

# Role of hyperhomocysteinemia in the pathogenesis of polycystic ovary syndrome

Urjumelashvili Manana<sup>1</sup>, Kristesashvili Jenaro<sup>2</sup>, Asanidze Elene<sup>3</sup>

## Abstract

**Background:** Polycystic ovary syndrome is the reason not only of infertility but also the one of the most important risk factors of miscarriage.

Until recent period hyperinsulinemia and hyperandrogenemia were considered in the pathogenesis of polycystic ovary syndrome, but in recent years, the studies have been reported that miscarriage in patients with polycystic ovary syndrome can be associated with hyperhomocysteinemia. Therefore, hyperhomocysteinemia may be considered as one of the newly identified characteristics of polycystic ovary syndrome.

Nowadays the matter of interest is to determine associations between hyperhomocysteinemia and metabolic syndrome and their contribution in the processes of ovulation, conception, pregnancy, pregnancy loss and live birth in infertile women with polycystic ovary syndrome. This data may give possibility to predict reduction in the ovulation rate and determination of the prognosis of miscarriages in women with polycystic ovary syndrome based on elevated homocysteine levels.

**Aim of the study:** We aimed to observe literature data to review the current understanding of the role of hyperhomocysteinemia in the pathogenesis of polycystic ovary syndrome and analyse of modern management of polycystic ovary syndrome.

**Materials and methods:** For this purpose following electronic databases were searched: Pubmed, Medline, Cochrane Library, Web of Science, EMBASE, Europe PMC, Science Direct, NCBI, Semantic Scholar, National Library of Medicine, Springer.

**Results:** 129 article was reviewed, 70 of them attracted our attention by their statistical significance and were analysed and discussed in our article.

**Conclusion:** Obtained controversial results do not allow specifying the role of hyperhomocysteinemia in the pathogenesis of polycystic ovary syndrome. That means the research in this direction should be continued because understanding the mechanisms of pathogenesis of polycystic ovary syndrome, is very important for effective management.

**Keywords:** polycystic ovary syndrome; PCOS, homocysteine, hyperhomocysteinemia, MTHFR

## Introduction

**R**ight to have a child is one of the most important human rights (13,14,18). However, due to infertility this right cannot be experienced by up to 50 million couples worldwide (17). According to WHO 2010 data about 12% of women were infertile (15, 16, 17), which leads to decreased quality of life of these people and their realization in the society.

Infertility is individual problem for individual couples even in countries with high birth rates while in Georgia, with amid alarmingly low birth rate, infertility is gaining special medical and social significance (17). Thus, identifying the causes of infertility based on the achievements of modern medicine and developing

highly effective management methods to overcome this problem is of state importance in Georgia.

Endocrine disorders are one of the leading causes of infertility in women. According to various studies rate of polycystic ovary syndrome (PCOS) in female infertility of endocrine genesis is 5-15% (19, 37). Clinically it is manifested by anovulation, oligo/amenorrhea, infertility, hirsutism, acne and obesity (3). 5-10% of clinical manifestations depend on race, ethnicity, environmental factors and phenotype (4).

Manifestation of polycystic ovary syndrome is not limited to reproductive disorders. It is associated with arterial hypertension, dyslipidemia, obesity, insulin resistance, and metabolic syndrome, leading to future health problems such as cardiovascular diseases and type 2 diabetes (2, 5).

Achieving pregnancy is not enough to fulfill the function of childbirth. It is very important to maintain this pregnancy, bring it to full term and give live birth.

Polycystic ovary syndrome is known to be one of

From the <sup>1,2</sup>Iv.Javakishvili Tbilisi state University; <sup>3</sup>University Geomedi  
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Address requests to: Urjumelashvili Manana  
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the most important risk factors not only for infertility but also for spontaneous abortion. In particular, the risk of spontaneous abortion in PCOS women is 40% (20). According to various studies, this rate varies between 25-73% (20, 21, 22).

Women with polycystic ovary syndrome (PCOS) are at higher risk for certain problems or complications during pregnancy. Complications of pregnancy commonly associated with PCOS could be a reason for these risks (71). PCOS is not only related to metabolic abnormalities, menstrual irregularity or infertility as previously reported, but becoming increasingly recognized the problems of gestational diabetes (GDM), pregnancy-induced hypertension, preeclampsia, premature delivery rate, neonatal birth weight, caesarean section rate, and rate and admission to an NICU, which are all considered to be adverse pregnancy outcomes of PCOS during pregnancy. The elevated risk for adverse obstetric complications that was observed in women presenting PCOS varied widely depending on the different phenotypes and features of PCOS. There have been a number of relevant studies performed in order to illustrate incidences of pregnancy and neonatal complications (72).

In 2011 Lucinda E Kjeruff et al and in 2013 by Jun Z Qin et al conducted an interesting studies. The purpose of these studies were to examine which maternal and neonatal complications are associated with polycystic ovary syndrome (PCOS) in pregnant women. The studies that were included compared pregnancy outcomes between women with PCOS and those without diagnosed PCOS. Primary outcomes included gestational diabetes mellitus, pregnancy-induced hypertension, and preeclampsia. Secondary outcomes included cesarean delivery rates, operative vaginal delivery rates, preterm delivery, small-for-gestational-age (SGA) infants and large-for-gestational-age infants. They found that PCOS in pregnancy was associated with higher rates of gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, preterm delivery, cesarean delivery, operative vaginal delivery, SGA, and large-for-gestational age. Only gestational diabetes mellitus, pregnancy-induced hypertension, preeclampsia, preterm delivery and SGA infants were found to be statistically significant. These metaanalysis confirms the higher association of pregnancy complications and PCOS compared with patients who do not have PCOS. They concluded that women with PCOS are at increased risk of adverse pregnancy and neonatal complications; this information may be vital in clinical practice for the management of pregnancy in women with PCOS. These women should be given notice of the additional risks their pregnancies may have, stronger surveillance and attention should be provided, as well as screening for these complications during pregnancy and parturition (72,73).

Regine P Steegers – Theunissen et al in case – control study they conducted in 2004 they evaluated that hy-

perhomocysteinemia was associated with an approximately 2 – fold to 3 – fold increased risk for pregnancy-induced hypertension, abruptio placentae, and intrauterine growth restriction. Cobalamin deficiency was associated with HELLP syndrome, abruptio placentae, intrauterine growth restriction, and intrauterine fetal death. Pyridoxal 5-phosphate deficiency increased the risk for pregnancy-induced hypertension 4-fold. These associations lost their significance after adjustment for time interval and maternal age. High red cell folate was associated with a decreased risk for abruptio placentae and intrauterine growth restriction. They concluded that hyperhomocysteinemia and vitamin deficiencies are largely determined by the interval between delivery and postpartum investigation and by maternal age. Time interval and maternal age should be considered in the risk estimation for vascular-related pregnancy complications (74).

### Diagnostic criteria of PCOS

Manifestation of polycystic ovary syndrome can begin during puberty and continue until postmenopause. PCOS is a major cause of menstrual dysfunction and hyperandrogenism in adolescents, leading cause of anovulatory infertility in the reproductive age, and in menopause it is a risk factor for development of diabetes mellitus, cardiovascular diseases, and adenocarcinoma (9).

Diagnosis of polycystic ovary syndrome at different stages was based on different sets of diagnostic criteria.

The first step in the study of polycystic ovary syndrome was to investigate its structure. With the development of histological and histochemical methods, its details were refined and the obtained results were published by Stein, Leventhal, and Lesnoi in 1928 – 1935 in their first publications (70). Stein and Leventhal syndrome was first described in 1935, which was characterized by irregular menstrual cycles, infertility, hirsutism, relatively rarely obesity and breast hypoplasia, and ovarian enlargement and cystic changes. Menstrual cycle disorders were in the form of primary or secondary amenorrhea, with anovulatory bleeding (69).

Quite practical classification for use in clinical practice was proposed by Krimaskaya in 1980, according to which 3 forms of PCOS were defined according to the source of hyperandrogenism (70):

1. Typical form - ovarian hyperandrogenism (primary polycystic ovaries);
2. Mixed form - includes ovarian and adrenal hyperandrogenism;
3. Central form - clinical manifestations of dysfunction of the hypothalamic-pituitary system, which regulates the function of the reproductive system.

In 1990, National Institutes of Health (NIH) established the diagnostic criteria for polycystic ovary syndrome, according to which diagnosis of polycystic ovary syndrome is based on the following criteria:

- Hyperandrogenism and / or hyperandrogenemia;
- Menstrual dysfunction.

In 2006, Androgen Excess and PCOS Society proposed the following PCOS diagnostic criteria:

- Clinically or biochemically detected hyperandrogenism;
- Ovarian dysfunction (oligo / anovulation and / or morphologically polycystic ovaries).

At present, diagnosis of polycystic ovary syndrome is based on the diagnostic criteria adopted at the Rotterdam ESHRE ASRM – Sponsored PCOS Consensus, Workshop, 2003, according to which diagnosis of polycystic ovary syndrome is made if at least two of the three criteria below are presented:

- Oligo / amenorrhea and / or chronic anovulation;
- Clinically and / or biochemically confirmed hyperandrogenemia;
- Multifollicular ovaries ( $\geq 12$  follicles of 2 - 9 mm diameter, or one or both ovary volume  $> 10$  m<sup>3</sup>) (6, 9).

According to this Consensus, thyroid diseases, hyperprolactinemia, androgen - producing tumors, adrenal hyperplasia, and Cushing's syndrome should be excluded.

The diagnosis of polycystic ovary syndrome in adolescents has difficulties as it is often associated with differentiation of PCOS with physiological pubertate, as physiological pubertate is characterized by such manifestations as menstrual cycle disorders, clinical manifestation of hyperandrogenism in the form of acne, multifollicular ovaries by ultrasound examination, and secondary insulin resistance, which is developed at the expense of elevated growth hormone (9).

At present, diagnostic criteria adopted at the Rotterdam ESHRE ASRM – Sponsored PCOS Consensus Workshop, 2003, are used for diagnosis of polycystic ovary syndrome in adolescents as well (9). However, these criteria do not take into account peculiarities of adolescent physiology, so different authors offer different diagnostic markers of polycystic ovary syndrome in adolescents (62,67).

According to Sultan and Paris, diagnosis of PCOS in adolescents is made, if at least 4 of the 5 criteria given below are present (67):

1. Oligo / amenorrhea or amenorrhea after 2 years from menarche,
2. Clinical hyperandrogenism,
3. Biochemical hyperandrogenism,
4. Insulinresistance or hyperinsulinemia,
5. Polycystic ovaries by ultrasound examination

By Carmina's proposal made in 2010, adolescent girls with PCOS should meet all three criteria according to Rotterdam criteria. Adolescent girls who have only 2 criteria are at high risk of syndrome development and require constant supervision (62). According to the ESHRE 2018 Guidelines, for diagnosis of PCOS in the adolescents whose gynecological age  $< 8$

years from menarche, use of ultrasound examination is not enough to make diagnosis, since this stage of life is physiologically characterized by multifollicular ovaries (68).

### Aim of the Study

Many researches on the polycystic ovary syndrome have been conducted. Despite the numerous studies, etiopathogenesis of PCOS is not yet fully specified. Understanding the mechanisms of pathogenesis of polycystic ovary syndrome and its effective management is very important.

Until recent period hyperinsulinemia and hyperandrogenemia were considered in the pathogenesis of polycystic ovary syndrome, but in recent years, the studies have been reported that spontaneous abortions in patients with polycystic ovary syndrome are associated with hyperhomocysteinemia, therefore, hyperhomocysteinemia (HHCY) may be considered as one of the newly identified characteristics of PCOS (20, 21, 22, 37).

So we aimed to observe literature and to review the current understanding of the role of hyperhomocysteinemia in the pathogenesis of polycystic ovary syndrome.

### Materials and Methods

For this purpose following electronic databases were searched: Pubmed, Medline, Cochrane Library, Web of Science, EMBASE, Europe PMC, Science Direct, NCBI, Semantic Scholar, National Library of Medicine, Springer. 129 article was reviewed, 70 of them attracted our attention by their statistical significance and were analysed.

### Results

In recent years, hyperhomocysteinemia is considered to be the main characteristic of polycystic ovary syndrome. Homocysteine is a non – protein  $\alpha$  - amino acid and homologous to amino acid cysteine. Its pathway covers remethylation to methionine or trans-sulfuration to cystathionine, as shown on Figure 1.

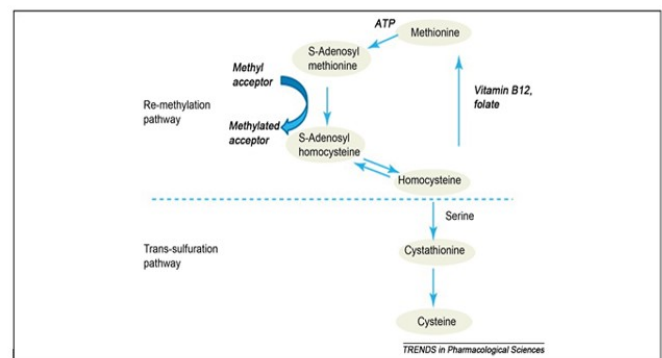


Figure 1 Homocysteine metabolism, ref. (33)

The first pathway of metabolism needs folate and vitamin B12, while the second pathway requires pyridoxal 5'-phosphate (PLP). These both ways of synthesis are strengthened by S-adenosyl methionine (SAM), which is moderator of methylenetetrahydrofolate reductase (MTHFR) and inhibitor of cystathionine- $\beta$ -synthase (CBS). These metabolic pathways are impaired during either cystathionine- $\beta$ -synthase (CBS) mutation or vitamin B6 deficiency, or blocking of remethylation cycle, which leads to accumulation of homocysteine in the blood plasma. As a result of blocking of remethylation cycle, increase in the level of homocysteine in the blood can be due to folate and vitamin B12, as well as MTHFR deficiency (37).

It is known that Hcy and insulin have the ability to induce each other by inhibiting hepatic cystathionine- $\beta$ -synthase (CBS) that results in hyperhomocysteinemia leading to compensatory hyperinsulinemia by inducing insulin resistance. This may impair activity of the MTHFR or CBS enzymes, leading to abnormal deposition of homocysteine in plasma (37).

Bar-on H et al. believe that PCOS-associated insulin resistance leads to hyperhomocysteinemia with impact of insulin on cystathionine- $\beta$ -synthase (26). These results of the study coincided with data of several other researches. In particular, correlation between homocysteine levels and insulin resistance in patients with PCOS was detected in De Pergola's et al. study (27).

It is established that several factors affect homocysteine level in blood serum. These factors include age, gender, smoking, physical activity, chronic inflammatory process, diet, and insulin (10). Normally, homocysteine levels are higher in men than in women and increases with age from 10.8 mmol/L at the age of 40–42 to 12.4 mmol/L at the age of 65–67. Hyperhomocysteinemia is classified as mild (15–30 mmol/L), intermediate (31–100 mmol/L) and severe (>100 mmol/L) (50).

In studies conducted by Hui Chang in Chinese population the level of homocysteine in blood serum >12  $\mu$ mol/l is considered as hyperhomocysteinemia (36).

Patients with hyperhomocysteinemia are prone to damage to endothelial cells, which causes an inflammatory process in blood vessels and in turn contributes to the development of atherogenesis, that can result in ischemic tissue damage (3). Besides the fact that hyperhomocysteinemia correlates with blood clots formation, infarctions, it is an important risk factor for development of many diseases, such as thrombosis, cerebrovascular diseases (Alzheimer's disease, brain atrophy and bone fractures, osteoporosis, femoral shaft fracture) (21, 22, 23, 24, 34, 26, 27). Hyperhomocysteinemia is also associated with early pregnancy loss, in particular, hyperhomocysteinemia increases hypercoagulability of pregnancy and likelihood of development of thrombosis in the blood circulation sys-

tem and, as a result, adverse pregnancy outcomes (6). On the early terms of pregnancy, including preimplantation period, hyperhomocysteinemia contributes to early pregnancy loss due to impaired implantation through interfering with endometrial blood flow and its vascular integrity, while at late terms promotes such complications as preeclampsia (PE), preterm labor (PTL), placental abruption, intrauterine growth restriction (IUGR) (6,20). In addition, hyperhomocysteinemia is associated with fetal neural tube defects (NTDs) (6).

In recent years, it was established that the development of pregnancy losses is due to the mutations of thrombophilia genes in mother. In difference with previous years data, new studies have been shown that MTHFR genes mutations contribute to second trimester losses, as well as are the risk factors for early pregnancy losses. As mentioned above, hyperhomocysteinemia, conditioned by MTHFR genes mutations contribute to early pregnancy loss due to impaired implantation through interfering with endometrial blood flow and its vascular integrity (11) (20).

Over the last decade quite a lot of studies were conducted to determine the rate of hyperhomocysteinemia in women with PCOS. In addition, it was studied association of hyperhomocysteinemia with such PCOS characteristics as insulin resistance, increased androgen levels and obesity (3, 11, 26, 34). However, obtained diverse results do not allow specifying the role of hyperhomocysteinemia in the pathogenesis of PCOS and therefore, addition of any recommendation in patient's management based on homocysteine indicators is limited, which indicates the need for further comprehensive research in this direction (3, 34, 37).

All above mentioned has been raised the interest to study correlation of hyperhomocysteinemia with insulin resistance and PCOS biochemical markers. According to the case-control studies conducted in 2013 by Sachan Rekha and in 2018 by Pranita Maharjan with co-authors, blood serum homocysteine indicators were significantly high in both, women with PCOS who had excess weight, as well as with a normal body mass and were in positive correlation with HOMA index (37, 38). In their study conducted in 2013, Murri et al. found associations of hyperhomocysteinemia with 3 of 5 criteria of the metabolic syndrome established by 2003 Rotterdam ESHRE / ASRM-Sponsored PCOS consensus workshop group: insulin resistance, elevated arterial pressure, and increased low density lipoproteins (36).

Similar correlation between increased homocysteine levels and insulin resistance was found in studies conducted in 2011 by Caglar, G. S. et al. and in 2012 by Rajagopal G. et al. (46, 47).

As it was mentioned above, according to data by Pranita Maharjan et al., one of the case-control studies conducted in 2018 established significant increase in homocysteine levels in both, patients with PCOS who had excess weight, as well as with a nor-

mal body mass. The same study revealed positive correlation between hyperhomocysteinemia and insulin resistance. At the same time, Esmailzadeh, S. et al. and Rosolova et al. independently of each other have established inverse relationship between homocysteine levels and insulin resistance parameters, in particular, high fasting IRI levels, high triglycerides, BMI, blood pressure and PAI - 1, and decreased low – density lipoproteins in blood serum (37, 39, 40). They also obtained statistically reliable data -- negative correlation between SSPG and homocysteine level in blood serum (37). At the same time, several authors did not find association between homocysteine levels and insulin resistance (41, 42, 43, 44, 45).

Research conducted by Rojeen\_Rasheed\_Suleiman and Dhia\_Mustafa\_Suleiman, staff members of the laboratory of the College of Health and Medical Technologies in Shekhan, Duhok Polytechnic University, Iraq, is noteworthy (28). The aim of researchers was to evaluate homocysteine levels in patients with PCOS. Through a case – control study (50 patients with PCOS by Rotterdam criterion and 40 healthy women), they have studied homocysteine levels in the blood serum with the use of Cobas 6000. Their results have shown that the level of homocysteinemia is significantly higher and average level of homocysteine in blood serum is higher in women with PCOS than in healthy women. This may be result of insulin resistance due to the impact of insulin on cystathionine  $\beta$  - synthase. Percentage prevalence of hyperhomocysteinemia was statistically reliable in PCOS patients compared to the control group. However, significant difference between homocysteine levels in normal and high BMI was not found. Study, conducted by Guzelmeric K, Alkan, et al., also found that high BMI is associated with increased homocysteine levels (25, 28).

The authors believe that based on the results of their study increased homocysteine levels in blood serum can be considered as PCOS biomarker (28).

These results match the results of the studies conducted by Al – Gareeb et al. and Maleedhu P. et al., significant increase in homocysteine levels in both, PCOS patients who had excess weight, as well as with a normal body mass, compared to respective control groups was detected (41,48).

However, Palomba S. et al. received opposite results. Their study have not found significant differences between homocysteine levels in patients with polycystic ovary syndrome and in the control group (49).

Obtaining different data from studies may be due to the fact, that homocysteine levels vary according to age, populations, diet and many other factors, and therefore no threshold norms have been set.

Interesting study was conducted by Hui Chang et al. The goal of their study was to determine associations between hyperhomocysteinemia and metabolic syndrome and their contribution to the processes of

ovulation, conception, pregnancy, pregnancy loss and live birth in infertile women with polycystic ovary syndrome. This data may give possibility to predict reduction in the ovulation rate and determination of the prognosis of miscarriages in women with PCOS based on elevated homocysteine levels. Participants of the study were divided into 3 groups according to

homocysteine levels ( lower tertile - HCY  $\leq$  6,09  $\mu\text{mol/l}$ , middle tertile - HCY 6,10 - 9,33  $\mu\text{mol/l}$ , upper tertile - HCY  $>$  9,34  $\mu\text{mol/l}$ ). High BMI was observed in the upper tertile group of homocysteine. Lower tertile group showed increase in FSH and trend of decrease in free testosterone. No significant difference between the ultrasonography data in all three groups was found. Statistically significant differences were observed in ovulation rate, in particular the inverse relationship between homocysteine level and ovulation rate in the middle and upper tertile compared with the lower tertile. Ovulation, conception, pregnancy, second and third trimester pregnancy losses and live birth rates in the group of patients with metabolic syndrome after adjusting treatment were statistically significantly lower than in the control group. Negative effect of high levels of homocysteine on ovulation rate was no longer observed after normalization of sex hormone levels. Based on above they concluded that the effect of hyperhomocysteinemia on ovulation was due to the action of homocysteine on sex hormones. Authors indicate that elevated serum homocysteine levels in blood serum are associated with sporadic anovulation and hormonal changes, indicating impaired ovulatory function. These data are consistent with Michels et al. 2017 opinion, who found correlations between elevated homocysteine levels and decreased total estradiol levels (51). Possible reason for tendency for estradiol levels to decrease in women with hyperhomocysteinemia is that elevated levels of homocysteine in the follicular fluid may suppress estradiol production and affect dominant follicle development, oocyte maturation, and fertilization in PCOS women who use assisted reproductive technologies.

Interesting was the meta – analysis conducted by Yuming Meng et al., which included 34 studies involving a total of 1718 study and 1399 control subjects. Meta – analysis aimed at establishing in PCOS women associations of high homocysteine levels with biochemical characteristics of PCOS. Based on obtained results researchers suggested that high levels of homocysteine in PCOS women were not associated with obesity, insulin resistance status or androgen levels. They also found that metformin treatment does not reduce homocysteine levels in PCOS patients (34).

Therefore, studies to determine significance of hyperhomocysteinemia in the pathogenesis of PCOS should take into account the fact that hyperhomocysteinemia may also be caused by other factors. In particular, as mentioned above, association of hyperho-

homocysteinemia with MTHFR gene mutations has been determined (3,50). Thus, in cases of PCOS, it should be considered appropriate to exclude MTHFR C677T and MTHFR A1298C genes mutations to avoid erroneous results in patients with PCOS, as well as inclusion of this component in the study in PCOS patients.

When conducting the study to determine the genesis of hyperhomocysteinemia, it is important to consider that polymorphism of MTHFR gene is characterized by population differences. The rate of MTHFR gene mutations in Egyptian women with recurrent idiopathic pregnancy loss was 63% (64, 65); In southern Italy, 78% of cases of recurrent pregnancy loss of unknown genesis one or more thrombophilic abnormalities were detected. The rate of MTHFR C677T gene mutation in Northern Europe is 32.7%, in Southern Europe - 62.5 - 79.2%, in Africans - 11.9%, in East Asian countries - 1.1 - 16.1%, in West Asian countries 47.7%, in Hispanic - 47.9% (64,66). However, studies conducted in Georgia in previous years indicate that MTHFR gene mutations are quite common in Georgian population, in particular, the prevalence of MTHFR C677T gene mutations in Georgia is 46.1% (12, 64).

As mentioned above, high rate of MTHFR C677T gene mutation has been found in Georgian population, but MTHFR A1298C gene mutations in women with pregnancy losses and in the control group has not been studied (12), while there are literature data that thrombosis and pregnancy losses develop in MTHFR A1298C compound heterozygous as well as in MTHFR C677T homozygous. And in women with PCOS, correlations between homocysteine levels and insulin, antimullerian hormone and androgen levels manifested by hyperhomocysteinemia have been established in a small group without excluding genetically induced hyperhomocysteinemia (9).

Since hyperhomocysteinemia is associated with MTHFR gene mutations, it is interesting, is the hyperhomocysteinemia and MTHFR gene mutations in case of polycystic ovary syndrome just coincidence, or could hyperhomocysteinemia be an independent factor in the pathogenesis of polycystic ovary syndrome.

Highly interesting study was conducted by Talieh Kazerooni et al., designed to study pathogenesis of recurrent pregnancy losses (RPL) in patients with polycystic ovary syndrome and establish associations with thrombophilias. Four groups were identified: 1. PCOS and RPL; 2. PCOS without RPL; 3. RPL without PCOS and control group. In the study they attempted to identify the role of hyperandrogenism, insulin resistance, and hyperhomocysteinemia in patients with PCOS and recurrent pregnancy loss. In the study they found that patients with PCOS and RPL had significantly higher levels of testosterone, DHEA-S, Hcy compared to patients without PCOS and RPL. Miscarriages in patients with PCOS were associated with hypofibrinolysis (PAI – Fx was defined) and de-

creased insulin sensitivity. Elevated homocysteine levels were also found in patients with pregnancy loss compared to healthy individuals. Significantly high levels of homocysteine were found in PCOS patients with RPL compared with patients with PCOS only, thus indicating the role of hyperhomocysteinemia in the pathogenesis of RPL in case of polycystic ovary syndrome. According to the authors, insulin resistance in polycystic ovary syndrome and, consequently, hyperinsulinemia leads not only to hyperandrogenemia, but also to hypofibrinolysis and hyperhomocysteinemia. This, in turn, increases the risk of developing recurrent pregnancy loss (5).

### Conclusion

Obtained controversial results and the fact, that in most of these studies genetic causes of hyperhomocysteinemia are not excluded, do not allow specifying the role of hyperhomocysteinemia in the pathogenesis of polycystic ovary syndrome. That means the research in this direction with exclusion of genetic factors and taking into account population characteristics should be continued because understanding the mechanisms of pathogenesis of polycystic ovary syndrome, is very important for its effective management.

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