

CROATIAN INTERNATIONAL PUBLICATIONS

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Vukasovic A, Grbesa D, Nikuseva Martic T, Kusec V, Miskovic B, Serman A, Soken N, Serman L. Glycosylation pattern and axin expression in normal and IUGR placentae. *J Matern Fetal Neonatal Med.* 2014;1-18.

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Objective: The aim of this study was to investigate the protein glycosylation pattern and AXIN1 protein expression in human placentae of normal pregnancies and compare them with placentae of pregnancies complicated with intrauterine growth restriction (IUGR). **Methods:** A total of 38 placentae (17 placentae of IUGR fetuses from singleton pregnancies and gestational age-matched 21 control placentae from normal singleton pregnancies) were collected from the Clinical Hospital Sveti Duh, Department of Gynecology and Obstetrics, Zagreb, Croatia. Gestational age was determined according to the last menstrual period (LMP) and by ultrasound measurements. Expression of glycoproteins was measured by Western blotting with SNA, UEA-I, PHA-E and DBA lectins as probes whereas expression of AXIN1 was determined by Immunohistochemistry. **Results:** Comparison of detected sugars revealed differences in protein glycosylation between normal and IUGR placentae. Higher expression of AXIN1 protein located mostly in the cytoplasm of syncytiotrophoblast and to a lesser extent in its nuclei was found in IUGR placentae. **Conclusion:** Results of our study suggest that changes in glycoprotein content may contribute to restricted placenta growth and development. Higher expression of AXIN1 protein in IUGR placentae indicates a role of Wnt/ β -catenin signaling pathway in pathology of placental development.

Tomicic M, Starcevic M, Ribicic R, Golubic-Cepulic B, Hundric-Haspl Z, Jukic I. Alloimmune neonatal neutropenia in Croatia during the 1998-2008 period. *Am J Reprod Immunol.* 2014;71(5):451-7.

Department of Platelet and Leukocyte Diagnosis and Hemostasis, Croatian Institute of Transfusion Medicine, Zagreb, Croatia.

PROBLEM: The aim of this study was to estimate the incidence of the disease and to analyze laboratory data of 23 newborns undergoing serologic testing for alloimmune neonatal neutropenia (ANN) during the 1998-2008 period in Croatia. **METHOD OF STUDY:** Laboratory data on 23 newborns undergoing serologic testing for ANN during the 1998-2008 period and epidemiologic data on the number of live births in Croatia were analyzed. Laboratory testing for ANN included serologic screening of maternal and neonatal sera and granulocytes (neutrophils) by immunofluorescence (IF) method. The monoclonal antibody immobilization of neutrophil antigens (MAINA) was employed to determine anti-HNA antibody specificity. **RESULTS:** Anti-HNA antibodies were detected in seven (54%) of 13 cases of serologically positive ANN. Only anti-HLA class I antibodies were demonstrated in four (31%) of 13 cases. In the 2007-2008 period of prospective data collection, the number of serologically verified ANN cases was one case per 17,323 live births. Results of the prospective study conducted at Maternity Ward, Department of Gynecology and Obstetrics, Sestre milosrdnice University Hospital Center yielded the ANN incidence of one case per 2843 live births. **CONCLUSION:** Monitoring of neutrophil count in neonatal blood and serologic testing for ANN in case of isolated neutropenia in the newborn contributed considerably to timely detection of ANN.

Kasum M, Simunić V, Vrčić H, Stanić P, Orešković S, Beketić-Orešković L. Follicular progesterone elevations with ovulation induction for IVF. *Gynecol Endocrinol.* 2014;19:1-5.

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The purpose of this review is to analyse the sources and effects of follicular progesterone elevations during ovarian stimulation, with the underlying mechanisms and preventive strategies on the *in vitro* fertilisation pregnancy outcome. In the early follicular phase, a flare-up effect of gonadotrophin releasing hormone (GnRH) agonists and incomplete luteolysis in GnRH antagonist regimens can result in significant elevations of progesterone. In the late follicular phase, progesterone elevations in GnRH analogue cycles are the result of the ovarian stimulation itself, driven by high follicle stimulating hormone dosage, estradiol levels, the number of follicles and oocytes. It seems that progesterone elevations ($>$ or $=$ 1.5ng/mL or 4.77nmol/L) have a detrimental effect on the outcome of pregnancy, accelerating the endometrial maturation. The most appropriate choice to avoid the negative effects of follicular progesterone elevations is to cancel fresh embryo transfer and to transfer frozen-thawed embryos in natural cycles. To prevent follicular phase elevations it might be preferable to use milder stimulation protocols, earlier trigger of ovulation in high responders and single-blastocyst transfer on day 5. The optimal GnRH analogue protocols during the entire stimulation period appear to be the long agonist as well as "long" and long GnRH antagonist regimens.

Kruljac I, Solter D, Vrkljan AM, Solter M. Remission of Graves' disease is not related to early restoration of euthyroidism with high-dose methimazole therapy. *Endocr Res.* 2014;15:1-4.

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Introduction and aims: The most recent hypothesis postulated that early restoration of euthyroid state in patients with Graves' disease changes the course of the disease and leads to better disease control. Therefore, we analyzed the efficacy of methimazole therapy and the course of disease in patients with restored euthyroidism and in patients with

active disease on first control visit. **Patients and methods:** We included 63 patients with total T4 level >190 nmol/L or T3 >7 nmol/L and diffuse goiter with no previous episodes of hyperthyroidism. All patients received initially high doses of methimazole (60-80 mg) followed by a rapid dose reduction. **Results:** Ten percent of patients were excluded from the study due to side effects. Two different groups emerged after 5 weeks of treatment with same dose of methimazole: group 1 with active disease (48%) and group 2 with restored euthyroidism. Further controls on 12th, 24th and 68th weeks of treatment showed no difference in remission rates, number of iatrogenic hypothyroid episodes, and number of exacerbations between the two groups, regardless of methimazole dose. There was no association between age, gender, thyroid hormone levels, and remission and exacerbation rates. **Conclusions:** Initially, higher methimazole doses with rapid progressive decrease to maintenance dose result in similar remission rates and are followed by similar incidence of adverse side-effect as fixed low dose therapy. Our results indicate that neither an early restoration of euthyroidism nor the difference in methimazole doses influence the course of Graves' disease.

Mirić M, Turkalj M, Nogalo B, Erceg D, Perica M, Plavec D. Lung diffusion capacity in children with respiratory symptoms and untreated GERD. *Med Sci Monit.* 2014;12;20:774-81.

Department for Anesthesiology, Reanimatology and Intensive Care Medicine, University Hospital Center Zagreb, Zagreb, Croatia; Department of Pediatric Allergology and Pulmonology, Children's Hospital Srebrnjak, Reference Center for Clinical Immunology in Children Appointed by the Ministry of Health and Social Welfare of the Republic of Croatia, Zagreb, Croatia.

Background: Gastroesophageal reflux disease (GERD) is associated with many respiratory disorders, among which, chronic cough, laryngitis, and asthma are among the most common. We investigated lung function, including gas diffusion capacity, in children with poor asthma control or chronic laryngitis with untreated GERD. **Material and Methods** A total of 71 children, aged 6-17 years, with chronic respiratory and other symptoms suggestive for GERD, were enrolled and divided into 2 groups: chronic laryngitis and asthma. **Participants:** underwent 24-hour pH monitoring and lung function assessment, measurement of single-breath diffusing capacity of the lung for carbon monoxide (DLCO), and fraction of exhaled nitric oxide (FENO) measurement. **Results:** 24-hour pH monitoring was

positive for GERD in 92.1% of preselected children with asthma and 90.1% of children with chronic recurrent laryngitis. All flows (PEF, MEF75, MEF50, and MEF25) were significantly lower in the asthma group, while FENO and DLCO were significantly lower in the laryngitis group. A significant inverse relationship was found between DLCO and all reflux indexes in the laryngitis group. Each unit change of Johnson-DeMeester score and Boix-Ochoa score increased the odds for significantly lower DLCO in laryngitis patients by 3.9% and 5.5%, respectively. Conclusions: In children with uncontrolled asthma and chronic laryngitis, the regurgitation of gastric contents due to GERD contributes to poor asthma control and aggravation of chronic laryngitis. Despite having normal lung function, the gas diffusion capacity should be controlled in patients with GERD and chronic laryngitis, and it might be the very first abnormality in distal airways.

Gasparovic H, Petricevic M, Kopjar T, Djuric Z, Svetina L, Biocina B. Impact of dual antiplatelet therapy on outcomes among aspirin-resistant patients following coronary artery bypass grafting. Am J Cardiol. 2014;113(10):1660-7.

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Coronary artery bypass grafting is pivotal in the contemporary management of complex coronary artery disease. Interpatient variability to antiplatelet agents, however, harbors the potential to compromise the revascularization benefit by increasing the incidence of adverse events. This study was designed to define the impact of dual antiplatelet therapy (dAPT) on clinical outcomes among aspirin-resistant patients who underwent coronary artery surgery. We randomly assigned 219 aspirin-resistant patients according to multiple electrode aggregometry to receive clopidogrel (75 mg) plus aspirin (300 mg) or aspirin-monotherapy (300 mg). The primary end point was a composite outcome of all-cause death, nonfatal myocardial infarction, stroke, or cardiovascular hospitalization assessed at 6 months postoperatively. The primary end point occurred in 6% of patients assigned to dAPT and 10% of patients randomized to aspirin-monotherapy (relative risk 0.61, 95% confidence interval 0.25 to 1.51, $p = 0.33$). No significant treatment effect was noted in the occurrence of the safety end point. The total incidence of bleeding events was 25% and 19% in the dAPT and aspirin-monotherapy groups, respectively (relative risk 1.34, 95% confidence interval 0.80 to 2.23, $p = 0.33$). In the subgroup analysis,

dAPT led to lower rates of adverse events in patients with a body mass index >30 kg/m² (0% vs 18%, $p < 0.01$) and those <65 years (0% vs 10%, $p = 0.02$). In conclusion, the addition of clopidogrel in patients found to be aspirin resistant after coronary artery bypass grafting did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events. dAPT did, however, lower the incidence of the primary end point in obese patients and those <65 years.

Lozo M, Lojpur M, Madden D, Lozo P, Banic I, Dujic Z. The effects of nitroglycerin, norepinephrine and aminophylline on intrapulmonary arteriovenous anastomoses in healthy humans at rest. Respir Physiol Neurobiol. 2014;199C:19-23.

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We have investigated the effects of the intravenous infusion of nitroglycerin (NTG), norepinephrine (NE) and aminophylline (AMP) on the opening and recruitment of intrapulmonary arteriovenous anastomoses (IPAVA) in healthy humans at rest. In ten volunteers saline contrast echocardiography was performed during administration of two doses of the NTG ($3\mu\text{gkg}^{-1}\text{min}^{-1}$ and $6\mu\text{gkg}^{-1}\text{min}^{-1}$) and NE ($0.1\mu\text{gkg}^{-1}\text{min}^{-1}$ and $0.25\mu\text{gkg}^{-1}\text{min}^{-1}$) as well as 30min following the administration of AMP at rate of 6mgkg^{-1} . Echocardiography was used to assign bubble scores (0-5) based on the number and spatial distribution of bubbles in the left ventricle. Doppler ultrasound was used to estimate pulmonary artery systolic pressure. Using a Finometer the following hemodynamic parameters were assessed: heart rate, stroke volume, cardiac output, total peripheral resistance as well as systolic, diastolic and mean arterial pressure. The most important finding from the current study was that nitroglycerin, norepinephrine and aminophylline in the applied doses were not found to promote IPAVA opening in healthy humans at rest.