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Effect of homocysteine on pregnancy: A systematic review

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ABSTRACT

Research purpose was to put together the available pieces of present scientific data and to close the gap in the knowledge of Hcy levels in pregnancy and its association with some pregnancy complications. Scientific data were taken from research papers published between January 1990 and December 2017, and found on the Internet (PubMed, ClinicalKey and Embase databases) by the following tags entered in English, Russian, French and German languages: *pregnancy*, *homocysteine*, *pregnancy complications*, *pregnancy loss*, *preeclampsia*, *intrauterine growth restriction*, and *placental abruption*. The review showed that Hcy levels range in uncomplicated pregnancy. Upon that, Hcy level tends to decrease during the second and third trimesters. Some studies have revealed a link between polymorphism and abortion. Sufficient data were obtained indicating the relationship between HHcy and PE. Placental abruption was also associated with high Hcy levels increasing the risk 5.3-fold, but still there are data not supporting the hypothesis that Hcy levels correlate with placental abruption.

1. Introduction

Despite the fact that homocysteine was first described in 1932, primary publications on the link between the increased homocysteine concentration and pathological conditions (cardiovascular diseases, pregnancy pathologies, neuropsychiatric disorders) appeared only in recent decades [1,2].

Homocysteine (Hcy) is a non-protein amino acid made from methionine that lost its terminal methyl group. It can be converted back to methionine using 5-methyltetrahydrofolate and methylcobalamin [3]. Hcy metabolism is at the crossroad of two pathways: remethylation pathway generating methionine (it requires folates and vitamin B12), and a pathway of transsulfuration to cysteine that requires pyridoxal-5′-phosphate [4]. The Hcy molecule is not removed during remethylation and transmethylation reactions, but it converts to cysteine during transsulfuration [5], supported by two vitamin B6-dependent enzymes: cystathionine β-synthase (CBS) and cystathionine gamma-lyase (CTH). CBS catalyzes the condensation of Hcy with serine to form cystathionine, while CTH breaks down cystathionine into cysteine and α-ketobutyrate. Aside from its role in protein synthesis, cysteine is a glutathione precursor, a strong antioxidant and a central compound in detoxification of many xenobiotics [6]. In most tissues, Hcy is either remethylated through methionine synthase or removed from the cell. The liver is the main organ of degradation of excess methionine and in maintaining homocysteine at adequate levels via a unique set of enzymes, including MAT I/III, CBS, CTH, BHMT, GNMT (glycine N-methyltransferase). One of the central mechanisms for regulation is that high levels of S-adenosylmethionine inhibit MTHFR and activate CBS [6]. Thus, an excess of methionine results in higher levels of S-adenosylmethionine (SAM) during homocysteine degradation by transsulfuration. Conversely, if methionine levels are low, for example during fasting, low SAM levels do not activate CBS and do not inhibit MTHFR activity, thereby leading to remethylation of homocysteine back to methionine.

There are three main HHcy causes: 1) Genetic defects in the enzymes of Hcy metabolism – 5, 10-MTHFR 677C → T mutations that inhibit homocysteine conversion to methionine; T133C, p.I278T and p.T191M mutations of the CBS gene [7,8]. 2) Nutritional disorder, resulting in a deficiency of folate or vitamin B12. Folate deficiency can result from malabsorption syndromes, alcoholism and liver diseases. Since the source of vitamin B12 is meat and dairy products, vegetarians are more prone to B12 deficiency [9,10]. 3) Impaired renal function – although the exact mechanism of homocysteine accumulation in patients with renal insufficiency is not understood completely, possible cause may be a defective clearance and/or a decrease in extrarenal metabolism [11,12].

As recent epidemiological studies indicated, Hyperhomocysteinemia (HHcy) is a condition associated with an increased risk of vascular disease induced by Hcy metabolism disorder. Severe HHcy is triggered by rare genetic defects leading to CBS, MTHFR

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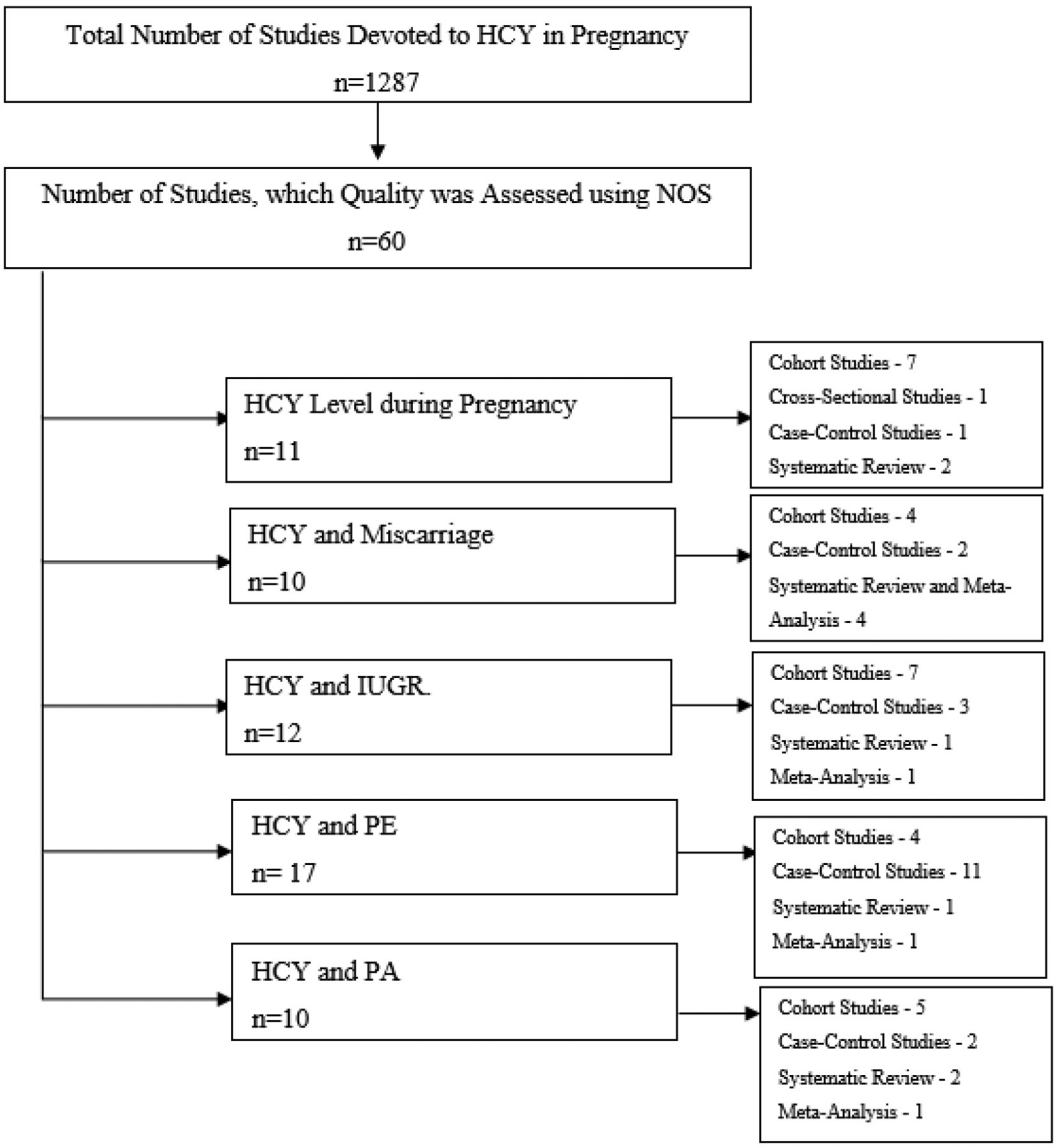

Fig. 1. Studies selection.

on enzyme deficiency In the last case, these are enzymes involved in the synthesis of Methyl B-12 and Hcy methylation. The mild HHcy observed under fasting conditions is caused by a moderate deterioration of the methylation pathway (folate/B12 deficiency or the lack of MTHFR thermal stability) [13,14].

HHcy results in endothelial damage. It increases the oxidative stress and stimulates ROS production during the autoxidation process, catalyzed by metal cation (such as copper and superoxide anion) that reacted with NO to form peroxynitrate. The latter reduces NO bioavailability. At the same time, oxidative stress activates matrix metalloproteases disturbing the extracellular matrix metabolism. HHcy also increases collagen accumulation that leads to vascular fibrosis [15–18]. Endothelial cell injury in HHcy leads to decreased protein C activation and inhibits thrombomodulin expression, which decrease contributes to local procoagulant state [19,20]. Such a damage also reduces the fibrinolytic activity [21]. Leukocyte migration and platelet adhesion result in microthrombi formation and tissue hypoxia. Similarly, HHcy induces the CD11B/CD18 expression. These proteins form a docking complex enabling the interaction between inflammatory cells and the endothelium, thereby causing damage and loss of endothelial cells [22–24].

Elevated Hcy levels during pregnancy were associated with complications, such as preeclampsia (PE), early pregnancy loss, placental abruption (PA), intrauterine growth restriction (IUGR), venous thrombosis, etc. These levels are linked to the effect of Hcy on vascular endothelial function, elevated pro-oxidant and thromboembolic activities [25–29]. Metabolic disorders that happen when the intima of placental vessels is disturbed are characterized by a change in the metabolism pattern of long-chain polyunsaturated fatty acids (LC-PUFAs). [Disorders] contribute to higher platelet aggregation via a decrease in the synthesis of endothelium-derived relaxing factor and nitric oxide, as well as via tissue factor induction and stimulated proliferation of smooth muscle cells. These factors lead to hemodynamic placental disorders that may be a key factor in pregnancy complications associated with endothelial placental dysfunction [30,31].

Research purpose was to put together the available pieces of present scientific data and to close the gap in the knowledge of Hcy levels in pregnancy and its association with some pregnancy complications.

2. Materials and methods

2.1. Research design

The studies, published between January 1990 and December 2017,