Ali Farid’s Updated Innovation in Women Reproduction

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ABSTRACT: In this review we introduced for the first time in literature FAMHS 2016 as a new marker for prediction of ovarian reserve which is a dimeric glycoprotein of 2 not identical amino acid φ and B- chain, have 2 types of receptors trans membrane heterometric protein and C-kit, and this lead to Farid New hypotheses with its impact on reproductive medicine. Platelet rich plasma (PRP) and leukocyte Platelet rich fibrin, and its uses in refractory repeated fetal loses, ICSI and during gynecological surgery.

In the field of Adenomyosis we introduced a new equation for Diagnosis and prognosis, in the treatment many lines of treatment rank from different types of IUD, Local drugs, Oral tablets, Auto thereby, direct injection in the uterus of Interferon, Pegasses, Bee Venom, Platelet rich Plasma (PRP), Visanne, Dichloacetic acid (DCA), Pigment epithelium Derived factor and mobile phone. Farid Intelligent Balloon by Its five types which is a new Modality in the treatment of infertility cases report related to all these invocations were presented.

All these lines of treatment passed phase I of investigation with no significant complications and excellent cost Benefit ratio and respect all Ethical guide lines.

1. FAMHS 2016

We discovered a new marker for prediction of ovarian reserve, it is not AMH, nor SCF [47, 52] it is FAMHS 2016, it is a dimeric glycoprotein a member of the transforming growth factor Beta super family has a relation to growth and differentiation.

1.1 Pharmacokinetics, Pharmacokinetics dynamics and Pharmacogenetics of FAMHS 2016

It is present (FAMHS 2016) in inactive form. It is a precursor for AMH, SGF the factor which control its production is not clearly known there may be autocrine and a paracrine mechanism. [85]. It is composed of 2 not Identical amino acid α-chain which is identical to AMH [51], with a M.W 140 KDa it is synthesized as a precursor of 560 amino acid containing a 25 amino acid leader and β-chain similar to SCF [19], with a 165 amino acid, and a MW 35 k Da. So the total M.W: 175 k Da which is the sum of AMH and SCF. [75]. bee venom can affect this compound and release one or two of it's component (AMH Like, SGF like) [2-6]. During the proteolytic process release of AMH causing down regulation of SGF and decrease of SGF causes up regulation of AMH (Figure 3), [85]. Combination of SGF + PBMNC SGF + Bee venom a new modality of ovarian failure treatment [2-6]. Gene location is on the short arm of chromosome 19 (closed to the gene of AMH, it is not located on the x or y chromosome. [34, 29, 71 and 85].

Amino acid of the gene: 701 amino acid which is identical to both amino acid of AMH and SCF, it is a unique gene. [81]. Two types of FAMHS 2016 RECEPTORS: [44], the first one Trans membrane hetero metric protein similar to that of AMH. And the second C-kit receptor [38], which is similar to that of SCF; has a multifold signaling components [50, 53, 63 and 65].

Gene encoding the receptors located on chromosome (12), gene of the receptor composed of 2 45 amino acid. Our new factor is produced as precursor protein which lead to final growth factor by proteolytic processing. [79, 80]. The following technique used for gene and receptors detection of FAMHS 2016: protein sequence analysis and oligonucleotide probe syntheses, preparation and screening of the CDNA library, Screening of the cosmid libraries DNA sequencing, RNA analysis (Northern Analysis, S1 analysis, Genomic southern analysis) Cloning of FAMHS 2016) Gene Fluorescence in situ hybridization, Reverse transcription polymerase chain Reaction, immunohistochemistry,
enzyme linked immunosorbent Assay (ELISA) and Immunoblotting. [10, 21, 29, 34, 44 and 51].

2. FARID NEW HYPOTHESES

A new hypothesis was put after we discovered FAMHS 2016: That this big molecule encode both AMH and SCF and these 2 factors connected together by disulfide bridges this was proved by mass spectrometric analysis according to surface – Enhanced laser adsorption/Ionization time of flight mass spectrometry (SELDI-TOFMS the analysis of date was performed using a genetic algorithm (clin protocol S1.0 software MALDI-TOF MS Based (Figure 2) [1, 10, 54 and 70].

![Figure 1 Chemical structure of FAMHS 2016](image)

![Figure 2](image)

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Figure 3: Proteolytic process of AMH 2016

Figure 4: Inverse relation between AMH, SGF

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This means that there is inverse relation between AMH, SGF (Figure 4). This hypothesis will open a new era in reproductive Medicine, in the treatment aging ovary, ovarian failure and Poor ovarian response, in IVF failure, and in the relation between inflammation and poor ovarian function (Figure 5) [20]. It will open and solve the problem of the Assay of AMH which Lead to gene II assay [81]. Open a new ear in the treatment of endometriosis (in which there is increased AMH and AMHR II mm RNA [54]. Lastly it will open a new line of treatment of pre term labor acting on inhibition of SGF/C-Kit pathway lead to significant decrease of histamine level.

2.1 Platelet-rich plasma (PRP)

Platelet-rich plasma (Abbreviation: PRP) is blood plasma that has been enriched with platelets. As a concentrated source of autologous platelets, PRP contains (and releases through degranulation) several different growth factors and other cytokines [28].

PRP was first developed in the 1970s PRP therapy began gaining popularity in the mid-1990s [87].

We recorded her a case report of spontaneous ovulation and pregnancy in 48 old female with AMH< 10.001 and six time failure of IVF treated by intraovarian and subcutaneous bee venom injection.

Figure 5 Relation between inflammation and poor ovarian function

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2.2 Pharmacokinetics and dynamics of (PRP)

The efficacy of certain growth factors in healing various injuries and the concentrations of these growth factors found within PRP are the theoretical basis for the use of PRP in tissue repair. The platelets collected in PRP are activated by the addition of thrombin and calcium chloride, which induces the release of the mentioned factors from alpha granules. The growth factors and other cytokines present in PRP include: Transforming growth factor beta, Fibroblast growth factor, Insulin-like growth factor 1, Insulin-like growth factor 2, vascular endothelial growth factor, epidermal growth factor, Interleukin 8, Keratinocyte growth factor, and Connective tissue growth factor [22, 60].

There are, at present, two methods of PRP preparation approved by the U.S. Food and Drug Administration. Both processes involve the collection of the patient's whole blood citrate dextrose) before undergoing two stages of centrifugation (TruPRP) (Harvest) designed to separate the PRP aliquot from platelet-poor plasma and red blood cell. Therapeutic PRP concentrates the platelets by roughly five-fold [39].

There is no report in the literature dealt with the use of PRP & Leucocyte and platelet rich fibrin) in the field of obstetrics and gynecology we succeeded to treat 5 cases with ovarian failure after laparoscopic ovarian drilling, 6 cases of ovarian endometriosis, 4 cases of uterine Adenomyosis by PRP with satisfactory result the technique was ultrasound direct injection of PPR through the ovaries and uterus. We used this Line of treatment in 10 patients to stimulate the process of healing during myomectomy. There is no complications recorded in this line of treatment and the cost benefit ratio was excellent [10, 33]. Also In a case report of repeated first trimester loses (18 times) with continuation of pregnancy and in repeated failure of ICSI 15 times by direct injection in the uterus at the time of ovum pick up [10].

2.2 Upt Dated in Adenomyosis (Diagnosis and Treatment)

**Diagnosis**

We introduced a new equation for diagnosis depending on (VEGF, x mirco RNA x Cancer antigen 125 (CA125)). Weight of the uterus had a high sensitivity and specificity for diagnosis and prognosis more then (one) (1) give the diagnosis and prognosis [10].

**Treatment of adenomyosis**

IUD Cupper silver Nickle, Propolis IUD, Bee venom IUD [8, 9] and GNRH IUD [10].

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Local

Vaginal valporic acid [56, 58], combined valporic + trichostatin, Vaginal statin, Vaginal propolis, Intrauterine amnion, and Vaginal curcumin [9, 10].

Oral

Demethylation agent [57], Curcumin, Propolis, Statin, TNF-alpha inhibitor, Matrix metalloproteinase inhibitor, Spirulina platens, Purslane, Soybean, DDB, DDB + statin [9, 10]. Cabergoline, Bromocriptine [36], and Metformin [68].

Auto therapy


Direct injection in the uterus by Interferon, Pegasus, Bee venom, Platelet rich Plasma (PRP), Visanne Ointment, Dichloroacetic acid (DCA) Through Laparoscopy, Hysteroscopy and Ultrasound-guided [10].

Pigment epithelium Derived Factor (PEDF)

PEDF is a multifunctional protein with antiangiogenic antitumornigenic, antioxidant, anti-inflammatory antithrombotic, and neuroprotective properties, it is the most potent inhibitor of stem/progenitor cell associated neovascularization [10]. We introduced for the first fine in literature the use of PEDF in endometriosis, fibroid, ovarian hyper stimulation syndrome and in adenomyosis [15].

Mobile Phone

Pharmacokinetics and dynamics of all previous Modalities

Inactivation and reduction of antigenic gene expression inhibits growth and decreasing the size of endometritis lesions [36], inhibition of adenomyotic stromal cell proliferation, increase in AMP protein kinase activation, apoptosis of ectopic endometrial cells by activating caspase – 3 Expression, direct effect on adenomyosis. Downregulation of Estrogen receptors, Reduction of prostaglandin, Production within endometrium and myometrium, reducing pain, decrease in uterine volume and increase in blood & flow resistance), Inducing apoptosis and reduce aromatase expression extra ordinary aromatase
activity is noted in uterine adephynosis [25]. So there is improvement in adenomyosis symptoms (pain, pressure effect, hypermenorrhea), high selectivity for binding to progesterone receptors, inhibitory effect on certain cytokines, direct inhibition of cellular proliferation stimulation of apoptosis, bind to dopamine receptors 2 VEG FR2 inactivation, reduction of micro RNA, significant increase in AMP – Protein kinase activation (similar to Metformin), Direct effect on adenomyosis foci, Interrupts pulsatile LH secretion, prevent dysperistalism and oxytocin receptor over expression which increased in Adenomyosis [62]. Stimulation of uterine endometrium adult stem cells which exhibit functional pluripotent potential in the direction of treating adenomyosis [67] and affection of mitochondrial membrane potential. adenomyosis is an epigenetic disease (hypermethylation) act as Demethylation agent increase PR – B gene, protein. Reduce estrogen receptors isoform which increase in adenomyosis [61] and reduced Gap junction proteins [15].

3. FARID INTELLIGENT BALLOON: A NEW MODALITY IN REPRODUCTIVE MEDICINE [10]

3.1 The need for Farid intelligent balloon catheter

We come across the difficulty of delivery of a new drug to its target action, that it would be unstable, non-soluble in ordinary delivery technique could not cross a cellular or tissue barrier, hence we introduce the balloon covered by a drug which we can used by its direct effect, not through its systemic effect. Also, to reduce the dose, and the toxicity of the drug used. The way we introduced the drug can be used by other roots except the balloon, so the balloon act as a vehicle to a drug to come in direct contact to the cells.

3.2 Types

It is classified according to the material which used and covered the balloon into the following types [15]:
Type I: Completely covered by Bee venom ointment.
Type II: Completely covered by Bee propels ointment.
Type III: Completely covered by magnetic material.
Type IV: Completely covered by visanne ointment.
Type V: Mixed type (mix one of previous material in a single balloon.)
3.3 **Usage**
According to indication [15].

**Description**

It is a 2 ends branched silicon catheter and has two lumens with inflatable balloon at the upper end of the two lumens. One of the two lumens is big in size for drainage, the outer is small for balloon inflation and is connected to one way valve to allow injection of fluid to inflate the balloon and prevent flow back, the material is latex silicon coated surface or completely silicon. It is sterilized by ethylene oxide and stored at room controlled temperature and designed for single use and should be stored in a dark place. Length 56-60 cm according to the length of uterus. Ensure that the bladder is empty. Cleanse the cervix and vagina with antiseptic solution. The procedure must be carried under complete aseptic condition, duration of the balloon (silicon type) range from 30 minutes to 3 weeks according to the indication of usage.

The balloon should be inflated with sterile liquid such as sterile water, sterile saline or lactated ringer solution; the balloon should never be inflated with any gas. The amount
inflated is variable depending upon indication and size of uterine volume. Excessive force should be avoided when inserting the balloon into the uterus.

Method of application
- Trans-vaginal placement.
- Trans-abdominal placement during any operation when the uterus is opened

Pharmacokinetics and dynamics and pharmacogenetics

By its tamponade effect can affect the genetic nature of the cell. It affect protein connexin which connect the cell together, strong progestational effect, Moderate antigonadotrophic effects [7, 15], no androgenic, glucocorticoid, mineralocorticoid activity. Inhibit protein kinase activity, suppressing cyclin digene expression normalize natural killer cell activity [48]. It has CD 147 like action which had apoptosis [69]. It attenuates nuclear factor KB activation, cyclooxygenase 2 expression and prostaglandin E2 [49], Micro RNA expression and their relation to angiogenic factors miRNAs (miR-156, -16, -17 -5p, -209, 21, 125a 221, 222, vascular endothelial growth factor A thrombospondin I, miR-17-92- miR-17-5P) moreover reduced microvascular density [59, 82], trapping of reactive diacarbonyl compound (methyl glycoxol MGO, glyoxal (GO) which causes production of advanced glycation end products (AGEs) [35], inhibition of macrophage migration inhibitory factor (MIF) [83], Acton ephrin A, B system [43], Stimulation of histone deacetylase inhibitors (Yuki Kawano et al., 2011), It inhibit hypoxia mediated activation of ErK/2 and Akt resulting in decrease expression of hypoxia inducible factor -1a (Michael Morcos and Xueliang Du, 2008), Reduce the activity of matrix metalloproteinase 2 and 9 [66]. Affection of mitochondrial biomarkers by using surface enhanced laser desorption / ionization time of light mass spectrometry [86]. Correction of mitochondrial displacement D-loop, it is known that there is association of mitochondrial displacement D-loop alteration and endometriosis [78]. Increasing expression of glyoxalase 1-reduces ROS production and increases life span, Reduced advanced glycation end products. Reduction of methyl glyoxal which has injurious effects on maturation of oocytes fertilization, fetal development via apoptosis [84]. Antitumor, antioxidant antibacterial, antiviral, antifungal and anti-inflammatory activities [66], Affection of telomerase and telomere length [42], Stimulation of pigment epithelium derived factor (PEDF) that possesses a potent antiangiogenic activity [31], Induce apoptosis and G0/G1 cell cycle arrest [48, 66]. It has antithrombotic, antihuman immunodeficiency virus activities [76], Suppression of the polo like kinase /activity [66], inhibits certain enzyme activities such lipoxygenases cyclooxygenase, glutathione S

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transferase, xanthine oxidase [30]. It affects the inner portion of the myometrium or the junctional zone (JZ). An altered JZ has also been found in women with endometriosis and adenomyosis, its role on the eutopic endometrium in adenomyosis and endometriosis (immunodysfunction) and there are alternation of adhesion molecules, cell proliferation and apoptosis, an increase in cytokines and inflammatory mediators, presence of oxidative stress and anomalies in free-radical metabolism, alternation in uterine receptivity and a role for the epigenetic mechanism [26]. It affects nuclear receptor and co-regulators of nuclear receptor (NR). SRC-1 is a major co-regulators involved in endometriosis and 70 KD isoform of SRC-1. Selective inhibition of SRC-1 can be used in the treatment of endometriosis, collectively. The NR/NR co-regulator functional axis plays a critical role in the pathogenesis and hence discovery of new treatment for nuclear receptor [41]. It affects kisspeptin-GNRH pathway [77]. It affects endocannabinoids (eCBs) and anandamide (AEA) which is important for fertility (Rapino et al., 2014). It affects ion channels in the endometrium which regulate endometrial receptivity and embryo implantation. Till now more than 14 types of ion channels had been expressed in the endometrium or cells of endometrial origin [74]. It affects water channels aquaporins (AQPs). The interplay between AQPs and other ion channels is important for regulating uterine luminal fluid volume [45]. It stimulates galactin and galactin -1 [24].

Contraindications
1. If there is allergy to any component of the device.
2. Purulent infection of the vagina, cervix or uterus.

Supposed clinical application:
• Asherman's syndrome, endometriosis, Adenomyosis, endometrial receptivity, fibroid, uterine arteriovenous aberration, intrauterine adhesions, increase success rate after IVF.
• By this intelligent balloon we introduced a new item in the treatment called the

Treatment at distance
The author carrying now clinical trials of all previous indications with a very promising result.

Complications
Till now, no report of any complication to the patients used this innovation.

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Cost benefit ratio
A very satisfactory cost benefit ratio of this innovation. (Successful IVF after 21 failure Treated by Farid Intillegent Balloon type 2)

Introduction
Uterine arteriovenous malformation are rare with an unknown incidence in the medical literature. Till now about 120 cases were recorded. The first case was reported 1926 by dubreuil uterine arteriovenous malformation is abnormal connection between arteries and veins> we introduced anew more descriptive name which was arteriovenous aberration [18]. It may be congenital or acquired traumatic it may be asymptomatic or represented by severe vaginal bleeding [73]. A report in medical literature dealt with this condition as a cause of idiopathic IVF failure. We represented here a case of 21 times IVF failure treated by Farid balloon catheter type 2 and ending by delivery of living male 3.5 kg.

Subject and method
41 years old female with unexplained infertility subjected to 21 trial of failed IVF in different centers was subjected to gray scale and colored Doppler ultrasound, MRI, CT and radiographic angiography we come to final diagnosis of congenital uterine arteriovenous malformation treated by Farid balloon type2 left for 10 days and removed before embryo transfer.

Result
Complete resolution of uterine arteriovenous malformation and delivery of a living male fetus 3.5 kg.

Discussion
This is the first reported case in the medical literature of uterine arteriovenous malformation as a cause of failed IVF, again this is the first case in the medical literature that used Farid intelligent balloon in the treatment of this condition the previous medical treatment of this condition rank from methylergonovein maliate,15 methyl prostaglandin f2alpha,estrogene and progesterone, oral contraceptive pill, GnRH agonist and danazol [73] laparoscopy had a place using bipolar coagulation and interferon [18], uterine artery

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immobilization all these measures used when preservation of fertility was needed but when was not needed hysterectomy is the standard treatment so in conclusion uterine arteriovenous malformation should be searched for any case of idiopathic repeated failure of IVF Farid intelligent balloon type 2 is a noval treatment of this condition.

4. CONCLUSION

We introduced the following innovations FAMH S2016, Platelet–rich plasma, updatated in Adenomyosis (Diagnosis and Treatment) and FARID Intelligent Balloon together with a case report related to each previous topic, definitely all these innovation help to improve fetomaternal welfares and health.

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