Medical and Research Publications
International Open Access

Review Article **Journal of MAR Case Reports (Volume 7 Issue 1)**

Will Exploration for Role of Kisspeptins Answer the Modes by which Transgenerational Transmission of Polycystic Ovary syndrome (PCOS) Occursto find a way of Avoidance of Inheritance of PCOS?- A Short Communication

Dr Kulvinder Kochar Kaur [1]*, DR Gautam Nand K Allahbadia [2],
DR Mandeep Singh M.D.DM [3]

1. Obstt & Gynae, Specialist Reproductive Endocrinology & Infertility Specialist.

2. M.D. (Obstt & Gynae), D.N.B, Scientific Director, Ex-Rotunda-A Centre for Human Reproduction 672, Kalpak Garden, Perry Cross Road, Near Otter's Club, Bandra (W)-400040MUMBAI, INDIA.

3. (Std) (Neurology), Consultant Neurologist, Swami Satyanand Hospital Near Nawi Kachehri, Baradri, Ladowali road, Jalandhar-144001, Punjab, India, JALANDHARPUNJAB.

Corresponding Author: Dr Kulvinder Kochar Kaur, M.D, Obstt & Gynae, Specialist Reproductive Endocrinology & Infertility Specialist.

Received Date: February 15, 2023

Published Date: March 01, 2023

Introduction

Polycystic ovary syndrome (PCOS) possesses a minimum of the following 2 components;namely hyperandrogenism(HA),irregular or absence of menstrual cycles(alias oligomenorrhea/ amenorrhea) or ovaries with polycystic morphology.It impacts 15-20% women in the reproductive period that impacts their fertility along with cardiometabolic health**[**1**]**. Regarding escalating fecundity assisted reproductive technology(ART) is the usual requirement; however,irrespective of the mode of conception women undergoing pregnancy usually encounter escalated risk of pregnancy induced hypertension (PIH),preeclampsia , maternal gestational diabetes mellitus(GDM) , spontaneous preterm birth, requirement for lower segment caesarean section (LSCS)delivery hence robust maternal morbidity.In total 60-70% of PCOS mother's daughters go on to have a hereditary acquisition of PCOS in view of genetic ,epigenetic along with generational aid that influences fetal HA generation;that is a generational characteristic shared as a precedence for all PCO phenotypes**[**1**]**. It is not astonishing that in view of PCOS multi billion dollars expenditure is placed on the United States government alone; however, it has not been feasible to attain a cure in view of its complicated generational etiopathogenesis.

The placenta of neonates born to PCOS women have been believed for considerable time to be implicated in contribution to the generational initiation of PCOS in addition to morphological along with functional intactness that gets influenced by maternal HA, obesity, GDM along with chronic low grade inflammation resulting in the reduction of uteroplacental perfusion, placental inadaequacy along with insufficient aromatization of androgens**[**1,2**]**. Animal model studies have provided direct validation regarding how maternal HA is implicated in inducing placental inadaequacy formed by maternal gestational testosterone (T) escalation **[**1**]**. Female rhesus monkeys progeny receiving exposure to gestational T display the maximum detailed PCOS-like adult phenotypes inclusive of numerous metabolic dysfunctions like diseases type2 diabetes mellitus (T2DM) which are correlated with PCOS**[** 1**]**. Male monkeys belonging to the same species (spp), having akin exposure to maternal HA further display equivalent insulin resistance (IR) along with pancreatic beta βcell dysfunction equivalent to T exposed females along with simulate glucocontrolling dysfunctions illustrated by male relatives of PCOS women**[**1**]**.

At the time of hyperandrogenic pregnancies in monkeys the villous hemochorial placenta displays decreased placental blood volume **[**3**]** along with probably placental blood flow,aiding in a comparatively hypoxic fetal milieu**[**3,4**]**. Adding diet induced maternal obesity (DIO) to the hyperandrogenic pregnancies in monkeys results in escalated maternal gestational weight accrual as

well as body fat [3,4], in addition to maternal hyperglycemia, along with IR[3], besides reduction in maternal expression of placental glucose transporters as well as diminished placental angiogenesis[4]. At the time of latter part of gestation, female rhesus monkey fetuses are hypolipidemic[1], lesser in size along with possess greater fat accrual[3], while male fetuses are longer as well as possess greater weight accrual[3]. Regarding the gestational T exposed neonates female rhesus monkeys, 50% are hypoglycemic ; despite equal birth weight for both sexes[1,4], as well as infant females display exacerbated weight accrual in addition to epigenetic alterations in white adipocytes which take place prior to besides being correlated with impaired adipogenesis along with hyperlipidemia[1].

Sun et al.[5], in a recent clinical observational study escalated our insight regarding placental function inadaequacy along with morphology at the time of hyperandrogenic PCOS pregnancies and advanced it further.This illustration besides validating PCOS placental morphological in addition to steroidal pathophysiology, further illustrated hormonal as well as metabolic reprogramming of the infants having exposure[5]. Clinical reference of Chinese women having pregnancy with a single fetus,no correlated pregnancy induced hypertension, GDM or any other endocrine conditions along with delivered by LSCS at term were enrolled from the prior to the pregnancy utilizing Rotterdham's PCOS criteria with exclusion of other endocrine conditions [5].

The age matching of PCOS women was carried out in women without PCOS , however they possessed mean overweight before pregnancy in contrast to controls. Nevertheless, indications for LSCS were not provided along with histories regarding utilization of ART, parity, prior pregnancy complications smoking along with medicines were not available. Canonical of the hyperandrogenic PCOS women with pregnancy along with as compared to control women, weight accrual was much greater in contrast to advocated guidelines as well as was equivalent to 40% higher in case of PCOS women[5]. On attainment of term gestational age (GA) PCOS women possessed escalated quantities of circulating cholesterol along with apolipotropin B, along with controls- with equivalent glucocontrolling paradigm quantities of circulating cytokines, other than decreased quantities of anti inflammatory interleukin-10 (IL-10) [5].In toto these blood paradigm pointed to a hyperlipidemic, proinflammatory maternal milieu [see figures 1-3].

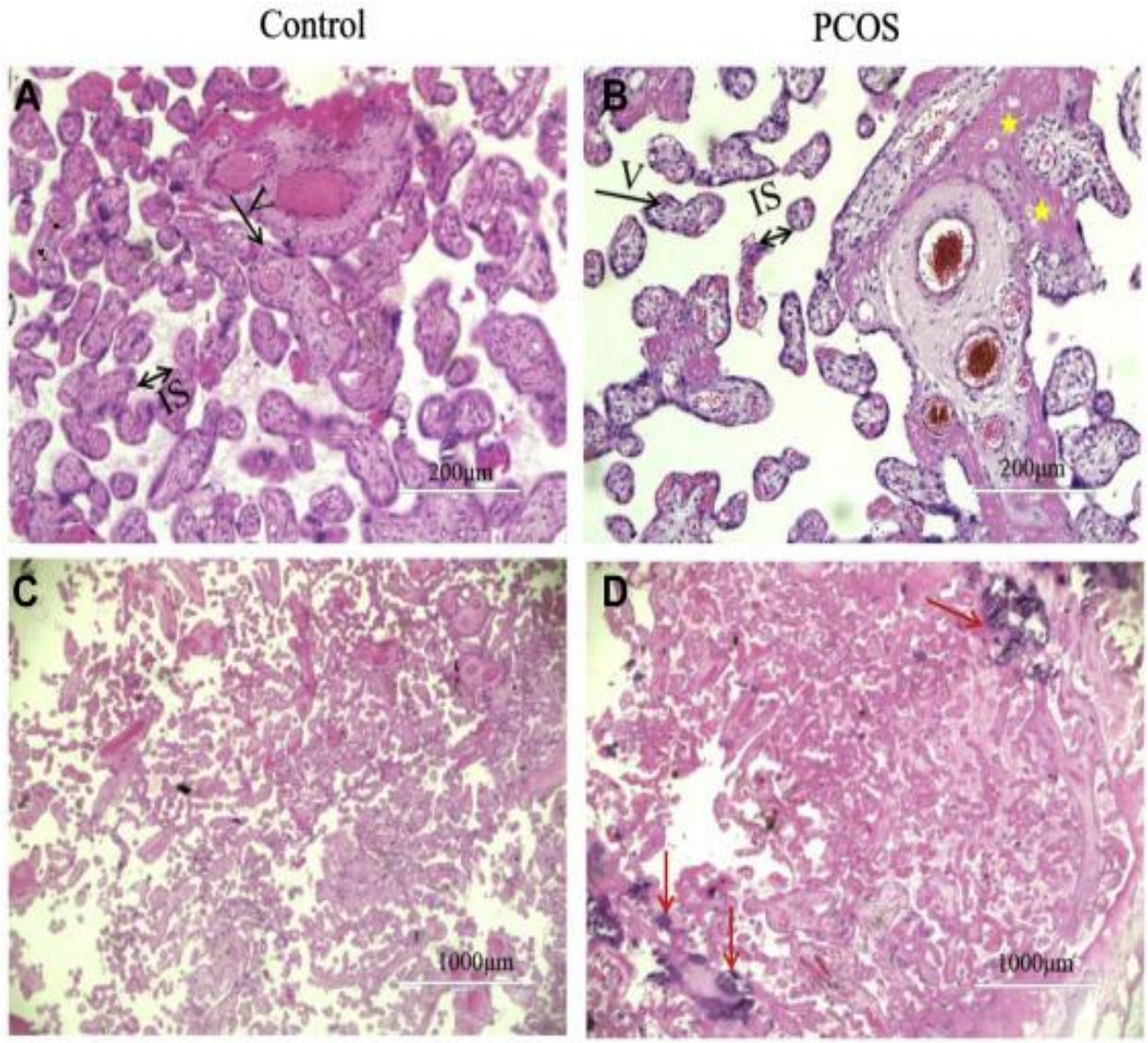


Figure 1 Courtesy ref no-5-Placental and Umbilical cord morphology. (A–D) The placental villus in the control group (A and C) and PCOS group (B and D) using hematoxylin and eosin staining. The yellow star in B demonstrates infarction (fibrinoid deposition around villus); the red arrow in D demonstrates calcification in placenta. Images were taken at 20x (A and B) and 4x (C and D) magnifications.

Scale bar = 200 μm (A and B), scale bar = 1000 μm (C and D). PCOS = polycystic ovary syndrome; V = villus; IS = intervillous space.

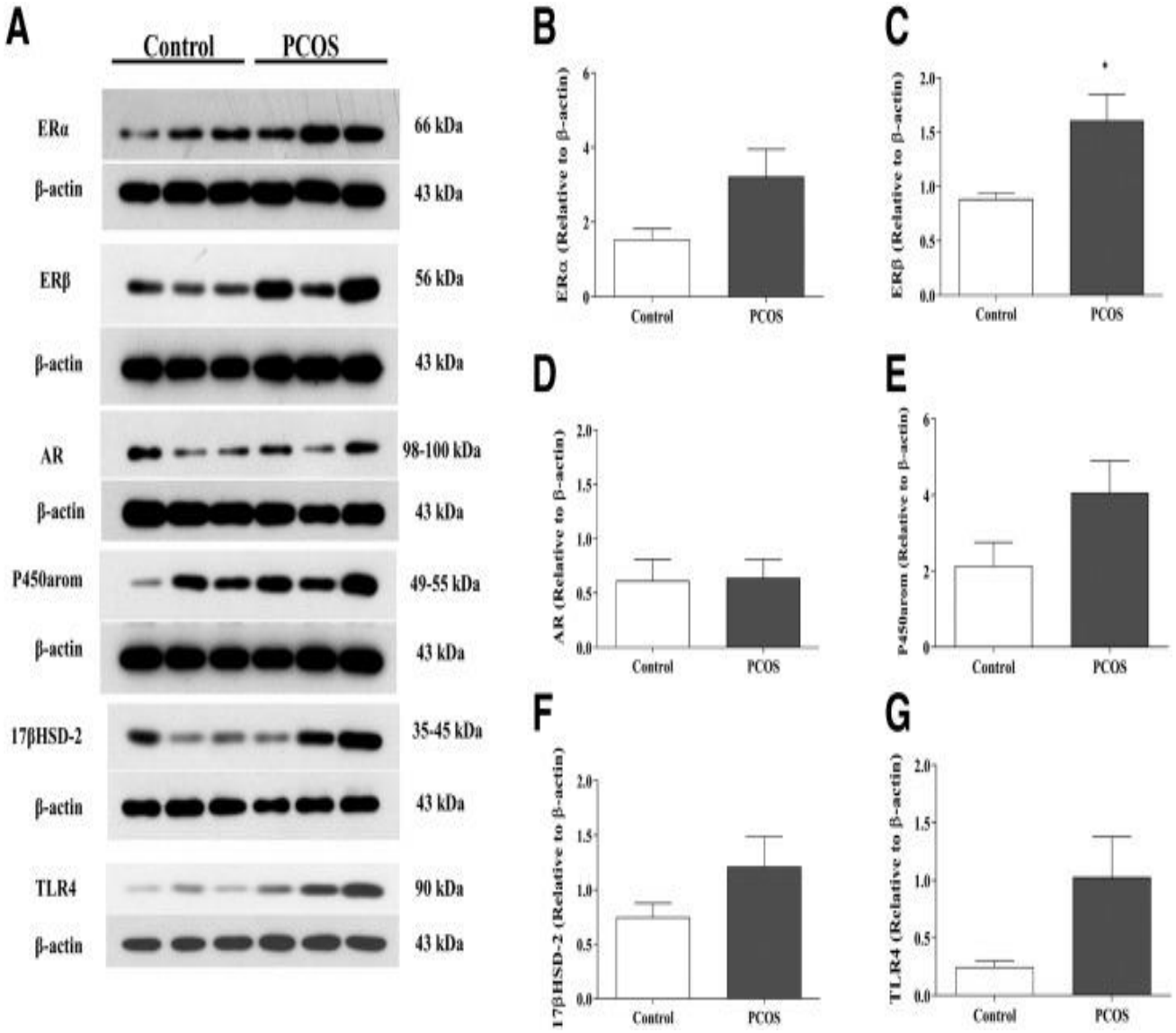
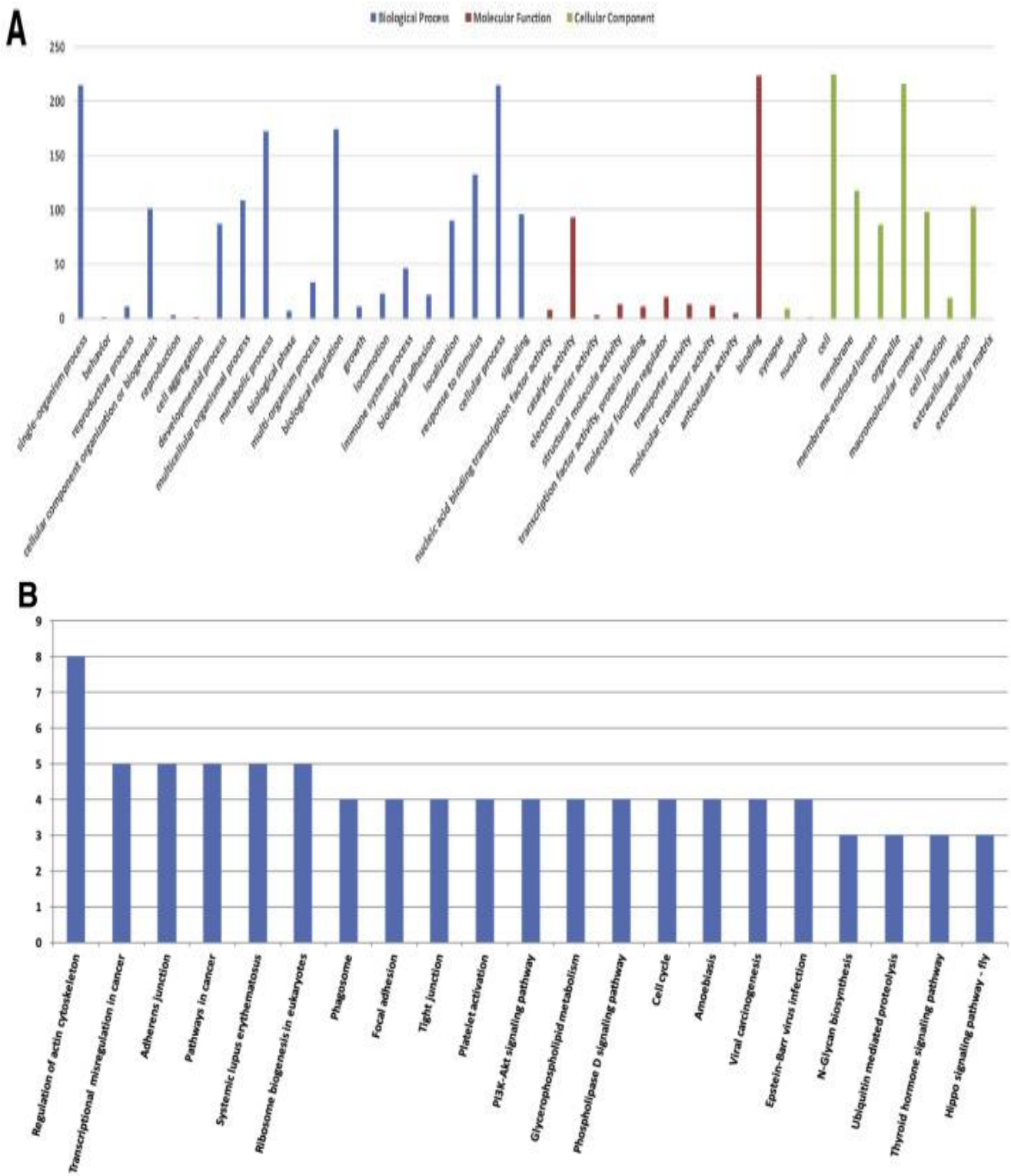


Figure 2 Courtesy ref no-5-Placental protein levels of ERα, ERβ, AR, P450arom, 17β-HSD2 and TLR4 in the control and PCOS groups. (A) Representative blots of ERα, ERβ, AR, P450arom, 17β-HSD2, and TLR4 protein expression. (B–G) Densitometric analyses of ERα (B), ERβ (C), AR (D), P450arom (E), 17β-HSD2 (F), and TLR4 (G) protein expression. The placental ERα, ERβ, AR, P450arom, 17β-HSD2, and TLR4 proteins were measured using Western blot. The final data were normalized using β-actin protein expression. Data are mean ± SEM, n = 3. Significant differences were determined using Student's t test.

**P<.05. PCOS = polycystic ovary syndrome; ERα = estrogen receptor alpha; ERβ = estrogen receptor beta; AR = androgen receptor; P450arom = aromatase; 17β-HSD2 = 17β-Hydroxysteroid dehydrogenases type 2; TLR4 = toll like receptor 4.*


A
Biological Process
Molecular Function
Cellular Component
250
200
150
100
50
0
single-organism process
behavior
reproductive process
cellular component organization or biogenesis
reproduction
cell aggregation
developmental process
multicellular organismal process
metabolic process
biological phase
multi-organism process
biological regulation
growth
locomotion
immune system process
biological adhesion
localization
response to stimulus
cellular process
signaling
nucleic acid binding transcription factor activity
catalytic activity
electron carrier activity
structural molecule activity
transcription factor activity, protein binding
molecular function regulator
transporter activity
molecular transducer activity
antioxidant activity
binding
synapse
nucleoid
cell
membrane
membrane-enclosed lumen
organelle
macromolecular complex
cell junction
extracellular region
extracellular matrix
B
9
8
7
6
5
4
3
2
1
0
Regulation of actin cytoskeleton
Transcriptional misregulation in cancer
Adherens junction
Pathways in cancer
Systemic lupus erythematosus
Ribosome biogenesis in eukaryotes
Phagosome
Focal adhesion
Tight junction
Platelet activation
PI3K-Akt signaling pathway
Glycerophospholipid metabolism
Phospholipase D signaling pathway
Cell cycle
Amoebiasis
Viral carcinogenesis
Epstein-Barr virus infection
N-Glycan biosynthesis
Ubiquitin mediated proteolysis
Thyroid hormone signaling pathway
Hippo signaling pathway - fly

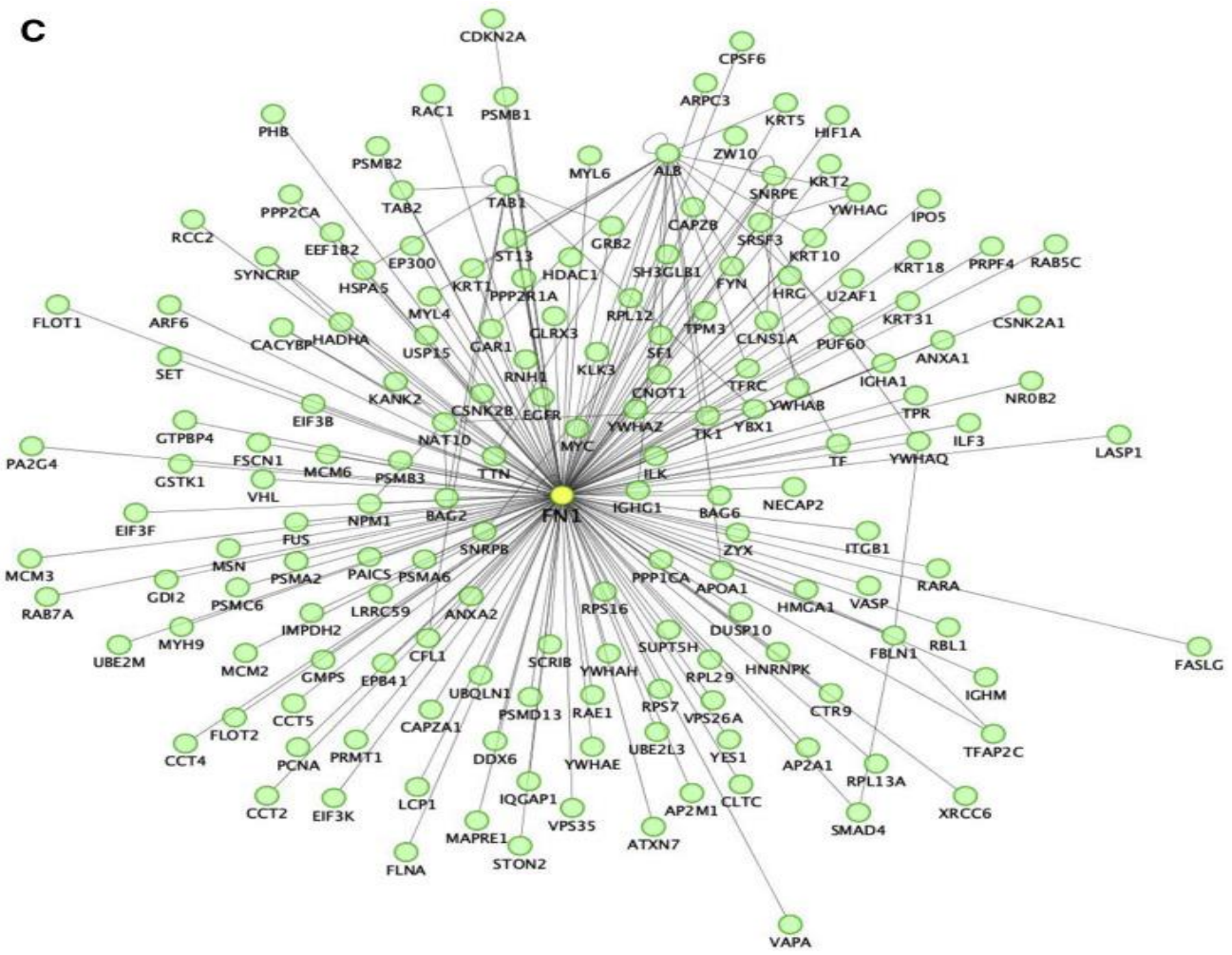


Figure 3 Courtesy ref no-5-GO analysis and KEGG pathway analysis. Proteins were classified according to biological processes, molecular function, and cellular compartment. **(A)** Functional classification at level 2. **(B)** KEGG pathways with more than four proteins are involved. The horizontal bars represent the number of differentially expressed proteins involved in each pathway. **(C)** Protein-protein interactions between FN1 and its associated proteins in the network.

GO = Gene Ontology; KEGG = Kyoto Encyclopedia of Genes and Genomes.

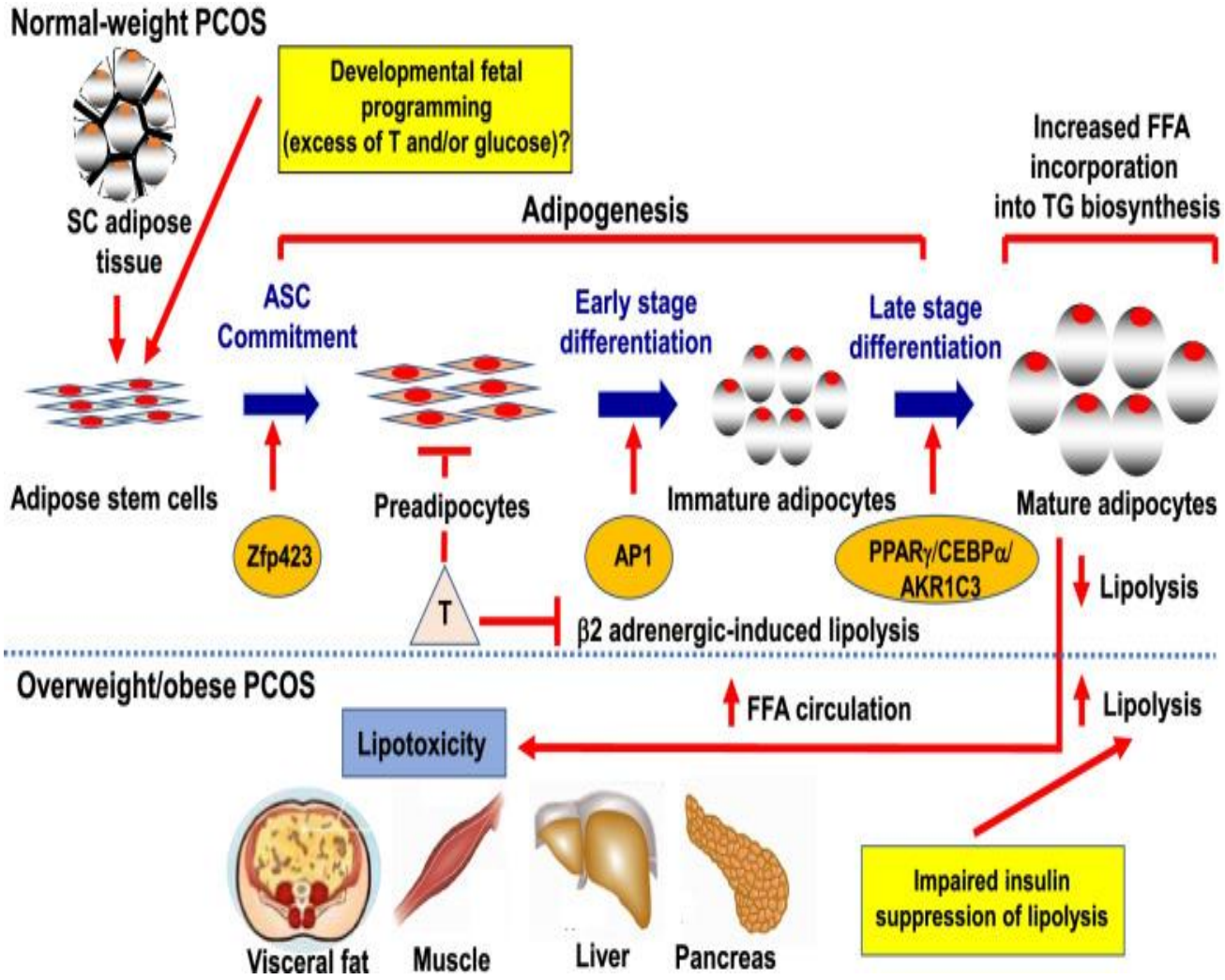


Figure 4 Courtesy ref no-14-Altered molecular pathways of subcutaneous (SC) abdominal adipogenesis in polycystic ovary syndrome (PCOS) as a risk factor for lipotoxicity. In normal-weight PCOS women, exaggerated adipose stem cell (ASC) development to adipocytes occurs via androgen-independent mechanisms [13,15]. Simultaneously, androgen escalation hampers early-stage adipogenesis, decreases insulin-stimulated glucose uptake, promotes lipid storage and impairs catecholamine-stimulated lipolysis [16-20], favouring abdominal fat deposition and increased energy availability through hyperandrogenism and insulin resistance, respectively. These same traits are worsened in overweight/obese PCOS women who have greater preferential abdominal fat accumulation, hyperandrogenism, and systemic insulin resistance [21], along with impaired insulin suppression of lipolysis [21,22], promoting ectopic lipid deposition and lipotoxicity [23].]

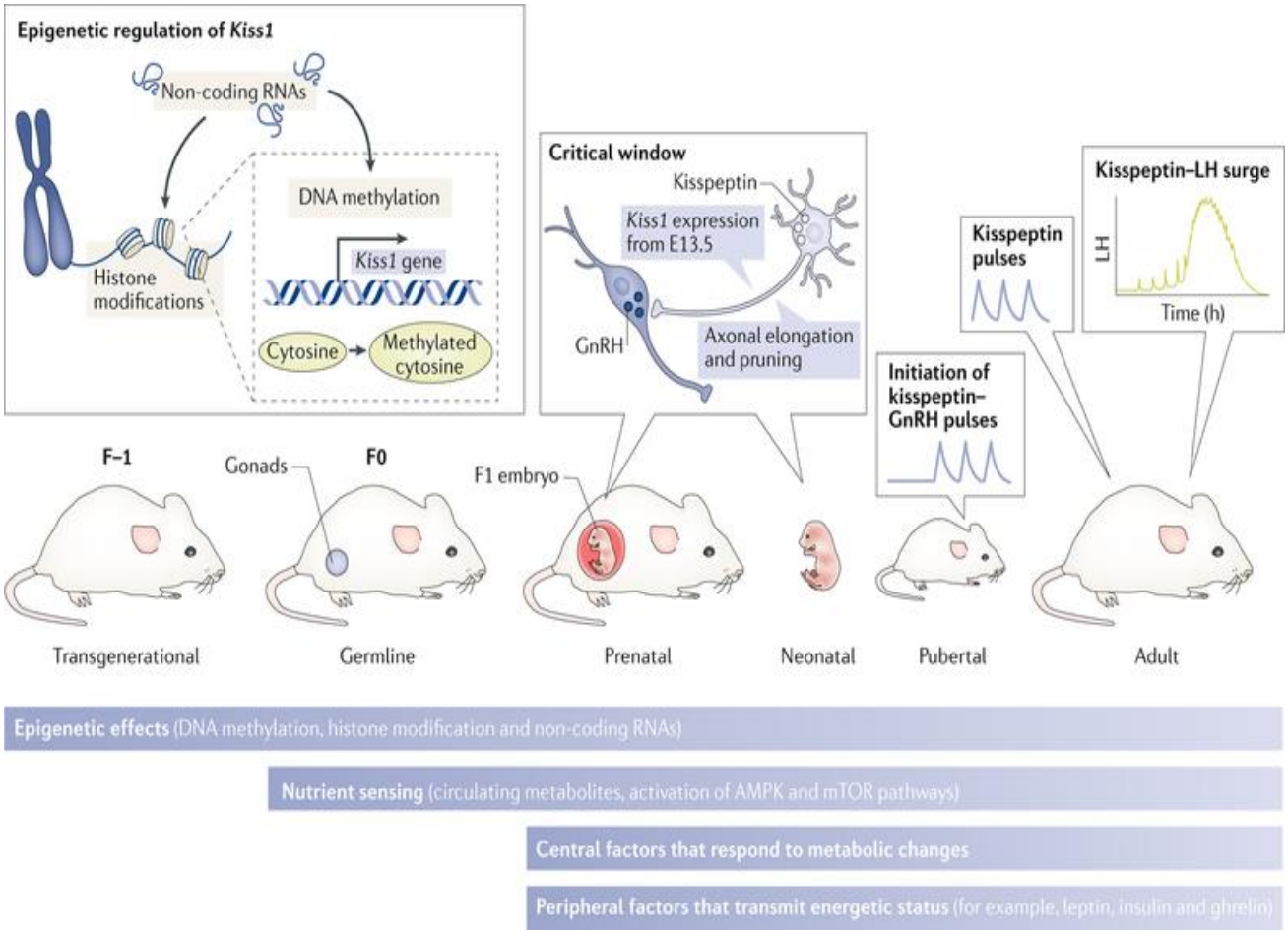


Figure 5 Courtesy ref no-30-Levels of metabolic regulation of kisspeptin neurons throughout development.

Schematic representation of the different developmental stages in which metabolic factors might affect the expression of the Kiss1 gene. First, epigenetic effects (DNA methylation, histone modification and non-coding RNAs) might permanently affect the expression of Kiss1. This effect can occur transgenerationally or at any stage of development. Second, during the perinatal period there is a critical window in which conformational changes in kisspeptin neurons might happen as a consequence of the exposure to metabolic factors. These pre-existing modifications (epigenetic and conformational during development) might determine the timing of the activation of kisspeptin neurons (puberty onset) and their function in adulthood (luteinizing hormone (LH) pulses and surge). Nonetheless, during and after development, kisspeptin neurons can still be regulated by metabolic factors at different levels: epigenetic, nutrient sensing and central and peripheral factors. AMPK, 5'-AMP-activated protein kinase; E13.5, embryonic day 13.5; GnRH, gonadotropin-releasing hormone; mTOR, mammalian target of rapamycin.

In view of maximum of the offsprings born were male infants in women with as well as without PCOS in addition tooverall study people were comparatively few ,the sex bias of the progeny prevented statistical evaluation for daughters only. Placental weights, birth weights along with birth lengths were parallel with the latter being canonical for GA[5].

Fetal umbilical cord blood paradigms pointed to hyperlipidemia in progeny of PCOS women in the context of escalated quantities of cholesterol along with high density lipoprotein (HDL) , along with adrenal HA[5]. On restricting evaluation to male progeny, sex hormone binding globulin (SHBG) was decreased, whereas Dehydroepiandrosteronesulphate (DHEAS)was escalated in infants of PCOS women in contrast to babies born to control women.The way predicted from prior display[1,2] placentae from term GA hyperandrogenic PCOS pregnancies exhibited infarction along with intravillous fibrin deposits,calcification as well as intervillous space in view of requirement for adapting to hypoxic fetal milieu[5]. Clarification was not there regarding which placental areas got sampled . In view of remarkable variation regarding intraplacental intactness besides functionality is of botheration. Placentas which got sampled from PCOS women in contrast to controls, however illustrated escalated protein expression of estrogen receptor β; nevertheless showed corresponding quantities of estrogen receptor-α(ER-α), androgen receptor, aromatase, 17βhydroxyteroid dehydrogenase2 along with toll like receptor 4 (TLR4) [5].

Escalated placental estrogen receptor β has been correlated with enhanced placental generation of vasoconstrictive prostanoids along with calcification correlated vascular damage,hence might point to aberrant vascular structure as well as working hence placental working is decreased .Additionally, proteomic isolation of decreased placental fibronectin generation in placentas of PCOS women[5], points to decreased intercellular cell adhesion along with villous remodelling amongst PCOS placentas along with little involvement with uterine endometrium. Hence on coincidental with escalated placental expression of estrogen receptor β, decreased placental fibronectin expression might aid in the common occurrence of PIH,preeclampsia, decreased placental oxygen along with nutrients exchange in PCOS women with pregnancy[1,2]. These kinds of placental molecular foundation might provide innovative understanding in the context of differential metabolic fetal reprogramming of the male as well as females progeny that induces adult metabolic phenotype correlated with familial PCOS[1]. Nevertheless, without the extra insight regarding placental impairment at the time of pregnancy it is tough to gather the way structural metabolically disturbances bring about fetal hyperandrogenism(HA). Still the strong points validating this work is no main pregnancy associated

in addition to LSCS complications occured uniformly, that probably provides insight regarding occasional placental function inadaequacy **[**6**]**.

Earlier we had reviewed the roles of PRDM, EBS/Y box protein 1 (YBX1) to control Bone morphogenetic protein7 (BMP7) inobesity &IR showing that PR (PRD1–BF–RIZ1 homologous) domain containing 16(PRDM16) binding is highly abundant at a broad set of brown fat selective genes. PRDM16 physically binds to MED1 a component of the Mediator complex and recruits it to superenhancers at brown fat selective genes.

Deficiency in PRDM in BAT reduces MED1 binding at PDRM16 target sites along with results in an elemental alteration in chromatin architecture at key brown fat selective genes. Thus PRDM controls chromatin architecture and superenhancers activity in BAT. PRDM16 interacts with MED1 at brown fat specific genes to facilitate gene transcription .The binding of MED1 to PRDM16 is apparently direct in view of these factors possess the capacity of binding together in vitro as purified proteins. MED 1 is a component of the Mediator complex which plays a crucial part in regulatory genes expression via various modes . Mediator bridges enhancer regions along with correlated transcription factor complexes with RNAII polymerase and the transcriptional machinery at the promoters.Harms et al. suggest that PRDM16/PRDM3 binds to chromatin at enhancers, many of which are super enhancers(SE) in BAT selective genes via peroxisome proliferator activated receptor γ (PPARγ) and CCAAT/enhancer binding protein (C/EBP β) along with other factors. At these areas PRDM16 recruits MED1/Mediator and by doing this organizes higher order chromatin architecture along with facilitate some brown specific target genes without impeding the chromatin binding of other transcription factors, including PRDM16 crosstalking partners like PPAR γ and C/EBP β**[**7**]**. The result of Harms et al.**[**8**]** indicated that AT ppargac α PRDM16 facilitates an active chromatin hub that links at least two enhancer elements of the promoter area, differentiation of at certain brown fat specific target genes without impeding the chromatin binding of other transcription factors, including prdm16 interacting partners PPARγ and C/EBP and likely other factors. At these regions PRDM16 along with MED1disrupts a higher order chromatin architecture. Furthermore Lida et al.**[**9**]** demonstrated a direct interaction of PRDM16 with MED1 subunit of the Mediator complex through the zinc finger domains. This gets recruited by enhancer of brown fat specific UCP1 genes through this crosstalkwith the enhancer of the thyroid hormone receptor (TR) driven transcription in a biochemically defined system in a mediator based manner**[**9,reviewed in 10,11**]**..

Further recently we had reviewed if any role of flutamide is existent in identification of PCOS women.This androgen effect in PCOS correlated with changed newly generated s/c abdominal

adipocytes in vitro,that gets augmented more in s/c adipose by intracellular alpha keto reductase (AKK IC3) modulated testosterone (T) formation from androstenedione (A4)that facilitates storage of TG,as observed in case of women with normal weight PCOS by an inverse association amongst serum total T/ A4 ratio along with fasting serum TG quantities. This observation takes place in parallel with catecholamines stimulated lipolysis in case of s/c abdominal adipose tissue represents another property of PCOS in fat depot**[**12**]**.

Recently DumesicDA group**[**14**]** that has been actively working on how the PCOS transmission from PCOS mothers to their offsprings takes place be it male or female gender resulting in metabolic dysfunction, further postulated how overexpression of PPARγ and CEBPa in certain PCOS s/c abdominal stem cells are associated with upregulation of AKR1C3 at the time of adipocyte maturation in vitro.These findings are parallel with an inverse association of serum total T/A4 ratio with serum TG quantities in normal weight PCOS women **[**rev in 12**]**, along with pointed to decreased TG turnover in S/C adipose of these individuals facilitates insulin sensitivity **[**rev in 12**]**. AKR1C3 gene expression along with activity are normally greater in preadipocytes along with adipose of gluteal in contrast to omental fat, with gluteal fat facilitating androgen activation (i.e., AKR1C3), and omental cells favoring androgen inactivation (i.e., aldo-ketoreductase AKR1C3-mediated androgen activation by fat depot, combined with hyperandrogenemia along with and preferential intra-abdominal fat accrual , probably impact bodyfat distribution along with function in normal-weight PCOSwomen via a programmedmode to balance glucose-insulin homeostasis with fat accretion **[**13**]**.

Additionally, certain PCOS candidate genes, like thyroid adenoma associated (THADA) along with insulin receptor(INSR), have been correlated with metabolic syndrome(MetS) along with dysfunctional glucose regulation in PCOS along with and type 2 diabetes**[**rev in 14**]**.Thus summarizing along with positing how in the last 2 millenia , menstrual irregularity, male-kind phenotype and decreased fertility have been detailed in women validate how these clinical characteristics were frequent in the earlier era. Recent observations in normal weight hyperandrogenic PCOS women illustrated that escalated lipid accrual by the s/c abdominal adipose stem cells(ASC's) at the time of generation of in vitro adipocytes in vitro takes place combined with diminished insulin sensitivity along with favoured accrual of considerable lipolytic intraabdominal fat in vivo . This kind of PCOS phenotype might be an evolutionary metabolic adaptability regarding balancing energy with storage with glucoseat disposal besides fatty acids oxidation(FAO) regarding ideal energy use at the time of reproduction. They tried to incorporate foundational endocrine-metabolic alterations in healthy, normal-weight PCOS women with akin PCOS-like traits existent in animal models where tissue

differentiation finishes at the time of fetal life in humans for validation of the evolutionary posit that PCOS possesses ancient along with generational origins[see figure 4].

We had further reviewed earlier the part of AMH as an early predictor of PCOS in perimenarchal girls in preventing associated comorbidities[24].Furthermore Ibanez et al.[25], illustrated that if early insulin sensitization was done it avoided the conversion of precocious pubarche to PCOS[25]. Although weight loss in overweight/obese women with PCOS through lifestyle intervention medication use and/or bariatric surgery can improve their metabolic-reproductive function [rev in 14], long-term effects of these clinical therapies remains uncertain, while gestational use of some medications are either contraindicated (i.e., antiandrogens) or associated with childhood adiposity and insulin resistance (i.e., metformin) [rev in 14]. A more efficacious approach might be to identification of young girls at risk for PCOS, probably by determining facial sebum quantities[rev in 14], anogenitaldistance [rev in 14] as well as /or circulating AMH quantities [rev in 14] in early life, and then initiate relevant interventions before puberty. This kind of clinical approach for the treatment of PCOS shifts the approach from disease treatment to preventive intervening , emphasizingon early along with proper lifestyle choices besides the generation of innovative therapies; however long-termactiond of these clinical therapies remains unsure.

Conclusion

Recently we had reviewed role of glucose transporter GLUT4, along with endoplasmic reticulum (ER) as well as inflammatory stress,in DMgeneration[26] . Uptake of glucose in muscles along with ATs are based on the insulin responsive glucose transporter GLUT4 that gets encoded by the soluble carrier family 2 member 4 (SLC2A4)gene,that got cloned 3decades back[27]. Subsequently it got clarified that GLUT4 possesses a foundational part in plasma glucose clearance dysfunction along with glycemia homeostasis[27]. Moreover, alterations in expression of GLUT4 have been correlated with glycemic regulation,with diminished GLUT4 taking part in susceptibility to hyperglycemia.In view of that here SLC2A4/ GLUT4 control of muscles GLUT4 along with ATs glycemic regulation in DM. Conversely, combinations of IR along with compensatory hyperinsulinemia (in case of T2D)or hyperinsulinemia induction by insulin therapy(in case of T1D) have further been revealed as possessing the capacity of resulting in injury to different organ systems.As early as 1993 Robenaum etal.[19] had presented regarding diminished GLUT4 transporters existed in PCOS[19],despite that we still do not have answers till date for IR correlated with PCOS.Thus we had reviewed how till date it has become clear in DM regarding the dysfunctional glucose homeostasis along with generation of

neurodegenerative conditions take place secondary to AGEs stimulated ER stress along with inflammatory stress.Blockade of stimulated ER stress along with inflammatory stress under certain experimental conditions in particular tissues have shown remarkable improvement of glycemic regulation or avoidance of CVD generation or its propagation.Hence dependent on hampering of ER along with inflammatory stress greater work was needed regarding small molecule hampering agents acting in the form of probable targets for the avoidance of along with generation of therapies for DM or its complications. Furthermore roles of melatonin, nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain- containing 3 (NLRP3) ,nutraceuticals were needed for DM complications both micro as well as macrovascular. Similarly we had further reviewed role of therapeutic targeting of macrophages polarization status in the treatment of obesity induced insulin resistance ,chronic inflammation**[**28**]**. Studying macrophages polarization status in utero might give more insight regarding avoidance of metabolic programming for IR generation in later life. Furthermore, considering the role of kisspeptins in reproduction along with nutritional control in view of their particular roleon control of GnRH secretion along with nutritional control,the former via estrogen receptor(ER)-α receptors present in various hypothalamic nuclei**[[**28,29**]**,latterin rodents **[**rev in ref 30**]** (see figure5) and this part needs to be explored in human &neonatesof monkeys programmed in utero if the evolutionary theory of metabolic adaptation is correct.

References

1. DumesicDA,Hoyos LR,Chazenbalk GD,Naik R,Padmanabhan V,AbbottD.Mechanisms of intergenerational transmission of Polycystic ovary syndrome. Reproduction 2019;159:R1-13.

2. KosterMP,DeWilde MA,Veltman VerhulstSM,Houben ML,Nikkels PG,VanRijnBB,etal. Placental characteristics in women with Polycystic ovary syndrome. Hum Reprod 2016;32(1): 147-53.

3. Bishop CV, Stouffer RL,Takahashi DL, Mishler EC, WilcoxMC,SlaydenOD,etal.Chronic hyperandrogenimia and western style diet beginning at pubertyreduces fertility and increases metabolic dysfunction during pregnancy in young adult female Macaques. Hum Reprod 2018;33: 694-705.

4. KuoK, Roberts VHJ,Gaffney J, Takahashi DL, Morgan T, LoJO, etal. maternal high fat diet consumption and Chronic hyperandrogenimia are associated with Placental dysfunction in female rhesus Macaques Endocrinology 2019; 160: 1937-49.

5. Sun M, Sun B, QiaoS, Feng X, Zhang S, et al. Elevated maternal androgen is associated with the dysfunctional placenta and lipid disordersin PCOS newborns. Fertil Steril 2020;113(6):1275-85.

6. AbbottDH.Does a compromised placenta contribute to transgenerational transmission of metabolic dysfunction in Polycystic ovary syndrome. Fertil Steril 2020;113(6):1165-66.

7. Chen W, Roeder RG. Mediator dependent nuclear receptor function. Semin Cell Dev Biol. 2011;22(7):759–768.

8. Harms MJ, Lim HW, Ho Y, et al. PRDM 16 binds MED and controls chromatin architecture to determine a brown fat transcriptional program. Genes Dev. 2015;29(3):298–307.

9. Lida S, Chen W, Nakaidai T, et al. PRDM16 enhances nuclear receptor– dependent transcription of brown fat–specific Ucp1 gene through interactions with Mediator subunit MED1. Genes Dev. 2015;29(3):308– 324.

10. Seale P. Transcriptional Regulatory circuits Controlling Brown fat Development and Activation. Diabetes. 2015;64(7):2369–2375.

11. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Advances in BAT physiology for understanding and translating into Pharmacotherapies for obesity and comorbidities. MOJ Drug Des Develop Ther. 2018;2(5):166–176.

12. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Identification of Women of Polycystic Ovary Syndrome (PCOS) AtRisk for Generation of Metabolic Disease in Normal Weight PCOS: Is There a Role of Flutamide?- AShort Communication. CPQ Medicine, (2023); 14(2), 01-06.

13. Cole B, Hensinger K, Maciel GA, Chang RJ, Erickson GF. Human fetal ovary development involves the spatiotemporal expression of p450c17 protein. J Clin Endocrinol Metab. 2006;91(9):3654–61

14. DumesicDA, Chazenbalk GD ,Padmanabhan V,AbbottD. Polycystic ovary syndrome as a plausible outcomes of evolutionary metabolic adaptation. Reprod Biol Endocrinol 2022;20:12.

15. Leung KL, Sanchita S, Pham CT, Davis BA, Okhovat M, Ding X, et al. Dynamic changes in chromatin accessibility altered adipogenic gene and total versus de novo fatty acids synthesis in subcutaneous adipose stem cells of normal weight Polycystic ovary syndrome(PCOS) women during adipogenesis: evidence of cellular programming. Clin Epigenet 2022; 12(1):181.

16. Arner P. Effects of testosterone on fat cell lipolysis:species differences and possible role in Polycystic ovary syndrome. Biochemie 2005;87(1):39-43.

17. Chazenbalk GD, ,SinghP, Irge D, AbbottDH, DumesicDA. Androgens inhibit adipogenesis during human adipose stem cells commitment to pre adipocyteformation. Steroids 2013;78(9):920-6.

18. Carbould A. testosterone treatment induces insulin resistance in subcutaneous adipocytes in women. J Gynaecol 2007;192(3):585-94.

19. Rosenbaum D, Harber RS, Dunaif A. Insulin resistance in polycystic ovary syndrome: decreased expression of GLUT-4 glucose transporters in adipocytes. Am J Phys. 1993;264(2 Pt 1):E197–202.

20. O'Reilly MW, Kempegowda P, Walsh M, Taylor AE, Manolopoulos KN, Allwood JW, et al. AKR1C3-mediated adipose androgen generation drives lipotoxicity in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2017;102(9):3327–39.

21. Dumesic DA,ObenfieldSE,StenerVictorinE,MarshalJC,LavenJS,Legro RS.Scientific statement on the diagnostic criteria , epidemiology, pathophysiology and molecular genetics of Polycystic ovary syndrome. Endocrin Rev 2015;36:487-525.

22. Manneras-Holm L, Leonhardt H, Kullberg J, Jennische E, Oden A, Holm G, et al. Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance. J Clin Endocrinol Metab. 2011;96(2):E304–11.

23. Chang RJ, Dumesic DA. Polycystic ovary syndrome and Hyperandrogenic states. In: Strauss III JF, Barbieri RL, editors. Yen and Jaffe's reproductive endocrinology: physiology, pathophysiology and clinical management. 8th ed. Philadelphia: Elsevier Saunders; 2018. p. 520–55.

24. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Role of Antimullerian Hormone as an Early Predictor of PCOS in Perimenarchal Girls-Role in Preventing Associated Comorbidities. J Gynecol 2019, 4(1): 000175.

25. Ibanez L, Ferrer A, Ong K, Amin R, Dunger D, et al. Insulin sensitization early after menarche prevents progression from precocious pubarche to poly cystic ovary syndrome. J Pediatr 2004); 144(1): 23-29.

26. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. 'An update on Mechanistic Modes in AGEs Stimulated & ER and Inflammatory Stress- Modulated Control of the GLUT4 expression(SLC2A4 promoted)and Atherogenesis in Diabetes mellitus -A Narrative review''. Mathews J Cytol Histol. 6(1):21:1-25.

27. James DE,Strube M,Mueckler M. Molecular cloning ion characterization of an insulin regulatable promoted glucose transporter. Nature 1989;338:83-7.

28. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. 'An update of use of therapeutic targeting of macrophages polarization status in the treatment of obesity induced insulin resistance ,chronic inflammation and type2 Diabetes mellitus-A Narrative Review''

29. Kulvinder Kochar Kaur,Allahbadia GN,Singh M..Kisspeptins in human reproduction—future therapeutic potential. J Assist Reprod Genet 2012;29(10):999-1011. DOI 10.1007/s10815-012-9856-1.

30. Kulvinder Kochar Kaur,Allahbadia GN,Singh M. Has The Enigma of Steroid Feedback Effects on GnRH Liberation Been Resolved with the Illustration of Estrogen Receptor-A on the Hypothalamic Kisspeptins Neurons-A Narrative Review. Int Gyn & Women's Health 5(4)- 2023. IGWHC.MS.ID.000218. DOI: 10.32474/IGWHC.2023.05.000218.

31. Navarro VM . Metabolic regulation of Kisspeptin-the link between energy balance and reproduction. Nat Rev Endocrinol 2020;16(8):407-20.