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REVIEW ARTICLE

Endometrium receptivity in premature ovarian insufficiency – how to improve fertility rate and predict diseases?

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ABSTRACT

More empathized approach is required and is obligatory to women with premature ovarian insufficiency (POI) interested for pregnancy. In order to improve fertility rate in POI patients our suggestions would be: (1) To decrease FSH value to 10–15 IU/L by increasing estrogen. Oocyte donation can be suggested after a minimum of six month interval from FSH between 10–15 IU/L and when no dominant follicles are found. (2) To perform oral glucose tolerance test (OGTT). Insulin sensitizing agents has to be included, when indicated, 3–6 month before pregnancy. (3) TSH has to be 1–2.5 mM/L during 3–6 months before pregnancy. (4) Tests for thrombophyllia (Leiden V, FII, MTHFR, PAI) have to be obligatory. They are less expensive than those repeated *in vitro* fertilizations. Therapy has to be included according to the indications. (5) In order to regulate disturbed immune response in POI patients with endometriosis oral contraceptive therapy is needed for atleast six months prior to the pregnancy. (5) Encourage the patients and advice them about healthy life style and eating habits. (6) Add other drugs, when they are indicated. Complex interplay between endocrine, immunological, haematological, and psychological factors are very often underdetected in POI patients. It is very important to find out the real time for oocyte donation after correcting all the disturbances, improving endometrium receptivity and reaching women's acceptable psychological status. Untreated disturbances induce cardiovascular diseases, diabetes mellitus, thyroid diseases, coagulopathioes etc.

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Introduction

Premature ovarian insufficiency (POI) is characterized by oligomenorrhoea for atleast 4 months, follicle stimulating hormone (FSH) above 40 IU/L, estradiol below 50 pmol/L in women younger than 40 years of age [1]. Fertility rate sharply decreases. Current guidelines advice oocyte donation to POI patients explaining that pregnancy with their own oocytes is almost impossible. Such an approach is highly dissapointing for the patients and some of them become depressive. Very often they insist on the trial with their own oocytes. So, can we offer them any other suggestions, increased endometrium receptivity and more empathized approach?

Pregnancy represents perfect biological test for woman's health. All disturbances during pregnancy can be diagnostic tool for prediction of diseases in the later stages of life.

Endometrial receptivity is the ability of the uterus to accept and develop a new embryo [2]. Two thirds of implantation failures can be explained by the lack of uterus receptivity [3]. During the luteal implantation phase, corresponding to cycle day 20–24, or 7–9 days postovulatory, endometrium is receptive to the oncoming blastocyst [4]. Morris et al. [5] found significantly more viable pregnancies occured among the patients with estradiol/progesterone in the range 7.36–12.22 (pM/L:nM/L) in midluteal phase.

In the menopausal women one year after the last menstruation about 1000 oocytes are still present in the ovaries. Some of them are of good quality but most are not. Successful rate of oocyte donation is not so high and *in vitro* fertilization (IVF) has to be repeated due to underdiagnosed endometrial endocrine, immunological and haematological disorders.

In a study of Letru-Konirsch H et al., endometrium was previously prepared with adequate dosages of estradiol and progesterone combined with pentoxifilline and tocopherol resulted in 30–50% pregnancies with fresh embryos and 15–25% with frozen thawed embryos [6]. Our study, performed on 350 infertile POI patients, showed 10% pregnancy rate in well prepared POI patients with their own oocytes [7].

Trying to understand POI patients, giving them realistic chances and discretely modifying the current point of view, we would like to emphasize on the crucial factors increasing fertility rate in POI patients and suggest a real cut off time for oocyte donation.

Estradiol

Low estradiol in POI induces many other disturbances. Conventional substituion of estradiol is not sufficient for inducing dominant follicle growth and adequate endometrial responsiveness. Estradiol actions are mediated via:

- Genomic pathway by nuclear receptors α and β;
- Non genomic more rapid like estrogen receptor (ER)α and G protein coupled ER1 (GPER).

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Estradiol receptor alfa promotes mitogenic activation and proliferation while ER beta protects endometrium from undesired action of ERalfa [8].

Estradiol down regulates FSH receptors and luteinizing hormone receptors (LH) [9]. It increases response of FSH and number of LH receptors previously induced by FSH. One of the important goal of estradiol therapy is to decrease the high endogenous FSH, which is ineffective in the stimulation of folliculogenesis, and possibly ameliorates the down regulation or desensitatation of diminished FSH receptors. Estradiol improves vascularization and endometrial flow, sensitizes and differentiates granulosa cells, stimulates endometrial proliferation, myometrium receptivity, production of the cervical mucus and directly influences an immune response. Estradiol receptors are expressed in various lymphoid tissue cells, lymphocytes, macrophages, and dendritic cells. It decreases activated T lymphocytes, improves autoimmunity, activates effector helper T lymphocytes and macrophages, facilitates the maturation of pathogenic autoreactive B cells [10]. Releasing of a few FSH receptors may diminish the autoimmune process and possibly lower the levels of autoantibodies.

In Taylor's study [11] 46% of the POI patients ovulate at least once during 12 months upon receiving appropriate estradiol therapy. The main principle of endocrinology is to replace insufficient hormones. In order to create optimal endocrine millieu for remaining follicle growth we suggested higher doses of estradiol trying to decrease FSH to 10–15 IU/L. Clinical experience and higher pregnancy rates allowed us to suggest the following: in a case that during 6 months no dominant follicles were obtained with day 2 FSH 10–15 IU/L the best solution would be oocyte donation. Well estrogenized brain of POI women allowed them to accept this solution even more having in mind that all other tissues are well prepared, esspecialy endometrium. In the untreated patients increasing FSH and low estradiol induces menopausal symptoms and sings with acute and chronic complications (cardiovascular diseases, higher mortality rate, osteoporosis, psychiatric disturbances etc).

Insulin

Uterine glucose metabolism plays an important role during implantation, embryo development, and pregnancy. Obesity and hyperinsulinism decrease implantation rate [12]. The regulation of glucose uptake in tissues and cells requires glucose transporters GLUT 4, regulated by androgen receptors and/or insulin receptors Akt/Tor signaling network.

When treating insulin resistance with metformin, energy metabolism in the cells is altered [13]. It lowers the glucose leves by inhibiting hepatic gluconeogenesis and opposing the actions of glucagon. The primary site of action for metformin is mitochondria [14]. The inhibition of mitochondrial complex I of the electron transport chain induces drop in energy charge, resulting in adenosin triphosphate (ATP) decrease, adenosin monophosphate (AMP) increases bounding P-site adenylat cyclase enzyme and inhibition of activity leading to defective cAMP protein kinase A (CAMPK) signaling on glucagon receptor. AMPK is energy sensor and a master coordinator of an integrated signaling network that comprises of metabolic growth pathways acting in synchrony to restore cellular energy balance. They switch on catabolic pathways that generate ATP and switch off anabolic pathways. Stimulation of 5'-AMP activated protein kinase confers to insulin sensitivity, mainly by modulating lipid metabolism. Metformin increases glucosae uptake in the skeletal muscles. It blocks insulin receptor/R/3K/Akt/mTOR signaling in the hiperplastic endometrial tissue inducing GLUT4 expression and inhibits AR expression [15].

Insulin resistance and hyperinsulinism induces obesity, increases androgen and plasminogen activator inhibitor and decreases glycodelin, insulin like growth factor binding protein 1 (IGFBP 1) and uterus vascularity decreasing endometrium receptivity (Table 1). Hyperinsulinism increases LH directly in the pituitary [16]. Metformin suppesses food intake by increasing levels of glucagon-like peptide 1, interaction with ghrelin and leptin on the hypothalamic levels [17]. It decreases PAI and proinflammatory cytokines by enhancing CD8 + T cell memory by altering fatty acid metabolism [18]. Insulin resistance with increasing LH in the menopause play role in adrenal tumorigenesis [19] showing us that early detection can protect from many diseases.

Having in mind important multiorgan effects of hyperinsulinism and specially, detrimental effects on endometrium receptivity we suggest that oral glucose tolarence test has to be routinely performed by 75 mg of glucose and glycemia, and insulin have to be detected in 0,30,60,90, 120 minutes. Area under the curve has to be calculated because HOMA index has a very limited value. Insulin resistance has to be treated with adequate dose of metformin at minimum 3–6 months prior to pregnancy and later, during pregnancy with proper dietary regimen in order to avoid miscarriages.

Untreated patients gain weight, develop metabolic syndrome and, during following few years, diabetes mellitus with all complications (retinopathy, neuropathy, nephropathy etc).

Embryo quality

Trypsin, a serin protease, is released by preimplanted embryos, elicit Ca 2^+ signaling in the endometrial epithelial cells. Competent human embryos trigger short-lived oscilatory Ca 2^+ fluxes inducing genes involved in implantaton and postimplantation development. Low-quality embryos cause a heightened and prolonged Ca 2^+ response. The decidualizing endometrium secretes serine protease inhibitors to limit embryo derived proteolytic activity. The acquisition of the secretory phenotype upon decidualization depends on the massive expansion of the estrogen receptors [20]. Optimal concentrations of estradiol and progesterone are crucial for early steps of embryo implantation and development.

Immunological parameters

Sexual steroids control the implantation process, a cascade of cytokines, growth factors, and adhesion molecules [21]. The progression of implantation and pregnancy require immunological tolerance which allows embryo survival. Hypoestrogenism in POI directly influences immune response. The large population of lympho-myeloid cells, found in endometrium, play variety of roles in the implantation process. Cell signaling pathways and specific proteins are involved in maturation, differentiation and functionality of the endometrium. Proteins expressed in luminal and glandular epithelia are: cadherins, beta-catenin, CD166/ALCAM, glycodelin A, leukemia inhibiting factor, stem cell factor and its receptor c-kit, epidermal growth factor (EGF), mucin 1, integrin alfaVbeta3, insulin like growth factor (IGF) etc.

Stromal protein changes, induced by cytokines, altering vascularization are: interleukin-6 (IL-6), interleukin 11 (IL-11), vascular

Table 1. Some effects of insulin resistance.

Increased	Decreased
Body mass index	Glycodelin
Androgens	Insulin like growth factor binding globulin 1
Plasminogen activator inhibitor	Uterine vascularity
Uterine vascular resistance	

endothelial growth factor (VEGF), transforming growth factor (TGF), CD 34, CD31/PCAM-1, CD44, matrix metalloproteinase proteins MMP and transcriptional regulators FOXO1, HOXA10 [22].

Biomarkers related to endometrium receptivity and implantation are: HLA-G, pinopodes (morphological markers of endometrial receptivity which persists for 24–48 h between days 19–21 of the cycle), integrins, L-selectin, heparin binding epidermal growth factor, chorionic gonadotropin, Notch 1, mucus, calcitonin, prostaglandins, HOX genes, insulin like growth factor-II (IGF-II), leukemia inhibiting factor (LIF), IL-6, interleukin 1 (IL-1), cadherin, cyclin Eap27, granulocyte colony stimulating factor 1, glucocorticoid-regulated kinase 1. It is secreted by the granulosa cells at ovulation and during the luteal phase. It may promote materno-fetal tolerance or influence oocytes own mRNA levels and its potential for selfrepairing [23,24]. According to the structural and functional abnormality cell adhesion molecules are devided into gropus: cadherins, mucins, selectins, integrins (the best marker of endometrial receptivity), and immunoglobulin superfamily [25].

IL-6 is a cytokine classically known to induce immunoglobulin production in the activated T cells and expriming paracrine-autocrine role during the periimplantation period. It is an essential cortico releasing hormone-independent stimulator of adrenal axis during immune system activation.

Selectins and mucins play a role in leading the blastocyst to a receptive endometrium while integrins and cadherins serve as adhesion molecules for nidation.

Pregnancy hormones suppress detrimental alloresponseveness while proofing tolerance pathway. This includes the reduction of the Ag-presenting capacity of the dendritic cells, monocytes, macrophages, as well as the blockage of natural killer (NK) cells, T and B cells [26].

Women with unexplained infertility have a lower levels of CD8 + T suppressor/cytotoxic and CD 56+ (NK) cells and higher levels of CD4+ (T helper/inducer) cells [27].

Natural killer cells (NK) secrete an array of cytokines important for an adequate local immunoregulation, angiogenesis, placental development, and pregnancy [28]. A proper balance between IL-12,IL-18,IL-15 and NK activation is required.

Endometrial glycodelin expression is an important predictor of pregnancy outcomes. Glycodelin is a major gycoprotein induced by progesteron and secreted from the secretory and decidual endometrium during the luteal phase [29]. It has apoptotic and antiproliferative effects on T lymphocytes and immunosuppresive and inhibiting effects on NK cells. Glycodelin A protects embryo from maternal immune system during imlantation. Glycodelin induces apoptosis of monocytes before their differentiation into macrophages through mitochondrial pathway without affecting fagocytic activity. Low glycodelin is associated with growth retardation of endometrium and early embryo loss, as well as reccurent pregnancy loss. Hyperinsulinism and insulin resistance lowers circulating glycodelin. Metformin therapy increases glycodelin threefolds during the luteal phase [30]. Insulin like growth factor binding globulin 1 influences endometrium receptivity, as well. It facilitates adhesion process at the fetal-maternal interface during the periimplantation period and metformin increase IGFBP1 [31].

Table 2. Some important pathological factors in endometriosis.

Increased	Decreased
Interleukin 6, Interleukin 8	Number of blastomeres per embryo
Tissue necrosis factor alfa	Glutathione
Atilaminin 1 antibodies	CYP19A1 in cumulus cells
Zona pellucida antibodies	All trans-retinoic acid synthesis
Beta-2-glicoprotein	mDNA copy numbers
Inositol	
Cardiolipin	
Ethanolamin	
Thyoredoxin- binding protein 2	
Arrested embryo	
Superoxide dismutase 1 in cumulus cells	

Endometriosis

Endometriosis is inherited, autoimmune and life-long disease. This, not completely etiologicaly discovered diseases, is still underdiagnosed and undertreated. Patients with endometriosis can have inherited POI at the same time or arteficial POI due to cystectomy. Special treatment of endometrial receptivity is neccesary in this group of patients prior to IVF. In order to achieve pregnancy pretreatment of endometriosis has to be from the time of diagnosis confirmation continuously until the time of ovulation induction. Treatment with gonadotropin releasing hormone agonists after cystectomy have very limited time restricted values which induce undesired consequencies with recidivant endometriosis after stoping it.

Negative immune impact is seen on the level of Fallopian tube, oocyte quality, sperm function, fertilization, endometrial receptivity, implantation, and placentation. Endometriois exhibits toxic effects on gametes and embryos. Endometrial implants secrete pro-inflammatory cytokines (IL-1beta, IL-8, IL-6, TNFalfa). Such an abnormal follicular environment with high cytokines levels impairs fertility and increases rate of apoptosis in granulosa cells. Peritoneal macrophages show enhanced ability to phagocyte sperm. Excessive production of autoanbibodies to the endometrium impaires implanation rate and endometrial receptivity [32,33] (Table 2).

Homeobox genes HOXA-10 and HOXA-11 have been linked to the endometrial receptivity. Taylor has observed thtat HOX gene expression was altered in endometriosis resulting in endometrial molecular alterations and decreased receptivity [12]. In experiments on mices mutation in these genes increased normal implatation rate [34].

Antinuclear antibodieas can be positive in women with endometriosis, but differential diagnosis has to be made with other diaseses (systemic lupus erythematodes, rheumatoid arthritis. Hashimoto etc).

Xu B [35] showed that oocytes from women with mild endometriosis exhibited abnormal mitochondrial structure and decreased mitochondrial mass. They found reduced mDNA copy numbers because of the disorder of cytoplasmatic mauration. Mitochondria are derived exclusively from oocytes, and their activity appears to be essential for oocyte maturation, chromosome segregation and a capacity of development [36]. Patients with endometriotic lesions grade I/II had more autoantibodieas than those with stage III-IV. Glutathione positively correlated with number of high quality embryos. Glutathione peroxidase 3 and thyoredoxin binding protein 2 negatively correlated with the percentage of mature oocytes. There may be an imbalance in the thyol-redox system and increased level of inflammatory cytokines in the intrafollicular microenvironments of infertile patients with endometriosis which may affect the embryp [37]. De Ziegler [38] have shown that assistant reproductive technique outcome

followed by 6 months of oral contraceptive therapy in women with endometriosis achieve the same outcome as that one in control group of women without endometriosis, what was vonfirmed in our study [7].

Giorgi [39] found positive effects of antioxidants, L-carnitine, N-acetyl cystein in preventing meiotic oocyte damage. Use of N acetyl cystein and L carnitine prevents the damages.

To achieve better quality of life, prevent cysts growth and preserve the fertlity rate endometriosis has to be treated throught the life with oral contraceptives in order to change negative immune responses. Our suggestion is that minimum 6 months of oral contraceptive therapy is needed prior to *in vitro* fertilization and embryo transfer.

Untreated endometriosis induces dysmenorrhea, decreasing quality of life. Endometroid cysts enlargement require surgery resulting in lower ovarian reserve with all consequences.

Thrombophillia

Familial thrombophillia (including factor V Leiden mutation, acquired activated protein C resistance, antiphospholipid antibodies sy and hypofibrinolysis) contributed to reccurent pregnancy loss [40]. Detection of Leiden V mutation, factor II, MTHFR, and PAI is necessary in a set of tests finding the etiology of infertility due to the endometrial responsivity disorders. A point mutation in factor V Leiden activates protein C resistance. Activated protein C resistance, atiphospholipid antibodies, and hypofibrinolysis contributed to the implantation failure and early pregnancy loss. Thrombosis of spiral arteries and intervillous space on the maternal side of the placenta can impair adequate placental perfusion [41]. Plasminogen activator inhibitor is a major inhibitor of fibrinolysis, produced by endothelium and decidualized the endometrium, promoting pregnancy loss. Glueck CJ [17] found that increased PAI 1 action resulted in placental bed thrombosis and uterine vascular insufficiency in 67% women with misscarigies. Insulin resistance further increases PAI decreasing pregnancy rate. Costs of these tests are uncomparably lower than the repeated unseccussfull IVFs, repeated pregnancy loss and, consequently, psychological disturbances of women.

Untreated thrombophillias and insulin resistance can induce thrombosis later in the life, even with fatal outcome.

Thyroid gland hormones

Thyroid hormones increase lipid metabolism, thermogenesis, and lypolitic activity due to the increased beta 2 adrenergic receptor expression and cAMP activated hormon sensitive lipase activity. TSH receptors, needed for ovulation and maturation, are present on the unmateruted oocytes [42]. Thyreoreleasing hromone (TRH) has direct effects on the ovaries, increasing prolactin and TSH. Higher estradiol levels after ovuation induction decreases thyroxin and increases TSH.

In the infertile women with hypothyroidism, GnRH secretion, and peripheral estradiol metabolism are disturbed, pulsatility of LH is abnormal, prolactin is increased and hemostasis is defective (factor VII, VIII, IX, XI). Decreased clearence of androstendion to estron, 5 alfa/beta androgen metabolits and binding of gonadal steroids to SHBG were found. On the same time free steroid fractions, excretion of 2-oxyestrogens and peripheral aromatization are increased [43].

In order to achieve pregnancy TSH levels between 1–2.5 mmol/L are adviced for minimum 3–6 months prior to fertilization.

Untreated thyroid diseases induce cardiovascular, neurological, psychiatric and other complications.

Other factors

Dehydroepiandrosteron (DHEA) is converted to estradiol, which suppresses FSH. It increases testosterone production by the very early follicles stimulating androgen receptors allowing more preantral follicles to progress to more mature antral follicles [44]. As well, follicle sensitivity to gonadotropins and endometrium receptivity are increased. Gleicher [45] found that DHEA improves ovarian function by reducing aneuploidy and over time improving ovarian reserve. Genazzani AR gave an overview of DHEA actions on whole women's body [46]. ASPIRIN significantly improves uterine and ovarian blood flow velocity, implantation and pregnancy rate [47]. Low dose aspirin inhibits the synthesis of prostacyclin, thus explaining the increase blood flow velocity. ARGININE, nitric oxyde donor, improves the uterine flow and estrogen receptors [48]. PENTOXILFYLINE, TOCOPHEROL- Trental influences intracellular AMP [49]. Vitamin E 1000 IU/day during 6 to 8 months, with other agents improve fertility rate. SILDENAFIL -Selective inhibitor 5-phosphodiesterase, enzyme included in cGMP hydrolization, increases vasodilatation by decreasing cGMP degradaton, increases endometrium receptivity and decreases natural killer (NK) cells activity [50]. Sher and Fish [51] suggested 25 mg every 6 h vaginal suppositories in the proliferative phase. INTRALIPID - Lipid emulsion suppress abnormal NK cytotoxic activity in peripheral NK cells (7–14 days prior to the embryo transfer, every day) and once monthly later 20 weeks. Intralipid 20% intravenously (9 mg/ml total blood volume) corresponds to 2 ml of intralipid 20% diluted in 250 ml saline [52]. NEUPOGEN 30, GRANULOCYTE COLONY STIMULATING FACTOR, SCRATCHING modulate expression of genes regulating vascular remodeling in the endometrium, regulates immune response and cell adhesion in the endometrium.MELATONIN has additional positive effects on endometrial receptivity.

POI registry, with world wide clinical experiences, will encourage new scientific ideas and findings in order to further improvrment of pregnancy rate in POI [53].

Conclusions

Complex interplay between endocrine, haematological, immunological, and psychological parameters need to be tested trying to find out complete etiology of infertility and endometrium status. Prior to any *in vitro* fertilization procedure it is obligatory to prepare patients and find the best time for oocyte donation representing is final last solution for achieving pregnancy in women with POI. Decreased endometrial receptivity and first trimester misscarriages represent prediction markers for diseases later in the life.

Disclosure statement

No potential conflict of interest was reported by the authors.

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