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Decoding the Oxidative Stress-Hormone Connection: Unveiling the Hidden Culprits of Bad Obstetric History

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ABSTRACT

Bad obstetric history (BOH) include recurrent pregnancy loss, stillbirth, preterm birth, and intrauterine growth restriction (IUGR). It seems that oxidative stress impairs normal function of the placenta and materno-fetal interface which leads to adverse pregnancy outcomes. Hormonal imbalance is highly relevant to the cause of reproductive health, though disturbances in key hormones such as follicle stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL) can be very critical factors in BOH. This study investigated the impact of oxidative stress along with these hormones in the etiology of BOH and their implications in clinical management.

This was a case-control study carried out with hundred samples during the period of June 2023–August 2024 in Kerala. Clinically proven fifty women with bad obstetric history aged between 20–45 years were selected as test samples. Fifty women with a history of successful pregnancies were selected as control. Oxidative stress marker malondialdehyde (MDA), FSH, LH, and PRL were evaluated by the ELISA method. Data management and analysis were performed using Microsoft Excel, and Jamovi 2.5.3.

When BOH patients were compared to controls, their levels of MDA, FSH, LH, and PRL were significantly higher ($p < 0.05$). This study concludes that the combined impact of oxidative stress and elevated hormone levels (FSH, LH, and PRL) has a significant role in the development of BOH. Monitoring these biomarkers can be used to identify women at risk for adverse pregnancy outcomes and be helpful for effective diagnosis and treatment.

Keywords: *Bad obstetric history, Follicle stimulating hormone, Luteinizing hormone, Malondialdehyde, Oxidative stress, Prolactin.*

1. INTRODUCTION

Bad obstetric history is defined as a series of adverse pregnancy outcomes including repeated miscarriages, stillbirths, preterm birth, IUGR, or congenital anomalies. Oxidative stress, the imbalance between the reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates, indeed plays a significant role in the pathophysiology of BOH [1]. MDA, being the by-product of lipid peroxidation, serves as a reliable biomarker of oxidative stress that correlates with cellular injury and inflammation [2]. The role of MDA in obstetric complications can explain the potential approaches to its diagnosis and therapy, emphasizing the need for early detection and intervention in pregnancies for better outcomes [3]. Among the many factors that influence pregnancy, hormonal imbalances play a crucial role. Follicle-stimulating hormone, luteinizing hormone, and prolactin are the three main hormones responsible for controlling the reproductive function and

fertility of people. Any imbalance of these hormones tends to significantly affect ovulation, implantation, and maintenance of early pregnancy and is associated with BOH [4]. The role of oxidative stress, FSH, LH, and prolactin in bad obstetric history is what the present study attempts to find out.

2. MATERIALS AND METHODS

2.1 Study design

This was a case-control study that was conducted at Genetika, Center for Advanced Genetic Studies, Thiruvananthapuram. Clinically proven fifty women with bad obstetric history aged between 20–45 years were selected as test samples. These subjects were referred from various infertility centers in Kerala to Genetika for advanced genetic studies. Fifty women with a history of successful pregnancies were selected as control samples. The duration of the study was from June 2023–August 2024. Institutional ethical committee clearance was obtained (Ref. No. 17/2023/IECG).

2.2 Inclusion and exclusion criteria

Only natural pregnancies, i.e., without any medical support, were considered in the study population. Neither the cases nor the controls suffering from cancer or on prolonged medication were excluded. Consanguineous married subjects were also excluded.

2.3 Study procedures

After getting informed consent from all the study subjects, data was collected by using a pre-structured questionnaire. 7 - 10 ml of fasting venous blood was collected and a portion of the blood was transferred to sodium heparinized vacutainer for molecular studies and the remaining for biochemical tests.

The parameters that were included in the study are biochemical parameters, including fasting blood sugar (FBS) by the GOD-POD method and lipid profile (Total cholesterol, triglyceride, HDL, and LDL) by the CHOD-PAD method. Endocrinological parameters, including LH (kit name- Origin, Cat: OPK5296), FSH (Kit name-Origin, Cat: OPK1221), and PRL (Kit name-Origin, Cat: OPK1224), were determined by using sandwich ELISA method. Oxidative stress was detected by using the biomarker MDA by the competitive inhibition ELISA (Kit name-Origin, Cat: OPK8428) method.

2.4 Data management and statistical analysis

The sample size was calculated by using the following formula: Z^2pq/d^2 (unlimited population). Data management and analysis were performed using Microsoft Excel and Jamovi 2.5.3. The collected information was summarized using frequency/percentage for qualitative data and mean with standard deviation for quantitative data. The level of statistical significance was set at a two-tailed p-value of 0.05.

3. RESULTS

Table 1: Comparison of Demographic and Clinical characteristics between case and control group

		Control		Case		$\chi 2$	df	p
		N	%	N	%			
Occupational Type								
	Non Sedentary	38	76	25	50			
	Sedentary	12	24	25	50	7.250	1	0.007
SES								
	Upper	38	76	26	52			
	Lower	12	24	24	48	6.250		0.012
Religion								
	Hindu	37	74	37	74			
	Muslim	6	12	6	12			
	Christian	7	14	7	14	<0.001	2	1.000
H/o Diabetes								

	No	44	88	28	56		
	Yes	6	12	22	44	12.698	1	<0.001
H/o Hypertension							
	No	41	82	15	30		
	Yes	9	18	35	70	27.435	1	<0.001
H/o Dyslipidemia							
	No	43	86	29	58		
	Yes	7	14	21	42	9.722	1	0.002
H/o UTI							
	No	47	94	38	76		
	Yes	3	6	12	24	6.353		0.012
H/o COVID							
	No	47	94	20	40		
	Yes	3	6	30	60	32.972	1	<0.001
Obesity							
	No	46	92	25	50		
	Yes	4	8	25	50	21.418	1	<0.001
Parental consanguinity							
	No	48	96	36	72		
	Yes	2	4	14	28	10.714	1	0.001
Regular exercise							
	No	43	86	42	84		
	Yes	7	14	8	16	0.078	1	0.779

Table 1 listed the demographic and clinical characteristics of the participants with BOH (n = 50) and control groups (n = 50). The data suggested that sedentary lifestyle, lower socio-economic status (SES), history of diabetes, hypertension, dyslipidemia, urinary tract infection (UTI), COVID infection, obesity, and parental consanguinity were significantly associated with the condition in the case group. These factors needed to be explored further as potential risk contributors of BOH. On the other hand, variables like religion (P=1.000) and regular exercise (P=0.779) do not show significant differences between case and control.

Table 2: Comparison of biochemical, endocrinological, and biomarker parameters between control and case.

	Control (n=50)		Case (n=50)		t test	
	Mean	SD	Mean	SD	t	p
Biochemical parameters						
Fasting blood sugar (FBS)	85.6	12.8	130.1	46.7	-6.496	<0.001
Total cholesterol	163.3	19.8	235.7	46.7	-10.09	<0.001
Triglyceride	114.6	16.5	161.2	41.3	-7.41	<0.001
HDL cholesterol	50.7	6.0	43.9	8.8	4.547	<0.001

LDL cholesterol	89.7	20.1	159.6	46.3	-9.787	<0.001
Endocrinological parameters						
Follicle stimulating hormone (FSH)	9.29	3.22	24.33	7.80	-12.596	<0.001
Luteinizing hormone (LH)	8.31	2.10	21.78	11.35	-8.248	<0.001
Prolactin (PRL)	13.26	3.86	24.05	9.93	-7.158	<0.001
Biomarker						
Malondialdehyde (MDA)	1.92	0.78	4.88	0.86	-17.971	<0.001

The provided table (Table 2) presented a comparison of biochemical, endocrinological, and biomarker parameters between a control group (n=50) and a case group (n=50). The statistical analysis used was a t-test, which was appropriate for comparing means between two groups. The results indicated significant differences between the control and case groups for all measured parameters. The t-test values were all highly negative, and the corresponding p-values were all less than 0.001, suggesting strong statistical evidence against the null hypothesis.

Table 3: Binary logistic regression analysis of parameters associated with BOH

	B	S.E.	Wald	df	p	OR	95% C.I. for OR	
							Lower	Upper
FSH	0.026	0.191	0.019	1	0.891	1.027	0.71	1.49
LH	0.573	0.353	2.643	1	0.104	1.774	0.89	3.54
PRL	0.807	0.402	4.033	1	0.045	2.241	1.02	4.93
MDA	2.00	0.25	16.0	1	0.001	7.39	4.53	12.10
Constant	-22.81	9.99	5.213	1	0.022	0		

In this study, binary logistic regression (Table 3) was used to examine whether the levels of MDA, FSH, LH, and PRL helped to explain the BOH diagnosis. MDA was the strongest predictor with a highly significant p-value of 0.001. The odds ratio (OR) of 7.39 indicated that for every unit increase in MDA levels, the probability of being classified as a case increased by approximately 7.4 times. The confidence interval (CI) of 4.53 to 12.10 further supported the significance of MDA as a best biomarker, as the range did not cross 1, confirming its substantial impact. The regression coefficient (B) for FSH was small and non-significant with a p-value of 0.891, indicating that FSH did not significantly predict the probability of being a case. The OR was 1.027, with a 95% CI that crossed 1 (0.71 to 1.49), suggesting no clear effect of FSH on disease presence. The coefficient for LH showed a positive association with case status, but the result was not statistically significant (p = 0.104). The OR of 1.774 indicated that higher LH levels increased the probability of being in the case group, but since the confidence interval included 1 (0.89 to 3.54), this effect was not conclusive. Prolactin (PRL) showed a significant positive effect on the probability of being a case, with a p-value of 0.045. The OR of 2.241 suggested that for each unit increase in PRL, the chance of being in the case group increased more than twofold. The confidence interval (1.02 to 4.93) supported this finding as it did not include 1, indicating a significant predictor of disease status.

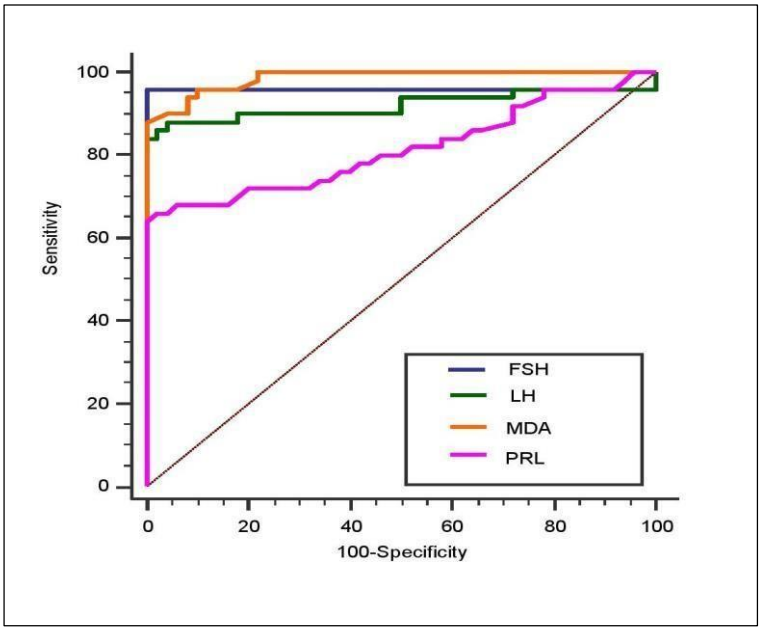
Table 4: Area under the curve (AUC) to measure predictive accuracy

	AUC	SE	95% CI
Follicle stimulating hormone (FSH)	0.96	0.028	0.901 to 0.989
Luteinizing Hormone (LH)	0.921	0.0338	0.849 to 0.965
Prolactin (PRL)	0.815	0.0453	0.725 to 0.886
Malondialdehyde (MDA)	0.986	0.00777	0.939 to 0.999

MDA exhibited almost perfect diagnostic accuracy with an AUC of 0.986, indicating it was an effective biomarker (Table 4). The extremely small standard error (SE) and narrow CI (0.939 to 0.999) emphasized the reliability and precision of MDA

as a best biomarker. The AUC of 0.96 indicated that FSH had excellent diagnostic accuracy as compared to other hormones like LH (AUC of 0.921) and PRL (AUC of 0.815). Comparison in terms of diagnostic accuracy based on AUC values was as follows: MDA > FSH > LH > PRL.

Figure 1: The ROC curve to predict BOH



Receiver operating characteristic **(**ROC) curve (Figure 1) illustrated the diagnostic performance of the biomarker MDA and the reproductive hormones FSH, LH, and prolactin by plotting the sensitivity (true positive rate) against 100-specificity (false positive rate). The diagonal line (dotted) represented a random classifier with no discriminatory power (AUC = 0.5). Curves closer to the top left corner indicated better performance. This ROC curve confirmed MDA as the most effective biomarker to predict BOH. FSH and LH also showed significant potential. The PRL curve was lower than those of FSH and LH, indicating lower diagnostic accuracy.

4. DISCUSSION

This study highlighted the complex interplay between oxidative stress and reproductive hormones in women with bad obstetric history. The results revealed that oxidative stress, as measured by MDA levels, and hormonal dysregulation, particularly involving FSH, LH, and PRL, were significantly associated with BOH. These findings suggested that both oxidative stress and hormonal imbalances contributed to adverse pregnancy outcomes.

Oxidative stress plays a crucial role in the pathophysiology of BOH. In this study, MDA levels were significantly higher in the BOH group compared to the control group (4.88 vs. 1.92, $p < 0.001$). MDA, a well-established biomarker of lipid peroxidation and oxidative damage, has been implicated in various reproductive disorders, particularly those affecting placental function [5]. The binary logistic regression analysis demonstrated that MDA had the highest odds ratio (OR = 7.39), indicating a strong association with BOH risk. Moreover, MDA had an almost perfect area under the curve (AUC = 0.986), signifying its high diagnostic accuracy as a biomarker for BOH.

The study also observed significant alterations in reproductive hormone levels in women with BOH. FSH, LH, and PRL levels were markedly higher in the BOH group compared to the controls. FSH and LH, which regulate the ovarian cycle, showed strong associations with BOH. Elevated FSH (24.33 vs. 9.29, $p < 0.001$) and LH (21.78 vs. 8.31, $p < 0.001$) levels were significantly correlated with the condition. While the logistic regression showed that LH had an odds ratio of 1.774, this result did not reach statistical significance, potentially due to sample size limitations. PRL, a hormone crucial for lactation and maintaining pregnancy, was significantly elevated in the BOH group (24.05 vs. 13.26, $p < 0.001$). PRL also emerged as a significant predictor in the regression analysis (OR = 2.241, $p = 0.045$), indicating that higher PRL levels increase the risk of BOH by more than twofold.

This study underscores the importance of considering both oxidative stress and hormonal dysregulation when evaluating women with BOH. The significant increase in MDA levels along with the altered hormone profiles suggests that oxidative stress may exacerbate hormonal imbalances, further impairing reproductive outcomes [6-8]. It is plausible that oxidative

stress triggers hormonal dysregulation, contributing to ovarian dysfunction and impaired follicular development, and miscarriages.

The interaction between oxidative stress and reproductive hormones can also impact placental development. Excess ROS could impair the endocrine function of the placenta, leading to abnormal hormone production, including FSH, LH, and PRL, which are vital for successful implantation and pregnancy maintenance [9, 10]. By disrupting the hormonal milieu, oxidative stress may create a vicious cycle that perpetuates poor reproductive outcomes in women with BOH.

The findings of this study have important clinical implications for managing BOH. Monitoring oxidative stress markers, particularly MDA, along with reproductive hormones, could enhance the early identification of women at risk for adverse pregnancy outcomes [11, 12]. Future research should focus on elucidating the molecular pathways through which oxidative stress interacts with the reproductive endocrine system. Investigating the efficacy of antioxidant treatments in combination with hormone regulation therapies could provide a novel approach for preventing BOH [13, 14]. Additionally, larger studies with diverse populations are needed to confirm the generalizability of these findings and to explore other potential biomarkers for BOH.

5. CONCLUSION

This study concludes that the combined impact of oxidative stress and elevated hormone levels (FSH, LH, and PRL) has a significant role in the development of BOH. MDA emerged as the most reliable biomarker, demonstrating high predictive accuracy for BOH. Elevated levels of FSH, LH, and PRL further underscore the role of hormonal dysregulation in adverse pregnancy outcomes. Future research should aim to develop targeted interventions that address both oxidative stress and hormonal disturbances to improve pregnancy outcomes in women with BOH.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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