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Article

Homocystine as a Diagnostic Marker for Preterm Labor

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Abstract: Preterm labor poses significant risks to maternal, fetal, and neonatal health worldwide, with elevated homocysteine levels identified as a potential marker for its diagnosis. This case-control study conducted at the Department of Obstetrics and Gynecology, AL-Yarmouk Teaching Hospital, included 90 pregnant women divided into two groups: 40 with threatened preterm labor (group A) and 50 without signs of labor (group B). Serum homocysteine levels were measured using ELISA, revealing a significantly higher mean level in the preterm group (1.769±0.687 nmol/ml) compared to controls (0.810±0.261 nmol/ml) (p=0.001). At a cutoff point of 1.096 nmol/ml, homocysteine exhibited a sensitivity of 80%, specificity of 86.4%, positive predictive value of 84.3%, and accuracy of 83% for predicting preterm labor. This study underscores the potential of homocysteine measurement as a screening tool in conjunction with other tests to identify high-risk patients for preterm labor, thus aiding in timely interventions and improved maternal and neonatal outcomes.

Keywords: Preterm labour, serum, homocystine, screening, test.

1. Introduction

The incidence of preterm labour has been rising, largely due to [1] (Increased of assisted reproductive technology, Increased in multiple pregnancies and Increased in preterm labor inductions.in a Study done in Iraq [2] Hyperhomocysieinemia in pregnant women has been associated with various placental pathologies like recurrent pregnancy loss , Abruption placentae& in another preeclampsia study associated with Fetal growth restriction and stillbirth [3]. The probable mechanism by which hyperhomocysteinemia affects pregnancy and placental implantation is by inhibition of trophoblast functions and cell death [4]. In the non-pregnant control group the mean homocysteine concentration (in micromoles per liter) was 5.6 at 8 16 weeks' gestation, 4.3 at 20-28 weeks' gestation, 5.5 at 36-42 weeks' gestation, and 7.9 while during pregnancy it it is significantly lower in all 3 trimesters of pregnancy compared with non-pregnant controls .The primary goal of treatment is to lower blood levels of homocysteine to normal. Treatment may consist of giving supplements of folic acid, vitamin B-12, and/or vitamin B-6; this combination ensures that methionine synthase cofactor stores are adequate, thereby promoting normal tetra-hydrofolate metabolism and re-methylation of homocysteine to methionine [5]. It also may include anticoagulant medications (blood thinners), such as aspirin, clopidogrel, heparin, low-molecular weight heparin, or warfarin, to prevent blood clots. Patients with the severe form of hyperhomocysteinemia (homocystinuria) are often treated with high doses of vitamin B-6 or betaine, and the amount of methionine consumed in the diet may be restricted [6] .

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2. Materials and Methods

A case-control study was conducted at the Department of Obstetrics and Gynecology of Al-Yarmouk Teaching Hospital through a period of 2 years from October 2018 to October 2020. The study protocol was approved by the scientific council of Obstetrics and Gynecology /Arabic Board for Medical Specializations. The study included 90 pregnant women in the third trimester of pregnancy. Patients were collected from the consultant clinic and inpatient obstetric ward of Al Yarmouk Teaching hospital. Those women were informed about the nature of the study, and verbal consents taken from all of them.They were divided into two groups :

(group A) includes 40 pregnant women with threatened preterm

Labor.

(group B) includes 50 pregnant women of comparable gestational age

without signs or symptoms of labour, serum samples were collected form patient.

3. Results

The study included 90 pregnant women 40 women in case group 50 women in control group Patient in both group (case & control) were tested for homocystine Independent 2 sample t test in table 1 showed that the mean maternal age in preterm group (29.1±5.5 year) was significantly higher than that of control group (22.2±5.6), p value=0.001. The mean of gestational age in preterm group (31.2±6.6 week) was significantly lower than that of control group (38.3±1.3), p value=0.001. No significant difference between mean number of parities in cases and control group, p value=0.543. There was significant association between history of previous preterm deliveries and possibility of occurrence of preterm delivery, p value= 0.002. Regarding abortion history, association was found between two group, p value= 0.09. Showed that the mean homocysteine level in preterm group (1.769±0.687 nmol\ ml) was significantly higher than that of control group (0.810±0.261 nmol\ ml) p value=0.001. At cutoff point of =1.096 one can predict preterm labour with a sensitivity =80%, specificity=86.4%, positive predictive =84.3%& accuracy =83% .

4. Discussion

The study included 90 pregnant women 40 women in case group 50 women in control group Patient in both group (case & control) were tested for homocystine Independent 2 sample t test in table 1 showed that the mean maternal age in preterm group (29.1±5.5 year) was significantly higher than that of control group (22.2±5.6), p value=0.001. The mean of gestational age in preterm group (31.2±6.6 week) was significantly lower than that of control group (38.3±1.3), p value=0.001. No significant difference between mean number of parities in cases and control group, p value=0.543. There was significant association between history of previous preterm deliveries and possibility of occurrence of preterm delivery, p value= 0.002. Regarding abortion history, association was found between two group, p value= 0.09.

Table 1 The Demographic Characteristics Of The Study Group

		N	Mean	Std. Deviation	P value
Maternal age in years	case	40	29.1	5.5	0.001
	control	50	22.2	5.6	
Gestational age in weeks	case	40	31.2	6.6	0.001
	control	50	38.3	1.3	
Partiy	case	40	1.9	0.69	0.543
	control	50	1.9	0.46	
Previous Hx of preterm	case	40	0.85	0.47	0.002
	control	50	0.08	0.04	
Previous Hx of abortion	case	40	0.75	0.25	0.09
	control	50	0.4	0.2	

Table 2 showed that the mean homocysteine level in preterm group (1.769±0.687 nmol\ml) was significantly higher than that of control group (0.810±0.261 nmol\ml) p value=0.001.

Table 2. Mean Of Homocysteine Between Case And Control Group

Real outcome	N	Mean	Std. Deviation	P value
Case	40	1.769nmol\ml	.687	0.001
control	50	0.810 nmol\ml	.261	

Homocystine , at the cutoff point of =1.096 one can predict preterm with Sensitivity =80%,Specificity=86.4%,PP-ve=84.3%, Accuracy =83%, as shown in table 3 and figure 1.

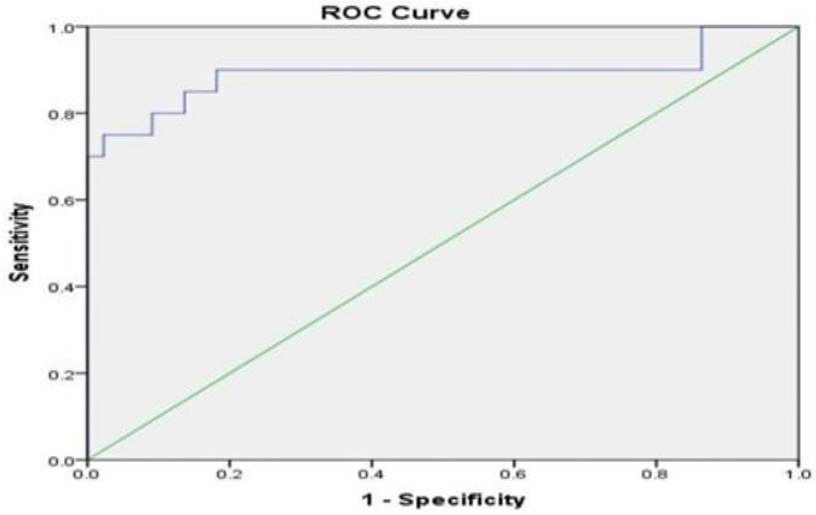

Figure 1. The ROC curve of homocystine level to detect preterm Total Area Under the curve=0.892, p value =0.001.

Gestational age at delivery in case group who tests positive for homocystine 28 case deliver preterm and 4 of them continue till term while in control group 5 deliver preterm and two deliver term. In patient with negative tests for homocystine in case group two deliver preterm and 6 deliver term while in control group three of them deliver preterm and 40 continue till term.

Table 3. Accuracy ,Sensitivity ,Specificity ,PP-ve , PP+ve.

	Case	GA at delivery	Control	GA at delivery	Total
Test Positive	32	28(28-36^{+6})w 4 > 37w	7	5(28-36w) 2 37w	39
Negative	8	2(28-36^{+6})w 6 > 37w	43	3(28-36w) 40 > 37w	51
Total	40		50		90
Sensitivity=80%,Specifcity=86%,pp+ve=82%,pp-ve=84.3%,accuracy=83					

Outcome of screening test using homocysteine level as predictor for preterm delivery. There was significant intermediate negative correlation between homocysteine level and gestational age, r=-0.534, p value=0.001, intermediate significant positive correlation between homocysteine level and maternal age, r=0.304, p value=0.004 as showed in table 4.

Table 4 Correlations between homo cysteine level and gestational age in week at time of delivery ,maternal age in year.

	Gestational age in week	Maternal age in year
Homocystine Pearson Correlation	-.543**	.304**
Sig. (2-tailed)	.000	.004
**. Correlation is significant at the 0.01 level (2-tailed)		

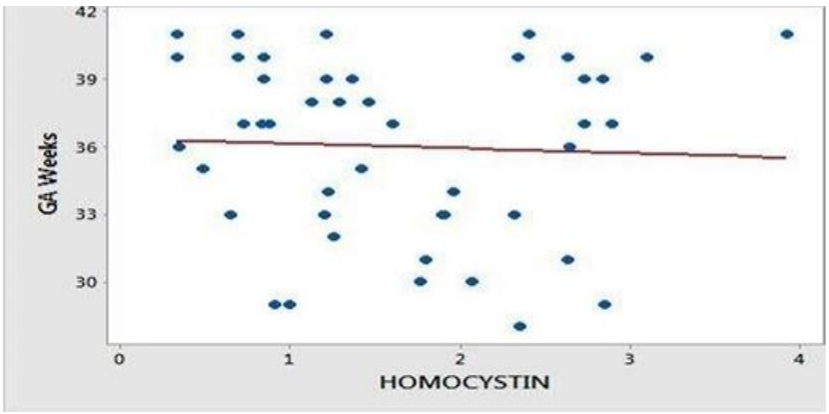

Figure 2. Correlation between homocysteine level and Gestational age in Weeks Homocystine level increase with maternal age while its higher among women who deliver preterm as showed in figure below.

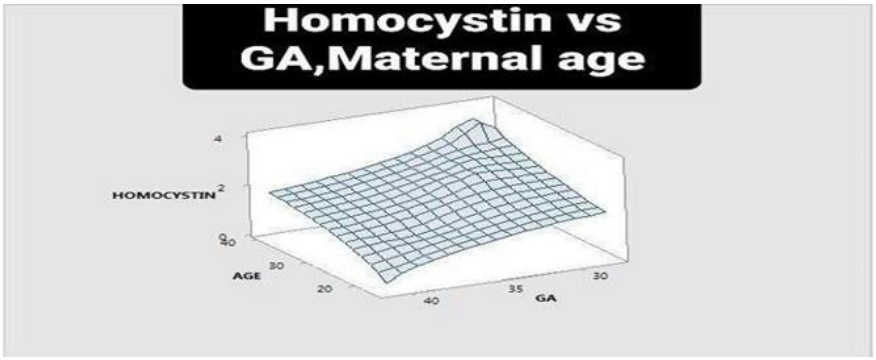

Figure 3.Three Dimensional mish surface plot showing that homocystine in X axis versus GA and maternal age

Table 5 showed the mean of homocysteine in patients with history of more than one previous preterm was found to be significantly higher than that found in history of single or no previous preterm history, p value=0.006. No significant difference between presence of previous abortion and the mean of homocysteine level, p value=0.778.

Table 5. Differences Between Means Of Homocysteine According To Studied Variables.

		N	Mean	Std. Deviation	P value
Previous preterm	No	60	1.1092	0.67333	0.006
	One	22	1.3447	0.68073	
	>1	8	1.8975	0.37192	
Abortion	No abortion	48	1.2561	0.68001	0.778
	Abortion	42	1.2148	0.70542	

Preterm labour is one of the complex and rapidly growing health issue in the developing world of which the causative factors are still uncertain [7] . The incidence rates are higher in underdeveloped countries (11.8%) compared to those most developed (9.3%) [8]. Preterm birth is considered a syndrome that can be initiated by numerous mechanisms such as inflammation and intrauterine infection, utero-placental ischemia and hemorrhage, uterine over distension, cervical insufficiency, hormonal disorders, and other immunologically mediated processes[9]. This health problem would be interesting one for the researchers. The study of homocysteine has introduced the link between metabolic (biochemical) and genetic factor's relationships with PTL. Since the association between homocysteine and PTL has been traditional decades ago, very few researchers targeting the same have been conducted till now [10]. The current study, showed significant difference with a p value of (0.001) between control and study group with regard to maternal age, women with preterm birth were older than control one , This is agree with a study done in Italy which found clear indication that mother with advanced age contributed to an increased risk of preterm delivery [11]. While in a study done in Finland 2017 found that advanced maternal age not associated with an increase in the probability of preterm delivery [12]. The present study revealed that gestational age in preterm group was lower than term group , p value was (0.001) which is expected with current protocol to compare homocysteine level between term and preterm group . In a study done in Egypt 2018 included 200 women found gestational age where significantly lower in preterm delivery group compared to the term delivery group. Significantly higher total maternal serum homocystine level were noted in the preterm delivery group [13]. With regard to woman parity the current study showed no significant association between study and control group with a p value of (0.543) which is similar to a study done in Italy at 2019 [14]. On the other hand in a study done in Taiwan (2013) [15] and other study done by Koullali Bouchra (2020) showed significant association between high parity and spontaneous preterm birth . This possibly points to other factors that may contribute to a higher risk of spontaneous preterm birth in high parity woman in these studies, one of the factors that may play a role could be a damaged cervix. The cervix plays an important role in maintaining pregnancy. It was well known that damage to the cervix, for instance by dilatation and curettage or loop excisions of the cervix for premalignant lesions, contributes to a higher risk of spontaneous preterm birth. The risk of such procedures being performed is higher in women at higher parity, which may be an explanation for the association of parity and spontaneous preterm birth [9]. In the present study there was significant difference, p value was (0.001) between control and study group with regard to previous history of preterm delivery. This finding was in concordance with findings of a study done in Italy 2019 by Granese Robarta who found preterm birth associated with higher proportion of history of a prior PTB [10] . This finding agreed by majority of studies dealing with the same subject, like two studies from Canada2008 and Brazil2020 [16] found similar results. History of abortion in present study was significantly associated with pregnancy outcome p value was (0.09). The result was similar to a study done by J S Brown et al which studied the association between previous abortion and the risk of low birth weight and preterm births [17], and in a study done by Hardy Ghislain et al who showed a significant increase in the risk of preterm delivery in women with a history of previous abortion (2011) [18] . While in a study done in Scotland at (2013) found that women with history of abortion no longer raises a woman's risk of having a premature baby during a subsequent pregnancy [19] . The present study found that homocysteine level in the serum of preterm labor group was significantly higher when compared to that in the control group .This agreed by many studies dealing

with the same subject .The three studies from India done by Chamotra Shaina (2020) [20], Surya Panikar(2021) [9],Dhobale Madhavi (2012)[21]found similar results. A high concentration of homocysteine can result from its defective excretion by a pregnant woman's kidneys .Other researchers proposed that a high concentration of homocysteine can bring weakness of the collagen structure through damaging transversal bindings which then leads to a weakness of the connective tissue .This process can stimulate preterm rupture of fetal membranes and causing preterm.

5. Conclusion

Our study elucidated a significant elevation in homocystine levels among women delivering preterm compared to those continuing pregnancy to term, underscoring its potential as a screening marker for identifying high-risk patients for preterm labor. The observed association between homocystine levels and preterm delivery suggests its utility as an adjunctive tool alongside existing diagnostic tests. Incorporating homocystine measurement into clinical practice may aid in early identification and intervention, thereby potentially mitigating adverse maternal and neonatal outcomes associated with preterm birth. However, further research is warranted to validate our findings across diverse populations and to explore the optimal integration of homocystine screening into existing diagnostic protocols for preterm labor.

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