Original Article
Diagnostic value of HAMD combined with determination of hormonal levels at different pregnancy stages

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Abstract: Objective: To explore the diagnostic value of Hamilton Depression Scale (HAMD) combined with the determination of hormonal levels at different pregnancy stages. Methods: 744 women in early pregnancy, 946 in middle pregnancy, and 881 in late pregnancy were retrospectively assessed. Among them, 492 had depression. HAMD scores and estradiol levels in all patients were recorded, and their values in the diagnosis of depression during different pregnancy stages were analyzed. Results: With the development of depression, the estrogen levels of pregnant women in the early, middle, and late pregnancies gradually and consistently decreased, with statistically significant differences (P<0.05). The HAMD scores of pregnant women in early, middle, and late pregnancies gradually and consistently increased, with statistically significant differences (P<0.05). The diagnostic accordance rate, sensitivity, and specificity of estradiol levels, HAMD scores, and HAMD scores combined with estradiol levels in diagnosing depression at different pregnancy stages were statistically significant (P<0.05). The diagnostic accordance rate, sensitivity, and specificity of HAMD scores and estradiol levels combined with HAMD scores in diagnosing depression at different pregnancy stages were higher than those of estradiol alone (P<0.05). The diagnostic coincidence rate and specificity of estradiol levels and HAMD scores in diagnosing depression in the late pregnancy were higher than those in the early pregnancy. Conclusion: Estradiol levels combined with HAMD scores are useful tools for diagnosing depression at different pregnancy stages, and further studies are necessary for their promotion and application in clinics.

Keywords: Pregnancy stages, HAMD, estradiol, diagnosis, depression

Introduction

Depression is a mental disorder with the highest incidence in the recent years. In 2020, depression is expected to be another disease burden worldwide following cerebrovascular diseases [1-3]. With the increasing social development, progress of medical technology, and transformation of modern medical model, medical workers are more and more concerned on the maternal psychological health during pregnancy in addition to previous postpartum mental healthcare problems [4, 5].

Estradiol is a steroid estrogen containing two subtypes, alpha and beta estrogen, with the highest levels and strongest activities in women [6, 7]. Studies have shown that estradiol regulates the level and activity of neurotransmitters and participates in the regulation of neuronal

excitability and protection of neuronal functions [8, 9]. In the meantime, the Hamilton Depression Scale (HAMD) was confirmed in clinics to better evaluate the degree of depression and was the most extensively used method for the clinical evaluation of depression [10, 11]. However, HAMD has some limitations in application as well, because evaluators should be systematically trained and the patients should have certain abilities in understanding and will be greatly affected by the subjective awareness of the evaluators, whereas the serological diagnosis can effectively avoid these deficiencies [12, 13].

In this study, we retrospectively analyzed the data of 2,571 pregnant women and their HAMD scores combined with hormonal levels to diagnose depression.

Table 1. General information of 2571 pregnant women

	Clinical data (n=2571)
Age (year)	28.2±4.5
Termination of pregnancy cycle (week)	37.4±2.1
Delivery mode [n (%)]	
Cesarean	1157 (45.0)
Eutocia	1414 (55.0)
Neonatal weight (Kg)	3.1±0.5
Systolic pressure (mmHg)	126.52±11.35
Siastolic pressure (mmHg)	78.44±7.47
Pregnancy [n (%)]	
First trimesters	744 (28.9)
Second trimesters	946 (36.8)
Third trimesters	881 (34.3)
Depression [n (%)]	
Mild depression	291 (11.3)
Moderate depression	176 (6.8)
Severe depression	25 (1.0)

Methods and materials

Clinical data

A total of 2,571 pregnant women who were gynecologically examined in Yuncheng maternity and child health hospital were retrospectively analyzed, including 744 in the early, 946 in the middle, and 881 in the late pregnancy; among them, 492 experienced depression: 291 with mild, 176 with moderate, and 25 with severe depression. Inclusion criteria: time of pregnancy, i.e., early, middle, and late pregnancy, was <12 weeks, ≤28 weeks, and >28 weeks, respectively. The time of pregnancy was confirmed based on the date when HAMD scores and estradiol levels were determined, and the variation did not exceed 1 week. All women were in a singleton pregnancy and in primiparas without organic diseases and abnormal blood system functions. The antenatal examination prompted the absence of fetal abnormalities, mental illness history, and hereditary mental illness, and the medical records of all the pregnant women were complete; Exclusion criteria: pregnant women who terminated the pregnancy due to exfetation and spontaneous abortion as well as embryo damage and those who gave premature birth were excluded. The study was approved by the medical ethics committee of Yuncheng maternity and child health hospital, and the informed consent was signed by the subjects or their family members.

Determination of estradiol levels

The estradiol level was detected using enzyme-linked immunosorbent assay and the nurses collected peripheral blood samples of pregnant women on an empty stomach in the morning. The estradiol kit was purchased from the Shanghai Zeye Biotechnology Co., Ltd. At first, the standard curve of estradiol level was established; the blank, standard, and sample holes were set up; 25 μL reference standard and quality control samples were added to the enzyme-labeled hole, which was previously coated with estradiol antibody; and 200 μL of enzyme conjugates were added. Warmly incubate for 120 min at 24°C, flush three times, remove the uncombined enzyme, and add 100 ml of substrate to develop color and let it stand for 15 min keeping away from lights at room temperature. During the 15 min, null with the blank hole, read the absorbance value (OD) of each hole at 450 nm wavelength on the microplate reader, and the estradiol levels in the sample were positively correlated with the OD value. Three groups of repeated holes were set up, and the experiment was repeated three times.

HAMD

The HAM-D is an observer-rated scale that evaluates core symptoms of depression. While there are multiple versions of the HAM-D, versions consisting of 17-21 items (including two, two-part items, weight and diurnal variation) are most common in clinical trials. In this study, it consists of 17 items with Likert scale of either 0 to 4 or 0 to 2. Scores can range from 0 to 54. HAMD scores can be used in place of a self-report when a patient is unable to read. It can also be used when there are concerns about the accuracy of the patient's self-report. The 17 items were completed by pregnant women independently. The scores of healthy, mildly depressed, moderately depressed, and severely depressed pregnant women were <7, 7-17, 17-24, and >24, respectively [12, 13].

Statistical analysis

The SPSS 19.0 (Asia Analytics Formerly SPSS China) was used for the statistical analysis. The

Table 2. Detection result of estradiol levels (pmol/L)

	First trimesters	Second trimesters	Third trimesters	Statistic	P value
Normal	409.3±35.6	784.6±39.7	1613.1±53.8	396.321	<0.001
Mild Depression	395.6±32.7[a]	765.1±38.4[a,d]	1539.1±51.5[a,d]	62.870	<0.001
Moderate Depression	368.4±30.6[a,b]	732.8±36.5[a,b,d]	1472.8±49.2[a,b,d,e]	40.992	<0.001
Severe Depression	315.7±27.5[a,b,c]	647.2±35.2[a,b,c,d]	1389.7±46.9[a,b,c,d,e]	6.658	0.036
Statistic	52.249	16.074	18.509		
P value	<0.001	0.001	<0.001		

Remark: a: compared with healthy pregnant women, P<0.05; b: compared with mildly depressed pregnant women, P<0.05; c: compared with moderately depressed pregnant women, P<0.05; d: compared with women in early pregnancy, P<0.05; e: compared with women in middle pregnancy, P<0.05.
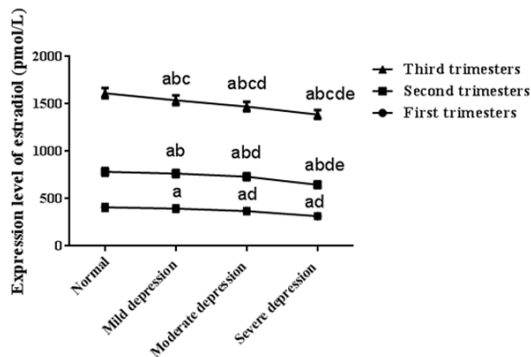

Figure 1. Expression level of estradiol (pmol/L). a: compared with healthy pregnant women, P<0.05; b: compared with mildly depressed pregnant women, P<0.05; c: compared with moderately depressed pregnant women, P<0.05; d: compared with that during early pregnancy, P<0.05; e: compared with that at middle pregnancy, P<0.05.

enumeration data were expressed in [n (%)], and the chi-square test (χ^2) was used to compare the rates. The measurement data were expressed as $\overline{x}$±sd, and the comparison between each group was performed using rank sum test. The differences among multiple groups were analyzed with means of variance analysis, and the least significant difference test was used to compare the two groups. The diagnostic values of HAMD scores and hormonal levels were analyzed based on the work curve of the subjects. P<0.05 implied the statistical significance.

Results

General information

The study included 2,571 pregnant women with the average age of 28.2±4.5 years and pregnancy termination cycle of 37.4±2.1 weeks, and pregnant women giving premature birth were excluded. Pregnant women who under-

went caesarean section accounted for 45% (1,157 cases), whereas those who underwent spontaneous vaginal delivery accounted for 55% (1,414 cases). The average weight of the newborns was (3.1±0.5) kg, and women who delivered abnormal newborns were excluded; the systolic and diastolic pressures were 126.52±11.35 mmHg and 78.44±7.47 mmHg; 784 patients (30.5%) were in early pregnancy, 946 (36.8%) in middle pregnancy, and 881 (34.3%) in late pregnancy. Finally, 492 patients were diagnosed with depression, including 291 with mild (11.3%), 176 with moderate (6.8%), and 25 with severe (1.0%) depression (**Table 1**).

Determination result of estradiol level

The estradiol levels between the healthy, mildly depressed, moderately depressed, and severely depressed pregnant women were significantly different (P<0.05). The estradiol levels in the middle and late pregnancies were higher than those in the early pregnancy (P<0.05), and those in the late pregnancy were higher than those in the middle pregnancy (P<0.05). With the development of depression, the estrogen levels of women in the early, middle, and late pregnancies decreased and were continuously declining, and the difference between the two groups was statistically significant (P<0.05) (**Table 2**, **Figure 1**).

HAMD score results

The HAMD scores were not significantly different between the healthy, mildly depressed, moderately depressed, and severely depressed pregnant women at different pregnancy stages (P>0.05). With the progression of depression, the HAMD score of pregnant women in early, middle, and late pregnancies gradually and continuously increased, and the difference

Table 3. HAMD scores

	First trimesters	Second trimesters	Third trimesters	Statistic	P value
Normal	5.32±2.13	5.72±2.02	5.71±2.04	2.614	0.074
Mild Depression	11.36±4.11[a]	12.15±3.98[a]	11.94±3.86[a]	1.476	0.229
Moderate Depression	20.41±6.21[a,b]	19.86±5.98[a,b]	20.65±5.72[a,b]	1.827	0.162
Severe Depression	26.32±5.61[a,b,c]	25.96±5.58[a,b,c]	26.13±5.65[a,b,c]	2.151	0.124
Statistic	2743.728	3384.730	2731.301		
P value	<0.001	<0.001	<0.001		

Remark: a: compared with healthy pregnant women, P<0.05; b: compared with mildly depressed pregnant women, P<0.05; c: compared with moderately depressed pregnant women, P<0.05. Analysis of depression diagnostic value of estradiol and HAMD at different pregnancy stages.

Table 4. Depression diagnostic value of estradiol and HAMD at different pregnancy stages [n (%)]

		Estradiol	HAMD	Estradiol combine HAMD	Statistic	P value
First trimesters	Precision rate	396 (53.2)	621 (83.5)[c]	617 (82.9)[c]	227.240	<0.001
	Sensitivity	91 (61.4)	121 (85.2)[c]	129 (90.8)[c]	35.391	<0.001
	Specificity	305 (50.7)	500 (83.1)[c]	488 (81.1)[c]	195.104	<0.001
Second trimesters	Precision rate	543 (57.4)	799 (84.5)[c]	788 (83.3)[c]	236.523	<0.001
	Sensitivity	105 (58.3)	149 (82.7)[c]	160 (88.9)[c]	52.609	<0.001
	Specificity	438 (57.2)	650 (84.9)[c]	628 (82.0)[c]	187.593	<0.001
Third trimesters	Precision rate	540 (61.3)[a]	772 (87.6)[a,c]	747 (84.8)[c]	213.861	<0.001
	Sensitivity	94 (55.3)	138 (81.2)[c]	149 (87.6)[c]	52.734	<0.001
	Specificity	446 (62.8)[b]	634 (89.2)[b,c]	598 (84.1)[c]	166.910	<0.001
$X^2$1	Precision rate	10.756	6.312	1.203		
P1 value		0.005	0.043	0.548		
$X^2$2	Sensitivity	2.514	0.894	0.815		
P2 value		0.284	0.640	0.665		
$X^2$3	Specificity	19.379	10.914	1.266		
P3 value		<0.001	<0.001	0.531		

a: diagnosis accordance rates difference compared with that at early pregnancy, P<0.05; b: specificity difference compared with that at early pregnancy, P<0.05; c: compared with estradiol diagnosis, P<0.05.
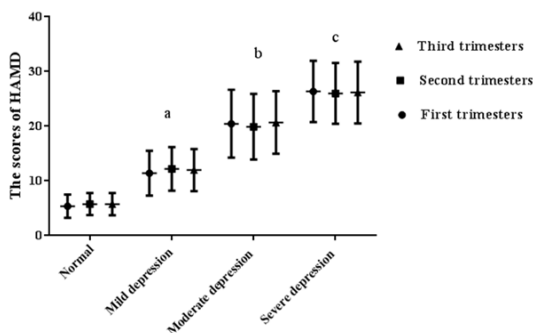

Figure 2. The HAMD scores. a: compared with healthy pregnant women, P<0.05; b: compared with mildly depressed pregnant women, P<0.05; c: compared with moderately depressed pregnant women, P<0.05. The diagnostic value analysis of estradiol levels and HAMD scores at different pregnancy stages.

between the two groups was statistically significant (P<0.05) (**Table 3**).

Diagnostic value of estradiol levels and HAMD scores

The diagnostic coincidence rate, sensitivity, and specificity of estradiol levels, HAMD scores, and estradiol levels combined with HAMD scores were significantly different in diagnosing depression at different pregnancy stages (P<0.05). The diagnostic coincidence rate, sensitivity, and specificity of HAMD scores and estradiol levels combined HAMD scores in diagnosing depression at different pregnancy stages were higher than those of estradiol levels alone (P<0.05), and the diagnostic coincidence, sensitivity, and specificity of HAMD scores and estradiol levels combined with HAMD scores in diagnosing depression at different pregnancy stages were not statistically significant (P>0.05). The diagnostic coincidence rate and specificity of estradiol levels and HAMD

scores in diagnosing depression at different pregnancy stages were statistically significant (P<0.05). The diagnostic coincidence rate and specificity of estradiol levels and HAMD scores alone in diagnosing depression at the late pregnancy were higher than those in the early pregnancy and were not statistically different from those in the middle pregnancy (P>0.05). The diagnostic coincidence rate, sensitivity, specificity of estradiol levels combined with HAMD scores and the sensitivity of estradiol levels and HAMD scores alone for the diagnosis of depression at different pregnancy stages were not statistically significant (P>0.05) (**Table 4**, **Figure 2**).

Discussion

Depression is a common mental disorder with the highest suicide incidence in psychiatry. At present, the doctor visiting and treatment rates of depressed patients are lower due to prejudice and other reasons [14, 15]. For many women, the duration of pregnancy is the most important period in their lives; however, approximately 10% of pregnant women suffer from depression, and if they are not diagnosed immediately, unpredictable effects on the mother and fetus may occur [16, 17]. At present, depression is mainly diagnosed based on various depression scales, such as HAMD, which requires more medical workers and patients' time, and currently an objective laboratory method for the diagnosis of depression is not available [18]. This study retrospectively analyzed the estrogen levels and HAMD scores of 2,571 pregnant women and analyzed their diagnostic values at different pregnancy stages to provide reference values for the clinical diagnosis of depression.

This study included a total of 2,571 patients in our hospital from March 2014 to July 2015 based on the inclusion and exclusion criteria, including 492 depressed patients accounting for approximately 19.1%, which is to some extent different from the study of Shariat [19] that reported 30% of the pregnant women investigated were depressed. This difference may be associated with the sample size of both studies considering that they only 283 pregnant women were included as subjects and may also be associated with the increasing concern on mental health of perinatal pregnant women in the recent years, which may lead to the decreased incidence of depression [20]. The estradiol levels in all healthy pregnant women significantly increased with the pregnancy progression, which was consistent with the related reports [21, 22] that the placenta also secreted a large amount of estradiol, causing a physiological increase of estradiol levels in pregnancy [23]. However, at different pregnancy stages, the estradiol levels of depressed pregnant women were significantly reduced, which further decreased with the exacerbation of depression. Hormone replacement therapy has been a controversial antidepressant treatment, and many studies have also found that estradiol can effectively improve the symptoms of depression [24, 25], which also indirectly validates our results that depressed patients have lower estradiol levels. It is also reported that significant changes in estradiol levels during pregnancy will affect the changes in neurotransmitters and regulate the mood of the brain, which trigger the pregnant women to feel depressed and further induce depression [26, 27], implying that estradiol is closely associated with depression and may play an important role in the diagnosis and treatment of depression in pregnant women.

We analyzed the diagnostic values of estradiol and HAMD in depressed pregnant women. We firstly organized the results of HAMD score in 2,571 pregnant women and found that with the increasing incidence of depression, the HAMD scores in early, middle, and late pregnancies gradually and continuously increased, which was similar to the results of related reports [28, 29], and our results also demonstrated that the HAMD scores of healthy, mildly depressed, moderately depressed, and severely depressed pregnant women were not significantly different at various pregnancy stages, which implied that the difference in pregnancy stages would not affect the assessment of depression severity, and HAMD is reliable. We speculate that the changes in estradiol levels may not be a major factor that induced depression. At present, the mechanism of depression remains unclear, and the interaction between the genes and environment or stress time is an important cause of depression [30, 31]. The fluctuation of estradiol levels caused by pregnancy and other physiological changes is higher, and the fluctuation caused by depression may not be obvious

in pregnant women, which limited the diagnostic value of estradiol in pregnancy and maternal depression [32]. Based on our results, the diagnostic coincidence rate and specificity of estradiol levels in diagnosing depression during the late pregnancy were higher than those during the early pregnancy, and further increase in estradiol levels weakens its effects on depression, increases the rate of missed diagnosis, and further increases the specificity. Therefore, the diagnostic value of estradiol to diagnose depression at different pregnancy stages remains to be explored, and its diagnostic value in non-pregnant women may also be considered and should be further analyzed in future studies.

In conclusion, the estradiol levels combined with HAMD scores can significantly diagnose depression at different pregnancy stages, and further studies were necessary to explore its promotion and application in clinics.

Disclosure of conflict of interest

None.

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