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REVIEW ARTICLE

UPDATED INNOVATION IN INFERTILITY

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Peripheral blood mononuclear cells,
Yeast betaglycan, Dineogest, CD 147.

ABSTRACT

In this review we introduced for the first time in literature a new drug FSLYM 192050, patent No. 698/2014). A new method for treatment of infertility (Glyoxalase – 1 loaded Bee venom nano particles targeted with a follicle stimulating hormone peptide as a new modality in the treatment of female and male infertility). A new (name, theories, treatment) for old problem (intravenous leiomyomatosis) again we introduced Bee venom Bee propolis, Zamzam Water, Eye Tears, and EPREX, in the treatment of many reproductive aberration and updated treatment of endometriosis (NANO GOLD, NANO SILVER, Peripheral blood mononuclear cells, Yeast betaglycan, and anti CD 147 Anew mechanism of action of Dineogest) all these innovations help to improve a fetomaternal health and well being and will cause a revolution in the field of treatment of infertility.

INTRODUCTION

(1) FSLYM 192050

Patent No 698/2014
A New Substance prepared in the laboratory using multiple biochemical reactions include:
* cell culture and cytotoxicity assay, DNA fragmentation for detection of cell apoptosis flow cytometry, stable free radical scavenging capacity cell culture, RT- PCR, Zymography, flouorometric assay, cell invasion and motility assay, NHR spectral evidence, HPLC analysis and LC/ESI – MS Method.

Pharmacokinetic properties

- **Absorption and distribution**

  Fully absorbed after oral administration, Oral bioavaibility being 95%, Absorption is rapid, Compared with the fasting state a high fat meal did not markedly alter the bioavaibality of oral dose, 95% bound to albumin in plasma apparent volume of distribution is 45L.

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- **Metabolism and elimination**

  Fully metabolized by hydroxylation, Cytochrome P450 (CYP) 3 A4 is the major enzyme involved in metabolism, Metabolites are rapidly cleaved from the plasma, Terminal elimination half life of single or multiple dose is 10 hours, Metabolic clearance rate from serum is 64 ml/min, The main route of excretion is urine, Bulk of metabolites elimination is the first 24 hours, Half life of excretion of urinary metabolites is 14 hours, 63% → eliminated in urine, 23% → in feces.

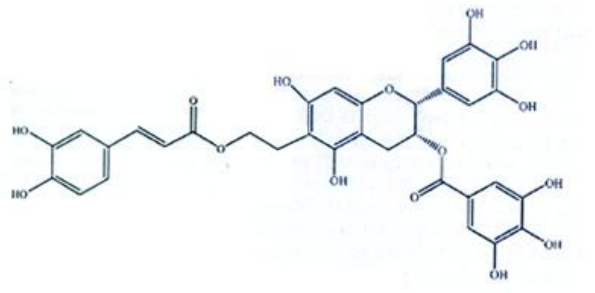
- **Drug interaction**

Not excreted in milk, No drug interaction, No effect with renal or hepatic impairment.

- **Contraindication :** No contraindication
- **Cost:** Excellent cost benefit ratio.
- **DOSE:** 45 mg/kg/over 8 weeks.

Pharmacodynamic properties

Moderate affinity for human progesterone receptors (invitro), Highly selective for progesterone receptor, Antagonistic activity on androgen receptor, Neither agonist nor antagonist activity on glucocorticoid or mineralocorticoid receptors, Does not activate estrogen receptors (α, β)



Chemical structure ofFSLYM192050

In vivo

Strong progestational effect, Moderate antigonadotrophic effects, No androgenic, glucocorticoid, mineralocorticoid activity, Inhibit rises in serum estradiol by inhibiting the development of ovarian follicles, It is moderately suppresses serum estradiol levels and affection of endometrial wave 15, Dose dependent activity, Inhibit protein kinase activity (Jian-Xin Chen, *et al.,* 2009), Suppressing cyclin digene expression (Jian-Xin Chen, *et al.,* 2009), Normalize natural killer cell activity(Jian-Xin Chen, *et al.,* 2009), No effect on bone mineral activity, after 6 months: no effect on liver, lipid, carbohydrate metabolism (Jian-Xin Chen, *et al.,* 2009), Delay in oocyte aging in mice (Jinmiao Liu *et al.,* 2012) (Evanthia Diamanti *et al.,* 2007) (Carla Tatone *et al.,* 2008) (Ying- Jing Chang *et al.,* 2010), It this inter leukin had a myolysis effect, CD 147 which had Apoptosis (Pietro Sanulli *et al.,* 2013), It attenuates nuclear factor KB activation, cyclooxygenase 2 expression and prostaglandin E2 (Jing-Jing Zhang *et al.,* 2011), 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 (Luis A. Ramon *et al.,* 2011) (Wakana Abe *et al.,* 2013), Trapping of reactive diacarbonyl compound (methyl glycoxol MGO, glyoxal (GO) which causes production of advanced glycation end products (AGEs) (ExanthiaDiamanti-Kandarakis- Christina Pipri istratiosPaatsonuris, 2007), Inhibition of macrophage migration inhibitory factor (MIF) (Warren *et al.,* 2011), Acton ephrin A, B system (HarukoFujii *et al.,* 2011), Stimulation of histone deacetylase inhibitors (Yuki Kawano *et al.,* 2011), It inhibit hypoxia mediated actvation 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, 9. (Nishida *et al.,* 2006), Affection of mitochondrial biomarkers by using surface enhanced laser desorption / ionization time of light mass spectrometry (Xinoyon Ding *et al.,* 2012), Affection of iron storage in peritoneal macrophages it is known that iron storage is increased in the peritoneal macrophages in patients with endometriosis and correlates with iron over load in peritoneal fluid and serum (Jean- ChirstopheLousse *et al.,* 2009), Correction of mitochondrial displacement D-loop, it is known that there is association of mitochondrial displacement D-loop alteration and endometriosis (Suresh Govatati *et al.,* 2013), Increasing expression of glyoxalase 1-reduces ROS production and increases life span (Xiaofang Peng *et al.,* 2011), Reduced advanced glycation end products (Xiaofang Peng *et al.,* 2011) (Evanthia Diamanti-Kandarakis and Ilias Katsikist 2008), Reduction of methyl glyoxal which has injurious effects on maturation of oocytes fertilization, fetal development via apoptosis (Xiaofang Peng *et al.,* 2011), Anticancer cell metastasis by down regulation of matrix metalloproteinase expression (Jing-Jing Zhang *et al.,* 2011) (Jian-Xin Chen *et al.,* 2009), Antitumor, antioxidant antibacterial, antiviral, antifungal and anti-inflammatory activities (Nishida *et al.,* 2006), Affection of telomerase and telomere length (Hapangama *et al.,* 2008), Stimulation of pigment epithelium derived factor (PEDF) which is a 50 kDa secreted glycoprotein that possesses a potent antiangiogenic activity (Dana Chderland *et al.,* 2013), Induce apoptosis and G0/G1 cell cycle arrest (Nishida *et al.,* 2006) (Jian-Xin Chen *et al.,* 2009), It is considered as apoptosis inducing agent (Nishida *et al.,* 2006), suppressing antiapoptotic proteins (Nishida *et al.,* 2006), It has antithrombotic, antihuman immunodeficiency virus activities (Seerin *et al.,* 2006), Suppression of the polo like kinase / activity (Nishida *et al.,* 2006), Suppression of mitochondrial tumour necrosis factor receptor associated protein expression (Carla Tatone *et al.,* 2008), Activation of MAP kinases (Carla Tatone *et al.,* 2008), Inhibits certain enzyme activities such lipoxygenases cycloxygenase, glutathione S transferase, xanthine oxidase (Carla Tatone *et al.,* 2008).

Supposed Therapeutic Indications

Endometriosis, Fibroid, PCO, Failed IVF, Premature ovarian failure, Improve endometrial receptivity, Poor ovarian response, Improved endometrial thickness, It can be used in the field of medicine and surgery industrial, agriculture and nano technology

Glyoxalase-1 loaded Bee venom nano particles targeted with a follicle stimulating hormone peptide as a new modality in the treatment of female and male infertility

We come across the difficulty of delivery of a new drug to it's target action that it would be unstable, non soluble. In ordinary delivery technique, could not cross a cellular or tissue barrier, hence the nano particles for drug delivery which are sub microscopic particles with dimensions in the range of 100-300 nm. By encapsulating drug in a polymer, the stability, permeability, bio distribution small circulation time of therapeutics can be changed (Borgmann *et al.,* 2011) via signaling molecules or ligands that are bound to the surface nano particles targeting to specific or cell types occurred. (Mahfouz *et al.,* 2010). Decreased glyoxalase-1 activity causes increased methylglyoxal (MG) which modifies proteins resulting in increase Mitochondrial ROS production increased ROS levels would further inhibit glyoxalase-1 and ultimately limit life span (Evanthia Diamanti *et al.,* 2008), (Micheal Noros *et al.,*)increased serum advanced glycation product (AGES) which demonstrated in PCO, and endometriosis this (AGES) lead to decreased glyoxalase-1 activity which increased methylglyoxal (MG).

In female infertility especially in old age and poor responder and (Evanthia Diamanti *et al.,* 2008), (Micheal Noros *et al.,* 2010), (Reddy and Labhasetwar, 2009), (Reddy *et al.,* 2008)in male infertility elevation reactive oxygen species have been found which correlated with decreased sperm motility, increased

(Aitken *et al.,* 1988) damage cell membrane peroxidation, DNA frag mention lose of fusion with oocyte. in female it correlated with poor response, congenital malformation, (chromosomal, DNA fragmentation and in fertility, Hence come delivery of Antioxidant (naturally occurring) Glyoxalse-1 which prevents mitochondrial protein modification and enhance life span this enzyme detoxifying methylglyoxal-1 (MG) increasing expression of glyoxalsase-1 reduce reactive oxygen species (ROS) and increase life span.

Nano particles were formulated with the use of a multiple emulsion solvent evaporation technique which have been described previously (Reddy and Labhasetwar, 2009)100 mg bee venom and 5 mg DMT with 50 reg dye (coumin 6) (Reddy *et al.,* 2008) were dissolved in 1 ml chloroform. The dye was incorpoerated (Aitken *et al.,* 1988), (Segretain *et al.,* 2010) into nonoparticles as a fluorescence markers to analyze nonoparticle cellular uptake, nanoparticles were conjugated by a two step epoxy method. Glyoxalase-1 activity was measured with the use of glyoxalase-1 assay kit. The analysis of glyoxalase-1 release from the nanoparticles as described (Jain, 2001; Hu *et al.,* 2012) previously. We used both mouse sertoli cell line and mouse ovarian cell line.

The protective effect of glyoxalase-1(Sahoo and Labhasetwar, 2005) loaded bee venom nanoparticle was tested after inducing oxidative stress in culture. The innovation in this method which differ from previous method lies in (Borgmann *et al.,* 2011) uses of Bee venom as a nano particles which is the first time to find nano particle to augment the action of FSH (Mahfouz *et al.,* 2010) . The use glyoxlase-1 loaded biodegradable nano particles so this method can be used in female who have poor responder, old age, and to improve fertilization in those who have elevated reactive oxygen species and infertility and sub fertility PCO, endometriosis, unexplained infertility. In male: to protect stertoli cells from oxidative stress, and to salvage testicular cells after torsion. Based on these data many enzyme can be used which regulate the oxidative stress like: superoxide dismutase, histone decacetylase inhibitors, pyrrolidine dithiocarbonate which attenuate Nuclear factor K-B. (Heneweer *et al.,* 2011; Zhang *et al.,* 2012; Wu and Yotnda, 2011) Devonc- Snow - Lisy *et al.* (2014)

BEE Venom

Due to it's unique composition Bee venom used in the treatment of many diseases but what is a new is it's place in infertility (Franklin and Baer, 1975; Gauldie *et al.,* 1978; Habermann and Reiz, 1965). For the first time in the literature we introduced bee venom in gynecology and obstetrics.

In Gynecology

Treatment of PCO (Ali *et al.,* 2000), Fibroid Uterus (Ali *et al.,* 2000) Endometrios is (Ali *et al.,* 1998), induction of ovulation, we can separate bee venom gonadotrophin (All *et al.,* 1999) with a pregnancy rate more than human menopausal gonadtrophin, in the treatment of adenomyosis bee venom used as Phytoestrogen (Ali, 2000), to correct Leukemia (Ali, 1999) inhhitory factor LIF, in Idiopathic Repeated. Abortion, unexpelained (Ali, 1998), (All *et al.,* 1999), (Ali *et al.,* 1999), (Ali, 1999) recurrent spontaneous abortion treatment of premature ovarian failure, correction of$_1$, (high) FSH (Ali, 1999), bee venom improves ovarian responsiveness, uterine and ovarian blood flow, velocity, implantation and pregnancy rate in patient undergoing treatment of invitro fertilization (Ali, 2000),(Ali, 2000), proximal tubal obstruction. (Ali, 1999) Postoperative: To prevent adhesion formation (Ali *et al.,* 2000) and reformation, to treat and prevention of keloid formation (Ali, 2000). In Pelvic inflammatory disease, in the treatment of cervical sperm antibodies. (Ali, 2000) Induction of ovulation in old age, and to increase pregnancy rate after artificial insemination and in Poor responders (All *et al.,* 1999)

In gynaecological oncology

Treatment of human papilloma virus (Ali, 2000). Recurrent human papilloma (Ali, 2000) virus, treatment of CINI, II, III, Endometrial carcinoma (Nishida *et al.,* 2006), (Pietro Sanulli *et al.,* 2013) delivery after conservative treatment of endometrial carcinoma (Ali, 1999), (Ali and Ali, 2000).

In Contraception

IUD loaded with bee venom (Ali, 2000) Bee venom ointment as a local contraception the decisive factor is the dose between conception and contraception. (Franklin and Baer, 1975), (Gauldie *et al.,* 1978) Role of bee venom and Micro RNA and it's impaction on reproduction (ovarian function, implantation, gynecological re productive diseases, spermatogenesis (Franklin and Baer, 1975; Gauldie *et al.,* 1978; Habermann and Reiz 1965; All *et al.,* 1999)

In obstetrics (Ali *et al.,* 1998)

Anti Phospholipid syndrome. (Ali *et al.,* 1998) Idiopathic abortion;

Components of bee venom and their major characteristics (Habermann and Reiz, 1965)

Components	Mw	Contents (%Dry BV)	Major characteristics
Peptide melittin	2840	40-50	26 amino acid Enhance of PLA_2 activity Cytotoxic effects against cancer cells Anti-inflammatory and anti-arthritic effects
Apamin	2036	2-3	10 amino acid Inhibitgion of Ca^{2+} activated K^+ channel Cytotoxic effect against cancer Nociceptive effect Anti- inflammatory properties
MCD peptide	2588	2-3	22 Amino acid anti-inflammatory and analgenic effect Histamine release (low dose) histamine release inhibition (hig dose) anti- allergic effect
Adolapin	11.500	1	Inhibition of PLA_2 and COX activity Anti-inflammatory activity Analgesic effect
Protease inhibitor	9000	<0.8	

(Ali *et al.,* 1998) immunologic abortion, in the treatment of eclampatic fit and it's comparison with magnesium (Ali *et al.,* 2000) sulfate and Diazepam, to (Ali and Ali, 1999) stimulate lung maturity, Idiopathic Intra uterine growth retardation, to arrest preterm labour. (Songhee, 2007), (James Olcese, 2014)
To enhances human embryonic stem cell differentiation. To Germ like cell differentiation (Ali, 2011)

Method of intake: in obstetrics and gynecology: intradermal, local, ultrasound guided, laparascopically guided, intraamniotic (Chung *et al.,* 2004)

BEE Propolis

Due to it's biological properties which are antioxidant anti abnormal enzymatic activities, (lipoxygenases, cyclooxygenase, glutathione S-transferase and xanthine oxidase (Koshihara *et al.,* 1984; Michaluart *et al.,* 1999; Chan *et al.,* 1995) anti-inflammatory properties (Michaluart *et al.,* 1999; Chung *et al.,* 2004) apoptosis inducible functions (Wang *et al.,* 2005) , anti HIV replication (Kashiwada *et al.,* 1995; Fesen *et al.,* 1993), antimetastatic (Liao *et al.,* 2003). Anti MMP-2 and MMP-9. Anti Tumor, Anti Bacterial and Anti vascular (Chung *et al.,* 2004).

In gynecology

In the treatment of PCO, endometriosis, fibroid uterus, poor responder. To prevent formation and reformation of pelvic adhesions, keloid formation, Pelvic inflammatory disease, ovarian hyper stimulation syndrome. (Nishida *et al.,* 2006) ovarian failure (natural and chemical induced), To Increase the pregnancy rate after artificial insemination, in cervical spern antibodies. Asherman syndrome, intravenous leiomyomatosis. (Ali, 2012)

In Contraception: 1. Local (ointment, Pessary).
2.IUD loaded with bee propolis

In Gynaecoogical Oncology The same as bee venom (Ali, 2012)

In obstetrics Repeated abortion, Septic shock syndrome, Anti phospholipids syndrome, Any infection in obstetrics, (Ali, 2012)

Method of intake

Local, (oral syrup, tablet), direct ultrasound guided, direct laparoscopically guided. (Ali, 2012)

Zamzam water

Zamzam water well is located in the holiest mosque of the Muslims in the city of Makkah which is in the western province of the Kingdom of Saudi Arabic. The well is four thousand years old, millions of Muslims drink this water as sacred water especially during pilgrimage and Umrah each year. Zamzam water is unique in its natural characteristics (Ali, 2012), a total 34 elements have been found with calcium magnesium. Sodium and chloride, fluorides in the highest concentrations. Zamzam water has special optical parameters Zamzam is unique is its natural characteristic it has been proven that there are no microbs whatsoever in the water of Zamzam Its stimulate increased lactation (Naeem *et al.,* 1983), (El-Zaiat, 2005). No Aquaporins is needed for it's action and it stimulate Aquaporins production (Naeem *et al.,* 1983; (El-Zaiat, 2005; El-Kashef, 1994), we introduced Zamzam water for the first time in gynecology and obstetrics.

Zamzam water in Gynecology

CO, fibroid, endometriosis, Unexplained infertility, recurrent spontaneous abortion, pelvic adhesion formation and reformation, Cervical sperm (Ali Farid Mohamed Ali, 2009; Ali Farid Mohamed Ali, 2009; Ali Farid Mohamed Ali, 2009; Aly Farid M Ali and Erlemandocosmi, 2011), antibodies, cervical factor in fertility, poor responders, to increase pregnancy rate after Artificial insemination, to enhance human embryonic stem cell to germ like cell differentiation, (Aly Farid M Ali and Erlemandocosmi, 2011) To increase potency of peripheral blood mononuclear cell (PB MNC) and in IVF

In obstetrics

Intraamniotic injection for treatment of Idiopathic oligohydramnios

Method of Zam Zam water intake

Oral for 3 months 250 c.c, Addition to embryo media (sterile), Intrauterine before embryo transfer, Intraamniotic, laparoscopically guided and ultrasound guided.

EPREX

EPREX is a recombinant human erythropoietin (EPO) and has 165 amino acid sequence, the apparent molecular weight of erythropoietin is about 30.400 daltons we introduced it as a new modality of treatment of poor ovarian responders (Jannsen, 2010), (Ali Farid, 2012), and premature ovarian failure(Jannsen, 2010, Ali Farid, 2012) EPREX is contraindicated in patients with: Known sensitivity to mammalian cell derived products, and Uncontrolled hypertension The subcutaneous route of administration should be used. The recommended dose (Ali Farid, 2012) regimen is 600 IU/Kg EPREX given weekly for three weeks (days -21, -14 and -7). EPREX adverse effect include: hypertension anaphylactic reaction, and angio-oedema, nausea, vomiting, headache, and diarrhea (Jannsen, 2010; Ali Farid, 2012).

Bee Venom, Bee propolis, Zam Zam water and EPREX THEIR impaction on reproduction and poor ovarian responders

The Bologna criteria for poor ovarian responders POR: two OF the following three (Retti, 2011) characteristics must be met for satisfying the POR definition: (ExanthiaDiamanti-Kandarakis, 2007) advanced maternal age ≥ 40 years or other risk factor for POR (HarukoFujii, 2011) a previous POR (Luis *et al.,* 2011) an abnormal ovarian reserve test. We introduced for the first time

in the literature a new modalities for this difficult problem. Pretreatment with any of these may improve the ovarian (Akhtar *et al.,* 1993) sensitivity to FSH and follicular response to gonadotrophin treatment in previous low responder IVF patients. Also it may improve ovarian response to gonodotrophins in poor responder IVF patient with normal basal concentration of FSH or It's effect on apoptosis of cultured granu losa- Lutein cells this effect may correlate with embryo fragmentation and pregnancy rate(HarukoFujii *et al.,* 2011).

The improvement of delivery and live birth rates after ICSI in women age > 40 days by any of previous modalities appears to be mainly due to an improvement of oocyte developmental potential also the effect on the uterus cannot be excluded. One conmen action of all these that it inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome p 450 submit of the enzyme resulting in a blockade of androgens convection into estrogens with a subsequent increase in

Chemical composition of eye tears (1), (2), (3)

Material	Concentration
Electrolyte concentrations in the tear film of healthy subjects	
Sodium	133 mM
Potassium	25 mM
Calcium	0.80 mM
Magnesium	0.61 mM
Chloride	128 mM
Bicarbonate	33 mM
Nitrate	014 mM
Phosphate	0.22 mM
sulfate	0.39 mM
Small-molecule Concentrations in the Tear film	
Retinol	16 ng/mL
Vitamin C	177 ug/mL
Tyrosine	45 uM
Glutathione	107 uM
Glucose	26 ug/mL
Prostaglandin	82 pg/mL
Protein	
Protective/anti-infective	
Lactoferin	1.35-6.3 mg/mL
Lysozyme/muramidase	0.5-45 mg/mL
Phospholipase A2	30-55 ug/mL
Cenuloplasmin	0.76 mg/mL
cuZn superoxide dismutase	
SOD) Lysosomal enzymes	
Immune system/inflammatory	
sigA	166 ug/mL – 2.42 mg/mL
Secretory component	
sigM	5.6 ug/ mL
Complement components IL-1a	43 pg/mL
IL – 1B	30 pg/mL
IL – Ra (IL – 1 receptor antagonist)	295 ng/ml
IL-2	38 pg/ml
IL – 5	40 pg/ml
IL – 6	42 pg/ml; 4.5 pg/mg protein
FasL	0.30 ng/mL
Tumor necrosis factor – a (TINF-a) interferony-y	0.36 – 1.97 ng/mL
Material	91 pg/mL
Tear film maintenance	
Lipocalin (tear – specific prealibumin	0.5 – 1.5 mg/mL
(TSPA)	
Albumin	
MUC1	
MUC4 (Sialomucin)	Variable 0-200 ug/mL
MUC5AC	
MUC7	19-280 ng/mL
Cormeal health & wound healing	
Fibronectin	0.10 – 0.25 ng/Ml
Gm-CSF protein	63 pg/mL – 8 ng/mL
Transforming growth factor a (TGF-a)	2.98 ng/m 1; 55 pg/mL
Transforming growth factor B1 (TGF-B1)	0.5 ng/mL
Transforming growth factor B2 (TGF-B2)	
Tear hepatocyte growth factor (HGF)	
Keratocyte growth factor	0.71 – 1.7 ng/ml
Basic fibroblast growth factor (FGFB; FGF2)	0.1-1.7 ng/mL (variable)
Epidermal growth factor (FGF)	19 ng/mL
Platelet-derived growth	0.40 ng/mL
Factor BB	0.83 ug/mL
Insulin	0.13 – 0.31 ng/mL
Tenascin	
Neuropeptides	
Substance P	198 ng/min

Continue…….

Calcitonin gene-related peptide (CGRP)	0.3-0.06 1U/mL
Proteases/protease inhibitors	0.0073 1U/mL
Plasminogen activator (urokinase type)	
Plasminogen/plasmin	1-14 ug/mL
a 1-Antichymotrypsin	106 ug/mg tear
a 1-protease inhibtor	Protein
a 2- Macroglolin	5-10 ug/mL
Cystatins	0.84 ng/mg tear protein
Secretory leukocyte protease inhibitor (SLPI)	
Matrix metalloproteinase 2 (MMP – 2)	
Matrix metalloproteinase 3 (MMP-3)	
Collagenase – 2 (MMP – 8)	7.3 ng/mg or 7.2 U/mg
	Tear protein 3.3 ng/mL
Matrix metalloproteinase 9 (MMP-9)	
Tryptase	

intraovrian androgens (Akhtar *et al.,* 1993) it has been shown in cultured mouse pre antralfollicles that androgen stimulate follicle growth also androgens stimulate theca and granulose cell proliferation and inhibition of Apoptosis also androgen stimulate FSH receptor expression, Also it stimulate IGF1 and IGF-1 receptor gene expression how ever when concentration are too high they can reduce follicular health, Also there is asynergistical role of androgens with FSH to promote early follicular recruitments.

Any OF these substances expet Eprex has effect on oocyte and embryo yields, embryo grade and cell number in IVF all these agents have a beneficial effect on oocyte maturation: Statistically significantly increased estradial 17B secretion which stimulate protein Kinase (MAPK) cascade in the oocytes, improved cumulus expansion, polar body formation, blastocyst rate, reduced reactive oxygen species, increased level of gluatathione, it promote sirtuim-1 gene expression. (Vaskivuo *et al.,* 2001), (Mangyuan Liu and Xu Yin, 2013). A gain also these agents expect EPREX protect against age-associated infertility, loss of oocytes and follicles and reduced oocyte quality contribute to age associated ovarian aging and infertility accumulation of free radicals with age leads to DN A mutation, protein damage telomere shortening, apoptosis and accelerated ovarian aging expect EPREY have the effect through antioxidation as well as activating SIRtl and telomeras (Vaskivuo *et al.,* 2001; Mangyuan Liu *et al.,* 2013) We proved that these Agents Except Eperx act Through affection of telomere length. (Van Zglinicki *et al.,* 2005; Keefe and Liu, 2009; Liu and Keefe, 2002; Huang *et al.,* 2013; Starr *et al.,* 2008; Lavaranos *et al.,* 1999; Liu and Li, 2010; Liu *et al.,* 2007; Broekman *et al.,* 2007; Broekman *et al.,* 2009; Price *et al.,* 2012).

Eye Tears

Due to its unique chemical composition (Callender and Morrison, 1974; Ohkiashty *et al.,* 2006; William *et al.,* 1982) we introduce Eye Tears for the first time in the Treatment of Myoma, endometriosis PCO, prevention of pelvic Adhesion and in IVF (To improve endometrial receptivity) treatment of repeated implantation failure (Ali Farid Mohamed Ali, 2014).

Myoma utero Venous organ dissemination

(The King is dead, Long live the king)

We introduced this name for the first in literature this term enclosed the 2 terms commonly appeared in the literature benign metastastizing leiomyomatosis (Steiner, 1939) and intravenous leiomyomatosis (Du *et al.,* 2011) after our case report discovery. This case report in the first one to find in the literature due to the following points.

(1) Short time of appearance (45 day after myomectomy)
(2) Large number of myoma recorded 475 myoma. (Valdes Devesa *et al.,* 2013) It is present in all part of the body: skin, subcutaenous tissue (Mayerhofer *et al.,* 2004), rectus sheath, rectus muscle, omentum, mesentery, intestine (small, large, kidney, inferior vena cava, right atrium, right ventricle, lung, lymph node brain, bone (femoral), retroperitonal).
(3) Combination between intravenous leiomyomatosis and benign metastasizing leiomyomatosis. Ki67 index is essential to exclude leiomoysarcoma (Mayerhofer *et al.,* 2004; Gezginc *et al.,* 2011). We put four theories for explanation for the first in the literature (Beck *et al.,* 2012).

a) Stem cell theory

Mesenchymal cell can be differentiated to myoma cell and the stimulus for this differentiation is the surgical because in all cases reported and our case is that there is a history of previous myomectomy or hysterectomy.

b) Aquaporins AQPs theory (Zoul *et al.*, 2013)

Previous studies demonstrate significant role for passive water channels maintaining water homeostasis in cell membranes. we studied AQPs in all myona removed and follow up all cases for 20 years for intravenous leiomyomatosis, the only case which have intravenous leiomyomatosis have statistically increased level four AQPI, increased AQPI lead to spread of myome.

c) Chromosomal theory

We find chromosomal aberration in intravenous, in chromosome No. (3, 10, 11, 14).

d) Micro RNA theory (Luis A. Ramon *et al.*, 2011)

Utilizing mi RNA microarray analysis we formed eight down regulated Mi RNAs (including Mi R 1966) and for up regulated mi RNAs.

(4) A new line of treatment, the proposed previous medical lines of treatment were hormonal (Mohamed *et al.,* 2014). Which include:

(5) Progestin, aromatase inhibitor, gonadotrophin relasing hormone agonist Gn RH agonist. Now we introduced Bee propolis as (oral intake [1/2 gram/ 4 times daily for one month] as a new line of treatment (Ali *et al.,* 2012).

Updated treatment of endometriosis

We introduced for the first time in literature these new modalities of treatment of endometriosis

1. NANO GOLD (Ali Farid *et al.,* 2012), NANO SILVER (Ali Farid *et al.,* 2012) and combined NANO gold and NANO SILVER.
2. Peripheral blood mononuclear cells (laparosecopically direct injection or ultrasound direct injection (Ali Farid *et al.,* 2013).
3. Yeast betaglycan (Ali Farid *et al.,* 2010). And CD 147 (Ali Farid *et al.,* 2010).
4. FSLYM1920 (Ali Farid *et al.,* 2014).
5. A new delivery system for GnRH agonist (intravaginal Ring, intrauterine loop) (Ali Farid *et al.,* 2012).
6. Direct injection of GnRH agonist through laparosecopically and ultrasound guided (Ali Farid *et al.,* 2010).
7. a new mechanism of action of Dineogest through neutropine, milk fat globule, epidermal growth factor 8, aquaporin 9, Defnsins and block want/ CATENIN path way (Ali Farid *et al.,* 2014).
8. A new modality of treatment of Adenomyosis: vaginal Dineogest laparoscopic rubbing of uterus with Dineogest ointment (Ali Farid *et al.,* 2014).

First baby delivered in the world literature after peripheral blood mononuclear cell injection

1. In the cervix (Repeated abortion 12 times) date 9/3/2009 (Ali Farid *et al.,* 2010).
2. In the ovary (Aged women 53 years through laparosecopically direct injection in the ovary date 10/11/2013 (Ali Farid *et al.,* 2013).
3. In the testis (Azospernia) infertility for 25 years date 15/12/2014

Conclusion

Ten updated innovation, in infertility, we are still in the beginning of a long of road which we put the first stone in this road. All these innovation respect the ethical consideration and passed between phase (1) and phase (2) more and more controlled studies and more randomization are needed before we reached to the conclusion. We think that our patients deserve more work to reach to a safe drug and a safe line of treatment with high therapeutic value and with reasonable cost benefit ratio.

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