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Pregnancy Complications & Management Related to Polycystic Ovarian Syndrome: An Overview

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ABSTRACT

The background of Polycystic Ovary Syndrome involves majority of studies which shows various complications in pregnancy. These studies mainly focused on diagnosis of disturbance or abnormalities or imbalance in the menstrual cycle, infertility and hirsutism (development of male characteristics) or chemical imbalance (hyperaldosteronism) in women's. This might have attention towards pregnancy and child outcomes to achieve better pregnancy and reduce multiple pregnancies. Pregnancy related to Polycystic Ovary Syndrome shows or increased risks of various complications. It includes various metabolic problems like gestational diabetes, hormonal problems like hyperaldosteronism and also reproductive problems associated with women like miscarriage which able to increased risks in pregnancy. These complications show long term effects on those women as well as the delivered offspring. These pregnancy complications further leads to developed risks as metabolic dysfunction as well as reproductive dysfunction in offspring's. This topic summarize the knowledge and facts about Polycystic Ovary Syndrome, complications related to Polycystic Ovary Syndrome and management of complications related to Polycystic Ovarian Syndrome which include long term influence on the women health.

Keywords:- POCS, ovarian cysts, hyperandrogenism, miscarriage, gestational diabetes, pre-eclampsia, Caesar, maternal complications.

INTRODUCTION

As we know, Female reproductive system (FRS) plays an important role in the human life cycle mainly in first phase of life cycle which is a birth phase. As the birth phase starts from pregnancy. Pregnancy is nothing but a " process or sequence of an events begins with fertilization, proceed with implantation, embryonic development and ends with fetal development." [36] Pregnancy period takes place about 38 to 40 weeks after mother's last menstrual cycle. This pregnancy consists of various stages where fetus can develop. During pregnancy period different changes can be occurs in the females. Stages of fetal development starts with fertilization where genetic material of sperm and secondary oocytes are combined to form a single cell mass in uterine tube. [36]

After that it gets attached to the walls of endometria. In the 2nd week embryo is developed with release of hCG (Human Chorionic Gonadotropin) hormone. At the end of 3rd week primitive organs and nerve cells are developed. Organogenesis occurred in 4th- 8th week. At last stage which is a fetal period where brain and other body parts are fully developed. [36]

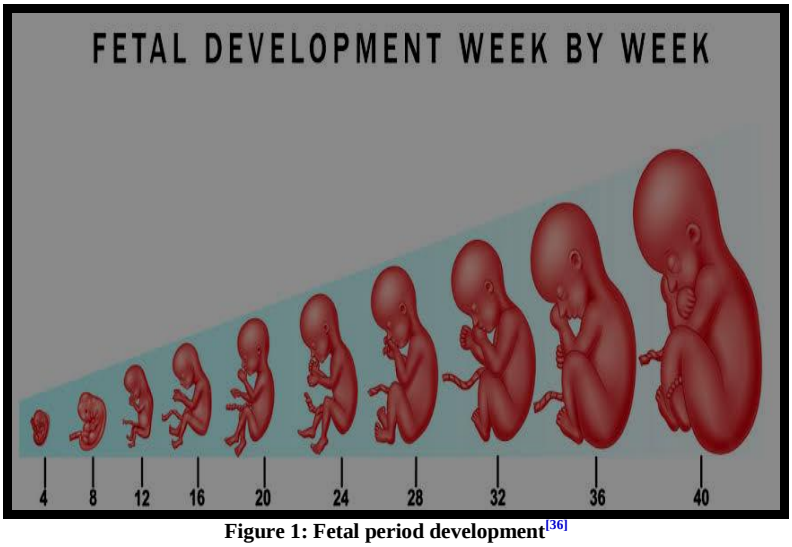

Figure 1: Fetal period development[36]

Polycystic Ovary Syndrome:-

A disorder develops during puberty and characterized by enlargement of ovaries with fluid filled sac (cysts) and tendency to have high levels of male hormone (androgen). [33] It is also called as STEIN-LEVENTHAL SYNDROME. [39] It is chronic anovulation and excess activity ovaries that involves ovarian dormancy or primary insufficiency. It's a common endocrinal disorder which may include reproductive, endocrine and metabolic alterations characterized by hypothalamic - pituitary - ovary axis dysfunction.[24] It is characterized by Oligominorrhoea, anovulation, hirsutism and obesity in young women.[30,28]

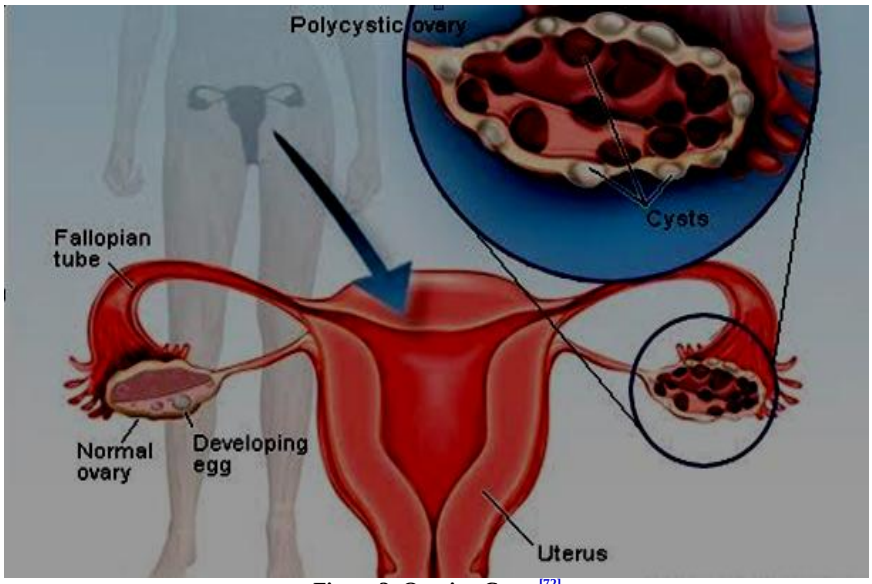

Figure 2: Ovarian Cysts [72]

Epidemiology of PCOS:-

It includes chemical abnormalities or chemical imbalance which causes high amount of androgen production, decreasing the production of follicle stimulating hormone (FSH). This results into swelling of ovaries. [6]

Another mechanism involves unbalanced release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) leads to inhibition of testosterone but level of LH responsible for secretion of androgen inappropriately which cause anovulation.[79] PCOS can also cause due to

genetic heredity.[61] Ovarian cysts are small fluid filled sac within ovary during polycystic ovary syndrome that occurs in both ovaries. Most women of reproductive age develop small cysts each month. A large cyst that come problems occurs in about 8% women's before menopause and about 16% after menopause. [79]

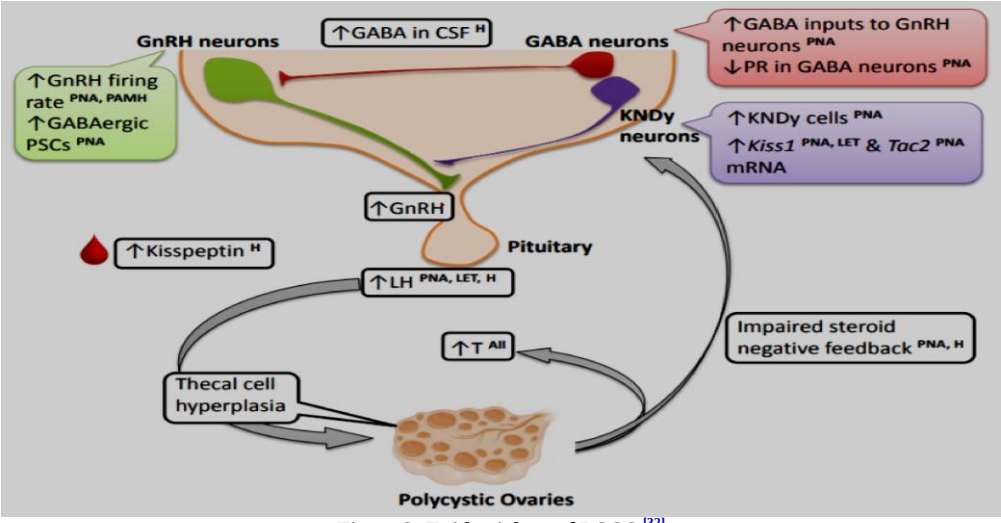

Figure 3: Epidemiology of PCOS [32]

Symptoms of PCOS:-

1) Trouble in conceiving pregnancy / Infertility [7]
2) Mood changes [72]
3) Acne [72]
4) Fatigue [72]
5) Insulin resistance/Diabetic condition [26, 28, 19]
6) High testosterone level [6]
7) Excessive body hair growth [72]
8) Weight changes and trouble losing weight [72]
9) Ovarian cysts [72]
10) Low sex drive [72]
11) Irregular or missed period [72]
12) Male pattern baldness thinning hair [72]

Pregnancy Complications related to PCOS :-

Multiple pregnancy -

Multiple pregnancies increased complications in prenatal morbidity observed in fertility treatment with special regards to women with PCOS affected by an ovulatory infertility. [114] Most complications are caused due to preterm delivery. [51] Multiple pregnancies are also related to obstetric and neonatal complications. Twin pregnancies increased 10 fold risk in newborn and 6 fold risk in premature delivery.[92,112] The rates of perinatal mortality in the meta - analysis shows followed difference in multiple pregnancy rates between women with PCOS and control Shown in table :

Table 1: Meta-analysis of PCOS[114]

Parameter	PCOS	Control	P-value
Total weight gain (kg)	14.8 (+- 3.5)	14.3 (+- 3.1)	Not significant
Gestational age at birth (weeks)	37.6 (+- 2.1)	38 (+- 1.9)	0.006
Impaired glucose tolerance	60	154	0.007
Gestational Diabetes Melitus	29	61	0.01
Pregnancy induced hypertension	20	32	0.002
Pre eclampsia	06	10	Not significant
Premature delivery	15	33	Not significant
Hypertension disorder in pregnancy	26	42	0.001

The women with the PCOS had higher risk of infants delivered preterm (Risk Ratio = 1.96), very preterm (RR = 1.82) and with low birth weight (RR = 1.39). After adjusting BMI and gestational age the difference were no longer statistically. [114, 64]

Pregnancy induced hypertension and pre-eclampsia:-

Cardiovascular disease occurs 8% of PCOS women. The meta-analysis gives conclusion of 3- 4 times increase the risk of pregnancy induced hypertension in PCOS pregnancies.[Table1,13,56,90] Higher studies give the retrospective design, not the significant effect it's only detected in the meta regression.[90] The PCOS pregnancies lead to increase the maternal obesity. The meta-analysis gives the result of 3-4 folds increase the risk of pre-eclampsia it is similar to the pregnancy induced hypertension (PIH).[13,56,90] In PCOS pregnancies the 50% of women's cause the pre-eclampsia as compared to the normal one.[Table 1] In the pre-eclampsia which increase the blood pressure after the 20th week of pregnancy. Pre-eclampsia damage the mother's organs are kidney, liver, and brain. Comparison between PCOS and High Density Proteins (HDP) the risk for increased the pre-eclampsia in PCOS women but the control group was not Body Mass Index (BMI) matched.[95] When the comparison between PCOS and non-PCOS women the higher risk of increase the PIH in PCOS women after the BMI matched. The pre-eclampsia is not treated on time leads to cause the eclampsia. The PCOS pregnancy requires the C-section deliveries, the higher risk for mother as well as baby i.e. miscarriage, multiple pregnancies etc. [114]

Gestational Diabetes Mellitus (GDM):-

The gestational diabetes is one of the diabetes which pregnant women get 40 to 50% of gestational diabetes complicates the PCOS pregnancies. [81, 83] GDM caused due to the adequate pancreatic β-cell functioning in PCOS women's. [102,116] Treating the GDM which reduces the maternal and neonatal complications. [88] The risk of GDM is three times higher with PCOS women's. [13, 56, 90, 83] The use of metformin reduces the pregnancy complications in 274 pregnancies of women with PCOS the showing of PCOS ratio is (17.6 and 16.9 %) in the use of metformin and placebo group. [85, 95, 124] Pregnant women with PCOS containing GDM ratio is (Odd Ratio 2.32, 95% Confidence Intervals 1.88 - 2.88). After adjusting the age, BMI, hypertension, smoking, and demographic factor the GDM ratio will be (OR 2.1, 95% CI 1.1- 3.9). [85,48] The pregnant women with PCOS having the gestational diabetes mellitus (GDM) whose baby having the greater risk of causing the type- 2 diabetes mellitus later in life.

Miscarriage :-

Recent studies indicate that PCOS women's are at risk of first trimester miscarriage. This is because of early pregnancy loss (EPL) occurs in 30-50% of PCOS women compared with 10-15% of normal women's. [37, 46] Determination of EPL rate is different in all women's which cannot be accessed. [99] There are various mechanisms of EPL which includes obesity, insulin resistance, hyperandrogenism, impaired fibrinolysis and endometrial dysfunction. [99, 28, 29] Reoccurrence or spontaneous pregnancy loss in PCOS which occurs in nearly 50% of total pregnancies is a frequent obstetric complication. [123,125]

Caesarean Risk :-

The women with PCOS also lead to increase complication in caesarean deliveries as compared with normal deliveries or deliveries of women's without PCOS. [42,103] Due to the hormonal in in women with PCOS the size of embryo also gets increased and hence the risk of C-section or caesarean delivery gets increased twice as compared to normal women's. [Table 1] Also other factors like obesity and GDM can increased the risk of caesarean

deliveries. [25,Table 1] The infants with caesarean delivery of women with PCOS can also susceptible towards the risk of shoulder dystocia (condition in which baby's shoulder get stuck during labor) due to larger size of infant.[117]

Continuous Preterm Delivery/Prenatal Delivery :-

The prenatal deliveries can do worst effect on infant as well as mother with PCOS compared to mother without PCOS. [96] this can be further leads to GDM, obesity and other maternal issues. [49] Prenatal deliveries can indicates adverse effects due to poor development of oocyte, embryo quality and intrauterine environment.[40] The prenatal delivery of women with PCOS having GDM history can leads to develop fetal macrosomia resistant into altered glucose metabolism and disturbed uterine blood flow. [7] In several studies indicates that increase in preterm delivery (PTD) before 37 weeks of gestation in PCOS women's as compared to women's without PCOS. In women with PCOS the risk of PTD with antimullerine hormone (AMH) value is >9.75ng/ml was 4-fold higher and 2- fold higher in AMH value >13.66ng//ml.[42]

Other maternal complications :-

In the PCOS pregnancies the higher risk is the caesarean delivery (OR 1.56, 95% CI 1.20 - 2.02) i.e. the vaginal delivery was quite not higher with the PCOS pregnancies. [13, 56]

Fetal/neonatal outcomes :-

In fetal/neonatal outcomes with the women with PCOS having chance to increases the 2- folds risk of preterm deliveries because of the labor pain of the placental insufficiency. [90] Premature delivery ratio was (OR 2.21, 95% CI 1.69 - 2.90). [21] The infants who are delivered prematurely can chance of meconium aspiration (OR 2.02, 95% CI 1.13 - 3.61). [80] Also the probability to increase 2-fold risk of small for gestational age (SGA) having the women with PCOS. [13,56,38] The meta analysis study report conclude the large for gestational age (LGA) and no differences found for the outcomes in PCOS and non-PCOS outcomes. [56] The only difference in fetal outcome for the fetal growth of gestational age neonates is lower in PCOS then the non-PCOS women (68.3 vs. 87.3%) whereas the incidence of SGA (15.9 vs. 6.3%). [83, 3]

Offspring health :-

Mother having the PCOS his offspring having higher risk of developing endocrine and cardiovascular disease in later life and also increase cardio metabolic risk because of the intrauterine environment. [54, 127, 11] According to the barker hypothesis the lifetime health can be related to intrauterine environment. [54,11,10,108] PCOS women's offspring having the risk of insulin resistance (IR), metabolic abnormalities, endothelial dysfunction, obesity, offspring adiposity in later life and develop the first decade of life.[14,59] The women who having the pcos whose daughter having little bit problems during the puberty time. If the concentration of dihydroepiandrostenedione sulphate is increases in the daughter then the onset of puberty and around 30% exacerbated adrenerche.[71,114] Having the greater risk of cause ovarian androgenism in adolescence, may it cause pre-pubertal, pubertal, and post-pubertal hyper insulinaemia later in life.[24,44,45] Women with pcos whose daughter having higher risk of autism spectrum disorders because of the high testosterone levels.[86,114] It has also higher risk for the metabolic and reproductive disorders.[69,108] Pre-pregnancy overweight preterm birth and birth weight of singleton newborn compared the overweight and normal weight pregnant women with PCOS.[23] The PCOS women gradually increase the baby weight in pregnancy.[83,84] i.e. the PCOS women are obese in during and after pregnancy. The gestational weight gain and obesity are important factor to influencing the offspring health. [22,113] The early metformin treatment can prevent or

delay the development of hirsutism, androgen excess, oligomenorrhoea and pcos but the initially the metformin treatment in PCOS with pregnant women has minor weight gain pregnancy compared with controls who received the placebo Gives the long term complication in the children whose mother having the PCOS.[18,124]

Pathophysiological considerations regarding PCOS pregnancy complications :-

Increased pregnancy complications in women with PCOS having some factor to influence chemical as well as biochemical characteristics of pregnancy outcomes. [114] This factor is independently playing a major role in pathophysiological adverse pregnancy outcomes in women with PCOS.

Relevance of the heterogeneous PCOS features :-

Hyperandrogenism ovarian dysfunction with related oligo-amenorrhoea and polycystic ovary morphology (PCOM) are main criteria for the diagnosis of PCOS.[58,60,97] In PCOS women's androgen level are higher in compared with the non-PCOS controls it increases throughout the pregnancy hyperandrogenism causes the pregnancy.[68,110,53,33] The hyperandrogenism or increased androgen synthesis during pregnancy in women with PCOS are an abnormal steroidogenic function of the placenta in women with PCOS was demonstrated.[31,70,118] Serum testosterone and sex hormone binding globulin (SHBG) concentration in women can significantly increase or decreased hemodynamic changes during development of pulmonary embolism (PE).[104,105,123,2,33] High level of androgen can affect the offspring weight, disturbance of maternal energy, hemostatic and nutrition transport change.[12,109] The women who conceive pregnancy after long time to pregnancy will increased risk of preterm birth (OR 1.31,95% CI 1.21-1.42).[73,114] Placental alterations causes direct effect of androgens on endometria and dysregulation of lipolysis or lipid metabolism.[17,52,117]

PCOS – related comorbidities :-

Obesity is the severe comorbity in the reproduction associated with PCOS.[62,117,77] Obesity increased the risk of miscarriage and also other risks of maternal complications like thromboembolism.[74,57] The women's with PCOS associated with visceral obesity increased 2-3 fold risk of PIH and PE which associated with the body fat.[101,119,1] Obese PCOS women also increased a risk of unplanned caesarean delivery.[9,27,124,129] Fetus of obese PCOS women having risks of neural tube defects , heart defects and omphalocele.[106,16,93] It also shows long-term effects on metabolic disorder like hyperinsulinaemia associated with IR which develops hypertensive disorders in pregnancy.[26,75] Women with PIH/PE elevates insulin level and cause uncomplicated pregnancy. [63]

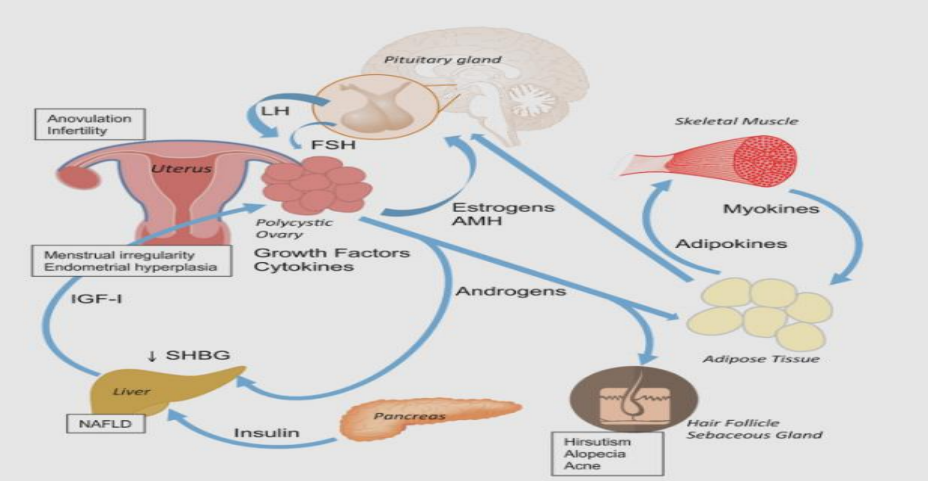

Figure 4: Schematic Representation of Pathological Complications [5]

PCOS- related infertility interventions :-

The anovulatory infertility can also leads to increased risk in complications related to PCOS pregnancy.[43,94] The pregnancies conceive and achieved after a time to pregnancy of more than 12 months probably ends premature delivery and infant having lower weight.[73] In obese women with PCOS consists a combination of hypocaloric diet and increased physical activity required for losing weight. This results into increase natural reproductive outcomes.[67,82] PCOS women having higher risk of preterm delivery due to ovulatory induction as compared to women without PCOS conceiving pregnancy (OR 1.45 95% CI 1.21-1.74).[87] IR is a typical characteristic of women with PCOS with prevalence ranging from 75-95% with respect to BMI in case of insulin sensitive biguanides particularly metformin on ovulatory induction.[114,115] Gonadotropins mediated ovulation induction indicated resistance or failure with clomiphene citrate.[121]

Hormone Independent alterations in Placenta :-

Hormone independent alterations are an important pathway in a nutrients transport of placenta for fetal growth in human with PCOS. [120] Effect of weight loss during pregnancy in obese women has a limited data.[35] According to data 2.9% of women's of reproductive age affected by pregestational diabetes specially type two diabetes mellitus.[41,4] Preconception care aimed at ensuring an adequate glycemic control which reduces risk of GDM. [122] In a case of women with PCOS associated with GDM metformin is an effective and safe as a medication, particularly for overweight and obese women.[8] Potential use of metformin over insulin suggested because maternal weight gaining pregnancy patient compliance an infant health.[97,58,111] Administration of metformin in pregnant women reduces uterine artery impedance between 12-19 weeks of gestation period.[100] Combinations of metformin with low molecular weight heparin (LMWH) reduce pregnancy loss in hyperhomocysteinaemia without any maternal side effect. [91, 19, 20]

Prevention and management in PCOS :-

There is no proper prevention to avoid PCOS syndrome but the PCOS women can get proper nutrition and weight management to avoid a complications such as diabetes, PIH and other cardiovascular diseases. [114] In the PCOS pregnancies the IR to cause the metabolic alteration as compared to normal pregnancies. In PCOS pregnant obese women having greater risk of preterm/neonatal delivery, intrauterine death and berth trauma as well as having greater risk of GDM and PE (RR 0.74, 95% CI 0.60-0.92) if it is avoid follow the dietary schedule to maintain the weight gain in pregnancy. [120] Before the conception developing higher risk of GDM in PCOS women depends on the fasting glucose level, androstindione, SHBG concentration and post history of type 2 diabetes. [114] In non-PCOS women related risk obesity, higher age, and particular ethnicity. The cholesterol, triglycerides, high density lipoprotein (HDL), B.P. and glucose level are confirmed before in pregnancies because there imbalance caused the preterm birth and shorter the gestational period. [66] In gestational period to maintain hygiene and total focus on the early change of proteins leads to dyslipidemia and to decrease hemoglobin level and hematocrit level because of these biochemical markers causes the higher risk of pregnancy complication in women with PCOS. [114] Metformin is antidiabetic drug which is used in the GDM. [98] It helps to maintain blood glucose level safely and effectively in the patient with GDM in non RCTs. [128, 78,130] In randomized controlled trials (RCTs) repeatedly use of metformin causes the decrease in maternal weight gains in pregnancy it also caused the uterine artery impedance in between the 12 to 19 weeks gestational period. [36] Hence, it does not show specific effect to reduce or prevent

PIH. Metformin is combine with LMWH to decrease pregnancy loss in limited women's associated with PCOS. As LMWH is prescribed alone to reduce pregnancy loss as well as coagulation. LMWH and Acetylsalicylic Acid (ASA) are combined to avoid spontaneous abortion in those women with hyperhomocystenemia.[19,20,85] Combination of oral contraceptives and anti-androgens reduce androgen level which helps to treat symptomatic endometrial problems.[69] Overall goals of therapy include severity of hyperandrogenic syndrome reduction of risk factors for GDM and cardiovascular disease and metabolic abnormalities management, planning to obtain safe pregnancy by improving quality of life achieved by multidisciplinary team providing patient center care.[Figure.5]

Metabolism:- Overweight and obese patient, weight loss is caused due to change in physical activity and nutritional alteration which leads to decrease insulin and androgen level results into glucose intolerance.[7] Metformin is commonly used drug which act as an insulin sensitizing and hypoglycemic agent in the PCOS women.[128,78] There is no evidence that metformin reduces BMI in women with PCOS compared with placebo.[78] The women who receive antiandrogens along with oral contraceptives will minimize the effect of metformin on BMI.[65] Liraglutyl is a glucagon like peptide receptor-1 agonist use for the treatment of type-2 diabetes and obesity which significantly helps in weight loss and reduces waist circumstance.[47] Myo-and D-chiro-inositol is insulin sensitizing agent works as an insulin singling secondary messenger and also as a possible alternative to metformin in IR associated PCOS women.[76]

Quality of life: - PCOS patient having large impact of psychological effect like depression, anxiety, and sleep disorders. [21] Psychological effect includes common symptoms like sleep disturbance, appetite change, fatigue and loss in interest in daily activities. Evolution of these is essential for better care and management for those patient associated with PCOS. [Figure.5]

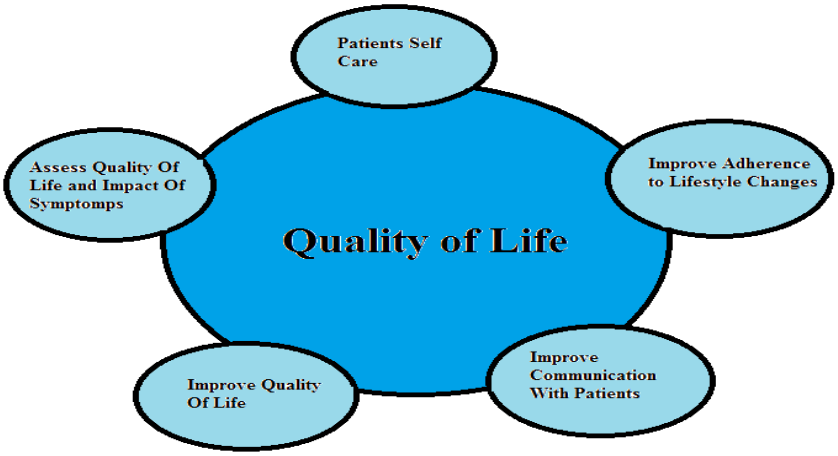

Figure 5: Objectives of assessing the quality of life[5]

Infertility: -

First line therapy includes folic acid supplement and cessation of smoking and alcohol consumption. Second line treatment includes ovulation induction. Clomiphene citrate is given as a reference therapy for ovulation induction in women with PCOS associated with infertility and anovulation. Metformin is not recommended in ovulation induction due to low live birth rate. [78, 89] Letrozole which is an aromatase inhibiter work as alternative to clomiphene citrate. [126, 34]

Patient Counselling with Psychological support:-

As we know, PCOS is a hormonal imbalance disorder which mainly affect at a gestational period of a women. So, to avoid or handle any complications regarding PCOS in pregnant women as well as in infant preconception counselling or advice regarding lifestyle, obesity and period of conceiving pregnancy should be required.[44] Most of the study indicates that women with PCOS associated with obesity or weight gain affected most by the metabolic, psychological and reproductive repercussion of PCOS.[90] PCOS women have low rate of pregnancy due to lower uptake of contraception and hence practitioner should counseled patient about appropriate use of contraception to avoid unplanned pregnancy.[43] In women with PCOS requires more psychological support like interpersonal communication, emotional as well as relational support.[50,55] The counselling should include things like exercise and nutritional counselling on hormonal, menstrual and reproductive function in women with PCOS.[15]

CONCLUSION

As pregnancy is an important event of women's life cycle. This topic highlights about major complications and management to avoid or handle complications related to women associated with polycystic ovarian syndrome. As the mechanism for PCOS is remain unclear till now but there is possible mechanism is chemical or hormonal imbalance in the women body. The main complications involves pregnancy complications, pathological complications and maternal or preterm delivery complications which will be seriously effect on the mother health as well as offspring/neonates health. Pregnancy in PCOS worsens the risk in physiological metabolic and inflammatory changes during gestational period. PCOS in pregnancy also effect on several co-morbidities and cofactors which increase absolute risk in the relevant threshold. The management of polycystic ovary syndrome involved various clinical, biochemical and proteomic markers as a potential diagnostic tool. Other things involved in the PCOS pregnancy are reproductive history including non-complicated and complicated pregnancies which cause long-term maternal and offspring health effects. Pregnancy complications in PCOS include long term maternal effects like ovarian steroidogenesis, development of type-2 diabetes mellitus, PE, cardiovascular disease. PCOS can also able to cause some phenotypic alterations. Integral management regarding to PCOS need to develop a multidisciplinary team which helps to provide lifestyle interventions and psychological support to patient. Some of the complications are explored but most of the complications remain unexplored. To explore this complications and treatment regarding to polycystic ovary syndrome is important future perspective for research.

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