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Original research article

To study hyperhomocsteinemia, hypothyroidism, and poor glucose metabolism in recurrent miscarriage in periconceptional period

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Abstract

Aim and Background: The occurrence of repeated pregnancy loss is a matter of significant concern for both the couple experiencing it and the medical professional providing treatment. In this study, we conducted an assessment of the periconceptional correlation between the combination of hyperhomocysteinemia, hypothyroidism, and impaired carbohydrate metabolism and recurrent pregnancy loss.

Material and Methods: A descriptive, prospective observational study was conducted between January 2022 to January 2023 to investigate a cohort of 590 consecutive pregnancies with two or more abortions, specifically from our Infertility clinic. All pregnant women underwent routine blood tests, examinations, and imaging procedures in accordance with the hospital's regulations. The study encompassed an examination of all patients in relation to the triad of hypothyroidism, hyperhomocysteinemia, and poor glucose metabolism.

Results: The prevalence of recurrent pregnancy loss was determined to be 5.65%. The majority of women surveyed reported having undergone two prior abortions. The majority of women experienced normal conception. The majority of women had a body mass index below 25. The study findings indicated that approximately 60 to 65% of women exhibited the presence of two variables. A total of 56% of female participants indicated the presence of the trio. Approximately 7% of the patient population experienced a subsequent abortion during the second trimester, with 66.6% of these cases exhibiting the presence of the triad relationship.

Conclusion: Investigation of these three variables in individuals diagnosed with recurrent pregnancy loss would facilitate prompt identification, ongoing monitoring, and vigilant observation, hence contributing to the prevention of obstetric problems. Implementing a straightforward nutritional intervention could potentially lead to improved maternal and fetal programming as well as effective risk management.

Keywords: Hypothyroidism, hyperhomocysteinemia, impaired metabolism of glucose, loss of pregnancy repeatedly

Introduction

Recurrent pregnancy loss is operationally defined by the American Society for Reproductive Medicine as the occurrence of spontaneous termination of two or more pregnancies. Approximately 15% of couples experience Recurrent Pregnancy Loss (RPL), which has notable implications for their relationship and overall well-being [1]. There is a direct association between recurrent pregnancy loss and various factors, including parental chromosomal defects, uterine structural anomalies, maternal thrombophilic diseases, and anti-phospholipid antibodies. Nevertheless, the underlying mechanisms responsible for the pathophysiology of the condition remain unidentified in around 50% of instances. Heritable thrombophilias exhibit a lower prevalence within our nation. The pathophysiology of recurrent pregnancy loss has been associated with several factors, including elevated levels of total homocysteine, hypothyroidism, poor carbohydrate metabolism, or a combination of these diseases [2, 3].

These factors have been identified as potential contributors to the development of RPL in situations where the underlying cause remains uncertain. Homocysteine is classified as a non-essential amino acid, which possesses the ability to undergo conversion into cysteine or be recycled into methionine [4], an amino acid that is considered important for human health. This conversion and recycling process is facilitated by the presence of specific B vitamins. There exists a disparity in homocysteine levels between males and females, with a commonly observed range of 5 to 15 micromol/l considered as normal. Hyperhomocysteinemia refers to a medical condition characterized by elevated levels of homocysteine in the blood, surpassing the threshold of 15 micromol/l. Hyperhomocysteinemia has been

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identified as a noteworthy risk factor for various disorders, including arterial and/or venous thrombosis, unfavorable pregnancy outcomes, congenital abnormalities, and vascular dementia. The range of numbers provided by the user is 7 to 12 [4, 5].

Thyroid hormones have a vital role in the development of the fetus. Thyroid hormone abnormalities and elevated levels of thyroid peroxidase antibodies have been found to disrupt the processes of folliculogenesis, spermatogenesis, embryogenesis, and fertilization, therefore playing a significant part in the occurrence of pregnancy loss. Thyroid diseases encompass two main conditions, namely hypothyroidism and hyperthyroidism. Euthyroid women are characterized as individuals who have normal thyroid-stimulating hormone levels throughout the initial trimester of pregnancy [6, 7].

Aberrant carbohydrate metabolism during pregnancy, including compromised glucose tolerance and gestational diabetes, is a moderately common condition that impacts approximately 2-5% of pregnancies [8]. Similar to other maternal illnesses linked to macrovascular dysfunction, impaired glucose metabolism is associated with increased maternal and fetal-neonatal morbidity. The present study is to assess the periconceptional correlation between the combination of hyperhomocysteinemia, hypothyroidism, and poor carbohydrate metabolism, and recurrent pregnancy loss. Additionally, this study aims to investigate potential nutritional risk factors for RPL. The objective of the present study was to assess the periconceptional correlation between the combination of hyperhomocysteinemia, hypothyroidism, and poor carbohydrate metabolism and RPL [9, 10].

Materials and Methods

A descriptive, prospective observational study was conducted between January 2022 to January 2023 to investigate a cohort of 590 consecutive pregnancies with two or more abortions, specifically from our Infertility clinic. All pregnant women underwent routine blood tests, examinations, and imaging procedures in accordance with the hospital's regulations. The study encompassed an examination of all patients in relation to the triad of hypothyroidism, hyperhomocysteinemia, and poor glucose metabolism.

Statistical analysis

The aforementioned criteria and clinical outcomes were extensively examined by examining the case records.

Results

The prevalence of RPL in the present investigation was found to be 5.65%. The age group with the highest number of women was 30-35 years. The highest proportion of women underwent two abortions. The majority of women achieved conception through natural means. A significant proportion of women exhibited a low body mass index at its greatest value. The prevalence of polycystic ovary syndrome was observed in 28.9% of individuals diagnosed with recurrent pregnancy loss. The categorization of patients based on the presence of particular antibodies and abnormalities.

Table 1: The distribution of RPL cases by age

Sr. No.	Age group	Number	Percent
1.	20-24	13	21.66
2.	25-29	15	25.0
3.	30-34	22	36.66
4.	35-39	09	15.0
5.	40-44	01	2.5
	Total	60	1.6

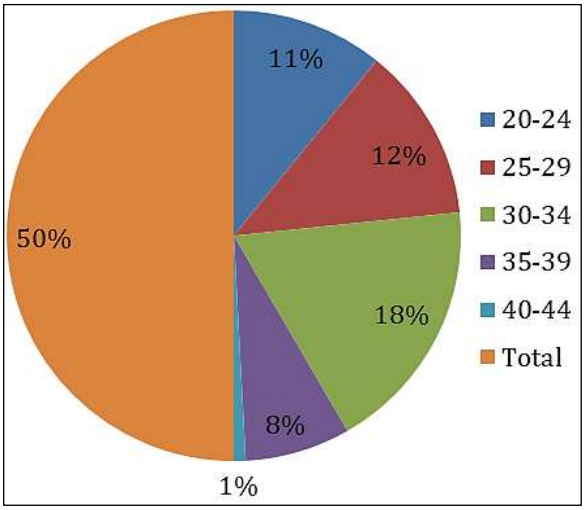

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Fig 1: The distribution of RPL cases by age

Table 1 and Figure 1 present the distribution of instances of RPL (Recurrent Pregnancy Loss) categorized by age. The data reveals that the highest proportion of cases is recorded within the age group of 30-34, while the lowest proportion is found in the age group of 40-44.

Table 2: Subjects are distributed according to the number of abortions

Sr. No.	Abortions (No.)	Number	Percent
1.	2	24	40.5
2.	3	20	33.33
3.	4	09	15.0
4.	6	07	11.66
	Total	60	100

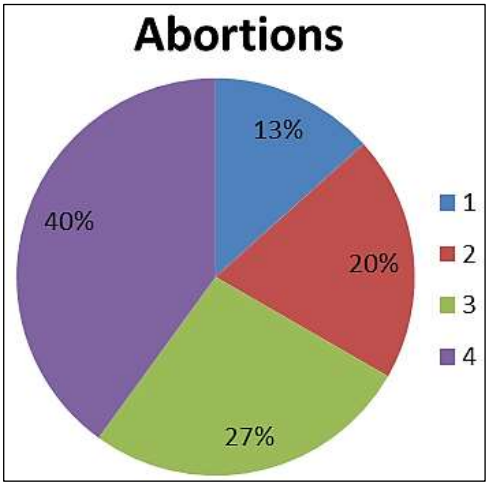

Fig 2: Subjects are distributed according to the number of abortions

Discussion

The study revealed a prevalence rate of 5.65% for recurrent pregnancy loss (RPL). On a global scale, the incidence of recurrent pregnancy loss (RPL) is estimated to range from 0.5% to 1% of all pregnancies. The prevalence of the observed phenomenon is substantial within our research, as the data has been gathered from a specialized facility for infertility treatment, where couples who are already experiencing infertility and pregnancy loss seek assistance. In the present investigation, it was shown that 46.7% of the female participants exhibited a body mass index below 25, while 35.6% fell between the BMI range of 26 to 29, and 15.6% had a BMI beyond 30. Both malnutrition and high body mass index have been found to be linked to infertility, including the occurrence of recurrent pregnancy loss [11, 12].

Table 3: RPL distribution of pregnancies by mode of conception

Sr. No.	Mode of conception	Number	Percent
1.	Normally	40	66.66
2.	Timed intercourse	06	10.00
3.	IVF/ET	10	16.66
4.	IUI	04	06.66

Table 4: BMI wise distribution of subjects

Sr. No.	BMI	Number	Percent
1.	0-25	20	33.33
2.	26-29	20	33.33
3.	>30	20	33.33
	Total	60	100.0

Table 5: RPL subjects distribution by presence of PCOS

Sr. No.	PCOS	Number	Percent
1.	Yes	30	50.0
2.	No	30	50.0
	Total	60	100.0

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Table 6: Subjects distribution by presence of condition

Sr. No.	Condition	Number	Percent
1.	Anti-nuclear antibodies	20	33.33
2.	Anti-thyroid peroxide antibodies	20	33.33
3.	Chromosomal Anomalies	15	25.00
	Uterine Anomalies	05	08.33

Table 7: Subjects distribution by the condition

Sr. No.	Condition	Number	Percent
1.	Hyper homocyteinemia	20	33.33
2.	Hypothyroidism	20	33.33
3.	Impaired carbohydrate metabolism	08	13.32
4.	Hypothyroidism and hyperhomocystenemia	02	03.33
5.	Hypothyroidism and impaired carbohydrate metabolism	02	03.33
6.	Hyperhomocystenemia and impaired carbohydrate metabolism	08	13.32

The study revealed that individuals who were underweight prior to pregnancy exhibited an increased likelihood of experiencing preterm birth, low birth weight, and intrauterine development restriction. The presence of a low body mass index among pregnant women can have implications for placental development and fetal growth, primarily stemming from inadequate nutrient availability. The distribution of extra weight and fat is a notable pathophysiological alteration observed in individuals with obesity [13]. The accumulation of adipocytes has been identified as a contributing factor to the development of insulin resistance, a condition that plays a significant role in the progression of several disorders, most notably diabetes mellitus. Adipocytes are also involved in the increase of reactive oxygen species and pro-inflammatory cytokines. This process is accountable for the impairment of blood vessels, resulting in the development of coronary artery disease and stroke. Additional potential pathways contributing to recurrent pregnancy loss in women with obesity include disruptions in the hypothalamic-pituitary-gonadal hormonal axis, compromised endometrial receptivity, diminished oocyte quality, and elevated levels of inflammatory markers [14-16].

In the conducted investigation, it was observed that 28.9% of instances of recurrent pregnancy loss exhibited concurrent polycystic ovary syndrome. Hence, the prevalence of recurrent pregnancy loss in individuals with polycystic ovarian syndrome is higher than average [17]. Nevertheless, the relationship between polycystic ovary syndrome and recurrent pregnancy loss is still not well understood, mostly due to the considerable variability observed across different research investigations. Previous studies have documented a notable association between the elevated occurrence of luteinising hormone hypersecretion and obesity in the syndrome, which has been identified as a potential risk factor for spontaneous abortion. Multiple studies have provided evidence of a potential correlation between insulin resistance and hyperhomocysteinemia, with a notable prevalence of the latter in women diagnosed with polycystic ovary syndrome [18-20].

Recent studies have shown evidence indicating that women with polycystic ovary syndrome may experience hypofibrinolysis, which is characterized by elevated levels of plasminogen activator inhibitor-1. This condition has been identified as a potential cause of recurrent pregnancy loss. The potential consequences of increased levels of plasminogen activator inhibitor-1 may be further exacerbated by elevated levels of homocysteine, ultimately leading to the development of thrombosis [21]. Therefore, polycystic ovary syndrome encompasses various complicating conditions that can potentially contribute, either independently or collectively, to the occurrence of thrombosis and ultimately result in recurrent pregnancy loss. The present investigation indicated a prevalence of 73% for hyperhomocysteinemia, 78% for hypothyroidism, and 78% for impaired carbohydrate metabolism among the patients. Furthermore, it was observed that a confluence of two factors was documented in around 60-65% of the patient population, while the coexistence of all three elements was reported by 56% of the patients [22, 23].

Hypothyroidism is a prevalent condition during pregnancy, and there exists a statistically significant correlation between hypothyroidism and recurrent pregnancy loss occurring before the 20th week of gestation. The guidelines established by the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology substantiate the correlation between thyroid dysfunction and the heightened likelihood of experiencing a miscarriage [24, 25]. According to current guidelines, there is a growing agreement that thyroid-stimulating hormone levels exceeding 2.5 mU/l should be regarded as an atypical finding in individuals experiencing recurrent pregnancy loss. The important determinants in reproductive pathophysiology are glycemic management and insulin sensitivity [26]. The association between impaired glucose tolerance, diabetes mellitus and insulin resistance with unfavorable reproductive outcomes, such as infertility, miscarriages, and bad pregnancy outcomes, has been well-established for a considerable period of time. Multiple investigations have demonstrated a biochemical and clinical correlation between miscarriage and suboptimal glycemic management and insulin resistance [27, 28]. During a typical pregnancy, the transfer of maternal circulating

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glucose to the fetus occurs through the fetoplacental circulation. However, maternal insulin, which is unable to traverse the placental barrier, does not accompany this process. Maternal glucose levels that are elevated in gestational diabetes mellitus elicit fetal hyperglycemia and reactive fetal hyperinsulinemia, resulting in impaired functioning of the endothelium in both the fetal microcirculation and macrocirculation. Therefore, the interconnectedness of hypothyroidism, hyperhomocysteinemia, and poor glucose metabolism together lead to recurrent pregnancy loss. Within our cohort, a total of three patients, or 6.91% of the patient population, experienced a subsequent abortion during the second trimester. Among these individuals, two patients specifically described the existence of a triad [27-29].

Conclusion

Examining these three variables in individuals diagnosed with recurrent pregnancy loss (RPL) would facilitate prompt identification, ongoing monitoring, and vigilant observation, hence contributing to the prevention of obstetric problems. Implementing a straightforward nutritional intervention could potentially lead to improved maternal and fetal programming as well as effective risk management. Through the provision of appropriate guidance to our adolescent population, we may contribute to the attainment of a secure future in terms of reproductive health. Further research is necessary to extrapolate the findings.

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Conflict of interest: None.

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