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Original Research Article

Peri conceptional association of the triad of hyperhomocsteinemia, hypothyroidism and impaired carbohydrate metabolism with recurrent pregnancy loss

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ABSTRACT

Background: Recurrent pregnancy loss is a cause of great concern to the affected couple as well as the treating physician. We evaluated the periconceptional association of the triad of hyperhomocystienemia, hypothyroidism, and impaired carbohydrate metabolism with RPL and to identify the potential risk factors for RPL which are probably nutritional.
Methods: Seven hundred ninety-six consecutive pregnancies with two or more abortions referring to our Infertility clinic were selected to be studied in a descriptive, prospective observational study in 2012-2014. All the pregnant women were subjected to routine blood tests/ examination/ imaging as per hospital protocols. All underwent TSH, FT4, GTT 75 gm (fasting and 2 h postprandial) as per routine antenatal workup. Additionally, fasting plasma homocysteine, antinuclear antibody, anti phospholipid antibody, anti- thyroid peroxidase antibody tests were performed for patients with RPL. All the patients were studied for the triad of hypothyroidism, hyperhomocysteinemia and impaired carbohydrate metabolism.
Results: The incidence of RPL was found to be 5.65 %. Majority of women (51.1%) were in the age group 30-34 years. Majority of the women (55.6%) had 2 previous abortions. Majority of women (57.7%) had conceived normally. Majority of women (46.7%) had BMI<25. PCOS was reported in 28.9% women. HHcy, hypothyroidism and impaired carbohydrate metabolism was found in 78%, 73% and 73% women, respectively. The presence of two factors was reported in 60 to 65% women. 56% women reported the presence of the triad. About 7% of the patients underwent repeat abortion in second trimester of which 66.6% had the association of triad.
Conclusions: Investigating these three factors in patients with RPL would help in early recognition, monitoring, and aggressive surveillance, which will help prevent obstetric complications. Simple nutritional correction may allow for better maternal and fetal programming and appropriate risk modulation.

Keywords: Hyperhomocysteinemia, Hypothyroidism, Impaired glucose metabolism, Recurrent pregnancy loss

INTRODUCTION

The American society for reproductive medicine (ASRM) defines recurrent pregnancy loss (RPL) as the spontaneous loss of two or more pregnancies.[1] About 15% of couples are affected by RPL, with significant consequences concerning their partnership and quality of life.[2,3] Parental chromosomal anomalies, uterine structural anomalies, maternal thrombophilic disorders and anti-phospholipid antibodies have been directly associated with RPL. However, in almost 50 % of cases, the pathophysiology remains unknown.[4] In our country, heritable thrombophilias are less common.[5] Among the undetermined cases, elevation in total homocysteine

(tHcy) levels (hyperhomocysteinemia; HHcy), hypothyroidism, impaired carbohydrate metabolism, or combinations of these three pathologic conditions have been described as playing a role in the pathogenesis of RPL. Homocysteine is a non-essential amino acid that can be converted into cysteine or recycled into methionine, an essential amino acid, with specific B vitamins. Homocysteine levels vary between men and women, with a normal range typically between 5 to 15 micromol/l. Hyperhomocysteinemia is when levels exceed 15 micromol/l.[6] Hyperhomocysteinemia (HHcy) has been underlined as an emerging risk factor for several diseases such as arterial and/or venous thrombosis, adverse pregnancy outcome, congenital malformations and vascular dementia.[7-12]

Thyroid hormones are very crucial for foetal development. Thyroid hormone disorders and high thyroid peroxidase antibodies (TPO-Ab) levels disturb folliculogenesis, spermatogenesis, embryogenesis and fertilisation, supporting a vital role in pregnancy loss.[13] Thyroid disorders can be either hypothyroidism or hyperthyroidism. Euthyroid women are defined as those having normal TSH (0.1-2.5 µIU/l) in first trimester. Subclinical hypothyroidism is defined as high TSH (>3.0 µIU/l) in the presence of normal levels of free T4 (0.8-2.0 ng/dl). Overt hypothyroidism is defined as high TSH (>3.0 µIU/l) with low Free T4 (<0.8 ng/dl).[14]

Abnormal carbohydrate metabolism during pregnancy, such as impaired glucose tolerance (IGT) and gestational diabetes (GDM), is a relatively frequent disease affecting 2–5% of all pregnancies. As with other maternal disorders associated with macrovascular dysfunction, abnormal carbohydrate metabolism is related to augmented maternal and fetal-neonatal morbidity.[15] Current study aims to evaluate the periconceptional association of the triad of hyperhomocystienemia, hypothyroidism, and impaired carbohydrate metabolism with RPL and to study the potential risk factors for RPL which are probably nutritional.

Aim

Aim of the current study was to evaluate the periconceptional association of the triad of hyperhomocystienemia, hypothyroidism, and impaired carbohydrate metabolism with RPL.

METHODS

Seven hundred ninety-six consecutive pregnancies with two or more abortions referring to Milann the fertility centre, Bangalore, India were selected to be studied in a descriptive, prospective observational study in 2012-2014. All the pregnant women were subjected to routine blood tests/ examination/ imaging as per hospital protocols. All underwent TSH, FT4, GTT 75 gm (fasting and 2 hr postprandial) as per routine antenatal workup. Additionally, fasting plasma homocysteine, antinuclear antibody (ANA), anti phospholipid antibody (APLA), anti thyroid peroxidase antibody tests were performed for patients with RPL. All the patients were studied for the triad of hypothyroidism, hyperhomocysteinemia and impaired carbohydrate metabolism.

Statistical analysis

The case records were analyzed systematically for the above-mentioned parameters and clinical outcomes.

RESULTS

The incidence of RPL in current study was 5.65%. The maximum numbers of women (51.1%) were in the age group 30-35 years. The maximum number of women (55.6%) had two abortions. The maximum number of women (57.77%) had conceived normally. A maximum number of women (46.7 %) had low BMI. 28.9% of RPL cases also had the presence of PCOS. The distribution of patients according to the presence of specific antibodies and anomalies is shown in (Table 7). The distribution of patients according to the presence of hypothyroidism, hyperhomocysteinemia, impaired carbohydrate metabolism or a combination thereof are as shown in (Table 8).

Table 1: The incidence of RPL.

Incidence of RPL	N	%
Total RPL	45	5.65
Other than RPL	751	94.34
Total pregnancies	796	100

Table 2: The age-wise distribution of RPL cases.

Age group (years)	N	%
20-24	4	8.9
25-29	11	24.4
30-34	23	51.1
35-39	5	11.1
40-44	2	4.4
Total	45	100.0

Table 3: Distribution of subjects by the number of abortions.

No. of Abortions	N	%
2	25	55.6
3	14	31.1
4	5	11.1
6	1	2.2
Total	45	100

DISCUSSION

The incidence of RPL in our study was found to be 5.65 %. Globally, RPL is reported to occur in 0.5%-1% of

total pregnancies.[16,17] The incidence is high in our study as the data has been collected from an Infertility Centre frequented by couples already suffering from infertility and pregnancy loss. In current study, 46.7% of women had BMI<25, 35.6% had BMI between 26 to 29, and 15.6% had BMI>30. Both undernourishment and high BMI are associated with infertility, including recurrent pregnancy loss (RPL).

Table 4: Distribution of RPL pregnancies by mode of conception.

Mode of conception	N	%
Normally Conceived	26	57.77
Timed Intercourse	5	11.11
IUI	3	6.66
IVF/ET	11	24.44

Table 5: Distribution of subjects by BMI.

BMI	N	%
0-25	21	46.7
26-29	16	35.6
30 and more	7	15.6
Total	45	100.0

Table 6: Distribution of RPL subjects according to the presence of PCOS.

Presence of PCOS	N	%
Yes	13	28.9
No	32	71.1
Total	45	100

Table 7: Distribution of subjects by presence of condition.

Presence of condition	N	%
Anti-thyroid peroxidase antibodies	10	22.2
Anti nuclear antibodies	8	17.8
Anti phospholipid antibodies	8	17.8
Uterine anomalies	5	11.1
Chromosomal anomalies	0	0

Pre-pregnancy underweight status was found to have a greater risk of preterm birth, low birth weight and intrauterine growth restriction. Having low BMI can affect the development of the placenta in pregnant women and affect the growth of the fetus due to a lack of nutrients. One of the significant pathophysiological changes in obesity is the distribution of excess weight and fat (adipocytes). The build-up of adipocytes is known to cause insulin resistance, which is responsible for the natural history of various diseases, particularly diabetes mellitus. Adipocytes also contribute to the escalation in reactive oxygen species (ROS) and pro-inflammatory cytokines. This phenomenon is responsible for the dysfunction of blood vessels, leading to coronary artery disease and stroke. Other possible mechanisms of recurrent pregnancy loss in women with obesity are disturbances in the hypothalamic-pituitary-gonadal hormonal axis, endometrial receptivity, oocyte quality, and inflammatory markers.[18]

Table 8: Distribution of subjects by condition.

Condition	N	%
Hypothyroidism	33	73
Hyper homocysteinemia	35	78
Impaired carbohydrate metabolism	33	73
Hypothyroidism+hyperhomocystenemia	28	62.2
Hypothyroidism+impaired carbohydrate metabolism	29	64.4
Hyperhomocysteinemia+impaired carbohydrate metabolism	27	60

In our study, 28.9% of RPL cases also had the presence of PCOS. Thus, the clinical association of RPL in polycystic ovarian syndrome (PCOS) is more than common. However, the incidence rate between PCOS and RPL remains uncertain due to its wide variation in different studies. The high prevalence of hypersecretion of luteinising hormone and obesity in the syndrome has been reported as a risk factor for spontaneous abortion. Several studies document a possible association between insulin resistance (IR) and HHcy, with the incidence of the latter being high in PCOS women. Recent reports attest the occurrence of hypofibrinolysis associated with high plasminogen activator inhibitor-1 (PAI-1) in women with PCOS as a cause of RPL. The effects of elevated PAI-1 may also be aggravated by elevated homocysteine, eventually causing thrombosis. Thus, PCOS involves numerous confounding factors that may contribute, individually or in combination, to thrombosis and ultimately lead to RPL.[19] In current study, hyperhomocysteinemia (HHyc), hypothyroidism and impaired carbohydrate metabolism were reported in 73%, 78% and 78% patients, respectively. In addition, a combination of two factors was reported in 60-65% of patients, and 56% of patients reported the presence of all three factors. A meta-analysis of studies between 1992 to 1999 by Nelen et al showed a significant association between HHcy and recurrent early pregnancy loss. More recently also, increasing evidence is available for the association of HHcy and RPL.[2,3] Inherited conditions such as gene polymorphisms; i.e. cystathionine beta synthase (CBS) or methylenetetrahydrofolate reductase (MTHFR) have been involved in explaining the pathophysiology of HHcy.[20,21] Acquired conditions such as folate and/or vitamin B6/B12 deficiencies due to dysregulation of their normal metabolism and/or low dietary intake are the modifiable causes of HHcy.[22,23]

Besides, recent studies have shown many non-enzymatic factors affecting homocysteine levels.[6,8] Insulin inhibits

hepatic CBS, an enzyme involved in the conversion of homocysteine to cystathionine, leading to elevated homocysteine levels. Insulin resistance seems to escalate the homocysteine levels.[24] HHcy interferes with endometrial blood flow and vascular integrity, resulting in increased oxidative stress in vascular endothelium and early pregnancy loss.[25]

Hypothyroidism is common in pregnancy, and there is a statistically significant relationship of hypothyroidism with recurrent pregnancy loss in <20 weeks of gestation.[25] The ASRM and ESHRE guidelines confirm the association between thyroid dysfunction and the risk of miscarriage. As per the guidelines, there is an emerging consensus that TSH values >2.5 mU/l should be considered as an abnormal result in RPL patients.[26] Glycemic control and insulin sensitivity are the most critical factors in reproductive pathophysiology. Impaired glucose tolerance, diabetes mellitus and insulin resistance (IR) have been long known to be linked to adverse reproductive outcomes, including infertility, miscarriages, and adverse pregnancy outcomes. Several studies have shown a biochemical and clinical association between miscarriage and poor glycemic control and IR.[27] In normal pregnancy, maternal circulating glucose can be delivered to the fetus via the fetoplacental circulation but is not accompanied by maternal insulin, which cannot cross the placental barrier. The high maternal glucose levels in GDM provoke fetal hyperglycemia and reactive fetal hyperinsulinemia, which lead to endothelial dysfunction within the fetal micro-and macro-circulation.[28] Thus, the triad of hypothyroidism, HHcy and impaired carbohydrate metabolism are interlinked and together contribute to RPL. In our cohort, three patients, i.e. 6.91% of patients, underwent repeat abortion in the second trimester, of which two patients reported the presence of triad.

CONCLUSION

Investigating these three factors in patients with RPL would help in early recognition, monitoring, and aggressive surveillance, which will help prevent obstetric complications. Simple nutritional correction may allow for better maternal and fetal programming and appropriate risk modulation. By proper guidance to our adolescent cohort, we can also help in achieving the safe future reproductive life. More extensive studies are required for the extrapolation of the results.

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