

# Seasonal Impact in the Frequency of Intrahepatic Cholestasis of Pregnancy

Cem Yaşar SANHAL<sup>1</sup>, Korkut DAĞLAR<sup>1</sup>, Özgür KARA<sup>1</sup>, Ayşe KIRBAŞI<sup>1</sup>, Dilek UYGUR<sup>1</sup>, Aykan YÜCEL<sup>1</sup>

Ankara, Turkey

## ABSTRACT

**OBJECTIVE:** To evaluate the presence of any seasonal variation in the frequency of intrahepatic cholestasis of pregnancy (ICP).

**STUDY DESIGN:** A total of 126 cases with ICP were compared with a cohort of 37614 pregnant women who delivered. The diagnosis ICP was performed on the basis of severe itching and the absence of dermal rash and any other hepatic disease, with the co-existence of elevated serum aminotransferase levels and/or serum bile acid concentration. For each month and season, observed and expected ICP rates were analysed and compared by using chi-square statistics. Multivariate logistic regression was performed to investigate certain parameters on cumulative risk.

**RESULTS:** A significantly lower frequency of ICP in winter (6/126 (4.8%),  $p=0.001$ ) and a significantly higher frequency in spring (44/126 (34.9%),  $p=0.034$ ) were detected. A 2.1 and 3.8-fold higher risk were found for the nulliparity and the twin pregnancy, respectively. Logistic regression analysis confirmed the significant (10-fold) decrease in the frequency of ICP in winter. The significance of spring did not persist after the adjustment.

**CONCLUSION:** Main outcome of the study points at seasonality in ICP frequency. Future studies in different populations may reveal data about factors that interact with seasonality and playing roles in ICP.

**Keywords:** Intrahepatic cholestasis of pregnancy, Season, Frequency, Variation

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## Introduction

Intrahepatic cholestasis of pregnancy (ICP), which occurs mostly in the second or third trimester of gestation in a previously healthy woman, is characterized by the co-existence of pruritis and elevated fasting serum bile acids and/or elevated transaminases.<sup>1</sup> Although being accepted as a benign and temporary condition which resolves with the ceasing of the pregnancy, ICP is still of major interest to contemporary perinatal medicine, particularly due to the adverse outcomes as preterm delivery, non-reassuring fetal status, meconium staining of the amniotic fluid and stillbirth.<sup>2</sup> The reported incidence of ICP varies between 0.1% and 15.6% in different geographical parts of the world.<sup>3,4</sup> The reason for this difference is unknown. Recent studies about the etiology of ICP revealed multifactorial origin involving genetic and hormonal factors. It was also suggested that environmental factors may have roles in the expres-

sion of the disease.<sup>5</sup> However, like the causes of the variations in the incidence, the certain etiology of the ICP is still unknown.

An abiotic or biotic factor that has influences on living organisms is defined as an environmental factor. Temperature, amount of sunlight and pH of the water soil constitute most of the abiotic factors.<sup>6</sup> Climatic and seasonal alterations have major effects on abiotic factors, and this issue has been taking on accumulating academic interest in order to enlighten the unknown associations between the gestational diseases and environmental factors.

It was previously reported that ICP occurred more commonly in colder months.<sup>7,8</sup> This knowledge is relatively old and was determined in diminished population. Furthermore, climates are divided in to 5 groups or classes due to the aspects of the native vegetations namely: Tropical/megathermal; Dry; Temperate/mesothermal; Continental/microthermal; Polar and alpine.<sup>9</sup> We performed our study in order to evaluate the presence of any seasonal variations in the frequency of ICP in a hospital of a city with continental climate.

## Material and Method

The protocol of this prospective cohort study was approved by the ethics committee for human studies of Zekai Tahir Burak Women's Health Care, Training and Research Hospital and informed consent was taken from the participants.

<sup>1</sup>Department of Perinatology, Zekai Tahir Burak Women's Health Care, Training and Research Hospital, Ankara, Turkey

Address of Correspondence: Cem Yaşar Sanhal  
Department of Perinatology, Zekai Tahir Burak Women's Health Care, Training and Research Hospital, Ankara, Turkey  
cemsanhal@yahoo.com

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During the 24-month-period, from July 2013 to July 2015, women who were referred to Zekai Tahir Burak Women's Health, Education and Training Hospital for the perinatal care, were enrolled in the study. The hospital is a tertiary referral center in the capital of Turkey, Ankara. A total of 126 cases with ICP were compared with a cohort of 37614 pregnant women who delivered. The diagnosis ICP was performed on the basis of severe itching and the absence of dermal rash and any other hepatic disease with the co-existence of the elevated serum aminotransferase levels and/or serum bile acid concentration ( $>10 \mu\text{mol/L}$ ). The accurate date of ICP diagnosis was determined due to the onset of symptoms and serum abnormalities.

Seasons were defined as winter (December, January, February), spring (March, April, May), summer (June, July, August), and fall (September, October, November). According to the Köppen climate classification, Ankara borders on a dry summer continental climate with a warm summer subtype and is near the borderline of a semi-arid climate.<sup>10</sup> Ankara has cold, snowy winters and hot, dry summers. Rainfall occurs mostly during the spring and autumn.

SPSS statistical software for Windows, version 17.0 (SPSS, Inc., Chicago, Ill., USA) was used for statistical analysis. Normal distribution for continuous variables was assessed with the Kolmogorov - Smirnov test. Comparisons of parametric variables between groups with normal distributions were performed by Student's *t* - test. The Mann - Whitney U test was used for comparisons of continuous variables that did not have normal distributions. A chi-square test or Fisher's exact test (for pairwise comparisons) was performed for nominal or ordinal variables between groups where appropriate. The seasonal impact in the frequency of ICP was assessed by chi - square test. The rate of monthly and seasonal number of newly diagnosed cases with ICP / monthly number of deliveries were calculated. In addition for each month and season, the observed and expected ICP rates were analysed and compared using chi - square statistics. Multivariate stepwise logistic regression with backward elimination was performed to investigate certain parameters on cumulative risk of ICH within groups. The model consisted of winter, spring, nulliparity, twin pregnancy and male fetus. A *p*-value  $<0.05$  was considered significant.

Table 1: Demographic characteristics of groups<sup>a</sup>

	ICP (n=126)	Control (n=37614)	<i>p</i> value <sup>b</sup>
Age (years)	28.3±5.6	28.3±5.9	0.960
Parity (number)	0 (0-2)	1 (0-11)	<b>0.001</b>
Birth weight (grams)	2877±502	3110±637	<b>0.04</b>
Duration of gestation (weeks)	36.4±1.9	37.9±4.8	<b>0.013</b>
Twin pregnancies (number, %)	8 (6.3)	630 (1.7)	<b>0.04</b>
Still birth (number, %)	0 (0)	272 (0.7)	1.0
C/S (number, %)	76 (60.3)	19754 (52.5)	0.272

ICP: Intrahepatic cholestasis of pregnancy, C/S: Cesarean section

a: Data are expressed as median (min-max), mean ± standard deviation and number, % where appropriate. b: *p* <0.05 indicates significant difference

## Results

Table 1 demonstrates the demographic characteristics of the groups. The cases in the study group had a significantly lower number of parity, delivered earlier and also had lower neonatal birth weight. The rate of twin pregnancies were higher in patients with ICP.

Table 2 denotes the results of chi-squared tests of seasonal variation. Compared to other seasons, a significantly lower frequency of ICP for winter (6/126 (4.8%), *p*=0.001) and higher frequency of ICP for spring (44/126 (34.9%), *p*=0.034) were detected. The monthly number of cases and seasonal trend of ICP are depicted in Figure 1 and Figure 2, respectively.

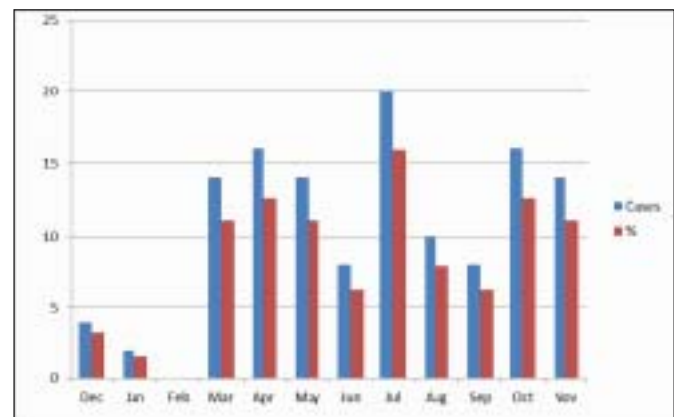


Figure 1: Monthly number of ICP cases

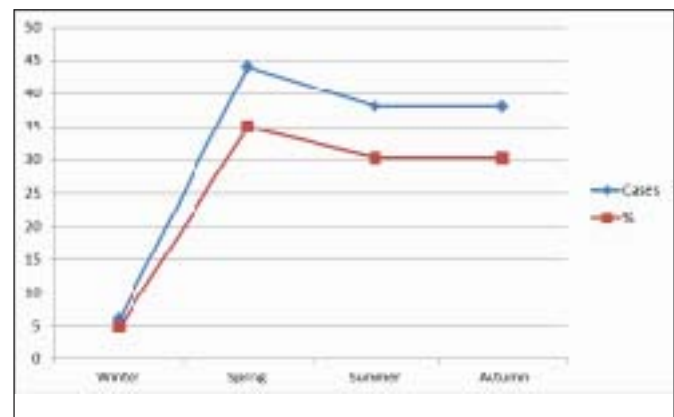


Figure 2: Seasonal trend of ICP

The findings of logistic regression models are shown in Table 3. A 2.1 and 3.8-fold higher risks were found for the nulliparity and twin pregnancy, respectively. The winter made a significant (10-fold) decrease in the frequency of ICP. The significance of the effect of the spring on ICP did not persist after the adjustment.

## Discussion

In this study, we evaluated the relation between the seasons and the ICP frequency of our hospital. We found that the number of new cases with ICP was significantly lower in winter and higher in spring. Moreover, the effect of the winter (but not for spring) on this result remained significant (an approximately 10-fold lower risk) after adjusting for potential confounders in logistic regression model. Additionally, nulliparity and twin pregnancy were associated with higher risks for ICP.

Earlier studies from Scandinavia and Chile had shown evidence of seasonality in ICP, especially higher risks for colder

months.<sup>7,8</sup> These results seem contradictory to our findings. However, the data were established in lands that belong to different groups in Köppen climate classification<sup>10</sup> regarding Ankara, and the reason of the conflict may be due to the alterations in the winter characteristics of different climates. From this point of view, our study reveals the preliminary data of a pregnancy population living in a continental climate.

Despite the extensive research, much of the pathogenesis of ICP is still unknown. The former data pointed a genetic tendency in the etiology. A 5 to 12-fold increased risk of ICP development in the mothers, parous sisters and daughters of the index patients denoted evidence about the issue.<sup>11</sup> The gene deficiency of ATP-binding cassette subfamily B member 4 (ABCB4) membrane transporter, which plays role in the bile acid export metabolism, was also reported to be in association with cholestatic liver diseases.<sup>12</sup> Moreover, heterozygosity of the common ABCB11 mutations and the mutations of the other phospholipid transporter encoding gene, ATP8B1, were both shown to be involved in a number of patients with the

Table 2: Results of chi-squared tests of seasonal variation performed on monthly and seasonal frequencies for cases of ICP during the study period

	ICP (n: 126)		Control (n:37614)		p <sup>a</sup>
	Observed	Expected	Observed	Expected	
<b>Winter</b>	6 (4.8%)	28.4	8450 (22.5%)	8465	<b>0.001</b>
December	4 (3.2%)	9.8	2938 (7.8%)	2932	0.237
January	2 (1.6%)	10	2982 (7.9%)	2974	0.063
February	0 (0%)	8.6	2570 (6.8%)	2562	<b>0.021</b>
<b>Spring</b>	44 (34.9%)	29.8	8860 (23.6%)	8875	<b>0.034</b>
March	14 (11.1%)	9.8	2924 (7.8%)	2928	
0.324					
April	16 (12.7%)	9.6	2858 (7.6%)	2864	0.146
May	14 (11.1%)	10.4	3078 (8.2%)	3081	0.398
<b>Summer</b>	38 (30.2%)	34.2	10176 (27.1%)	10180	0.580
June	8 (6.3%)	10.6	3172 (8.4%)	3170	0.552
July	20 (15.9%)	12.2	3664 (9.7%)	3672	0.102
August	10 (7.9%)	11.2	3340 (8.9%)	3339	0.793
<b>Autumn</b>	38 (30.2%)	30	8952 (23.8%)	8960	0.237
September	8 (6.3%)	10.2	3060 (8.1%)	3058	0.605
October	16 (12.7%)	20.4	3028 (8.1%)	3033	0.176
November	14 (11.1%)	9.6	2864 (7.6%)	2868	0.334

ICP: Intrahepatic cholestasis of pregnancy, a:  $p < 0.05$  indicates significant difference

Table 3: Impact of factors on intrahepatic cholestasis of pregnancy

Characteristics	Crude odds ratio	Confidence Interval	Adjusted Odds ratio	Confidence Interval
Winter	0.172	0.054-0.547	0.171	0.054-0.546
Spring	1.741	1.036-2.926	1.227	0.730-2.63
Nulliparity	2.264	1.370-3.742	2.067	1.249-3.421
Twin pregnancy	3.913	1.410-10.857	3.751	1.346-10.451
Male fetus	1.518	0.915-2.516	1.474	0.887-2.443

*Bold typeface indicates significance*

progressive intrahepatic cholestasis, because of the decrease in the folding ability of the bile salt export pump protein.<sup>13,14</sup>

Although the dysregulations from seasonal patterns take part in the occurrence of some cardiovascular, autoimmune and psychiatric illnesses,<sup>15-17</sup> the effects of seasonal variations on human tissue functions are not broadly studied. However in 2015, Dopico et al. showed the different seasonal expression profiles of more than 4000 protein-coding mRNAs in white blood cells and adipose tissue, and also the international alterations of the cellular composition of the blood that varies by season, which could explain the gene expression periodicity.<sup>18</sup> In our opinion, the findings of this interesting study are critical for the enlightening of the diseases like ICP, which may be influenced by the genetic mutations and also present with seasonality. In other words, seasonal variations may generate the transitory decompensation of the heterozygous circumstance for genes encoding hepatobiliary transport elements which deteriorate during the course of gestation, and resulting in ICP.

Incomplete illumination in the pathogenesis of ICP enforced the researchers also to investigate the immunologic and hormonal base of the disorder. As demonstrated in our study, the increased risk of twin pregnancies,<sup>19</sup> and the usual third trimester onset when the serum levels of estrogen reach their peak,<sup>20</sup> may connote the association between hormones (mainly estrogens and progesterone) and ICP. It is known that the immunologic balance of the normal pregnancy is ensured by the interaction of CD4 (+) and CD8 (+) T cells, in which the CD8 (+) T cell activity is more prominent.<sup>21</sup> It was also ascertained that the high levels of estrogen decreased the activity of CD8 (+) T cells that might lead to ICP.<sup>22</sup> A population based trial exploring the seasonal variation of estradiol levels reported the significant differences in the total and free estradiol monthly means; highest level in June and nadir in November.<sup>23</sup> Although being conducted in non-pregnant women and in a city (Tromsø, Norway) with different climate properties regarding Ankara, this study and the estrogen effect on T cells revealed the necessity of new trials exploring the seasonal change in the serum levels of sex hormones in pregnant women and the potential immunologic - tissue effects of these changes in ICP.

Furthermore, seasonal variations have some confirmed effects on maternal levels of non-hormonal compounds. A remarkable higher rate of vitamin D deficiency in pregnant women during the winter season was reported in a study performed in Ankara.<sup>24</sup> This finding is important because Vitamin D and its receptor control important steps in bile acid detoxification.<sup>25</sup> On the other hand, it also reveals a contradiction about one of the most significant result of our study denoting the potential protective effect of winter against the occurrence of ICP.

Afterall, there are some limitations of our study. First, the major finding indicating the significantly lower number of ICP cases in winter, can not be generalized. The reason of this en-

tity is the distinct climate and winter characteristics in divergent geographic parts of the world. Second, the investigation of the interactions between seasonal variations and the potential factors for ICP as genetic mutations, sex hormones and non-hormonal substances, which were not examined in this study, may reveal more valuable data to unveil ICP etiology. And finally, the trials with longer durations and higher number of participants may declare more reliable findings about the main objective of this study.

The etiology of ICP is complex with genetic, endocrine, and environmental factors having major roles. In this study, we showed the seasonal variations in the number of new diagnosed cases with ICP. Further studies in different population and climates with the evaluation of all confounder factors in ICP etiology may reveal more informative data about the contention.

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