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OXIDATIVE STRESS AND PSYCHOLOGICAL STRESS AMONG SUBJECTS WITH RECURRENT PREGNANCY LOSS

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ABSTRACT

Recurrent pregnancy loss (RPL), known popularly as recurrent miscarriage, is a clinical condition of two or more failed pregnancies, affecting 12-15% of total pregnancies. Besides genetic and anatomical abnormalities, stress and anxiety impart a vital role in repeated abortions. The Perceived Stress Scale, an extensively used psychological tool for assessing the perception of stress in an individual, was taken for evaluating the role of psychological stress among subjects with RPL. The oxidative stress marker, malondialdehyde (MDA) and several other clinical parameters were also analyzed among 150 women with RPL and 110 healthy women with one or two children. The study concluded that RPL individuals are shown to have higher rates of oxidative and psychological stress with elevated MDA concentration and PSS score respectively.

Keywords: Recurrent pregnancy loss, Oxidative stress, Malondialdehyde, Perceived Stress Scale

INTRODUCTION

Recurrent pregnancy loss (RPL) is traditionally defined as three or more consecutive pregnancy losses before 20 weeks of gestation (Lee and Silver 2000). "The American Society for Reproductive Medicine (ASRM)" defined it "as a clinical condition of two or more failed pregnancies" (ASRM 2012). RPL otherwise called recurrent miscarriage (RM) is a frustrating condition affecting around 2-6% of infertile couple and 12-15% of all pregnancies (Moghbeli 2019). Homer (2019) denoted that, "despite intensive workup, no apparent cause can be identified in at least 50% of couples experiencing RPL". Patkiand Chauhan (2016) estimated, "a much higher prevalence of spontaneous miscarriage in the Indian women (32%)".

Genetic, anatomic abnormalities, immunologic, endocrine disorders, infectious, heritable and/or acquired thrombophilias and environmental factors are attributed to the etiological factors of repeated abortions (Kinsey et al 2015). Kicia et al (2015) pointed out that, "stress and anxiety happen to women experiencing a miscarriage, so a joint analysis of these two emotions is very important for maintaining good health in general". According to Gong et al (2013), "women who suffer from a history of repeated miscarriage experience with varying degrees of depressive symptoms that may be responsible for negative psychological impacts".

Perceived Stress Scale (PSS) in order to measure the degree to which life events are appraised as stressful. Hence, this method of assessing stress reflects the definition of psychological stress proposed by Lazarus and Folkman (1984). PSS is a widely used psychological instrument for measuring the perception of stress (Li et al 2002). "It is a 10-item self-report questionnaire and is designed to reflect how unpredictable, uncontrollable and overloaded respondents find their lives". Cohen (1994) employed a 5-point Likert scale (0 = never, 4 = very often). Scores can range from 0 to 40, with higher scores indicating a higher level of perceived stress.

Bedaiwy et al in 2002 explained that, "complications like spontaneous abortion, preeclampsia etc, develop in response of Oxidative Stress (OS)". Agarwal and Allamaneni (2004) have suggested that, "OS plays a major role in the normal functioning of the reproductive system and subsequent pathogenesis of female infertility". Torkzahrani et al (2019) identified, "by measuring serum OS markers, in women with spontaneous abortion & compare the level with normal pregnant women in first trimester". Risk factors for complications during pregnancy are gradually increasing. Recent studies showed that psychological stress, endocrinological, biochemical and lifestyle factors contribute to RPL, still the relation between psychological stress and oxidative stress related RPL is unclear. Hence the present study was undertaken to evaluate the role of oxidative stress and psychological stress among subjects with RPL.

MATERIALS AND METHODS

A total of 150 women with recurrent pregnancy loss were included in the test group and 110 healthy women with one or two children were selected as control subjects. Detailed demographic, clinical and lifestyle characteristics were recorded using well-structured proforma. Perceived stress scale (PSS) was employed to assess the women's stress status". A 5-point Likert scale (0 = never, 4 = very often) Cohen (1994) was used. Scores typically range from 0 to 40. Four ml of blood sample was collected by venipuncture and oxidative stress marker [Malondialdehyde (MDA)], T3, T4, TSH and Uric acid were analyzed among the study subjects by employing standard biochemical and hormone assay protocols. The concentration of MDA was evaluated based on the method proposed by Sato et al in 1979.

OBSERVATIONS AND RESULTS

The age range of study subjects was from 18 to 45 years. The mean age of test subjects and control subjects was 32.32±6.83 and 32.84±6.24 respectively and no statistical significance difference was observed (t= -0.627; p =0.265).

Table: 1 Distribution of mean MDA and mean PSS score among study subjects

Variables	Test subject (n=150)	Control Subjects (n=110)	t	p
Mean MDA	3.38±2.44	1.52±0.68	7.72	< 0.001
Mean PSS score	27.20±5.82	13.55±3.55	21.78	< 0.001

The observed mean MDA level of test subjects was 3.38±2.44µmol/L and 1.52±0.68µmol/L for control. A statistically significant difference between the mean MDA level of test and control subjects was observed with a p value <0.001 (t = 7.72). PSS score was categorized into three groups as low stress (scale: 0-13), moderate stress (scale: 14-26) and high perceived stress (scale: 27- 40). Test subjects showed a mean PSS score of 27.20±5.82 and the observed PSS score of control subjects was 13.55±3.55 (t=21.78; p <0.001).

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Table: 2 Distribution of mean MDA and mean PSS score according to demographic parameters among study subjects

Variables	Category	MDA (µmol/L)		PSS	
		Test	Control	Test	Control
Age (Years)	18-29	2.75	1.59	26.58	12.87
	30-39	3.68	1.61	27.2	13.55
	≥40	4.04	1.68	28.46	14.52
Birth order	≤3	3.19	1.45	27.13	13.39
	>3	4.21	1.79	27.51	13.59
Residence	Urban	3.39	1.55	27.98	13.76
	Rural	3.32	1.47	26.67	13.56
	Coastal	3.65	1.54	26.55	12.5
Occupational Type	Sedentary	3.55	1.59	28.26	13.62
	Non - sedentary	3.15	1.47	26.40	13.45
Socioeconomic Status	High	2.41	1.45	26.88	11.53
	Average	3.26	1.53	27.04	13.74
	Low	4.11	1.51	27.90	15.83
Consanguinity	Yes	3.40	0	27.51	0
	No	3.30	0	26.33	0
Duration of married life (years)	≤10	3.09	1.42	26.35	13.32
	>10	3.90	1.72	28.72	14

On the basis of age, the study subjects were categorized into three groups (18-29, 30-39 and ≥40 years). An elevated mean MDA (4.04µmol/L) and PSS score (28.46) was observed among test subjects with advanced age (≥40 years). Similarly an increased mean value of mean MDA (4.21µmol/L) and PSS score (27.51) was observed among test subjects with birth order >3. Based on residence, test subjects were grouped into three (as urban, rural and coastal). An elevated mean MDA level was observed among these subjects who reside in coastal areas (3.65µmol/L) whereas; test subjects who reside in urban areas showed an increased mean PSS score (27.98) when compared to the rest.

According to occupational type test subjects were grouped as sedentary and non-sedentary. Those who reported with sedentary type of occupation showed an elevated mean MDA value (3.55µmol/L) and an increased mean PSS score (28.26). In case of socioeconomic status (SES), test subjects reported with low SES showed comparatively an elevated PSS score and mean MDA value. The observed mean MDA level of test subjects with consanguinity was 3.40µmol/L and for test subjects without consanguinity it was 3.30µmol/L. The PSS score of test subjects reported with and without consanguinity were 27.51 and 26.33.

Test subjects with duration of married life ≤10 and >10 years showed a mean MDA level of 3.09µmol/L and 3.90µmol/L respectively. The observed PSS score of test subjects with duration of married life ≤10years was 26.35 and for test subjects with duration of married life >10years it was 28.72.

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Table: 3 Distribution of mean MDA and mean PSS score according to physiological parameters among study subjects

Variables	Category	MDA(µmol/L)		PSS	
		Test	Control	Test	Control
Abdominal circumference (cm)	≤100	3.42	1.52	26.83	12.40
	>100	3.29	1.58	27.35	13.60
Obesity	Yes	3.61	1.24	27.44	13.58
	No	2.94	1.54	26.75	13
Menstrual cycle	Irregular	3.41	1.56	27.91	13.75
	Regular	3.35	1.06	26.60	11
PCOS	Yes	4.34	1.56	27.45	13.75
	No	3.17	1.06	26.07	11
No. of gestation	≤4	3.01	1.53	27.05	13.55
	>4	4.01	1.10	27.29	13.66
No. of abortion	≤3	3.08	0	26.73	0
	>3	3.58	0	27.52	0

Test subjects with abdominal circumference >100cm showed a mean MDA level of 3.29µmol/L and for control subjects it was 1.58µmol/L. The observed mean PSS score of test subjects with increased abdominal circumference (>100cm) was 27.35 and for control it was 13.60. Test and control subjects reported with obesity showed a mean MDA concentration of 3.61µmol/L and 1.24µmol/L respectively. Moreover, the observed mean PSS score of test and control subjects with obesity were 27.44 and 13. Test subjects with obesity showed an increased mean MDA and PSS score when compared to the control subjects. Similarly, test subjects reported with irregular menstrual cycle showed an increased mean MDA level and mean PSS score than the control subjects.

The observed mean MDA level and mean PSS score of test subjects with PCOS were 4.34µmol/L and 27.45. According to the number of gestations, the study subjects were categorized into two groups (as ≤4 and >4). Test subjects with an increased number of gestations (>4) showed an elevated mean MDA concentration (4.01µmol/L) and high mean PSS score (27.29). Likewise, test subjects with more number of abortions (>3) showed an elevated mean MDA level (3.58µmol/L) along with high mean PSS score (27.52) when compared to the rest.

Table: 4 Distribution of mean MDA and mean PSS score according to clinical factors among study subjects

Variables	Category	MDA(µmol/L)		PSS	
		Test	Control	Test	Control
H/o UTI	Yes	4.46	1.53	27.49	13.61
	No	3.02	1.30	26.32	12.50
H/o	Yes	4.32	1.62	27.37	13.57

Endometriosis	No	3.24	1.52	26.05	13
FH/o BOH	Yes	3.57	1.54	27.84	13.46
	No	3.29	1.27	27.03	14.75
H/o Thyroid disorder	Yes	3.47	1.53	27.74	13.56
	No	2.96	0.39	24.65	12
Mental stress	Yes	3.67	1.59	27.41	13.56
	No	3.32	1.52	26.16	13.41
H/o Diabetes	Yes	4.20	1.55	27.28	13.65
	No	2.99	1.11	27.04	12.14
H/o Hypertension	Yes	3.39	1.53	27.56	19
	No	3.28	1.15	23.71	13.50
H/o Dyslipidemia	Yes	4.37	1.53	27.75	13.59
	No	3.26	1.46	27.14	13.18

Test subjects reported with H/o UTI, H/o Endometriosis, FH/o BOH, H/o Thyroid disorder, H/o Diabetes, H/o Hypertension and H/o Dyslipidemia showed an elevated mean MDA level of 4.46µmol/L, 4.32µmol/L, 3.57µmol/L, 3.47µmol/L, 4.20µmol/L, 3.39µmol/L and 4.37µmol/L respectively, when compared to the control group. Similarly, the observed mean PSS score of all these clinical parameters among test subjects was higher when compared with the control subjects.

The observed mean MDA level of test subjects reported with mental stress was 3.67µmol/L and for control it was 1.59µmol/L. Moreover, test subjects reported with mental stress showed an increased mean PSS score (27.41) than the control subjects (13.56).

Table: 5 Distribution of mean MDA and mean PSS score according to lifestyle characteristics among study subjects

Variables	**Category**	**MDA(µmol/L)**		**PSS**	
		Test	**Control**	**Test**	**Control**
Regular Exercise	Yes	3.31	1.66	26.46	13.62
	No	3.43	1.49	27.80	13.30
Alcohol consumption	Yes	6.78	0	27.28	0
	No	3.33	0	21.5	0
Dietary Pattern	Non-Veg:	3.57	1.52	27.24	13.58
	Veg:	1.64	1.50	26.86	13.12
Water intake per day	Good	3.03	1.46	27.17	12.6
	Average	3.43	1.55	26.03	13.44
	Poor	4.44	1.57	29.08	13.88

Test subjects without regular exercise showed an increased mean MDA level (3.43µmol/L) and mean PSS score (27.80). Similarly, test subjects reported with alcohol consumption, non-vegetarian dietary pattern and poor daily water intake level also showed an elevated mean MDA level and a high mean PSS score.

Table: 6 Distribution of mean MDA and mean PSS score according to endocrinological factors among study subjects

Variables	Category	MDA(µmol/L)		PSS	
		Test	Control	Test	Control
T3 (ng/dL)	≤159	3.58	1.53	27.47	15
	>159	3.08	1.36	26.68	13.45
T4 (µg/dL)	≤11.7	3.63	1.52	27.29	13.56
	>11.7	2.87	1.46	27.04	13.33
TSH(µIU/ml)	≤4.5	3.25	1.55	26.72	13.47
	>4.5	3.74	1.28	28.52	14.4

Test subjects with T3 level≤159ng/dL and T4 level ≤11.7µg/dL showed an increased mean MDA level and high mean PSS score. In addition to that, test subjects with TSH level >4.5µIU/ml showed an increased mean MDA concentration (3.74µmol/L) and higher mean PSS score (28.52) than the rest with TSH concentration ≤4.5µIU/ml.

Table: 7 Distribution of mean MDA and mean PSS score according to Uric acid level among study subjects

Uric acid (mg/dL)	MDA(µmol/L)		PSS	
	Test	Control	Test	Control
≤6	3.03	1.51	27.02	11
>6	3.96	1.77	27.51	13.70

Test subjects with uric acid level≤ 6mg/dL showed a mean MDA level of 3.03µmol/L and with uric acid level>6 mg/dL showed a mean MDA concentration 3.96µmol/L. The observed mean PSS score of test and control subjects was 27.51 and 13.70 respectively i.e, an elevated level of mean MDA and PSS score were observed among test subjects reported with uric acid concentration >6 mg/dL.

DISCUSSION

In the current study, RPL subjects showed an increased mean MDA level (3.38±2.44µmol/L) and mean PSS score (1.52±0.68) when compared to the control group. According to Lyu et al (2013), "the most common complication of pregnancy is spontaneous abortion which affects 50% of all fertilization and 12%-15% of clinical deliveries". Daglar et al (2016) found that, "serum MDA levels in women with abortion during first trimester were slightly higher than that in the women with normal pregnancy".

The study showed an elevated mean MDA concentration in subjects with advanced age on the comparison with young subjects. Silver et al in 2011 estimated that, "the risk is between 9% and 12% in women aged 35 years, but increases to 50% in women aged 40". Gatea et al (2012) observed that, "an elevated concentration of MDA was observed among women suffering from RPL, when compared to other healthy women". In the current study, the observed PSS score of test subjects was 28.46 and for control subjects it was 14.52. Comparatively an increased PSS score was observed in the test group than the control subjects.

Boots et al (2014) observed, "a higher frequency of miscarriages among obese women and their results supported non-genetic cause for obesity-related miscarriage". In the present study, test subjects with

obesity showed an increased mean MDA level of 3.61µmol/L than the control subjects with a mean value of 1.24µmol/L.

Rai et al (2000) described, "PCOS as a complex disorder involving abnormalities in interactions between the pancreas, the hypothalamus/pituitary, the ovaries, the liver and adipose tissues. Women with PCOS have a threefold higher prevalence of thyroid autoimmunity when compared with healthy age-matched controls". In the current study, PCOS was reported in both test and control subjects. However, an elevated mean MDA concentration and a high PSS score were observed among test subjects when compared with the control subjects.

Li et al (2002) mentioned that, "the incidence of endocrine abnormality in women with RPL is approximately 10-15%". Twig et al (2012) stated that, "there is a strong association between thyroid immunity and infertility". In the current study, it was observed that, the test subjects reported with H/o Dyslipidemia showed an increased mean MDA level of 4.37µmol/L than the control subjects (1.53µmol/L). Similarly, an elevated mean PSS score was also observed among test subjects reported with H/o Dyslipidemia.

Present study identified an elevated mean MDA concentration and PSS score in test subjects with irregular exercise, alcohol consumption, dietary pattern (non-vegetarian type) and poor water intake when compared to the rest. Furness et al. (2011) explained that, "changes in lifestyle characteristics like poor diet, lack of exercise or an exposure to pollutants may accelerate the process of inflammation, OS and ultimately DNA damage". Gaskins et al (2014) suggested, "a healthy diet for women before pregnancy as it has been related to conception chance as well as the pregnancy and infant outcomes".

Negro et al in 2007 revealed that, "hypothyroidism in pregnancy may not be always classical and many times it was very difficult to distinguish from the symptoms of normal pregnancy". Sarkar (2012) added that, "4% of young females were presented with autoimmune thyroid disorders and 15% were at risk because of the thyroid antibody-positivity". In the current study, it was observed that, test subjects with TSH concentration >4.5µIU/ml showed an elevated mean MDA concentration (3.74µmol/L) and high mean PSS score (28.52) than the rest with TSH concentration ≤4.5µIU/ml. In accordance with the study done by Vinita et al (2003) observed, "hypothyroidism in 1.44% of women with RPL in the Indian population". Rao et al (2008) found that, "hypothyroidism was one of the causative factors for abortion with RPL in the first trimester among Indian population".

It was observed in the current context that the test subjects with uric acid level >6 mg/dL showed a mean MDA concentration 3.96µmol/L and the observed mean PSS score of test subjects was 27.51. An elevated level of mean MDA and PSS score were observed among test subject reported with uric acid concentration >6 mg/dL.

Vázquez-Rodríguez and Rico-Trejo (2011) reported, "the increased risk of fetal morbidity and mortality with high levels of uric acid". The mean serum uric acid level in the abortion group was higher than that in the normal pregnancy group. Menon and Bonney (2014) had identified that, "uric acid plays a major role in the human body as an antioxidant and OS marker. Lowered uric acid level seems to elevated MDA level showing risk of Oxidative stress".

CONCLUSION

Oxidative stress plays a key role in the pathophysiology of different diseases and affects women's reproductive health and pregnancy outcome. The current study observed an increased PSS score along with an elevated MDA concentration in RPL women compared to control. The study revealed that the influence of demographic, lifestyle, clinical, physiological and endocrinological factors results in increase of PSS score and as well as MDA level among subjects with RPL. In conclusion, oxidative stress and psychological stress

were more prevalent among women with RPL. Hence, lifestyle modifications like healthy diet, regular exercise, weight management and reducing psychological stress will help to maintain the oxidative and psychological stress.

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