Mother and Child Health

The possible role of hyperglycemia in the development of retinopathy in preterm infants

Ertl T., Gyarmati J.

Department of Obstetrics and Gynecology, Medical School, University of Pécs, Édesanyák útja 17, Pécs, Hungary, H-7624

tibor.ertl@aok.pte.hu

Aim: The incidence of hyperglycemia among extremely low birth weight (ELBW) infants is about 20-86%, depending on the definition used. Hyperglycemic preterm neonates have reduced insulin synthesis and limited insulin secretory response to glucose. The disease is associated with higher rate of mortality, intraventricular hemorrhage, sepsis and necrotizing enterocolitis. Recently an association between hyperglycemia and retinopathy of prematurity (ROP) was suggested in very low birth weight (VLBW) infants.

Methods: We analyzed the incidence, etiology and related complications of hyperglycemia in 201 VLBW infants.

Results: The incidence of ROP and hyperglycemia was 34.5% and 17.2%, respectively. The gestational age, birth weight, Apgar score was significantly lower in ROP patients. ROP developed in 80% of hyperglycemic infants (OR:11.9; 95% CI:4.5-32.5; $p<0.0001$). Hyperglycemia may be an independent risk factor for ROP development. Insulin use in premature infants may increase the risk of ROP.

Conclusions: Severe ROP is a multifactorial vasoproliferative retinal disorder characterized by a first phase of impaired growth leading to insufficient vascularization. The second phase of ROP with subsequent pathologic neovascularization may lead to retinal detachment and blindness. Retinopathy induced by oxygen or diabetes share many pathophysiological similarities. Vascular endothelial growth factor is implicated in the genesis of both disorders and the therapeutic target of clinical trials to prevent ROP. Insulin like growth factor-1 deficiency, a common disturbance in VLBW infants, could also be responsible for glucose instability and ROP development. While retinal immaturity differentiates VLBW infants with ROP from adults with diabetic retinopathy, the similarities suggest that longitudinally stimulus, rather than an acute event, is more likely to result in ROP. Clarification of the mechanisms responsible for this association requires further human and animal studies.

Keywords: neonatal hyperglycemia, retinopathy of prematurity

HLA-G 14 bp insertion/deletion polymorphism and female reproductive health

Sosnina K. O., Zastavna D. V., Terpylyak O. I., [1]Stoika R. S.
Institute of Hereditary Pathology, NAMS of Ukraine,
79000, Lviv, Lysenko Str. 31a
[1]Institute of Cell Biology, NAS of Ukraine,
79005, Lviv, Drahomanov Str. 14/16
zastavna.d@ihp.lviv.ua

Aim: The immune status of pregnancy is one of the major reproductive problems, and major histocompatibility complex (HLA-system in human) plays a central role in it. HLA-G (non-classic HLA-antigen) is of particular significance there, since it is expressed at the very early stages of human embryogenesis. It was suggested that specific polymorphisms found in coding and regulatory parts of *HLA-G* gene and associated with its different expression, might be important for pregnancy prolongation. We consider that during the reproductive losses, principal role belongs to polymorphism insertion/deletion 14 base pairs at 3`UTR region of *HLA-G* gene, since it is known that this polymorphism directly affects the level of expression of this gene. In this study, we addressed *HLA-G* polymorphism in women with recurrent spontaneous abortion (RSA).
Methods: DNA was isolated from the peripheral blood cells and the villi of human fetus chorion. DNA was subjected to polymerase chain reaction and electrophoresis in agarose gel.
Results: A significantly higher *HLA-G* 14 bp insertion/insertion genotype frequency ($\chi^2 = 4.021$, $P<0.05$) in a group of women with RSA compared to the control group was established. Calculation of odds ratio (OR) showed more than 3-fold increase in the miscarriage risk in women homozygous for *HLA-G* 14 bp insertion/insertion genotype (OR = 3.41 CI -95%: 0.98-11.85). Significantly higher *HLA-G* 14 bp insertion/insertion genotype frequency ($\chi^2 = 4.881$, $P <0.05$) in a group of spontaneously aborted embryos was also established, and the risk of spontaneous abortions in homozygous *HLA-G* 14 bp insertion/insertion genotype was increased up to 3 times (OR = 2.75 CI-95%: 1.10 - 6.90). Taking into account the literature data on the association of homozygous genotype by the allele insertion (+) 14 bp with a decreased expression of *HLA-G* gene, we predict a particular role of the non-classic HLA-G antigen in prolongation of pregnancy in human, touching both woman and fetus.
Conclusions: The homozygous *HLA-G* 14 bp insertion/insertion genotype was found to be an important risk factor of the recurrent spontaneous abortions in women.
Keywords: recurrent spontaneous abortion (RSA), *HLA-G* 14 bp insertion/deletion

The presence of intra-amniotic inflammation determines different phenotypes of preterm prelabor rupture of membranes

Kacerovsky M.

Institute: Department of Obstetrics and Gynecology, Charles University in Prague, Faculty of Medicine Hradec Kralove, University Hospital Hradec Kralove,
Sokolska 581, Hradec Kralove 500 05, Czech Republic
marian.kacerovsky@gmail.com; Marian.Kacerovsky@seznam.cz

Background: Microbial invasion of amniotic cavity (MIAC) has extensively been related to neonatal morbidity and mortality in pregnancies with preterm prelabor membrane rupture (PPROM). However, the presence of an intra-amniotic inflammatory status seems to be as important as the identification of microorganism in the amniotic fluid for the occurrence of preterm delivery and neonatal complications. The management of women with PPROM in the Czech Republic is active. Therefore, placental pathology after delivery may represent placental status at the time of amniotic fluid sampling. The aim of the study is to evaluate the magnitude of the intra-amniotic inflammatory response in different subgroups according the presence of MIAC and histological chorioamnionitis.
Objective: To evaluate the influence of MIAC and histological chorioamnionitis on the magnitude of intra-amniotic inflammatory response in PPROM.
Study Design: A prospective cohort study was performed in 107 women with PPROM between 23+0-36+6 weeks' of gestational age. Twenty-six amniotic fluid proteins were assayed by multiple immunoassay.
Results: The rate of MIAC and histological chorioamnionitis was 44% and 57%, respectively. Intra-amniotic inflammatory response was significantly higher when histological chorioamnionitis and MIAC were simultaneously present. There were no differences on intra-amniotic inflammatory response between women with MIAC or histological chorioamnionitis alone and women without infection.
Conclusion: The presence of both histological chorioamnionitis and microbial invasion of amniotic cavity is determinant of intra-amniotic inflammatory response in women with PPROM
Key words: preterm delivery, intrauterine infection, intrauterine inflammation.

Preventing preterm birth: limitations and potential of animal models.

Falkay G. and Gaspar R.

Department of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged
H-6701, P.O. Box 121, Hungary

falkay@pharm.u-szeged.hu

Preterm birth is the most important direct cause of neonatal mortality and remains major challenge of obstetrics and global health. Intrauterine infection causes approximately 50% of early preterm birth. Our understanding of the regulation of parturition remains inadequate.

Are animal models relevant to key aspects of human parturition?

The scientific literature, largely derived from rodent animal models, suggests two major mechanisms regulating the timing of parturition: the withdrawal of the steroid hormones progesterone and proinflammatory response by the immune system. However, available evidence strongly suggests that parturition in the human has significantly different regulators and mediators from those in the most animal models.

Although animal models are not without their limitations in modelling human parturition, they have made important contributions to our current understanding of this complex process. Differences in how parturition is executed in common animal models and humans have been identified, but these differences should not discourage investigators from conducting further research to identify additional important similarities. Specific examples of the aspects of parturition in different animal models are summarized.

Congenital human cytomegalovirus infections as a cause of hearing loss in infants: Importance of maternal seroimmunity

Britt William, Boppana Suresh, Fowler Karen, [1]Yamamoto Aparecida, and [1]Mussi-Pinhata Marisa.

Dept of Pediatrics, Univ Alabama Birmingham, Birmingham, Al. USA
[1]Dept of Pediatrics, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil
wbritt@peds.uab.edu; wbritt@uab.edu

The **Aim** of this study was to determine the contribution of congenital human cytomegalovirus (HCMV) infection to the development of hearing loss in infants and children in maternal populations with intermediate and high HCMV seroprevalence.
Methods: Newborn screening for infants with congenital HCMV infections was carried out in (1) approximately 90,000 infants born in 6 hospitals in the United States and (2) in 2 hospitals in Ribeirao Preto, Sao Paulo, Brazil. The US maternal population contained women from groups with a high HCMV seroprevalence and women with an intermediate HCMV seroprevalence, together likely reflective of the overall HCMV seroprevalence in the US of about 60%. In contrast, the HCMV seroprevalence in the Brazilian maternal population was >96%. Newborns in both populations were screened within the first 7 days of life by a PCR assay and/or a virus immediate early antigen detection assay. Infection in infants that were identified using these assays were confirmed to be excreting HCMV by detection of HCMV in the urine within 3 weeks of life. Hearing function was asscessed by auditory brainstem responses during 1st year of life with at least 2 tests being completed by age 12 months.
Results: In congenitally infected infants identified by screening in the US population, the rate of hearing loss at birth was approximately 9.1%. Similarly, the rate of hearing loss in infants identified by screening in Brazil was 11.5% (10/85). Analysis of the severity of hearing loss in the Brazilian infants revealed that 7/10 (70%) had moderate to severe hearing loss. Moreover, in the Brazilian population we could document non-primary maternal infection in 6/10 and primary maternal infection in only 1/10 of infants with hearing loss.
Conclusions: These results demonstrate the hearing loss secondary to congenital HCMV infection occurs with a similar frequency in infants born to women with or without preconceptional immunity to HCMV. These findings suggest that conventional strategies of prophylactic vaccination will not have an impact on the contribution of congenital HCMV infection to hearing loss in infants and children.

Keywords: Human Cytomegalovirus, Congenital Infection, Hearing Loss

New gestational diabetes criteria and their impact on maternal and neonatal health

Ceauşu Iuliana

«Carol Davila» University of Medicine and Pharmacy, Bucharest, Romania
«Dr.I. Cantacuzino» Clinical Hospital, Department of Obstetrics and Gynecology,
iulianaceausu2004@yahoo.com

Background and aim: New criteria for the diagnosis of gestational diabetes (GDM) were recently proposed by the Consensus Panel of the International Association of Diabetes Pregnancy Study Groups (ICP 2010).
So the new GDM diagnostic criteria recommended by IADPSG identified a new group of GDM women that, classified normal with Carpenter and Coustan criteria, show metabolic characteristics and pregnancy outcome similar to those of GDM women.
We aimed to examine whether these new criteria (GDM-2010) select women and children at risk better than criteria of the Forth International Workshop Conference of GDM (GDM-1998) using the 2-hour 75g oral glucose tolerance test (OGTT).
Materials and methods: This was retrospective study in our clinic including 147 women underwent an 2-hour 75g-OGTT with gestational age 24^{th}-28^{th} weeks and were treated if at least one value according to the GDM-1998 was met or exceeded (GDM-1998) in keeping with the recommendations of the Romanian Diabetes Association at that time (2004-2006). We evaluated the impact of risk factors, different thresholds (GDM-2010 vs. GDM-1998) on fetal/neonatal complications and maternal postpartum glucose tolerance in pregnant women.
Results: 48% of all women were diagnosed according to GDM-ICP, whereas 46% according to GDM-1998. GDM-2010 identified a higher rate of obstetrical complications. We found 7.3 % more large for gestational age neonates ($p<0.01$), 3.5% more cesarean sections ($p<0.001$) and 4.8% more neonates with birth weight >4000g ($p<0.01$) than with the former criteria. The number of risk factors (GDM in previous gestations, intrauterine fetal demise, birth weight over 4000g, malformation, previous recurrent abortus, risk ethnic group, BMI, gestational hypertension, preterm delivery, age, family history for DM2, large for gestational age) detected by the GDM-ICP was increased by 3.1% ($p<0.0001$).
Conclusion: These results support the use of the new, more stringent criteria proposed by ICP for the diagnosis of GDM (GDM-2010), because they can detect more obstetrical complications than the former diagnostic criteria (GDM-1998) in a Central European population.
Keywords: macrosomia, large for gestational age, gestational diabetes mellitus

Congenital CMV and Neonatal HSV Infections in the Netherlands

Galama J. M., Gaytant M. A., van der [1]Meijdenb W. I., [2]Steegersc E. A.

Department of Medical Microbiology. Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands.
[1]Department of Dermatology and Venereology. Erasmus University Medical Center, Rotterdam, the Netherlands.
[2]Department of Gynaecology and Obstetrics. Erasmus University Medical Center, Rotterdam, the Netherlands.
J.Galama@mmb.umcn.nl

Congenital **cytomegalovirus** (CMV) and neonatal **herpes simplex virus** (HSV) infection are among the most serious complications of pregnancy and of the neonatal period.
Aim: to assess the incidence of congenital CMV and neonatal HSV infection for the Netherlands.
Methods: prospective study among 7793 newborns for congenital CMV infection and a retrospective surveys for neonatal HSV infections, including seroprevalence studies for CMV, HSV type 1 and type 2.
Results: For congenital CMV an incidence of 1/1000 was found, the lowest ever reported. The low incidence may be explained by a low CMV seroprevalence of 35% among the pregnant women. For neonatal HSV infection an incidence of 2.0-3.2/100,000 births was found over a period of 25 years (1981-2005). Neonatal HSV infections were mainly caused by HSV-type 1, probably due to primary infection.
Conclusions: Congenital CMV and neonatal HSV infections are not a major problem in The Netherlands. Preventive measures for neonatal HSV infection should take into account that HSV-1 has a more prominent role in certain populations than is commonly accepted.
Keywords: congenital, neonatal**,** cytomegalovirus, herpes simplex virus**,** infection, The Netherlands

Standardization and improvement measures in cases of medically assisted reproduction

Tihana Vešligaj, Siniša Šijanović
JJ Strossmayer University Osijek, School of Medicine, Department Obstetrics and Gynecology, 4, Huttlerova, HR31000 Osijek, Croatia
sinisa.sijanovic@os.htnet.hr

Aim: Infertility treatment is a complex procedure since it requires collaboration of several medical professions. This specific case shows how standardization and measures for improving o fan in vitro procedure could decrease complications and increase the number of successfully completed pregnancies.
Methodes: Data were derived from anamnesis and labaratory findings of patients hospitalized in department Obstetrics and Gynecology in Clinical Hospital Centre Osijek.
Results: In our description, standard protocol was applied on a patient who had to undergo in vitro fertilization procedure due to sterility. The patient developed the complication of ovarian hyperstimulation syndrome and despite the therapy her first pregnancy ended in miscarriage. When the conditions were favorable again, the in vitro procedure was repeated and it resulted in the birth of a healthy child.
Conclusions: Infertility is a disease which causes deep frustration. The most important factors are age, the effects of endometriosis and sexually transimitted diseases. Birth of a healthy child without any complications for the mother is considered a success. There are many fields in which actions may be undertaken in order to accomplish better results in a shorter period of time without complications. Normal egg cells and sperm are the prerequisites for success. Focus is on the gentler procotols in order to minimize the risk of complications. It has also been proven that oocyte vitrification does not increase the risk of congenital abnormalities. Finally, something that is not a part of medical profession, but limits it significantly – Law on Artificial Insemination. However, neither the encouraging advancement nor the success in treating infertility should be the reason or encouragement for women to postpone their reproduction until unfavorable age.
Key Words: infertility, in vitro fertilization, multiple pregnancy.

Preterm birth and cytokines balances

Pyrohova V., Shurpyak S., Petruh A.
Danylo Halitskiy Lviv National Medical University.
69, Pekarska str., Lviv, Ukraine, 79010
pyroh@mail.lviv.ua; shurpyak_serhiy@yahoo.com

Aim: A risk of pregnancy loss after the first abortion is 13-17%, which corresponds frequency of sporadic abortion in population, while after two preceding spontaneous abortion risk of pregnancy loss was 36-38%. For women, not having living children, probability of pregnancy loss higher and 40-45% makes after the third pregnancy miscarriages. 30-60 % all of premature births complicated the premature preterm rupture of membrane (PRM). Preterm rupture of membrane is a thorny obstetric problem many aspects of which largely remain unsolved.
Methods: For the exposure of immunological factors of premature births with the PRM conducted research of levels of IL-1в, IL-6, and IL-4 to the blood of women with the usual unmaturing of pregnancy.
Hundred expectant mothers are inspected in age from 18 to 39 years with the terms of pregnancy from 22 to 34 weeks. The concentrations of cytokines (IL-4, IL-6, IL-1в) in the blood determined by immunoferment method.
Results: Premature births, begun with the preterm rupture of membrane, are related to the enhanced concentration of proinflammatory cytokines and accordingly with the decline of activity of antiinflammatory cytokines. The table of contents of cytokines in the whey of blood for woman giving births with preterm rupture of membrane had reliable distinctions from the group of woman giving births with physiological pregnancy.
Level of IL-1β, which participates in initiation of childbirth, for woman giving births with the preterm rupture of membranes was in 3.4 time in relation to women with the uncomplicated pregnancy (226 ± 21 pg/ml against 62 ± 8 pg/ml, $p < 0,01$).
At the same time level of IL-4 made 5.8 ± 0.8 pg/ml, that was below the average values of norm in 4.2 times. For women with the normal flow of pregnancy a level of IL-4 in the whey of blood was 24.1±3.4 pg/ml. IL-4 is the natural inhibitor of inflammation and key cytokines, produced Th2-lymphocytes, which supports balance of Th1/ Th2.
Conclusions: At premature births, beginnings from the preterm rupture of membrane, activating of Thl results in blowing off tolerance and premature childbirth. The increase of level of IL-6 and IL-1β can a laboratory criterion, having a prognostic value of premature births, serve on a background the decline of level of IL-4.
Keywords: preterm rupture of membrane, pregnancy, cytokines

Pulsation of the fetal splenic vein – a potential ultrasound marker of histological chorioamnionitis and funisitis in women with preterm prelabor rupture of membranes

Musilova I., Kacerovsky M.

Department of Obstetrics and Gynecology, Charles University in Prague, Faculty of Medicine Hradec Kralove, University Hospital Hradec Kralove, Czech Republic.

7744.ivana@seznam.cz

Aim: The fetal spleen is involved in the response to intrauterine infection. The flow pattern of its vein is continuous under normal conditions. The aim of the study was to determine whether the presence of histological chorioamnionitis and funisitis is associated with a continuous or pulsatile flow pattern in fetal splenic vein.

Methods: We performed a prospective study including 79 women with preterm prelabor rupture of membranes. The splenic vein was identified in a transverse image of the fetal abdomen. The flow pattern was defined as continuous when no changes in velocity were found within a single cardiac cycle. The pulsatile flow was defined as a pattern with changes in velocity synchronised with fetal heart rate.

Results: The pulsatile flow pattern of the splenic vein was found in 47% (24/51) of women with histological chorioamnionitis. In contrast, 4% of women without histological chorioamnionitis displayed pulsatile flow pattern (1/28). The association between the presence of histological chorioamnionitis and pulsatile pattern was highly significant ($p < 0.0001$). The presence of pulsatile flow pattern had sensitivity of 47% [95% confidence interval (CI): 33-62%], specificity 96% (CI: 82-100%), positive predictive value 96% (CI: 80-100%), negative predictive value 50% (CI: 36-64%), and likelihood ratio13.2 (CI 1.9-92.3) for the prediction of histologic chorioamnionitis.

Conclusion: Ultrasound Doppler evaluation of splenic vein could be a non-invasive tool for the prediction of intrauterine inflammation in women with preterm prelabor rupture of membranes.

Keywords: Doppler, intrauterine inflammation, prenatal diagnostic, splenic vein

The impact of SNPs in *LEP* and *LEPR* on pregnancy outcome

Heffer M., Wagner J., [1]Muller A., Škrlec I., [2]Maver A., [3]Zibar L., [2]Peterlin B.

Department of Medical Biology, School of Medicine, J. J. Strossmayer University of Osijek, J. Huttlera 4, 31000 Osijek, Croatia
[1]Clinic for Gynecology and Obstetrics, University Hospital Centre Osijek, J. Huttlera 4, 31000 Osijek, Croatia
[2]Institute of Medical Genetics, University Medical Center Ljubljana, Šlajmerjeva 13, 1000 Ljubljana, Slovenia
[3]Clinic for Internal Medicine, University Hospital Centre Osijek, J. Huttlera 4, 31000 Osijek, Croatia
mheffer@mefos.hr;

Aim: Pregnancy is an energy demanding period postulating the maintenance of dynamic energy balance between the mother and the child. A specific combination of single nucleotide polymorphisms (SNP) in two synergistic genes involved in energy homeostasis – leptin (*LEP*) and leptin receptor (*LEPR)* may potentially become a risk factor for recurrent spontaneous abortion (RSA). The comparison was done between a group of female patients with more than three recurrent spontaneous abortions (RSA) and women with two or more successful pregnancies (SP).
Methods: The study was conducted on 145 women with SP and 178 women with RSA. The genotypes for *LEP* (rs7799039, rs2122627, rs11761556, rs10244329) and *LEPR* (rs1137101, rs7516341, rs1186403, rs12062820) were determined with the use of KASP SNP Genotyping system and ABI Prism 7000 SDS instrument. The statistical comparison was done with the use of Chi-Square Statistic. The haplotype frequencies and haplotype-disease associations were estimated with the use of haplo.stats package.
Results: The genotype frequencies at -2548 G/A in *LEP* promoter region were different in SP ($p = 0.60069$) and RSA group ($p = 0.03166$). The genotype AA is associated with RSA (OR = 1.58) and previously connected with higher levels of circulating leptin. The ancestral allele C in rs7516341 and a new allele T in rs1186403 of *LEPR* gene are protective. In the haplotype analysis, the combination of opposite alleles at the same position is associated with a higher risk of RSA ($p = 0.0087$).
Conclusions: The levels of leptin in placenta and fetal circulation are differently regulated. The mother's ability to produce certain levels of leptin affects placental growth more than the fetal. The normal development is equable for both and might have a potentially adverse effect unless balance is achieved. A particular mother's haplotype of LEPR indicates a new molecular mechanism behind RSA.
Keywords: recurrent spontaneous abortion, *LEP, LEPR*, SNP