İZOLE VE KOMPLİKE KOLESTAZLI GEBE KADINLARIN PERİNATAL SONUÇLARININ KARŞILAŞTIRILMASI

Comparison of Perinatal Outcomes in Pregnant Women with Isolated and Complicated Cholestasis

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ÖZET

Giriş: Gebeliğin intrahepatik kolestazı artmış gelişme geriliği, preeklampsi ve gestasyonel diyabet riski ile karşı karşıyadır. Çalışmamızın amacı izole kolestaz saptanan kadınlar ile diğer hastalıkların eklendiği kolestazlı kadınların perinatal sonuçlarını karşılaştırmaktır.

Gereç ve Yöntemler: tersiyer merkezde gerçekleştirilen retrospektif çalışmamızda 2 yıllık süreçte antenatal kliniğine başvuran kolestaz tanılı kadınlar dahil edildi. Ek hastalık bulunanlar grup 1, izole kolestazlı kadınlar grup 2 olarak değerlendirildi. Bu iki grup arasında maternal karakteristik özellikler, laboratuvar sonuçları ve perinatal sonuçlar karşılaştırıldı.

Bulgular: Çalışma süresince gerçekleşen 25101 doğumun 117'sinde kolestaz saptandı (%0.46). Bunların 57'sinde (%48,8) hafif, 38'inde (%32,4) orta, 22'sinde (%18,8) şiddetli kolestaz tablosu izlenmiştir. Yine bu kadınların, 79'unda (%59) GIHK izole olarak saptanmıştır ve kalan 38'inde (%32,4) ek morbidite; 10'unda gestasyonel diyabet (%8,5), 11'unda preeklampsi (%13,6), 21'inde (%17,9) intrauterin gelişme geriliği. Kolestaz saptanan gebelerde mekonyumla boyalı amniyon sıvısı ve prematür doğum oranı daha fazla, dolayısıyla doğum haftası ve doğum ağırlığı daha erken ve düşük saptanmıştır. Takipte en yüksek karaciğer enzimleri ve açlık safra asidi değerleri, düşük doğum haftası, mekonyumla boyalı amniyon sıvısı ve yenidoğan yoğun bakıma yatış oranı komplike kolestazlı gebelerde izole kolestazlı gebelere oranla daha yüksek saptanmıştır.

Sonuç: Ek hastalığın eşlik ettiği kolestazlı kadınlarda perinatal mortalite ve morbidite daha yüksek izlenmiştir. Bu nedenle komplike olmuş bu alt grubun daha yakın takibi ve erken gebelik sonlandırması uygun olabilir.

Anahtar Kelimeler: *Gebelik; Kolestaz; Perinatal sonuçlar*

ABSTRACT

Introduction: Intrahepatic cholestasis in pregnancy encounters the risks of increased development retardation, preeclampsia and gestational diabetes. The aim of our study is to compare the perinatal outcomes in women diagnosed with isolated cholestasis or with cholestasis complicated with accompanying diseases.

Material and Method: In our studies performed in a tertiary center, women applying to the antenatal clinic and diagnosed with cholestasis within a period of 2 years. Women with additional diseases were included in group 1, and those with isolated cholestasis were included in group 2. Maternal characteristics, laboratory results and perinatal outcomes were compared between these two groups.

Findings: Cholestasis was found in 117 pregnant women in the 25101 births given within the study period (0,46%). Of these, cholestasis was found mild in 57 (48,8%), medium level in 38 (32,4%) and serious in 22 (18,8%). ICP (intrahepatic cholestasis of pregnancy) was found as isolated in 79 of these women (59%), of the remaining women, 38 had comorbidities (32,4%), 10 had gestational diabetes (8,5%), 11 had preeclampsia (13,6%), and 21 had intrauterine growth retardation (17,9%). Meconium-stained amniotic fluid and premature labor rate were higher in pregnant women with determined cholestasis, and therefore, birth weeks and birth rate were lower. The rates of the highest liver enzymes and fasting bile acid values, lower birth weeks, meconium-stained amniotic fluid and admission of the neonatal in the neonatal intensive care unit were found higher in pregnant women with complicated cholestasis.

Conclusion: Perinatal mortality and morbidity were found higher in pregnant women with cholestasis complicated with accompanying additional diseases. Therefore, closer follow-up and early termination of pregnancy can be proper in this complicated subgroup.

Keywords: *Cholestasis; Perinatal outcome; Pregnancy*

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the pruritic liver disease specific for pregnancy, and pruritus in the entire body, which is more common in palms and soles, is accompanied by high levels of bile acids in the serum (1). Pathogeneses is not fully clear yeti and genetic factors; gestational hormones and environmental factors constitute the underlying factors (2). Risk factors include the family history ICP found in previous pregnancies, multiple gestation, use of progesterone and Hepatitis C (1,3,4).

ICP increases the risks of negative obstetric outcomes both for the mother and the fetus. While it is associated with increased spontaneous or iatrogenic preterm birth, meconium-stained amniotic fluid, fetal stress or even with sudden death risk for the fetus, it is associated with lack of sleep because of itching, increased postpartum bleeding, preeclampsia and risk of gestational diabetes (5-7). Together with this, it was found in recent studies that cardiovascular disease and immune-mediated cancer risks increase in women with ICP in long term (8).

Studies have shown that ICP increases the prevalence of preeclampsia and gestational diabetes 4 times respectively, in the advancing pregnancy (7). This can be related with the increased additional perinatal mortality and morbidity in the course of pregnancy. Therefore, in our study we have conducted in this tertiary center, we aimed at comparing the outcomes in pregnant women with isolated ICP and pregnant women with complicated ICP.

MATERIAL AND METHOD

In this retrospective case control study, pregnant women followed up in the Antenatal Clinic in Bursa Yüksek İhtisas Training and Research Hospital with the diagnosis of intrahepatic cholestasis of pregnancy between January 1, 2017 and March 31, 2019. A search for intrahepatic cholestasis of pregnancy (ICD-10: O26.6) was carried out in the electronic archive of our Hospital, and all the patients who has applied within this period were recorded. Data concerning the mother and the neonatal were obtained from written files. The study has been reviewed and approved by the Institutional Review Board of the Bursa Yuksek Ihtisas Training and Research Hospital (Decision dated 27/03/2019 and numbered 2011-KAEK-25 2019/03-26). The study was conducted in accordance with the Helsinki declaration. Written consents were received from all patients before the study.

Inclusion criteria of our study were determined as follows: 1) Mothers older than 18 years of age, 2) fasting bile acid value 10 μM or higher, 3) exclusion of other pruritic skin disorders of pregnancy or liver, and 4) termination of pregnancy in our hospital. Exclusion criteria included the following: 1) chromosomal or non-chromosomal genetic diseases, 2) chronic hypertension, 3) factors contributing to preeclamptic predisposition such as multiple gestation, vascular diseases, nephrotic syndrome or type 2 diabetes.

ICP diagnosis was made based on the presence of high levels of fasting bile acids and/or increased levels of liver enzymes starting with pregnancy with clinical recovery immediately after labor and not accompanied by rashes. Measurement of fasting bile acid levels and liver enzymes were repeated 7-10 days later in case of laboratory values inconsistent with clinical findings. Based on the levels of fasting bile acids, the disease was classified as mild (in the range of 10 and 40 μM), medium-level (in the range of 40 and 100 μM) or severe (100 μM or higher).

As indicated in the guidelines of the American Gynecology and Obstetrics Association (5); preeclampsia was defined as the systolic blood pressure 140 mmHg or higher found in 2 measurements with 4-hour intervals in follow-up visits following the 20th gestational week and/or diastolic blood pressure 90 mm Hg or higher accompanied by proteinuria and/or end organ damage (9).

Gestational diabetes diagnosis was made with two-step oral glucose tolerance test. In case the value at hour 1 in the 50-g loading test was higher than 135 mg, the 100-g test was performed and gestational diabetes was accepted in the presence of 2 or more high values. İntrauterine growth retardation was accepted in the presence of abdominal circumference and/or fetal

weight being lower than the 10th percentile. The study population was assigned in two groups as the pregnant women with ICP together with preeclampsia and/or gestational DM and intrauterine growth retardation (group 1) and pregnant women diagnosed with isolated ICP (group 2). Maternal characteristics (maternal age, gravida, week of cholestasis week, week of labor, period between the diagnosis of cholestasis and labor, etc.), laboratory characteristics (maximum fasting bile acids, liver enzymes) and perinatal outcomes (rate of admission to the neonatal intensive care unit, the rate of meconium-stained amniotic fluid, caesarian section rate in relation with fetal stress etc.) were compared among the pregnant women.

Statistical analysis was carried out using the SPSS 22.0 (IBM SPSS, version 22, IBM Corp. Armork, NY, ABD) program. Descriptive data were expressed as mean values and standard deviation. Kolmogorov-Smirnov test was used to determine the distribution of variables. Mann-Whitney U-test and Chi-square test were used to determine the qualitative and quantitative data, respectively. Fisher's test was used in cases where the Chi-square test was unable to meet the conditions. P value <0.05 was accepted as the limit of significance.

FINDINGS

Intrahepatic cholestasis of pregnancy was found in 117 women applying to our clinic throughout our study. Cholestasis incidence was determined as 0,46% based on the proportion with 25,101 labors between these dates. Mild cholestasis picture was observed in 57 women with cholestasis (48,8%), medium-level in 38 (32,4%) and severe cholestasis in 22 (18,8%). Again, among these women, isolated ICP was found in 79 (59%) and comorbidities were observed in the remaining 38 (32,4%). Gestational diabetes was present in 10 pregnancy cases complicated with cholestasis (13,6%) and intrauterine growth retardation was present in 21 (17,9%). When compared to the control group, no significant changes were found in women with cholestasis as regards the maternal age, gravida, gender, admission of the neonatal in the intensive care unit and perinatal mortality; however, rates of meconium-stained amniotic fluid and premature labor were higher, and therefore gestational weeks and birth weight were found as earlier and lower, respectively (Table 1).

Table 1. Comparison of pregnant women with cholestasis and control group

Mother age (years)	26.8 ±4.8	25.4±4.4	NS
Gravidity	2.4±0.7	2.5±0.8	NS
Birth week (weeks)	36.6±2.4	38.7±4.2	<0.05
Gender (girls%)	60 (%51,2)	65 (%55,5)	NS
Birth weight (gr)	2680±389	3145±482	<0.05
Preterm labor (%)	15 (%12,8)	5 (%4,2)	<0.05
Meconium-stained amniotic fluid (%)	12 (%10,2)	4 (%3,4)	<0.05
Admission to neonatal intensive care unit (%)	10 (%8,5)	6 (%5,1)	NS
Perinatal death (%)	1 (%0,8)	0 (%0)	NS
NS: Non- Significant			

In the subgroup analysis, cholestasis in previous pregnancies was more frequent, week of cholestasis diagnosis was earlier and the highest liver enzyme and fasting bile acid values were higher in the women with cholestasis complicated with comorbidities (Table 2).

Table 2. Comparison of demographic and laboratory characteristics of isolated cholestasis and complicated cholestasis pregnant women

	Complicated ICP (n=48)	Isolated ICP (n=69)	p Values
Mother age (years)	26.3 ± 4.1	27.1 ± 4.6	NS
Gravidity	2.6 ± 0.9	2.3 ±0.6	NS
Hepatitis C history	2 (%4,1)	3 (%4,3)	NS
Progesterone use	5 (%10,4)	8 (%14,4)	NS
ICP history	3 (%8,3)	2 (%2,8)	<0.05
ICP diagnostic week (weeks)	28.3 ±4.7	31.2 ± 3.1	<0.05
Laboratory criteria - ALT - AST - Fasting bile acid measurement	 175.5± 157.4 116.2 ± 92.2 83.7 33.1	 98.8 ± 52.7 70.2 ±46.1 27.1 ± 10.9	 <0.05 <0.05 <0.05
ICP: Intrahepatic cholestasis of pregnancy ALT: Alanine aminotransferase AST: Aspartate aminotransferase NS: Non- Significant			

Upon comparison of perinatal outcomes between the two groups, it was seen that labor week was earlier and numbers of meconium-stained amniotic fluid and admissions in the neonatal intensive care unit were higher in women with complicated cholestasis (Table 3).

Table 3. Comparison of perinatal outcomes of isolated cholestasis and complicated cholestasis pregnant women

	Complicated ICP (n=48)	Isolated ICP (n=69)	p Values
Birth week (weeks)	35.3 ± 2.6	37.5 ± 1.1	<0.05
Gender (girls%)	25 (%52)	35 (%50,7)	NS
APGAR Score <7 (5. Minute)	1 (%2)	1 (%1,4)	NS
Birth weight (gr)	2458.3 ± 402.4	2880.7 ± 389.2	<0.05
Meconium-stained amniotic fluid (%)	7 (%14,5)	5 (%7,2)	<0.05
Admission to neonatal intensive care unit (%)	7 (%14,5)	3 (%4,3)	<0.05
Perinatal death (%)	1 (%2)	0 (%0)	NS
NS: Non- Significant			

Perinatal death was observed in one woman in our study (0,8%). Obstetric history of this 37-year-old woman with 2 previous pregnancies revealed that she had been taken under follow-up in her 2nd pregnancy with the diagnosis of isolated cholestasis she gave birth to healthy babies in 36th and 37th gestational weeks. The level of the fasting bile acid was found as 39 μmol/L at the time of diagnosis in this pregnant woman who was referred to our clinic with cholestasis diagnosis at week 28 of pregnancy. Ursodeoxycholic acid therapy (500mg/day) was started and when values (61μmol/L) and pruritus increased 2 weeks later, ursodeoxycholic dose was increased to 1000 mg/day and cholestyramine was added to the treatment. When diabetic fetopathy was found (polyhydramnios and abdominal circumference over 95th percentile) in the ultrasonography taken in week 32, she was taken under blood sugar follow-up and she was diagnosed with gestational diabetes. Diabetic diet and insulin therapy were started; 1 week later she applied to the emergency service with the complaints of diminished fetal movements and it was observed that there were no fetal cardiac apex peats, and the fasting bile acids were found as 112 μmol/L.

DISCUSSION

In this retrospective case control study, we carried out in a tertiary center, low birth weights, preterm labor and meconium-stained amniotic fluid rates were found significantly higher in women diagnosed with ICP as compared to the control group. Moreover. Perinatal mortality and morbidity incidences in women diagnosed with ICP and comorbidities, perinatal mortalite, morbidity incidence and laboratory values were found higher.

Intrahepatic cholestasis incidence is increasing within the recent years in relation with the increased awareness and increased diagnosis. In their study in a tertiary center, Kırbaş and colleagues found cholestasis incidence as 0,5%. Consistently with their study, cholestasis center in our study was found as 0,46% (10).

Studies have shown that GDM incidence increases in the advancing stages of pregnancy in pregnant women diagnosed with ICP (11). In molecular studies also, it was found that irisin resulting in the decrease of blood glucose and lipid levels through the increase in insulin sensitivity has higher levels in women with ICP as compared to without ICP, and this hormone has even higher levels in more severe cases as compared to milder cases (10). The hypothesis of Martineu and colleagues 11) that GDM and ICP have similar etiologies is supported with the findings in the case report published by Elfituri and colleagues (12) indicating the improvements in fasting bile acids and ALT/AST values obtained with metformin administered for GDM therapy in a woman resistant against rifampicin and ursodeoxycholic acid. In parallel with these studies, GDM incidence was found 4,3 times greater as compared to the control group in our study, and the response to ursodeoxycholic acid in this group was higher.

Animal and human studies suggest that placental abnormalities in ICP including focal amniotic membrane thickening, small chorionic villi according

to the gestational age, increased oxidative stress in placenta, apoptosis and hypoxia essentially originate from placenta, and ICP has a similar etiopathogenesis with preeclampsia (12,13). In support of these studies, preeclampsia and intrauterine growth retardation included in placental disorders were seen more frequently in our study.

The issue that intrahepatic cholestasis increases the risk of sudden intrauterine death is continues to be controversial. Most of the intrauterine death cases reported in the literature are obtained from historical publications and case reports. More recent studies with larger populations have shown that intrauterine mortality rate does not increase in mild cases (fasting bile acids between 10 and 40). It was found that labor in week 36 and 37 with an active management improved perinatal outcomes without increasing the perinatal morbidity and mortality. In the case report published by Lu and Qi, sudden fetal death was reported in a woman with ICP complicated with diabetes within the 34th gestational week (15). Intrauterine death was observed in 1 case in our study group also. Like those in the literature, this this pregnancy was also complicated with gestational diabetes. Therefore, it can be claimed that pregnant women with ICP with fasting bile acid exceed 40 and complicated with preeclampsia, growth retardation and gestational diabetes should be followed more closely, and labor must be planned with an active management after 34th gestational week.
The main limitation of our study is related with its retrospective design. Influences of the single tertiary center of the study and limited number of the study group on ICP incidence are possible.

In conclusion, it was observed in pregnant women diagnosed with ICP complicated with comorbidities that laboratory results, perinatal mortality and morbidity rates were higher as compared to women with both isolated mild ICP cases and to women in the control group. Therefore, closer follow-up and preterm termination of pregnancy can be considered as proper in this complicated subgroup.

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