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Evaluation of Fetal Thymus in Pregnancies with Inflammatory Bowel Disease

İnflamatuar Bağırsak Hastalığı Tanılı Gebelerde Fetal Timusun Değerlendirilmesi

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ÖZ

Amaç: İnflamatuar barsak hastalığı (İBH) ile komplike olmuş gebeliklerde fetal timik-torasik oranı araştırmaktır.

Metod: Bu vaka-kontrol çalışmasına 28-40. gebelik haftalarında bulunan Ülseratif Kolit (ÜK) ve Crohn Hastalığı (CH) tanılı 26 hasta ile 26 sağlıklı gebe dahil edildi. Kontrol grubu, gebelik yaşı ile eşleşen komplikasyonsuz gebeliklerden seçildi. Ultrasonografik değerlendirme sonrasında demografik özellikler, hastalık tipi ve hastalık aktivitesi değerlendirildi. Timik-torasik oran (TTO), ön-arka timus ölçümünün intratorasik mediastinal çapa bölünmesiyle hesaplandı.

Bulgular: TTO ölçümleri vaka grubunda 0,32±0,02 ve kontrol grubunda 0,35±0,02 idi (p <.001). Vaka grubundaki hastaların %34,6'sı (n=9) gebelikleri boyunca en az bir kez atak geçirmişti. ÜK ve CH olan hasta grupları arasında medyan TTO değerleri açısından anlamlı fark yoktu. Gebelikte en az bir kez atak geçiren grupta TTO, atak geçirmeyenlere göre anlamlı olarak daha düşük bulundu (sırasıyla 0,31'e karşılık 0,34, p=.012).

Sonuç: Çalışmamız İBH'nın fetal TTO üzerindeki etkisini değerlendiren ilk çalışmadır. İBH'li gebelerde maternal akut ve kronik inflamasyon, intrauterin çevreyi değiştirerek fetal timus boyutunu etkileyebilir. Gebelikte geçirilen atakların fetal timus boyutunu etkileyebileceği düşünüldüğünde bu hastaların remisyonda tutulması ve yakından takip edilmesi çok önemlidir.

Anahtar Kelimeler: İnflamatuar barsak hastalığı, Ülseratif Kolit, Crohn hastalığı, Fetal timus, Timik-torasik oran

ABSTRACT

Objective: To investigate the fetal thymic-thoracic ratio in pregnancies complicated with inflammatory bowel disease(IBD)

Study Design: This case-control study included 26 pregnant women diagnosed with Ulcerative Colitis (UC) and Crohn's Disease (CD) and 26 healthy pregnant women at 28-40 gestational weeks. The control group was selected from uncomplicated pregnancies matched by gestational age. Demographic characteristics, disease type, and disease activity were assessed after ultrasonographic evaluation. The thymic-thoracic ratio (TTR) was calculated by dividing the anteroposterior thymus measurement by the intrathoracic mediastinal diameter.

Results: TTR measurements were 0.32±0.02 in the case group and 0.35±0.02 in the control group (p <.001). 34.6% (n=9) of the patients in the case group had an attack at least once during pregnancy. There were no significant differences in the median TTR values between UC and CD groups. TTR was significantly decreased in the group who had an attack at least once during pregnancy compared to those who did not (0,31 vs. 0,34, respectively, p=.012).

Conclusion: This is the first study to assess the impact of IBD on fetal TTR. Maternal acute and chronic inflammation in pregnancies with IBD may affect the fetal thymus size due to the intrauterine milieu. Considering that exacerbation during pregnancy also affects fetal thymus size, it is crucial to keep these patients in remission throughout the disease and follow up closely.

Keywords: Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, Fetal thymus, Thymic-thoracic ratio

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are categorized as inflammatory bowel diseases (IBD), which cause digestive disorders and inflammation in the gastrointestinal tract (1). Both diseases are often diagnosed in childbearing and mainly affect women of reproductive age. Although the etiopathogenesis of IBD is not yet fully understood, studies on this subject emphasize the role of genetic, environmental factors, and gut microbiota (2, 3). The interaction between these factors contributes to the inappropriate immune response. Stimulation of the immune system causes damage to the gastrointestinal tract and symptoms in different parts. While CD has a segmental, asymmetric, and transmural manner in the digestive tract, UC is generally characterized by mucosal inflammation that begins in the rectum and can expand to the proximal colonic segments (4).

Recent studies indicate that cytokines have a crucial role in controlling intestinal inflammation and its clinical symptoms associated with IBD, thus directly involved in the pathogenesis of IBD (5). Environmental triggers lead to excessive and aberrant cytokine response in the genetically sensitive host, thus resulting in subclinical or acute inflammation. The defective acute inflammatory response results in inadequate clearance of antigenic factors; therefore, mucosal immune cells such as macrophages and T cells respond by producing cytokines, ultimately establishing chronic gastrointestinal tract inflammation (6). The disproportion between pro-inflammatory and anti-inflammatory cytokines restricts the resolution of inflammation and leads to disease progression and tissue destruction. In addition to continuing inflammation, attempts to resolve inflammation by angiogenesis and induced remodeling by the immune system lead to the ongoing process of the disease with remissions and attacks. Women with disease exacerbation at conception have more potential to have an attack during pregnancy than those who become pregnant while in remission (7). So, patients with active disease had an increased risk of adverse pregnancy outcomes such as spontaneous abortion, small for gestational age, low birth weight, and preterm birth due to impaired nutritional uptake and absorption (8).

The fetal thymus is essentially an epithelial organ that provides an appropriate environment for developing T-lymphocytes. These T-lymphocytes mature over time and are called thymocytes, enabling the thymus to play a crucial role in systemic inflammatory processes(9). Chaoui et al. first described the anteroposterior fetal thymus and the intrathoracic mediastinal diameter in the three vessels' view to complete the thymic-thoracic ratio(10). Reference charts for thymus measurement have been developed, and it has been shown that fetal thymus size is not affected by gender and multiple pregnancies (11, 12). Previous studies have shown an association between fetal thymus measure and several maternal or fetal disorders. Small thymus measurements in fetuses diagnosed with congenital heart disease and 22q11 microdeletion, Down syndrome, and intrauterine growth retardation are some examples of fetal conditions (10, 11, 13). Small thymus size has been detected in pregnancy complications such as gestational diabetes mellitus, preeclampsia, and premature rupture of membranes (14-16). In addition, our previous studies showed decreased fetal thymic-thoracic ratio in various rheumatological diseases (17, 18). So, we aimed to obtain the fetal thymic-thoracic ratio in the pregnancies with IBD compared to a healthy control group.

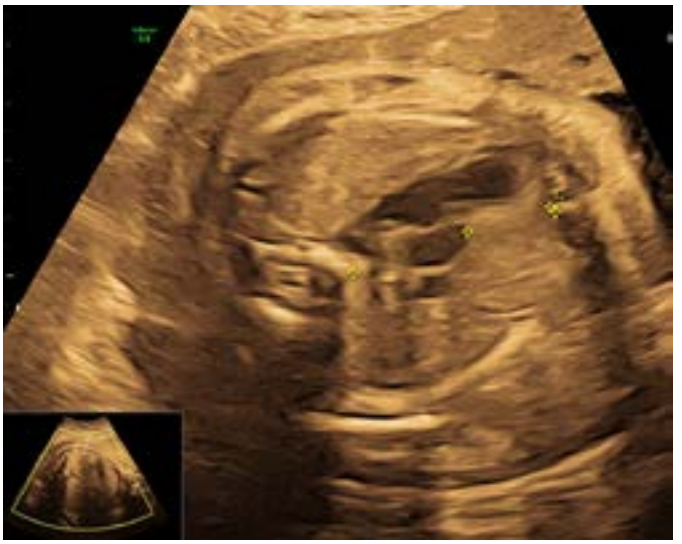
MATERIALS AND METHOD

We performed a case-control study on 52 pregnant women from 28 to 40 weeks gestation. All patients in our study were collected in the perinatology clinic of Ankara City Hospital in Turkey from July 2022 to January 2023. After approval from the Medical Research Ethics Department of Ankara City Hospital, this study was planned following the Declaration of Helsinki (E2-22-2142). All participants wrote the informed consent.

Pregnant women diagnosed with UC and CD before pregnancy and followed up in our clinic were included. Other chronic diseases, smoking, multiple pregnancies, pre-eclampsia, pregnancies with congenital structural or chromosomal abnormalities, and intrauterine growth restriction were excluded to minimize confounding effects. A blinded maternal fetal subspecialist (D.M.B.) performed all sonographic measurements using the 4-8 MHz convex transducer of Voluson E8 (G.E. Healthcare, Milwaukee, WI). Demographic characteristics, including age, gravidity, parity, abortus, pre-pregnancy body mass index (BMI), disease type, and disease activity, were assessed after ultrasonographic evaluation. The gestational week of all study groups was defined according to the last menstrual period or based on the measurement of first-trimester crown-rump length. An increased frequency in symptoms and at least one attack was set as having an attack during pregnancy. For the control group, healthy pregnant women matched by maternal age and gestational weeks were chosen randomly. None of our patients were treated with betamethasone administration before the sonographic evaluation.

Firstly, the homogeneous construction of the thymus was visualized in the anterior part of the mediastinum. In the three-vessel view, the distance between the posterior wall of the fetal chest and the transverse aortic arch edge was calculated to evaluate the anteroposterior diameter, as previously described (10). The intrathoracic mediastinal diameter was the distance of a parallel section drawn from the anterior border of the thoracic vertebral body along the epicenter of the aortic arch vessel to the inner edge of the sternum also measured. The thymic-thoracic ratio (TTR) was estimated by dividing the anteroposterior thymus by the intrathoracic mediastinal diameter (Figure 1).

Figure 1: The anteroposterior diameter of the fetal thymus (1) and the intrathoracic mediastinal diameter (2)



Measurements were repeated, and the average values of three measures were recorded.

All statistical analyses were performed using the Statistical Package for Social Sciences software version 17.0 (SPSS Inc, Chicago, IL). Normal distributed continuous variables are reported as mean ± standard deviation. Nonnormally distributed metric variables are presented as median (Inter Quartile Ranges). Demographic features of the study groups were compared using the Independent t-test and Mann-Whitney U test. The differences in TTR values between the case and control groups were evaluated using the Independent t-test. Mann-Whitney U test was also used in the comparisons made according to the type of disease and the presence of attacks. P-values≤0.05 were assessed as statistically noticeable.

RESULTS

This study included the case group comprising 26 patients, 15 UC and 11 CD, and the control group composed of 26 patients. Clinical characteristics of the study groups and fetal TTR measurements between case and control groups were presented in Table 1.

Table 1: Demographic and clinical characteristics of all participants

	Case group (n=26)	**Control group (n=26)**	**p-value**
Age (years)	28.5±5.6	29.8±4.5	.327*
Gravidity	3±2	3±2	.297†
Parity	1 (0-1)	1 (0-2)	.711†
Abortus	0 (0-1)	0 (0-0)	.063†
Pre-pregnancy BMI (kg/m²)	24.2±1	25.2±2.3	.079*
Gestational age (Weeks)	31 (29-33)	30 (28-33)	.901†
TTR	0.32±0.02	0.35±0.02	**<.001***
Attacks during pregnancy	9 (34.6%)		
Gestational age at birth (weeks)	38 (36-39)	38 (37-40)	.063†
Birth weight (gram)	2780 (2540-3010)	3240 (3010-3510)	**.031†**
Apgar 1st score	7 (6-8)	7 (7-8)	.412†
Apgar 5th score	9 (8-10)	9 (8-10)	.841†

Values are presented as mean± standard deviation and median (IQR (Inter Quartile Ranges)) or as counts (percentage)

The bold characters were used to define the significant "p" values p < 0.05.
Abbreviations: TTR; thymic-thoracic ratio

* Independent t-test

† Mann Whitney U test

Both groups had similarities in pre-pregnancy body mass index, age, gravidity, and abortion numbers. TTR values were 0.32±0.02 in the case group and 0.35±0.02 in the control group (p <.001). The birth outcomes of both groups were also compared. There was only one fetus in the case group who were admitted to the neonatal intensive care unit. 34.6% (n=9) of the patients in the case group had an attack at least once during pregnancy.

Table 2: Comparison of the thymic-thoracic ratios between subgroups

	UC (n=15)	**CD (n=11)**	**p-value**	**Attacks during pregnancy (n=9)**	**No Attacks during pregnancy (n=17)**	**p-value**
TTR	0.32 (0.31-0.34)	0.32 (0.31-0.36)	.813†	0.31 (0.31-0.32)	0.34 (0.32-0.36)	**.012†**

Values are presented as median (IQR (Inter Quartile Ranges))

The bold characters were used to define the significant "p" values p < 0.05.
Abbreviations: UC; Ulcerative colitis , CD; Crohn's disease , TTR; thymic-thoracic ratio

† Mann Whitney U test

Table 2 shows the comparison of TTR values in IBD subgroups. No significant difference in the median TTR values was observed between UC and CD groups. TTR was statistically significantly decreased in the group who had an attack at least once during pregnancy compared to those who did not (0,31 vs. 0,34, respectively, p=.012).

DISCUSSION

This study showed decreased fetal TTR in pregnant women with IBD. Although we found no difference between UC and CD groups, TTR was smaller in these patients than in controls. We also showed that pregnant women with at least one attack had a smaller TTR than those without during pregnancy.

During fetal development, various organs and systems are formed and matured. These processes can be disrupted and made vulnerable to inflammation. Inflammation may be caused by various factors during pregnancy, including infections, immune system dysregulation, or exposure to certain environmental factors (9). It is crucial to understand the impact of inflammation on the developing fetus, as it can significantly affect the development of various fetal organs. The thymus is a primary lymphoid organ susceptible to inflammation, stress, hormonal status, and the inadequacy of nutrition. The dynamics in the immune system and inflammatory processes trigger the fetal hypothalamic-pituitary-adrenal axis, resulting in the thymus's cellular density and composition (19). With the induction of apoptosis, changes begin with the reduction of cortical lymphocytes, followed by the disappearance of the corticomedullary demarcation line and atrophy in organ size. Therefore, the fetal thymus has been an essential source of research used to evaluate the effect of maternal inflammatory and oxidative conditions on the fetus. Hyperglycemia and metabolic disturbance caused by diabetes are stress factors for the fetus and decreased fetal thymus size has been observed in these patients (20). Glucose excess and metabolic disturbance seen in maternal diabetes cause a fetal stress cycle due to impaired oxygen transfer of the placenta. The reduced fetal thymus size observed in maternal diabetes has been associated with this vicious circle. The activated hypothalamic-pituitary axis and increased maternal cortisol transfer in preeclampsia have been associated with fetal thymus involution and decreased fetal thymus size in these patients (14). Small fetal thymus dimension is also demonstrated in various other stress-associated conditions in pregnancy, including fetal inflammatory response syndrome, chorioamnionitis, and malnutrition (21-23). However, in the absence of noticeable infection, thymocyte depletion and thymus involution in chorioamnionitis have been shown histologically. The decreased fetal thymus size observed after the COVID-19 infection also indicates that maternal inflammatory mediators may be able to trigger the processes affecting fetal thymus involution (24). In light of this information, it was thought that the fetus might undergo modifications in some organs in response to infection-induced stress factors, and changes in the fetal thymus structure, which is an organ sensitive to fetal stress, may play a role in this response.

Chronic inflammation, affected by the intrauterine environment, has been observed to impact fetal thymus size (25). Epigenetic changes leading to various diseases have been observed in the innate immune cells of fetuses exposed to in-utero maternal inflammation (26). Active inflammatory processes in women with IBD may interrupt appropriate placentation or restrict the placenta's ability to meet fetal needs, thus leading to the alteration of cellular components at the maternal-fetal interface (8). Increased levels of chemokines and cytokines in IBD may lead to changes in fetal immune response. Decreased fetal thymus size in IBD revealed in our study indicated the fetal response to inflammation. This finding was consistent with our previous study, which showed reduced fetal thymus in maternal autoimmune diseases (17). Contrary to this, a previous study found increased fetal thymus size in rheumatologic diseases (27). We think the retrospective design of this previous study may have influenced the results.

Abnormal and excessive cytokine formation in IBD causes a subclinical or acute reaction. In patients who fail to resolve acute bowel inflammation, chronic inflammation develops. The imbalance between proinflammatory and anti-inflammatory inhibits the resolution of inflammation and leads to disease exacerbation and tissue destruction (6). A recent meta-analysis indicated that IBD flares during the periconceptional period and pregnancy are related to an increased risk of adverse pregnancy outcomes such as spontaneous abortion, preterm birth, and low birth weight (28). The decreased fetal thymus size in those who had an attack in our study suggested the fetal effects of inflammatory load in these patients. This shows that pregnancy should be planned while the disease is in remission, and continuous disease control is essential even during pregnancy.

The strength of our study was that it was a prospective case-control design. The limitations of our study are that fetal thymus measurement was only given as thymus-thorax ratio, serum inflammation markers were not available, its relatively small number of patients, and postnatal thymic evaluation could not be performed.

CONCLUSION

To date, this is the first study to assess the influence of IBD on the fetal thymic-thoracic ratio. Maternal acute and chronic inflammation in pregnancies with IBD may affect the fetal thymus size due to the intrauterine milieu. Considering that exacerbation during pregnancy also affects fetal thymus size, it is crucial to keep these patients in remission throughout the disease and follow up closely.

Conflicts Of Interest

The authors have no conflicts of interest.

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