The Relationship of Placental Histology to Pregnancy and Neonatal Characteristics in Preterm Infants

Emel **ALTUNCU**[1], İpek **AKMAN**[1], Esin **KOTİLOĞLU**[2], **Alin BAŞGÜL**[3], Ziya **YURDAKUL**[1], Figen **DEMİR**[4], Zehra **KAVAK**[3], Emine **BAŞ**[2], Nejat **BOZKURT**[3], Hülya **BİLGEN**[1], Eren **ÖZEK**[1]

[1]*Division of Neonatology Unit, Department of Pediatrics, Faculty of Medicine, Marmara University, Istanbul, Turkey*
[2]*Department of Pathology, Faculty of Medicine, Marmara University, Istanbul, Turkey*
[3]*Department of Gynecology and Obstetrics, Faculty of Medicine, Marmara University, Istanbul, Turkey*
[4]*Department of Public Health, Faculty of Medicine, Marmara University, Istanbul, Turkey*

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Abstract

Objective: The microscopic and macroscopic features of placenta can contribute to the clinical understanding of premature delivery. The aim of our study was to relate the histopathological findings in the placentas of premature infants to pregnancy and explore its relation to neonatal morbidity.

Materials and Methods: Placentas of 86 singleton preterm infants were examined and the association between placental pathology and the initiator of the preterm delivery such as preterm labor (PTL), preterm premature rupture of membranes (P-PROM) and pregnancy induced hypertension (PIH) were evaluated. The findings associated with acute placental inflammation or placental evidence of PIH were correlated to the initiators of preterm delivery and the clinical findings of the neonates.

Results: The initiator of preterm delivery was PTL in 45%, P-PROM in 20% and PIH in 21% of the infants. Twenty percent of placentas had one or more findings associated with acute inflammation, 43% had findings associated with PIH, 23% had no identifiable pathology and 14% had other findings (intervillous thrombus, villous edema, etc.). Among mothers with placental evidence of acute inflammation, 56% had P-PROM, 38% had PTL and 6% had PIH. The mothers who had histological chorioamnionitis delivered at a younger gestational age than the mothers who had placental evidence of PIH (29 and 32 weeks, respectively; p=0.001). Histological chorioamnionitis was found to be more frequent in the placentas of infants with bronchopulmonary dysplasia (p=0.001).

Discussion: This preliminary study revealed that the placental pathological findings appear to be correlated to the initiator of preterm delivery. Examination of the preterm delivery placentas gains importance in determining the etiology of preterm delivery and morbidity in infants.

Keywords: placenta, prematurity, neonatal morbidity, histological chorioamnionitis

Özet

Preterm Doğumlarda Plasenta Histolojisi ile Gebelik ve Neonatal Özelliklerin İlişkisi

Amaç: Plasentanın mikroskopik ve makroskopik özellikleri, prematüre doğuma yol açan olayların anlaşılmasında yol gösterici olabilir. Bu çalışmada, preterm bebeklerin plasentalarındaki histopatolojik bulgular ile gebelik özellikleri karşılaştırılarak plasenta bulgularının neonatal morbidite ile ilişkisinin araştırması planlandı.

Materyal ve Metot: Seksen altı tekiz preterm bebeğin plasentası incelendi ve preterm doğuma yol açan başlıca nedenlerden preterm eylem (PTL), uzamış erken membran yırtılması (EMR) ve gebeliğe bağlı hipertansiyon (PIH) ile plasenta patolojileri arasındaki ilişki incelendi. Plasentada görülen enflamasyon ve hipertansiyonu düşündüren histopatolojik bulgular ile preterm eylem nedeni ve bebeklerin klinik bulguları ilişkilendirildi.

Corresponding Author: Dr. Emel Altuncu
Altunizade Tophanelioğlu Cad. 13/15,
Üsküdar, İstanbul, Türkiye
Phone : +90 216 327 10 10 / 411
GSM : +90 536 374 31 52
E-mail : emelkayrak@yahoo.com

Sonuçlar: Preterm doğumu başlatan nedenler, %45 olguda preterm eylem, %20'sinde uzamış EMR ve %21'inde PIH idi. Plasentaların %20'sinde akut enflamasyon bulgularından bir veya birden fazlası, %43'ünde gebeliğe bağlı hipertansiyonu gösteren bulgular, %23'ünde normal histoloji ve %14'ünde diğer histolojik bulgular saptandı. Plasentasında akut enflamasyon bulgusu olan annelerin %56'sında uzamış EMR, %38'inde preterm eylem, %6'sında PIH vardı. Plasentasında histolojik koryoamniyonit bulgusu olan annelerin bebeklerinin gestasyonel yaşı, plasentasında PIH bulgusu gösteren annelerin bebeklerinkinden daha küçüktü (sırasıyla, 29 ve 32 hafta; p=0.001). Bronkopulmoner displazi gelişen infantların plasentalarında akut enflamasyon bulgusuna daha sık rastlandı (p=0.001).
Tartışma: Plasentadaki patolojik bulgular ile doğumu başlatan nedenler arasında ilişki vardır. Prematüre bebeklerin plasentalarının incelenmesi, preterm doğumun etiyolojisinin belirlenmesi ve morbiditelerin izlemi açısından önemlidir.

Anahtar sözcükler: plasenta, prematürite, neonatal morbidite, histolojik koryoamniyonit

Introduction

Prematurity is the major cause of perinatal and neonatal mortality and morbidity. Seventy percent of all preterm deliveries are due to spontaneous onset of labor with or without rupture of membranes (1). Placenta provides a diary of the pregnancy. Pathological examination of the placenta can contribute to the clinical understanding of premature delivery, fetal growth restriction and neonatal morbidity (2).

It has been demonstrated that placental pathological findings correlate strongly with the initiator of preterm delivery which is either preterm labor (PTL), preterm premature of membranes (P-PROM) or pregnancy induced hypertension (PIH) (3). It has been shown that histological chorioamnionitis is associated with immaturity, premature rupture of membranes (PROM) and bronchopulmonary dysplasia (BPD) (4). Placental vasculopathy is found to be associated with decreased birthweight, lower 5th minute Apgar score and increased risk of necrotising enterocolitis (2).

In our study, we aimed to relate the placental morphology to features of the pregnancy, the fetus and the neonate. We also explored the relationships of placental pathological findings with the initiator of premature delivery and neonatal morbidity.

Materials and Methods

Sample

The placentas of singleton preterm babies of less than 37 weeks of gestation delivered at Marmara University Hospital in 2004 were evaluated following approval of institutional ethics committee. Maternal and neonatal medical records were retrieved to review pregnancy-related issues and neonatal morbidity and mortality.

Data on the pregnancy and the neonate

PIH was classified as gestational hypertension, preeclampsia, or eclampsia. Gestational hypertension was defined as a blood pressure equal to or greater than 130/90 mmHg on more than two occasions greater than six hours apart without proteinuria after 21 weeks of gestation. Preeclampsia was diagnosed as hypertension of equal to or greater than 130/90 mmHg with proteinuria of 1+ or 2+ on dipstick in two samples 6 hours apart or greater than 0.3 grams in a 24-hour urine collection. Eclampsia was defined as seizures in patients with preeclampsia (5). Delivery was considered as premature when it occurred before 37 weeks of gestation, as defined by the World Health Organisation (6). Gestational age was estimated using fetal ultrasound scan obtained before the 13th week of gestation when it was available or according to the date of the last menstrual period. PTL was considered as the initiator of the delivery if labor began while membranes were intact. PROM was defined as spontaneous rupture of membranes before the onset of labor. P-PROM was rupture of membranes before 37 weeks of gestation. Clinical chorioamnionitis was defined as maternal fever in the presence of additional two clinical findings (abdominal tenderness, fetal tachycardia, maternal leukocytosis, and/or foul smelling amniotic fluid).

A baby was classified as small for gestational age (SGA) if the birth weight fell below the 10th percentile for gestational age, based on the Lubchencho curves (7). BPD was defined as dependence on supplemental oxygen in the postconceptual 36 weeks. Respiratory distress syndrome (RDS) was diagnosed by the need for supplemental oxygen and ventilatory support associated with characteristic radiological findings. Early onset sepsis was designated as culture proven (bacterial growth in any culture) or clinical sepsis (any clinical signs like respiratory distress, hypotension and/or any abnormal laboratory findings like a left-shifted white blood cell count with an immature-to-total polymorphonuclear leukocyte ratio ≥0.2, leukocytosis, leukopenia, thrombocytopenia) diagnosed within the first 72 hours of life. Intraventricular haemorrhage (IVH) was detected by cranial ultrasonography performed in the first 10 days of life. Periventricular leukomalacia (PVL) was defined as necrosis of white matter dorsal and lateral to the external angles of the lateral ventricles by cranial ultrasound. Perinatal asphyxia was defined as presence of fetal distress during fetal monitoring, 5th minute Apgar score <3 and umbilical cord pH <7.2 or presence of multiorgan dysfunction. Early neonatal mortality was death of the newborn within the first week of life.

Collection and preparation of tissue

All placentas were received fresh and examined macroscopically for gross pathology such as color change of placental membranes, infarction, calcification, thrombus and bleeding. After fixation in 10% buffered formalin, appropriate samples were submitted for routine histological examination. These samples consisted of a membrane roll, two umbilical cord samples taken at 1 and 6 cm distal to the insertion point, two random full-thickness placental tissues, and sample(s) to represent any area of macroscopical pathology. The histopathological findings were classified as shown in Table 1 (8).

Interpretation of histological data

Data on placental histology were grouped as 1) acute inflammation; 2) placental correlates of PIH; 3) other pathological findings (composite group); 4) no identifiable pathology.

Findings associated with acute inflammation were opacification of the membranes with variable degree of inflammation in microscopical study. Grading of the inflammation was done according to Redline et al (9). Placental correlates of PIH were old infarcts, increased syncytial knots, and maternal decidual vasculopathy. Other pathological findings such as intervillous thrombus, villous edema, increased nucleated red blood cells in fetal vessels, retroplacental hemorrhage, chronic villitis of unknown origin and fibrotic villi were also recorded.

Statistical analysis

The neonatal data were expressed in terms of the median and the ranges. The Fischer's exact test and χ^2 test were used for the analysis of differences of quantitative parameters. Kruskal-Wallis test was used for the analysis of differences in continuous variables. Statistical significance was defined as $p<0.05$.

Results

Placentas of 86 preterm infants were examined. Twenty percent (n=17) of placentas had one or more findings associated with acute inflammation, 43% (n=37) had findings associated with PIH, 23% (n=20) had no identifiable pathology and 14% (n=12) had other pathological findings. The last group (n=12) was eliminated from the statistical analysis, as the histopathological findings were too infrequent to analyze. Of the 17 cases with placental findings associated with acute inflammation, 4 had umbilical cord inflammation as well.

Gestational age at birth was <23 weeks for 1% of infants, 24-27 weeks for 7%, 28-31 weeks for 38%, and ≥32 weeks for 54% of infants. The median gestational age and birthweight was 32.2 weeks (range, 22.5-36.6) and 1650 gram (range, 570-3000), respectively.

Demographic characteristics of patients according to the histopathological features of the placentas are given in Table 2. The findings of particular importance were the younger

Table 1. Definitions for gross and microscopical placental findings

Placental finding	Definition
Placental weight	Trimmed weight of the disc without umbilical cord and membranes
Membranes	Inflammation, meconium staining
Umbilical cord	Insertion, twisting, number of vessels, presence of thrombus/hemorrhage
Retroplacental hemorrhage	Retrolacental blood clot observed macroscopically (parenchymal indentation) or microscopic decidual and/or parabasal hemorrhage
Chronic non-specific deciduitis	Lymphocytes in the decidua
Fetal vessel thrombosis	Thrombosis of blood vessels in the cord, chorionic plate or stem villi
Infarction	Presence and extent of infarction involving the disc
Intervillous thrombosis	Laminated thrombosis in the intervillous space
Hemorrhagic endovasculitis	Obliteration of fetal vessels associated with red blood cell extravasation
Perivillous fibrin deposition (severe)	More than expected perivillous fibrin deposition around individual chorionic villi or when detected macroscopically
Segmental villous fibrosis (Avascular villi)	Villous stromal fibrosis involving portion of fetal lobules
Chronic Villitis	Lymphocytes and/or other mononuclear cells infiltrating chorionic villi
Villous maturation	Maturation of chorionic villi in the fetal lobule matched with gestational age: appropriate, accelarated or delayed
Syncytial knotting (increased)	Syncytial nuclei forming a multinucleated protrusion from the villous surface in >30% of terminal villi
Decidual vasculopathy (Maternal underperfusion)	One or more of the following lesions in the decidual vessels
Atherosis	Foamy macrophages in the intima of decidual arterioles and/or fibrinoid necrosis
Muscularisation	Persistence of muscle fibers in the decidual vessel walls

Modified from Kaplan C, Lowell DM and Salafia C (8).

Table 2. Demographic characteristics of patients according to the placental histopathological features

Maternal and neonatal characteristics	Placental histology			
	PIH (n=37)	Acute inflammation (n=17)	No identifiable pathology (n=20)	*p*
Gestational age (week)(Median; range)	32.5 (27.2-36.6)	29 (22.5-36.6)	33.3 (25-36.5)	0.001
Birthweight (g) (Median; range)	1720 (720-3000)	1300 (570-2370)	2040 (680-2700)	0.004
Maternal age, (Median; range)	30 (20-40)	27 (22-37)	30 (22-39)	0.78
Gravidity (Median; range)	2 (1-7)	2 (1-5)	2 (1-8)	0.72
Parity (Median; range)	2 (1-7)	1 (1-3)	1 (1-7)	0.53

Table 3. Initiators of preterm delivery stratified by placental histopathological features

Initiators of preterm delivery	Placental histology			
	PIH (n=31)	Acute inflammation (n=16)	No identifiable pathology (n=17)	Total
Preterm labor (n=33) (%)	45	19	36	100
P-PROM (n=15) (%)	20	60	20	100
PIH (n=16) (%)	82	6	12	100

Table 4. Neonatal morbidity stratified by initiators of preterm delivery

Neonatal morbidity	Initiators of preterm delivery			
	Preterm labor (n=33)	P-PROM (n=15)	PIH (n=16)	Other (n=10)
Respiratory distress syndrome (n=30)	10	9	7	4
Perinatal asphyxia (n=17)	5	3	3	6
Early onset sepsis (n=13)	4	6	2	1
Intraventricular hemorrhage (n=14)	6	2	3	3
Bronchopulmonary dysplasia (n=8)	-	5	3	-
Periventricular leukomalacia (n=3)	-	-	1	2
Early neonatal mortality (n=12)	7	1	1	3

gestational age and lower birth weight of the infants delivered by mothers with placental inflammation. Maternal age, gravidity and parity were similar between the groups. Forty-nine percent (n=21) of infants with findings associated with acute inflammation, 25% (n=11) of infants with placental findings associated with PIH and 26% (n=11) infants with no identifiable placental findings were male. There was no statistically significant difference between groups as regards the neonatal sex and route of delivery. Thirty-five percent (n=21) of infants with placental findings associated with PIH was SGA and the incidence rates of SGA were 41% and 15%, respectively, in infants with placental findings associated with acute inflammation and no identifiable pathology. The incidence rates of SGA infants were not statistically different between groups (p=0.17).

The initiator of preterm delivery was PTL in 45%, P-PROM in 20% and PIH in 21% of the infants. The rest (14%) of the patients were delivered due to other indications (abruption, or fetal distress, etc.). Initiators of preterm delivery stratified according to the histopathological features of the placentas are given in Table 3. Of the mothers with evidence of acute placental inflammation, 9 had P-PROM and 6 had PTL, this result was comparable to that of 1 mother who had PIH as the initiator of preterm delivery (p<0.001). Three mothers with histological evidence of chorioamnionitis had fever in the perinatal period and two patients had leukocytosis in addition to fever. These patients were treated with broad spectrum antibiotics intravenously. All mothers with P-PROM were treated with empirical intravenous ampicillin even if they did not have clinical symptoms.

Among the babies whose placentas were examined, 40% had RDS, 11% had BPD, 18% had early onset neonatal sepsis, 23% had perinatal asphyxia, 19% had IVH and 4%

Table 5. Distribution of neonatal outcomes in relation to histological chorioamnionitis

Neonatal morbidity	Histological chorioamnionitis		
	Positive (n=17)	Negative (n=57)	*p*
Respiratory distress syndrome (n=30)	40	60	0.004
Perinatal asphyxia (n=17)	41	59	0.518
Early onset sepsis (n=13)	62	38	0.160
Intraventricular hemorrhage (n=14)	42	58	0.075
Bronchopulmonary dysplasia (n=8)	75	25	0.001
Periventricular leukomalacia (n=3)	0	100	-
Early neonatal mortality (n=12)	33	67	0.454

Table 6. Distribution of neonatal outcomes in relation to placental correlates of PIH

Neonatal morbidity	Placental correlates of PIH		
	Positive (n=37)	Negative (n=37)	*p*
Respiratory distress syndrome (n=30) (%)	43	57	0.344
Perinatal asphyxia (n=17) (%)	47	53	0.782
Early onset sepsis (n=13) (%)	39	61	0.359
Intraventricular hemorrhage (n=14) (%)	36	64	0.235
Bronchopulmonary dysplasia (n=8) (%)	13	87	0.025
Periventricular leukomalacia (n=3) (%)	100	0	0.077
Early neonatal mortality (n=12)	33	67	0.207

had PVL. None of the patients had advanced necrotising enterocolitis. Neonatal mortality was 16%. Statistical analysis of neonatal morbidity in relation to the initiator of preterm delivery was not possible because the sample size was not big enough for subgroup analysis (Table 4).

Neonatal morbidity associated with histopathological evidence of acute placental inflammation is given in Table 5. Seventy-five percent of placentas of infants with BPD ($p<0.001$) and 36% of placentas of infants with RDS ($p<0.01$) revealed acute inflammation. In 4 patients with placental finding of umbilical cord inflammation, two neonates had IVH, RDS and perinatal asphyxia and they died within the first week of life; two others had early onset neonatal sepsis, one with RDS as well; both were treated with intravenous antibiotics.

BPD was detected less frequently with placental features of PIH ($p=0.02$); there was no correlation between histopathologic features of PIH and other neonatal morbidities (Table 6) ($p>0.05$).

Discussion

Preterm delivery is still one of the most important problems of modern obstetrics, accounting for 70% of perinatal mortality and nearly half of long-term neurological morbidity (10). Approximately 20-30% of preterm births are the result of a physician's decision to bring about the delivery for maternal or fetal indications, and the remainder follows spontaneous onset of labor or rupture of membranes (11).

Chorioamnionitis is a puerperal infection that exists in clinical and subclinical forms. This entity is believed to play a causative role in many cases of spontaneous preterm delivery. The relation between infection and preterm delivery is not consistent throughout gestation. Infection is rare in late preterm deliveries (at 34 to 36 weeks) but is present in most cases in which birth occurs at less than 30 weeks, as shown by histological examination of the fetal membranes after delivery (12). Similarly, in our study, the median gestational age of infants born to mothers with histological chorioamnionitis was significantly lower than infants of mothers with normal placental histology (29 vs 33 weeks, respectively). Intrauterine infection is often chronic, and it is usually asymptomatic until the labor begins or the membranes rupture. Even during labor, most women who are later demonstrated to have chorioamnionitis (by histopathological findings or culture) have no symptoms other than preterm labor (13). Only 5-10% of women who have microorganisms in the membranes have clinical chorioamnionitis. Therefore, identifying women with intrauterine infections is a major challenge. In our study, 3 out of 17 mothers with histological chorioamnionitis had clinical symptoms.

The examination of the placenta of preterm infants can provide information about intrauterine infection. Chorioamnionitis possesses well-recognized maternal and neonatal complications. Our study demonstrates that mothers with P-PROM have an increased risk of histological chorioamnionitis and the neonates born to

mothers with histological chorioamnionitis have an increased risk of BPD. Chorioamnionitis together with either prolonged mechanical ventilation or late onset neonatal sepsis has been shown to increase the risk of chronic lung disease (CLD) (14). Cytokinemia is evident in neonates of mothers with histological chorioamnionitis. In premature neonates cytokine networks and cascade activation of both pro-inflammatory and anti-inflammatory cytokines may not have reached the highest degree of specificity and interregulation, thus might lead to an increased risk of CLD (4).

The presence of umbilical cord inflammation has been shown to be a risk factor for clinical manifestations of the fetal inflammatory response syndrome including IVH and central nervous system echolucencies (PVL) in preterm infants (15-17). The risk of echolucencies may be related to the deleterious effects of inflammatory cytokines on developing oligodendroglial cells (18). In our study group, 4 patients had umbilical cord inflammation and 2 of them had IVH, none of them had PVL, so a statistical analysis could not be performed to search the effect of chorioamnionitis on PVL or IVH.

Chorioamnionitis can also pose adverse maternal outcome like uterine atony and pelvic infections. The management of chorioamnionitis consists of the use of broad spectrum antibiotics and the accomplishment of delivery. A better understanding of the relation between intrauterine infection and spontaneous preterm delivery will permit the clinical investigation of treatments which will also reduce the incidence of spontaneous preterm delivery and long-term morbidity and mortality associated with it (19).

Placenta has respiratory, nutritional, excretory, endocrine and immunological functions and most of cases of intrauterine growth retardation (IUGR) result from placental insufficiency. At least one histopathological alteration was observed in 95% of placentas of SGA infants. The specific findings included placental infarction, perivillous fibrin deposition and chronic villitis. Extensive perivillous fibrous deposition has been associated with the decrease of blood flow in the intervillous space and has been frequently associated with the presence of placental infarction. Chronic villitis is an inflammatory process of villous surface and it leads to a process of intrauterine malnutrition through the reduction of maternal-fetal exchange. Thus, both of the conditions cause restraint on the villous surface area of maternal-fetal exchange and even if they can not be accounted for a primary cause of IUGR, they can secondarily aggravate it (20). In our study, 35% of neonates born to mothers with placental vasculopathy were SGA in comparison to 15% of neonates born to mothers with no identifiable placental pathology, but this tendency was not statistically significant. Examining the placentas of SGA infants may help to look for disorders that may be directly or indirectly associated with the etiopathology of fetal growth restriction (20).

Infarction, decidual vasculopathy and snycytial knotting are features of placental underperfusion (21). Fibrinoid necrosis of decidual vessels, villous infarct and increased villous fibrosis are features of secondary villous damage. In our study, placentas of 82% of the patients with PIH had one or more of these histological findings. Zhang et al. have reported that placental infarction was seen in 32.3% and maternal atherosis and fibrinoid medial necrosis was seen in 21.4% of these placentas of mothers with PIH. Examination of placentas with PIH should be based on a combination of a number of histological changes (22).

In summary, this preliminary study shows that, placental pathology is a valuable link explaining how underlying risk factors of pregnancy result in adverse pregnancy outcome. Studies with larger sample sizes can provide additional information.

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3. Klinik Patrikte Kök Hücre ve Gen Tedavisi Kongresi

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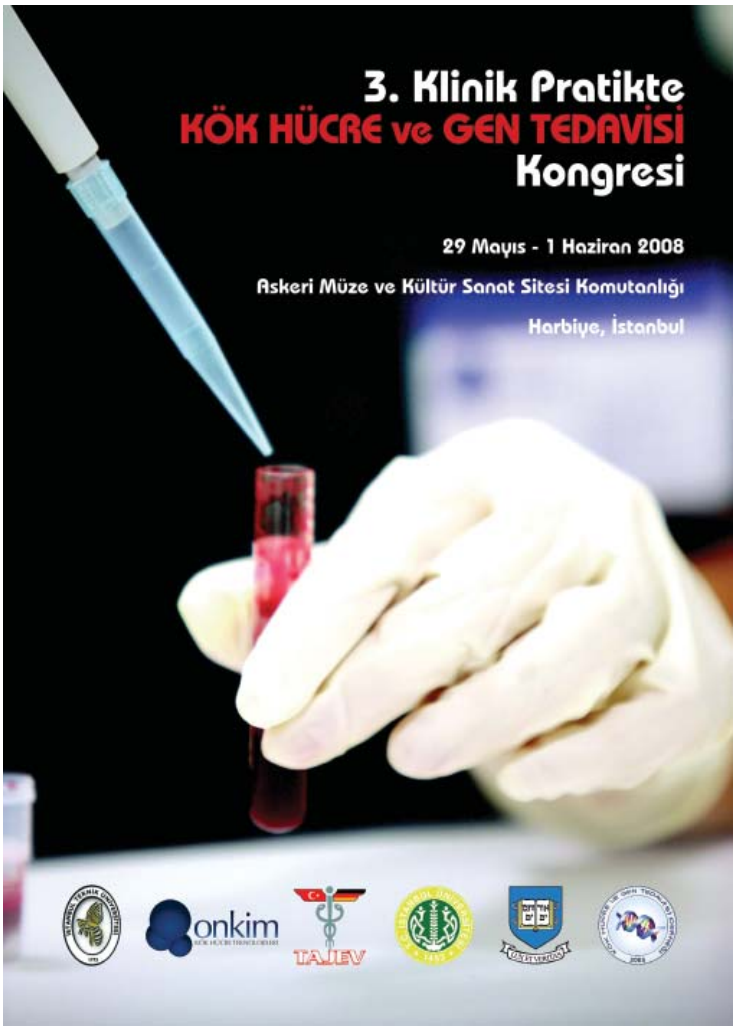
Değerli Meslektaşlarımız,

Kök hücre ve gen tedavisi ile ilgili ilk Ulusal Kongreyi 2004 yılında İstanbul Üniversitesi'nde başarıyla gerçekleştirdik. 1. Kongre'ye katılım ve ilgi, beklediğimizin çok üzerinde oldu ve katılımcılardan olumlu geri bildirimler aldık. 1. Kongre'de değişik disiplinlerde çalışan araştırmacı ve uygulayıcılar arasında bir köprü oluşturulması, genç araştırmacı ve meslektaşlarımıza araştırma olanakları ve konuları bakımından bir görüş kazandırılması, kök hücre ve gen tedavisi uygulamaları konusunda güncel bilgiler kazanılması gibi amaçlarımıza fazlasıyla ulaştık. Bütün bunların yanı sıra, etik değerler ve biyolojik tedavilerin hukuksal boyutunu da tartışarak, ülkemizin bu konuda izlemesi gereken yolu belirleyecek önemli çıkarımlar elde ettik.



Geçen zaman içerisinde gerek gen tedavisinde gerekse kök hücre tedavisinde önemli gelişmeler oldu. 3. Kongre'de, ilk toplantıdaki amaçlarımızın yanı sıra ağırlıklı olarak bu gelişmeler ele alınacaktır. Bu toplantıda alanlarında kendilerini kanıtlamış kök hücre biyologları, biyomedikal mühendisler ve klinik uygulayıcılar kök hücre ve gen tedavisi konusunda güncel gelişmeleri tartışacaklardır. İstanbul Üniversitesi, Kök Hücre ve Gen Tedavisi Derneği ve ülkemizin bu konuda temel taşlarından birisi durumundaki İstanbul Teknik Üniversitesi bünyesindeki Kök Hücre Araştırma ve Uygulama Merkezi Onkim'in, dünyanın bu konuda çalışan sayılı kurumlarının deneyim ve katkıları ile gerçekleşecek olan bu bilimsel şöleni sizlerle paylaşmak bizi son derece mutlu edecektir.

Saygılarımızla,

Prof. Dr. Erkut Attar
Kongre Sekreteri