyclogest
	Ring	10 mg/day[f]	Fertiring
Rectal	Suppository	200, 400 mg	Cyclogest
Uterine	IUD	38 mg	Progestasert
Intramuscular injection	Oil solution	2, 5, 10, 20, 25, 50, 100 mg/mL	Proluton
	Aq. susp.	12.5, 30, 100 mg/mL	Agolutin
	Emulsion	5, 10, 25 mg/mL	Di-Pro-Emulsion
Subcutaneous	Aq. soln. (inj.)	25 mg/vial	Prolutex
	Implant	50, 100 mg	Proluton
Intravenous	Aq. soln. (inj.)	20 mg/mL	Primolut

2. Estrodiol

Administration of estrodiol

Estradiol can be administered in a number of ways. Among them are oral, Rectal, by intramuscular or subcutaneous injection (in oil or aqueous), buccal, sublingual, intranasal, transdermal (gels, creams, patches), vaginal (tablets, creams, rings, suppositories), and as a subcutaneous implant. [43]

Dosage form

Emulsion, Spray, Tablet, Cream, Insert, Ring, Microspheres, Oil solution, Pellet, Patch, Gel pump, Gel packet, and Emulsion. [44]

Current marketed preparation and dose

Table 5: Available Forms of Estrodiol [45]

Route	Ingredient	Form	Dose	Brand Names
Oral	Estradiol	Tablet	0.1, 0.2, 0.5, 1, 2, 4 mg	Estrace, Ovocyclin
	Estradiol valerate	Tablet	0.5, 1, 2, 4 mg	Progynova
Transdermal	Estradiol	Patch	14, 25, 37.5, 50, 60, 75, 100 µg/d	Climara, Vivelle
		Gel pump	0.06% (0.52, 0.75 mg/pump)	Elestrin, EstroGel
		Emulsion	0.25% (25 µg/pouch)	Estrasorb
		Spray	1.53 mg/spray	Evamist, Lenzetto
Vaginal	Estradiol	Tablet	10, 25 µg	Vagifem
		Cream	0.01% (0.1 mg/gram)	Estrace
		Insert	4, 10 µg	Imvexxy
		Ring	2 mg per ring (7.5 µg/day, 3 months)	Estring
	Estradiol acetate	Ring	50, 100 µg/day, 3 months	Femring
Injection	Estradiol	Microspheres	1 mg/mL	Juvenum E
	Estradiol benzoate	Oil solution	0.167, 0.2, 0.333, 1, 1.67, 2, 5, 10, 20, 25 mg/mL	Progynon-B
	Estradiol cypionate	Oil solution	1, 3, 5 mg/mL	Depo-Estradiol
Implant	Estradiol	Pellet	20, 25, 50, 100 mg, 6 mon.	Estradiol Implants

Novel Approaches of Drug Delivery for Gynecological Disorder

1. Polymer– drug conjugate

Polymer–protein conjugates, such as Oncaspar and Neulasta, have been successfully used in clinical settings over the past ten years, and clinical trials involving polymer–anticancer medication conjugates have shown encouraging outcomes. This has raised interest in this developing discipline, along with the realization that nanomedicines may play a significant future role in cancer diagnosis and therapy. [46]

In 1975, the idea of polymer-anticancer conjugates was initially put forth [47] Typically, polymer–drug conjugates use the increased permeability and retention (EPR) effect to target certain tumors. [48]

2. Iron Deficiency Anaemia in Pregnancy [49]

a. Iron (III) Polymaltose complex

The iron (III) polymaltose complex (IPC) dextriferron is one of the numerous oral irons (III) composites that are currently accessible. It is in the category of slow-release medications because, in contrast to iron salts, the polymaltose, which functions as an envelope around the trivalent iron, permits a delayed release of iron from the complex and, as a result, a lower rate of adverse effects. Similarly, taking it with food increases its bioavailability. It is advised to take 100–200 mg daily.

b. Liposomal Iron

Due to its lack of direct interaction with the intestinal mucosa, liposomal iron, a preparation of ferric pyrophosphate linked to ascorbic acid and transported within a phospholipid membrane, is a new generation of oral iron that exhibits a high bioavailability and a low occurrence of adverse effects. There is little information on its use during pregnancy.

Future Perspective

1. Nanotechnology

Since a variety of uses in food technology, medical, and chemical manufacturing have been documented, the field of nanotechnology has grown remarkably. One promising avenue for nanomedicine is the use of gold nanoparticles as a useful vehicle for miRNA delivery techniques. Due to their shape plasticity, size flexibility, and potential for surface changes, gold nanoparticles are excellent candidates. Furthermore, research on repro-toxicology is being conducted to clarify the suitability and safety of these carriers for usage in the female reproductive system. More precisely, the microinjection of *in vitro* produced murine embryos did not result in any harmful effects, nor did the culture of porcine oocytes with different kinds of gold nanoparticles impact their maturation. [50]

2. Artificial intelligence (AI)

Artificial intelligence (AI) is the use of fine algorithms to mimic mortal cognitive capacities and to address difficult healthcare challenges including complex natural abnormalities like cancer. The exponential growth of AI in the last decade is verified to be the implicit platform for optimal decision- making by super-intelligence, where the mortal mind is limited to reprocess huge data in a narrow time range. Cancer is a complex and multifaced disorder with thousands of inheritable and epigenetic variations. [51]

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