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Clinical Importance of Serum BDNF (Brain Derived Neurotrophic Factor) Level for the Management of Pregnancies Complicated with Meconium-Stained Amniotic Fluid

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Abstract

Background: Meconium-stained amniotic fluid complicates pregnancies and is associated with high risk of neonatal meconium aspiration syndrome. Early detection of meconium-stained amniotic fluid is essential to prevent adverse neonatal outcomes.

Objectives: To investigate the relationship between poor neonatal outcomes of meconium-stained amniotic fluid and serum brain-derived neurotrophic factor (BDNF).

Patients and Methods: A case control study was carried out in the Department of Obstetrics and Gynecology of Azadi Teaching Hospital in Kirkuk, Iraq from 1st of March to 31st of August 2024 on a sample of 90 pregnant women. The case group included 45 pregnant women who underwent cesarean section due to fetal distress with meconium-stained fluid, and the control group included 45 pregnant women who underwent cesarean section due to fetal distress without meconium-stained liquor. The brain-derived neurotrophic factor was assessed in mothers and neonates from umbilical vein.

Results: Mean maternal and fetal cord (brain-derived neurotrophic factor) level was significantly lower among pregnant women with meconium-stained liquor compared to controls ($p<0.001$). The maternal BDNF cutoff for predicting meconium-stained liquor fetal distress was 1.76 ng/ml, showing an acceptable validity finding with sensitivity 100%, specificity 95.6% and accuracy 98.5%. The maternal and fetal brain derived neurotrophic factor levels were positively correlated with birth weight and APGAR score at both 1 and 5 minutes in neonates from pregnancies complicated with meconium-stained liquor.

Conclusion: Maternal and fetal cord serum brain-derived neurotrophic factors are decreased in fetal distress with presence of meconium-stained amniotic fluid.

Keywords: Meconium-stained amniotic fluid, Fetal distress, Brain-Derived Neurotrophic Factor.

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Introduction

Meconium-stained amniotic fluid (MSAF) during delivery is a marker of fetal stress. Neonates delivered through MSAF often require resuscitation and are at risk of meconium aspiration syndrome (MAS) (1). The word "meconium" originates from the Greek word mekoni, meaning "poppy juice" or "opium-like," referring to the belief that fetal exposure to meconium would lead to neonatal sleepiness or depression, a concept generally attributed to Aristotle (2). Meconium is content of the fetal colon, and primarily consist of water (72%-80%), exfoliated skin cells, lanugo, vernix caseosa, and gastrointestinal secretions. Its characteristics greenish-yellow color is due to the presence of bile pigments (3). MSAF occurs more frequently in post-term newborns. Its incidence increases with advancing gestational age. One study reported MSAF in 5.1% of preterm, 16.5% of term, and 27.1% of post-term deliveries. While the presence of MSAF is a prerequisite for the diagnosis of MAS, only 2% to 10% of babies born through meconium-stained fluid will develop MAS (4). MSAF is associated with fetal academia, chronic hypoxia (5), low umbilical artery pH and microbial invasion of the amniotic cavity in both term and preterm pregnancies (6, 7). MSAF is typically identified after membrane rupture or through amniocentesis. Detection of sonographic particulate matter in amniotic fluid via ultrasound may raise the suspicion of the MSAF. The diagnostic ultrasound features of MSAF include 1: a widespread echogenic pattern throughout the amniotic cavity; 2: a distinct contrast between the amniotic fluid and the umbilical vessels; and 3: layering of particles in the more dependent areas. However, these sonographic appearances are not specific to meconium, as similar pattern may occur with vernix or even blood (8). Maternal complications linked to MSAF include intra-amniotic infection, clinical chorioamnionitis, puerperal endometritis, post-cesarean infection, postpartum hemorrhage, and dehiscence of perineal lacerations (9). MSAF also poses a risk of various neonatal complications, including meconium aspiration syndrome (MAS), neonatal sepsis, pulmonary disease, and long-term neurologic impairment (eg, cerebral palsy) (10). MAS occurs in neonates who experience an intrauterine event that results in antepartum or intrapartum fetal hypoxia, triggering the passage of meconium, fetal gasping, and subsequent meconium aspiration prior to birth (11). Neurotrophies are a group of soluble molecules that are involved in various functions of the nervous system, including cell growth, differentiation, and neuronal plasticity (12). Among them, Brain-derived neurotrophic factor (BDNF) is one of the most extensively studied. BDNF plays a key role in regulating synaptic plasticity and long-term potentiation within the brain. Additionally, BDNF serves distinct functions during pregnancy, as it is essential for implantation and placentation (13). In the CNS, mature BDNF plays a key role in regulating both inhibitory and excitatory neurotransmission and in promoting neuronal growth. One of its primary functions during the early postnatal period is to sustain the survival of neurons that are not fully integrated in the neural network. Neurons that fail to establish adequate connections with others are prone to undergo apoptosis and eventually die. BDNF contributes to the structural and functional development of neuronal network formation by responding to afferent stimuli in the postnatal period (14). Altered BDNF production has been observed in intrauterine growth restriction, gestational diabetes, neonatal respiratory complications, and ischemic brain injury in newborns (15). Recent studies also indicate that BDNF might serve as a potential marker for predicting intrapartum neonatal hypoxia. BDNF can cross the blood-brain barrier, and its concentrations in cord blood closely reflect those in fetal brain (16). This study

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aimed to investigate the relationship between poor neonatal outcomes of meconium-stained amniotic fluid and serum brain-derived neurotrophic factor.

Patients and Methods

Study design: This case-control study was conducted out at the Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Kirkuk, Iraq, from March 1 to August 31, 2024. Oral informed consent was obtained from all participants, and confidentiality was maintained by coding names. Ethical approvals were secured from the Scientific Council of Obstetrics and Gynecology/Iraqi Board for Medical Specializations and the College of Medicine, University of Kirkuk (No. 66, 26\2\2025). A total of 90 pregnant women aged 16–40 years with 37–40 weeks' gestation and singleton pregnancies were enrolled. All participants were admitted in active labor and confirmed by an obstetrician. The case group (n=45) included women with MSL undergoing cesarean for fetal distress. The control group (n=45) comprised women undergoing cesarean for fetal distress without MSL.

Inclusion criteria: Singleton pregnancy, maternal age between 16 and 40 years, gestational age between 37 and 40 weeks, absence of any pre-existing medical conditions, and voluntary agreement to participate.

Exclusion criteria: Fetal congenital anomalies, multiple pregnancy, maternal medical diseases (pregestational or gestational diabetes mellitus, hypertension, preeclampsia, renal disease, cancer, chorioamnionitis, autoimmune disease, thyroid disease), smoking, in vitro fertilization, preterm labor, intrahepatic cholestasis, post term pregnancy, drugs(opioids/analgesics [morphine , fentanyl, meperidine], sedatives/anti histamines[promethazine, diazepam], regional anesthetics) and refusal to participate. The selected participants were interviewed by the researcher upon admission to the labor room. The collected data included maternal age, parity, and gestational age. Following obstetrical history, a physical examination of the maternal abdomen was conducted to measure symphysis-fundal height and assess fetal lie and presentation. Fetal heart rate (FHR) monitoring was conducted using continuous cardiotocography (CTG) for cases with antepartum or intrapartum risk factors, while intermittent auscultation was performed for the remaining participants. The diagnosis of fetal distress was based on FHR tracings. Due to the unavailability of fetal blood sampling, further confirmatory assessment was not performed. The meconium-stained fluid was diagnosed by the on-duty obstetrician through vaginal examination. Some women presented with rupture membrane, while others had intact membrane, and artificial rupture was done after admission. Fetal distress was diagnosed in participants based on fetal heart rate (FHR) monitoring. Some cases exhibited Category III FHR tracings, prompting the initiation of intrauterine resuscitative measures. These measures included left lateral recumbent positioning, rapid intravenous infusion of one liter of non-glucose crystalloid solution, and administration of maternal oxygen. Despite these interventions, no improvement in FHR tracings was observed. Consequently, cesarean delivery was indicated, with the timing and mode of delivery determined based on feasibility and maternal-fetal status. Participants with Category II FHR tracings were closely evaluated and continuously monitored. Intrauterine resuscitative measures were initiated. However, in some cases, no improvement was observed, and FHR tracing progressed to Category III in others; cesarean delivery was indicated. The reasons for fetal distress in the control group included antepartum hemorrhage, oligohydramnios, cord prolapse, cord around fetal neck, etc. Neonatal outcome was assessed by neonatal care unit physicians on duty. Neonates were assessed for birth weight, gender, Apgar score at 1 and 5 minutes,

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meconium aspiration syndrome, respiratory distress syndrome, other neonatal complications, and neonatal intensive care unit (NICU) admission. Neonates were followed up for 7 days Birth weight was classified as either normal (2.5-4 kg) or low (<2.5kg) (17). The APGAR score was categorized into normal (≥7), intermediate (4-6), and low (<4)(18). MAS is defined as unexplained respiratory distress in neonates born through MSAF (1). Fetal distress is defined as intrauterine depletion of oxygen and accumulation of carbon dioxide, leading to hypoxia and acidosis (19). The brain-derived neurotrophic factor (BDNF) levels were measured in maternal and umbilical cord blood samples.

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics were presented as mean ± standard deviation for continuous variables and as frequencies with percentages for categorical variables. Categorical data were analyzed using Chi-square or Fisher's exact test, while group means were compared using the independent t-test. Pearson correlation and ROC curve were used to assess associations and determine optimal cut-off values, with statistical significance defined as $p \leq 0.05$.

Results

Women age and gestational characteristics: Maternal age and gestational characteristics showed no significant differences were observed between study groups regarding age of pregnant women, parity and gestational age. Most women in both groups were between 20–29 years (46.7% in cases vs 55.6% in controls) and 30–40 years (42.2% vs 40%). Only a small proportion were <20 years (11.1% vs 4.4%). The age distribution is relatively similar between groups, with no obvious imbalance. This supports the statement that there is no significant difference in maternal age between the groups. With respect to parity, 24.4% of the case group and 26.7% of the control group were nulliparous, 75.6% of cases and 71.1% of controls were para 1–4, while none of the cases and 2.2% of controls were para ≥5. The difference was statistically not significant (P = 0.5). Regarding gestational age, 75.6% of participants in both groups were between 37–38 weeks, while 24.4% were between 39–40 weeks. No statistically significant difference was observed between the two groups (P = 0.6). (Table 1).

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Table 1. Distribution of maternal age and gestational characteristics according to study groups.

Variable	Study groups				P- value
	Case		Control		
	No.	%	No.	%	
Age					0.4
<20 years	5	11.1	2	4.4	
20-29 years	21	46.7	25	55.6	
30-40 years	19	42.2	18	40.0	
Parity					0.5
Nulliparous	11	24.4	12	26.7	
Para 1-4	34	75.6	32	71.1	
Para ≥5	0	-	1	2.2	
Gestational age					0.6
37-38 weeks	32	75.6	29	75.6	
39-40 weeks	13	24.4	16	24.4	

* Fishers exact test, ** Chi square test.

Neonatal outcomes: There was a highly significant association between low birth weight and MSL cases (p<0.001). A highly significant association was observed between low APGAR score at one minute and MSL cases (p<0.001). There was also a highly significant association between low APGAR score at five minutes and MSL cases (p<0.001). No significant differences were observed between study groups regarding fetal gender (p=0.5), fetal meconium aspiration syndrome (p=0.15) fetal respiratory distress syndrome (p=0.15), other neonatal complications and NICU admission (p=0.09). Although neonatal adverse outcomes were more frequent in MSL, the variation did not reach the statistical level of significance (Table 2).

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Table 2. Distribution of neonatal outcomes according to study groups. APGAR: A for appearance, P for pulse rate, G for grimace, A for activity, R for respiratory effort. NICU: neonatal intensive care unit.

Variable	Study groups				P-value
	Case		Control		
	No.	%	No.	%	
Birth weight					**<0.001**
Normal	25	55.6	44	97.8	
Low	20	44.4	1	2.2	
Fetal sex					0.5
Male	15	33.3	18	40.0	
Female	30	66.7	27	60.0	
Meconium aspiration syndrome					0.15
Yes	2	4.4	0	-	
No	43	95.6	45	100.0	
APGAR score at 1 minute					**<0.001**
<4	25	55	5	11	
4-7	12	26	10	22	
>7	8	17	30	66	
APGAR score at 5 minutes					**<0.001**
<4	23	51	6	13	
4-7	14	31	12	26	
>7	9	20	27	60	
Respiratory distress syndrome					0.15
Yes	2	4.4	0	-	
No	43	95.6	45	100.0	
Other neonatal complications (e.g. fits, hypoglycemia)					-
Yes	0	-	0	-	
No	45	100.0	45	100.0	
NICU admission					0.09
Yes	5	11.1	1	2.2	
[No	40	88.9	44	97.8	

* Chi square test, **Fishers exact test.

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BDNF levels: Both maternal and cord blood BDNF were significantly lower in cases complicated by MSL compared to controls group ($p < 0.001$). (Table 3, Figure 1and Figure 2).

Table 3. Distribution of BDNF levels in maternal blood and fetal cord blood according to study groups.

Variable	Study groups		P-value
	Case	Control	
	Mean±SD	Mean±SD	
Maternal BDNF (ng/ml)	1.4867±0.118	1.9068±0.017	**<0.001**
Fetal BDNF (ng/ml)	1.5±0.12	1.9079±0.022	**<0.001**
*Independent sample t-test.			

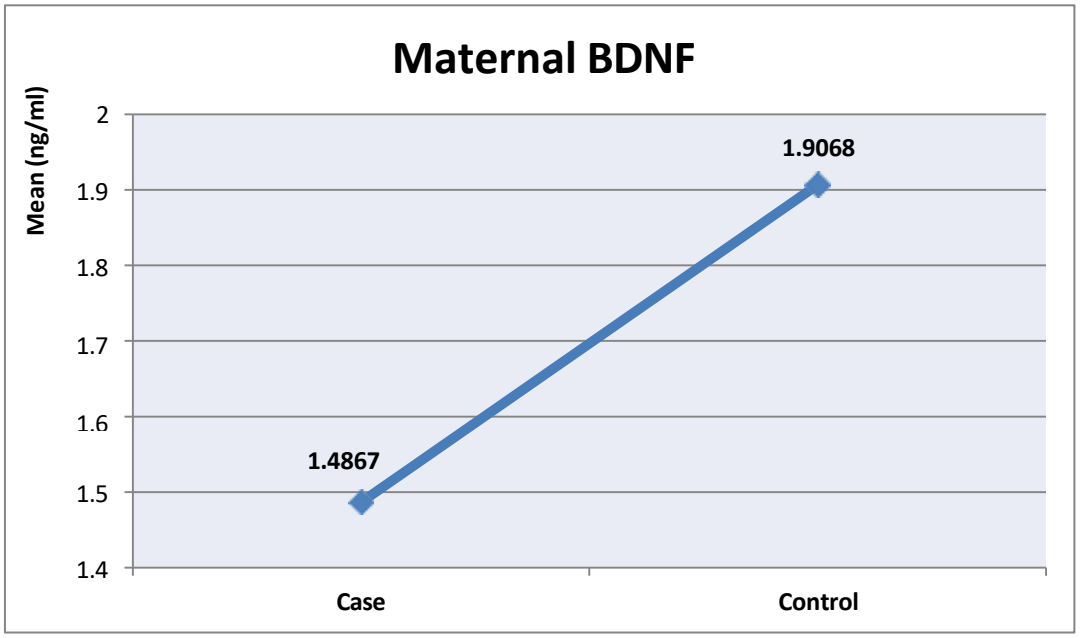

Figure 1. Maternal BDNF level in regard to study groups.

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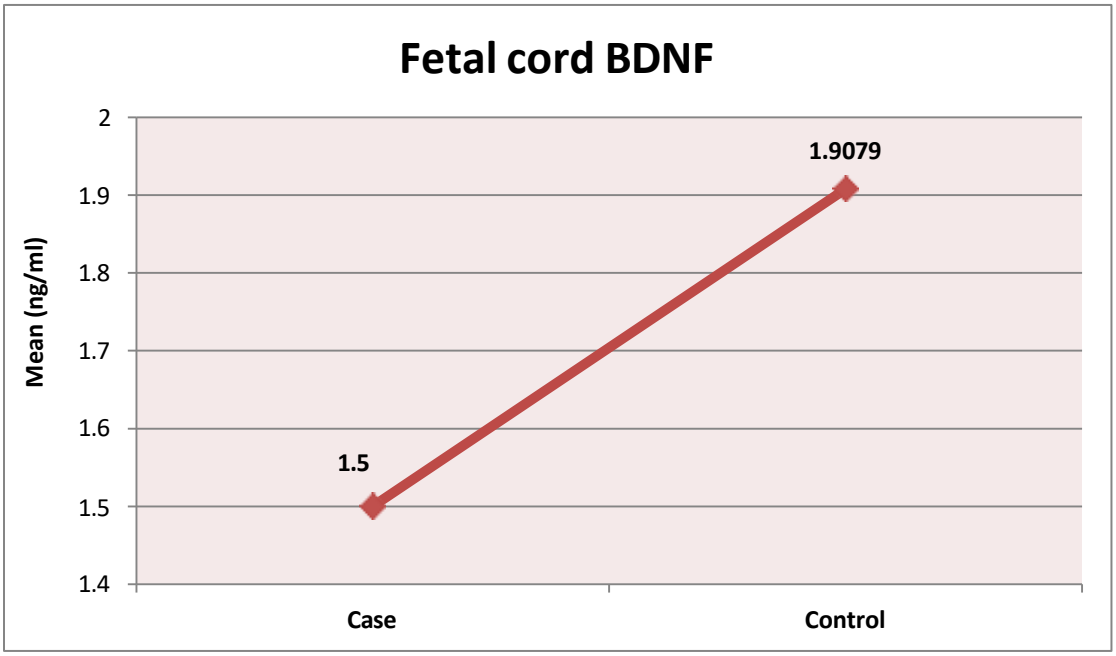

Figure 2. Fetal cord BDNF level in regard to study groups.

Cut off values of BDNF: The optimal maternal BDNF cutoff value for predicting of MSL fetal distress was (1.76 ng/ml) showing a high validity with sensitivity 100%, specificity 95.6%, and accuracy 98.5%. ROC curve of maternal BDNF in prediction of MS with fetal distress showed a value which is = 0.99, that's an excellent result, it shows that biomarker performs almost perfectly in distinguishing between the two groups (cases and controls). (Table 4 and figure 3).

Table 4. Maternal BDNF levels predicting MSL fetal distress.

Maternal BDNF	Sensitivity	Specificity	Accuracy
1.59 ng/ml	100%	88.9%	94.6%
1.76 ng/ml	**100%**	**95.6%**	**98.5%**
1.88 ng/ml	86.7%	97.8%	93.4%

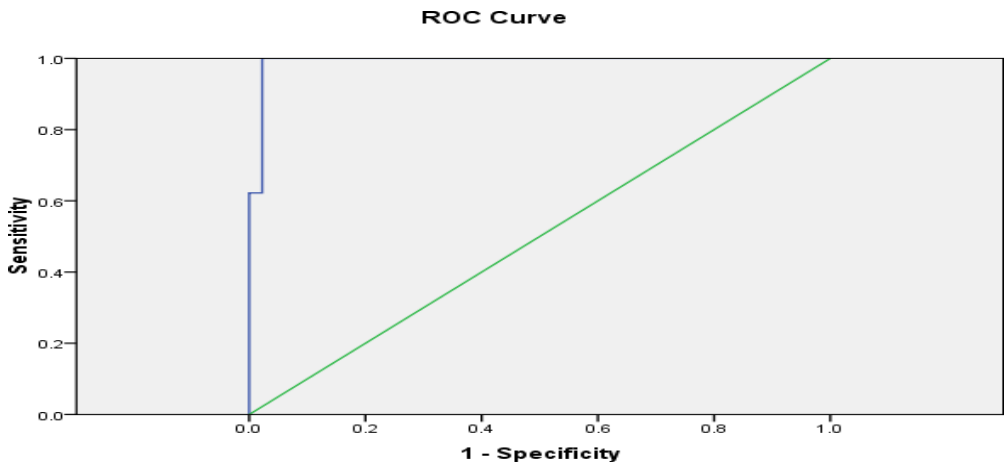

Figure 3. ROC curve of maternal BDNF in prediction of MSL fetal distress (AUC=0.99).

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Pearson correlation of BDNF levels: Maternal BDNF levels showed a positive correlation with neonatal birth weight in pregnancies complicated by MSL (p=0.03). Fetal BDNF levels were also positively correlated with neonatal birth weight. A moderate positive correlation was found between maternal BDNF and APGAR score at 1 minute (p<0.001). Fetal BDNF also showed a moderate positive correlation with APGAR score at 1 minute (p<0.001). Both maternal and fetal BDNF levels were moderately correlated with APGAR score at 5 minutes (p<0.001). No significant correlations were observed between BDNF levels and fetal gender, meconium aspiration syndrome, respiratory distress syndrome, or NICU admission. (p > 0.05). (Table 5).

Table 5. Pearson correlation of maternal and fetal cord BDNF levels with neonatal outcomes of pregnant women with MSL. MAS: meconium aspiration syndrome, RDS: respiratory distress syndrome, NICU: neonatal intensive care unit. APGAR: A for appearance, P for pulse rate, G for grimace, A for activity, R for respiratory effort.

Neonatal outcomes	Maternal BDNF (ng/ml)	Fetal BDNF (ng/ml)
Birth weight	r=0.4	r=0.3
	P<**0.001**^{S}	P<**0.001**
Fetal gender	r=0.12	r=0.2
	P=0.4^{NS}	P=0.1
Fetal MAS	r=0.02	r=0.08
	P=0.8^{NS}	P=0.6
APGAR score at 1 minute	r=0.5	r=0.4
	P<**0.001**^{S}	P<**0.001**
APGAR score at 5 Minutes	r=0.4	r=0.3
	P<**0.001**^{S}	P<**0.001**
Fetal RDS	r=0.02	r=0.08
	P=0.8^{NS}	P=0.6
NICU admission	r=0.03	r=0.07
	P=0.98^{NS}	P=0.6

Discussion

In this study, data showed no significant differences between mothers with MSL and controls regarding maternal age, parity, or gestational age. This contrasts with Addisu et al.'s findings, which linked advanced maternal age to increased MSAF risk. The discrepancy may be due to differing age distributions, as Addisu et al. included more older women (20). Our data revealed a presence of strong significant association between low birth weight and MSL cases (p<0.001 IU), aligning with Jain et al.'s findings (21). However, it contradicts Mohammad et al.'s results, which showed no significant difference in birth weight between thin and thick MSAF cases. The inconsistency may stem from differences in nutritional status and other community-specific risk factors (22). Additionally, no significant differences were found between the MSL and control groups regarding fetal sex, MAS, RDS, other neonatal complications, and NICU admission. These

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results align with Lee et al., except that they reported higher NICU admissions in MSL cases (23). In contrast, studies by Abdulghafor et al. and Gallo et al. reported poor neonatal outcomes such as fetal death, MAS, sepsis, and early neonatal death. MSAF has also been linked to maternal morbidities like chorioamnionitis and endometritis. Adverse outcomes are more common in resource-limited settings due to delays in care and limited NICU access (9, 24). The current study also found significantly lower maternal and fetal cord BDNF levels in MSL cases compared to controls ($p<0.001$), consistent with Kadioglu et al and Shchelchkova et al. BDNF is crucial for fetal neurodevelopment and neuroprotection. Low levels may indicate fetal hypoxia, oxidative stress, and impaired placental function, contributing to adverse outcomes in MSAF pregnancies (16, 25). The mean maternal BDNF level was significantly lower among pregnant women with MSL in comparison to controls ($p<0.001$). This finding is similar to the results of Shchelchkova et al.'s experimental study in Russia, which reported lower maternal serum BDNF level among cases with meconium-stained fluid and fetal distress (hypoxia) as compared to those without meconium-stained fluid (25). The optimal maternal BDNF cutoff value in the prediction of MSL fetal distress was (1.76ng/ml) with an acceptable validity finding (sensitivity 100%, specificity 95.6% and accuracy 98.5%). These findings agree with results of Flöck et al prospective cross-sectional study in Germany (26). BDNF role in protecting against hypoxia and oxidative stress is constant across different populations leading to similar finding regarding the predictive value of BDNF for fetal distress. Low level of BDNF in maternal and fetal circulation is associated with fetal distress in pregnancies with MSAF. A moderate positive correlation between maternal and fetal BDNF and low APGAR scores at 1 and 5 minutes in MSL cases was reported. This aligns with Nouri et al., who reported lower APGAR in cases at 1 minute but not at 5. The persistence of low scores in our study suggests prolonged neonatal compromise. Differences may be due to the severity or consistency of MSL across populations. Notably, the link between BDNF, birth weight, and MSL remains underexplored and needs further research (27). No significant correlation between maternal or fetal cord BDNF levels and fetal sex in MSL cases was shown ($p>0.05$), consistent with Antonakopoulos et al (28). This suggests that BDNF expression and regulation are likely independent of fetal gender, as neurotrophic factors are primarily influenced by placental and maternal physiological conditions rather than fetal sex hormones. Similarly, no significant association was observed between BDNF levels and meconium aspiration syndrome, aligning with Fung et al.'s findings (29), indicating that BDNF may not play a direct role in the pathogenesis of airway obstruction or inflammation resulting from meconium aspiration. Additionally, there was no significant correlation between BDNF levels and neonatal respiratory distress syndrome or NICU admission. These results are supported by Kadioglu et al.'s study in Turkey (16). Overall, BDNF levels did not significantly relate to key neonatal outcomes in MSL pregnancies. Low 5-minute APGAR scores are commonly seen in neonates born through MSAF, often due to perinatal asphyxia. However, other maternal conditions may also contribute, including SARS-CoV-2 infection, which has been linked to significantly lower scores (30). Maternal beta-thalassemia is another factor, potentially causing fetal hypoxia or growth restriction (31). Studies show systemic maternal illnesses are key contributors to low APGAR scores. Therefore, evaluating maternal comorbidities is crucial for proper interpretation and management.

Conclusion

The maternal serum and fetal cord blood brain-

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derived neurotrophic factor level is decreased in pregnant women with meconium-stained amniotic fluid. Birth weight and APGAR scores are correlated to levels of maternal or fetal cord brain derived neurotrophic factor level in pregnancies complicated with Meconium-Stained fluid. The lower levels of maternal brain-derived neurotrophic factor are predictors of fetal distress in meconium-stained fluid. Birth weight and APGAR scores are lower in cases with meconium-stained amniotic fluid. It was recommended for encouraging the physicians to adopt the use of maternal and fetal brain-derived neurotrophic factor in screening for fetal distress among pregnant with meconium-stained fluid and fetal distress. Low birth weight and low APGAR scores outcomes should be taken in consideration for pregnant with meconium-stained amniotic fluid. Supporting large sized multi-center studies on use of maternal and fetal brain-derived neurotrophic factor in screening and diagnosis of fetal distress among pregnant with meconium-stained fluid.

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Ethical clearance: From the Scientific Council of Obstetrics and Gynecology/Iraqi Board for Medical Specializations and the College of Medicine, University of Kirkuk no. 66 in 26\2\2025.

Conflict of interest: None.

Use of Artificial Intelligence (AI): The authors state they did not use any generative AI tools for creating or editing the manuscript's language.

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الأهمية السريرية لمستوى عامل التغذية العصبية المشتق من الدماغ في إدارة حالات الحمل المعقدة بالسائل الأمينوسي الملطخ بالعقي

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الملخص

الخلفية: يعتبر السائل الأمنيوسي الملطخ بالعقي من المضاعفات الشائعة للعديد من حالات الحمل، ويرتبط بزيادة خطر متلازمة شفط العقي لدى حديثي الولادة. يعد الكشف المبكر عن السائل الامينوسي الملطخ بالعقي امراً ضرورياً لمنع النتائج السلبية على صحة حديثي الولادة.

الأهداف: لدراسة العلاقة بين النتائج السلبية لحديثي الولادة الناتجة عن السائل الأمنيوسي الملطخ بالعقي ومستوى عامل التغذية العصبية المشتق من الدماغ في المصل.

المرضى و طرق العمل: هذه الدراسة هي دراسة حالة وشاهد أجريت في قسم النسائية والتوليد في مستشفى آزادي التعليمي في مدينة كركوك في العراق، خلال فترة من ١ مارس الى ٣١ اغسطس ٢٠٢٤, تضمنت العينة ٩٠ امرأة حامل (تضمنت مجموعة الحالات ٤٥ امرأة خضعت لعملية قيصرية بسبب ضائقة جنينية مع وجود سائل أمينوسي ملطخ بالعقي, بينما تضمنت مجموعة الشواهد ٤٥ امرأة خضعت لعملية قيصرية بسبب ضائقة جنينية بدون سائل امينوسي ملطخ بالعقي). تم تقييم عامل التغذية العصبية المشتق من الدماغ من خلال جمع عينات الدم من النساء الحوامل ومن الحبل السري لحديثي الولادة (الوريد السري) وإرسالها الى مختبر خاص. ثم قياس مستوى عامل التغذية العصبية المشتق من الدماغ باستخدام بطريقة الساندويش ELISA .

النتائج: كان متوسط مستوى عامل التغذية العصبية المشتق من الدماغ في دم الأمهات وحبل السرة أقل بشكل ملحوظ بين النساء الحوامل مع وجود سائل أمينوسي ملطخ بالعقي مقارنة بالمجموعة الضابطة .p value < 0.001كانت قيمة القطع المناسبة لمستوى BDNF في دم الأمهات للتنبؤ بالضائقة الجنينية مع وجود السائل الأمينوسي الملطخ بالعقي (١,٧٦نانوغرام/مل) مع نتائج صلاحية مقبولة (حساسية ١٠٠٪، خصوصية ٩٥,٦٪، ودقة ٩٨,٥٪) . كان متوسط عامل التغذية العصبية المشتق من الدماغ للأم والجنين مرتبطًا بشكل إيجابي بوزن الولادة ودرجة أبغار عند كل من الدقيقة الأولى والخامسة لحديثي الولادة بين النساء الحوامل مع وجود سائل امينوسي ملطخ بالعقي.

الاستنتاج: مستويات عامل التغذية العصبية المشتق من الدماغ في دم الأمهات وحبل السرة تتغير في حالات الضائقة الجنينية ووجود السائل الأمنيوسي الملطخ بالعقي.

الكلمات المفتاحية: السائل الامنيوسي الملوث بالعقي، الضائقة الجنينية، عامل التغذية العصبية المشتق من الدماغ.

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