# Effect of antenatal steroid treatment on fetal and maternal endocrine parameters

## 1. Summary

Strong evidence exists for the role of antenatal steroids in Respiratory Distress Syndrome (RDS) prevention, the protocol for the steroid administration is evidence based. Glucocorticoids are essential for pulmonary development in fetuses and preterm infants, but the effect is not limited to lung development.

The accelerated maturation of organs might be taken that „hormonal imprinting" effect of glucocorticoids.

The first part of dissertation deals with glucocorticoid receptors of human fetal lung. From the scientific point of view these results are not „novum". But the second part of dissertation deals with a new peptid, ghrelin and possible correlation with endocrine and anthropometric parameters during pregnancy.

Ghrelin plays an important role in the regulation of appetite and food intake and controls of energy balance. This peptide is produced predominantly by the stomach, whereas lower amounts are derived from the hypothalamus, kidney, heart, pancreatic cells, and the placenta in humans. The presence of significant ghrelin concentrations in human cord blood has been shown, but information about the ghrelin secretion during the fetal life is scarce. It is known that the hypercortisolism in humans decreases ghrelin levels in plasma and that serum cortisol exhibits a negative correlation with ghrelin. The physiological mechanisms behind this relationship are not known, but the glucocorticoids that are used in antenatal therapeutic settings may have an effect on ghrelin secretion.

The point of the present study was to compare acylated and total ghrelin concentration in premature infants and their mothers and to investigate the possible relationship between ghrelin and anthropometric and hormonal parameters, such as leptin, insulin, growth hormone and cortisol.

## 2. Introduction

In the 1972 Liggins and Howie were the first to propose the antenatal corticosteroids given to mothers at risk of preterm delivery. Glucocorticoids appear to have, besides the stimulation of surfactant, additional effects on pulmonary maturation. Since then, many other randomized controll and meta-analysis have reported the clinical benefits of antenatal corticosteroids. In 1994 the National Institute of Health declared a cosensus statement: all pregnant women between 24 and 34 weeks gestation, who are at risk of preterm delivery, should be candidates for antenatal treatment with corticosteoids. In Hungary Szabó and coworkers were the first to introduce the antenatal corticosteroid treatment in the clinical practice.

Antenatal corticosteroids also protect the newborn from intraventricular haemorrhagie and necrotizing enterocolitis especially in extremely low birthweight infants.

There is no evidence that the repeated courses of prenatal steroids have higher efficiency in the prevention of RDS, but several clinical studies observed, that increasing numbers of antenatal corticosteroid courses were associated with reduction in birthweight.

The exact mechanism of glucocorticoid-induced lung maturation is still unknown. In most species, including humans, a late gestational rise in fetal cortisol production is found combined with a high expression of glucocorticoid receptors in pulmonary tissues. Hypophysectomy in several species causes abnormal lung development, suggesting that low levels of cortisol are linked with an inhibition of pulmonary maturation.

We measured glucocorticoid receptor concentration in human lung cytosol from fetuses of gestational age 14-28 wk. The concentration of cytoplasmic receptor arranged according to the gestational age are presented in Fig.1. Characterization of the in vitro binding of glucocorticoid by lung cytosol showed a high affinity, saturable receptors for natural and synthetic glucocorticoids. In evaluating ontogeny of receptor in human lung tissue showed a decrease in the receptor number at the end of canalicular phase. This time is the end of cellular proliferation of the lung and there is a marked decrease in interstitial tissue.

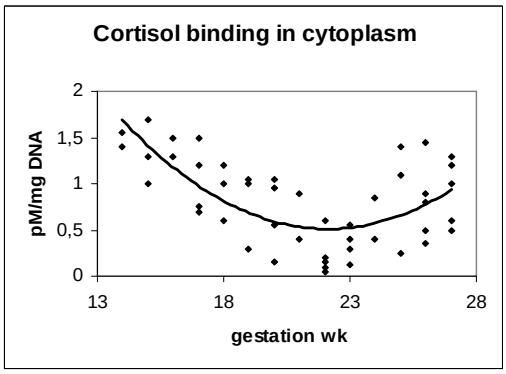



**Figure 1**. Cortisol cytoplasmic reception in human fetal lung n=47, Spearman k=0.015

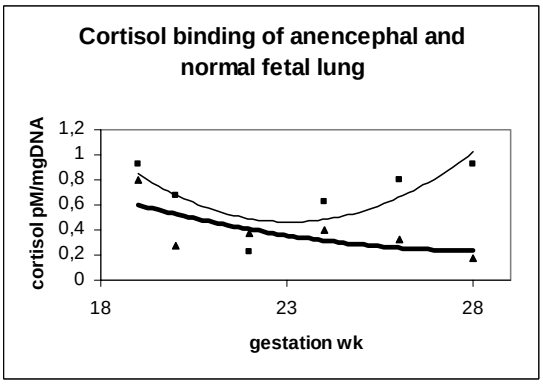


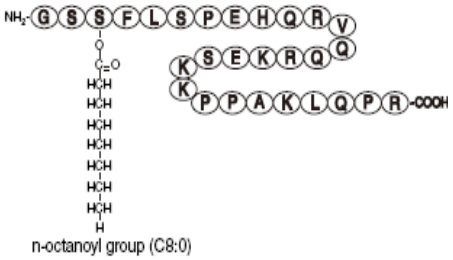

**Figure 2**. Mean cortisol receptor numbers in anencephal (▲) n=9 and normal (■) n=18 fetal lung

The cortisol binding examination of anencephal human fetal lung revealed the importance of hypothalamo-hypophyseal-adrenal axis in the normal development of cotisol receptors. (Fig.2.)

In 2002 a new hormone, ghrelin was idenfied in the neuroendocrine cells of human fetal lung. The extent of ghrelin expression differed according to the gestational age, the cut off point to separate the expression was the 18-20 week of gestation. It was declared, that the human fetal lung is an important source of ghrelin. It can be speculated that ghrelin may play a role in lung maturation and elongation.

The ghrelin was discovered in 1999, through a process of reverse pharmacology has been shown to be a natural ligand of the growth hormone secretagouge (GHS) receptor.

Structure of Ghrelin




It is a peptide hormone of 28 amino acids possessing an unusual octanoyl goup on the serin in position 3, which is crucial for its GHS activity. This peptide is produced predominantly by the stomach, whereas lower amounts are derived from the hypothalamus, pancreatic cells, kidney and placenta in humans. During the fetal life

after the stomach, the main source of ghrelin the neuroendocrine cells of lung and the pancreas B cells. Although in the beginning it was widely accepted that unacylated ghrelin was devoid of any biological activity , recently is considered as a peptide with wide range actions in different tissues. The best investigated ghrelin receptor, GHS-R1, has two variants, GHS-R1a and GHS-R1b, which result from alternative splicing of the same gene. GHS-R1a is expressed highly in the hypothalamus and pituitary and the octanoylation is essential for binding to it.

The octanoylated ghrelin has the GH-releasing effect and control of apetite, food intake and energy balance. The GHS-R1a and GHS-R1b and ghrelin are present in human endocrine pancreas suggesting that ghrelin may play a role in the glucose metabolism. Depending on the experimental conditions, ghrelin is reported to either inhibit or stimulate insulin secretion in humans. Ghrelin has both orexigenic and adipogenic effects and there is a negative correlation between total ghrelin and body mass index, insulin and leptin in lean and obese humans.

Ghrelin was detected in human placental tissue in 2001, and the receptor type GHS-R1b binding unacylated ghrelin was observed in placental and endometrial tissue. The presence of significant ghrelin concentrations in human cord blood has been shown but information about the ghrelin secretion during fetal life is scarce.

The source of ghrelin on cord plasma is unknown: it may have originated from the maternal compartment, may be secreted by the placenta or may come directly from the fetal tissues. Concentration of total ghrelin in cord blood of small-for-gestational age infants were significantly greater than in appropriate-for-gestational age at different times of gestation. The „catch-up growth" of infants is known, but the physiological mechanism behind it is unknown.

The possible role of ghrelin during pregnancy was examined in rat fetal development. The administration of acyl-ghrelin to female pregnant rats indicated that maternal acyl-ghrelin can easily transit to the fetal circulation. The prolonged maternal treatment with acyl-ghrelin during pregnancy significantly increased the average neonatal body weight at birth in comparisone to that of neonates delivered by saline-treated group. No signficant changes were observed after treatment with des-acyl ghrelin. When pregnant females treated with acyl-ghrelin consumed the same amount of food as saline-treated pregnant females, neonatal body weight was significantly greater in the ghrelin-treated group.

The multiple activities of ghrelin also include stimulatory effects on the corticotropic system, as systemic administration of ghrelin induces an increase in ACTH and cortisol levels in healthy subjets and shows a remarkable hyper-responsiveness of ACTH and cortisol secretion in patients with active Cushing's syndrome. It is known that the hypercortisolism in humans decreases total ghrelin levels in plasma and that serum cortisol exhibits a negative correlation with total ghrelin. The physiological mechanisms behind this relationship are not known, but the glucocorticoids that are used in antenatal therapeutic settings may have an effect on ghrelin secretion.

## 3. Objectives

The point of the present study was to compare acylated and total ghrelin concentration in premature infants and their mothers and to investigate the possible relationship between ghrelin and anthropometric and hormonal parameters, such as leptin, insulin, GH and cortisol.

## 4. Patients and methods

### 4.1 Patients

The 26 preterm infants (gestational age 25-35 weeks) and their mothers were involved in the study. Three women with twin pregnancies were included into the protocol together with their newborns. Mothers with pre-eclampsia, hypertension, or diabetes were excluded. Cesarean section was used for eight mothers.

The infants who were appropriate for gestational age participated in this study. It was defined as birth weight from -1.5 to + 1.5 S.D. of the mean birth weight in each gestational age according to current Hungarian standard. All mothers received betamethasone for the prevention of respiratory distress syndrome. The time interval between the steroid injection and the birth varied from 10h to 7 days.

### 4.2 Laboratory methods

Immediately after delivery, a venous cord blood sample was collected from newborns and also from mothers. The tubes containing EDTA with aprotinin were kept at 4°C before centrifugation and were centrifuged within 1h. The plasma samples were stored at -70°C. Acylated and total ghrelin, and leptin were measured with commercially available RIA kit (Linco Research Inc.USA). Cortisol, insulin and GH were assayed with RIA and IRMA kit (Isotope Ins.Hungary). Glucose was measured by glucose hexokinase method ( Merck ).

### 4.3 Statistical methods

Comparative analyses between maternal and fetal data were calculated by Mann-Whitney test. The correlations were analyzed by Spearman's correlation test. The Multiple Regression Model was created using stepwise method to verify the influence of different variables on fetal and maternal ghrelin levels. All statistical analysis were performed with SPSS 11.5 software, $p\langle 0.05$ was considered statistically significant.

## 5. Results

### 5.1 Anthropometric data and hormonal parameters

No signficant correlation was observed between anthropometric parameters (sex, mode of birth, gestational age, birth weight) and maternal and fetal hormonal parameters (acylated ghrelin, total ghrelin, cortisol, insulin, leptin). There was a significant correlation (Table 1) between placental weight and acylated ghrelin levels of neonates ($r=0.396$, $p=0.045$) and between placental weight and GH levels of neonates ($r=0.483$, $p=0.008$).

**Table 1** Spearman's correlation coefficient between the various studied hormones, glucose and anthropometric data in the fetus ∗ p⟨0.05

| | Acylated ghrelin | Total ghrelin | Cortisol | Insulin | Glucose | Leptin | GH |
|---|---|---|---|---|---|---|---|
| Gestational age | 0.266 p=0.190 | -0.221 p=0.268 | 0.480 p=0.010* | 0.131 p=0.498 | 0.005 p=0.980 | 0.362 P=0.075 | -0.195 p=0.310 |
| Birth weight | 0.038 p= 0.855 | -0.104 p=0.604 | 0.422 p= 0.025 | 0.247 p=0.196 | 0.008 p=0.968 | 0.334 p=0.103 | -0.304 p=0.109 |
| Placental weight | 0.396 **p=0.045*** | 0.158 p=0.431 | 0.149 p= 0.448 | 0.171 p=0.375 | -0.161 p=0.422 | 0.085 p=0.685 | 0.483 **p=0.008*** |
| Acyl-ghrelin | 1.00 | 0.050 p=0.812 | 0.547 **p=0.005*** | 0.004 p=0.984 | 0.213 p=0.306 | 0.076 p=0.737 | -0.009 p = 0.966 |
| Total Ghrelin | | 1.00 | 0.260 p = 0.200 | 0.039 p=0.846 | 0.154 p=0.453 | -0.243 p=0.264 | -0.234 p = 0.239 |
| Cortisol | | | 1.00 | -0.040 p=0.841 | 0.254 p=0.201 | -0.029 p=0.890 | 0.035 p = 0.861 |
| Insulin | | | | 1.00 | 0.509 **p=0.007*** | 0.184 p=0.379 | -0.367 **p=0.050*** |
| Glucose | | | | | 1.00 | -0.083 p=0.700 | -0.031 p=0.878 |
| Leptin | | | | | | 1.00 | -0.267 p=0.197 |
| GH | | | | | | | 1.00 |

## 5.2 Maternal and fetal hormonal parameters

The acylated and total ghrelin were detectable in all samples. Table 2 shows the maternal and fetal concentrations of ghrelin, cortisol, insulin, glucose, leptin and GH.

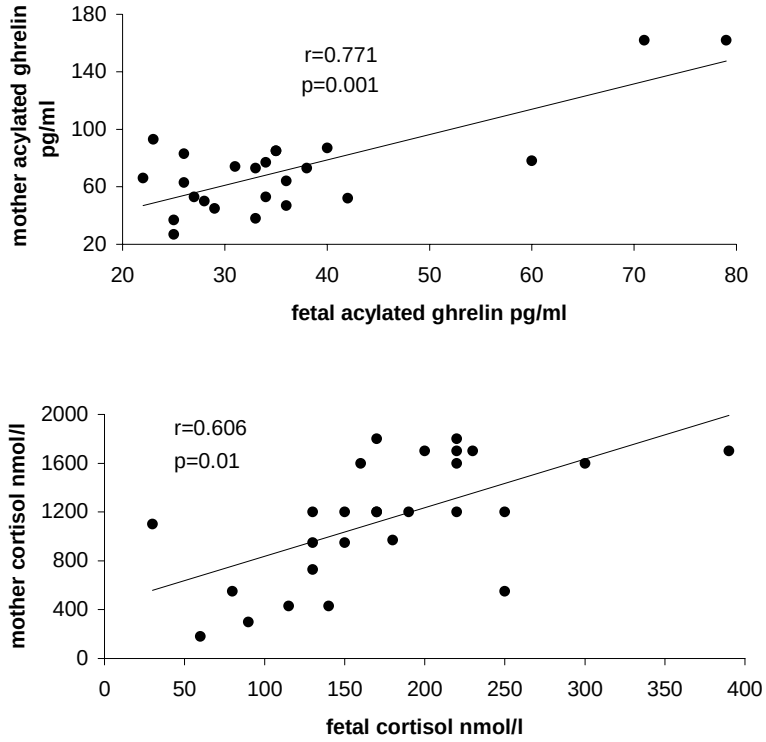
**Table 2** Maternal and fetal concentrations of ghrelin, cortisol, Insulin, glucose, leptin and GH

| | Maternal (n=23) | Fetal (n=26) |
|---|---|---|
| Acyl-ghrelin(pg/ml) | 73.1±33.1 | 36.5±14.6* |
| Total ghrelin(pg/ml) | 295.9±41.3 | 611.9±183.2* |
| Cortisol(nmol/l) | 1082.6±528.8 | 174.1±74.6* |
| Insulin(mU/l) | 44.2±43.5 | 15.4±15.6* |
| Glucose(mmol/l) | 7.4±2.3 | 5.6±1.2* |
| Leptin(ng/ml) | 28.9±13.3 | 0.86±0.76* |
| GH(μg/l) | 2.6±3.8 | 60.2±33.2* |

All data are presented as means±S.D.; n=number of cases, ∗p⟨0.01 versus mother with Mann-Whitney test

The mean level of acylated ghrelin concentration was higher in the maternal vein than in the cord vein (73.1 ± 33.1 vs 36.5 ± 14.6 pg/ml, p⟨0.01). Overall, there was a significant correlation (Fig.3) between the fetal and maternal acylated ghrelin levels (r=0.771, p⟨0.001). The total ghrelin concentration was higher in the neonates, than in the mothers (611.9 ± 183.2 vs 295.9 ± 41.3 pg/ml, p⟨0.01), but no significant correlation between the fetal and maternal total ghrelin levels was found.

**Figure 3** Correlation between paired maternal and fetal plasma acylated ghrelin and cortisol concentrations




## 5.3 Correlations among the various hormonal parameters

The bivariate correlations of cord vein hormones (Table1) show a significant correlations between the cord vein acylated ghrelin and cord vein cortisol levels (r= 0.547, p⟨0.005). Total and acylated ghrelin levels in the cord vein were unrelated to other studied hormones in the fetuses.

The bivariate correlations of mother vein hormones (Table 3) show a negative correlation between the total ghrelin and glucose (r = - 0.577, p ⟨ 0.003) and between the

total ghrelin and insulin (r = -510, p ⟨ 0.008 ). Acylated ghrelin levels in the mothers were unrelated to the studied hormones.

**Table 3** Spearman's correlation coefficient between the various studied hormones and glucose in the mothers ∗p⟨0.05

| | Acylated ghrelin | Total ghrelin | Cortisol | Insulin | Glucose | Leptin | GH |
|---|---|---|---|---|---|---|---|
| Acylated Ghrelin | 1.00 | -0.290 p=0.169 | -0.019 p=0.930 | 0.165 p=0.452 | 0.101 p=0.656 | -0.175 p=0.425 | -0.066 p=0.759 |
| Total Ghrelin | | 1.00 | 0.096 p=0.641 | -0.510 **p=0.008*** | -0.577 **p=0.003*** | 0.215 p=0.291 | 0.131 p=0.516 |
| Cortisol | | | 1.00 | 0.035 p=0.865 | 0.229 p=0.271 | -0.396 **p=0.041*** | 0.027 p=0.893 |
| Insulin | | | | 1.00 | 0.772 **p=0.0001*** | 0.047 p=0.820 | 0.087 p=0.665 |
| Glucose | | | | | 1.00 | -0.020 p=0.924 | 0.005 p=0.981 |
| Leptin | | | | | | 1.00 | -0.121 p=0.547 |
| GH | | | | | | | 1.00 |

The Figure 3 shows the significant univariate correlations between mothers and their fetuses in the case of acylated ghrelin (r=0.771, p⟨0.001) and the cortisol levels (r=0.606, p⟨0.01). The correlation between maternal and fetal cortisol concentrations remained significant after correction for the number of hours since the last injection of betamethasone.

### 5.4 Multivariate regression analysis

The Multiple Regression Model was created by use stepwise method, starting from all variables with a significant univariate correlation with any of the indices. Before the stepwise regression we examined with Spearman's correlation the relationship the fetal and maternal hormones and glucose (Table 4).

**Table 4** Spearman's correlation coefficient between mothers and fetuses ∗ p ⟨ 0.05

| Maternal<br>Fetal | Acyl-ghrelin | Total ghrelin | Cortisol | Insulin | Glucose | Leptin | GH |
|---|---|---|---|---|---|---|---|
| Acyl-ghrelin | 0.771<br>**p=0.001*** | -0.176<br>p=0.390 | 0.368<br>p=0.070 | 0.156<br>p=0.457 | 0.296<br>p=0.151 | 0.191<br>p=0.360 | 0.084<br>p=0.683 |
| Total ghrelin | -0.342<br>p=0.101 | 0.187<br>p=0.350 | 0.363<br>p=0.069 | 0.155<br>p=0.450 | 0.132<br>p=0.520 | -0.143<br>p=0.486 | 0.036<br>p=0.859 |
| Cortisol | 0.061<br>p=0.770 | -0.186<br>p=0.342 | 0.606<br>**p=0.01*** | -0.095<br>p=0.637 | 0.369<br>p=0.053 | -0.230<br>p=0.238 | -0.082<br>p=0.679 |
| Insulin | 0.144<br>p=0.482 | -0.296<br>p=0.120 | 0.020<br>p=0.921 | 0.279<br>p=0.151 | 0.390<br>**p=0.040*** | 0.140<br>p=0.476 | -0.178<br>p=0.356 |
| Glucose | 0.023<br>p=0.915 | -0.431<br>**p=0.025*** | -0.029<br>p=0.887 | 0.141<br>p=0.493 | 0.618<br>**p=0.001*** | 0.306<br>p=0.121 | 0.186<br>p=0.353 |
| Leptin | 0.119<br>p=0.599 | 0.068<br>p=0.748 | -0.233<br>p=0.263 | -0.244<br>p=0.251 | -0.180<br>p=0.390 | 0.325<br>p=0.134 | -0.178<br>p=0.356 |
| GH | 0.067<br>p=0.743 | 0.078<br>p=0.687 | -0.159<br>p=0.420 | -0.143<br>p=0.469 | -0.132<br>p=0.504 | 0.070<br>p=0.722 | 0.283<br>p=0.137 |

The summary of the stepwise multivariate regression analysis for fetal acylated ghrelin and maternal total ghrelin as dependent variables and the placental weight, maternal acylated ghrelin, fetal cortisol and the maternal glucose, maternal insulin, fetal glucose as independent variables is presented in Table 5.

**Table 5** Multiple regression model with indices of fetal acylated and maternal total ghrelin as dependent variables β denotes the regression slope *p⟨0.05

| | Fetal acylated ghrelin | Maternal total ghrelin |
|---|---|---|
| | $R^2$=0.639 | $R^2$=0.184 |
| Maternal acylated ghrelin | β=0.733, p=0.0001 | |
| Maternal cortisol | β=0.286, p=0.038 | |
| Maternal glucose | | β=-0.467, p=0.019 |

The adjusted $R^2$ was 0.639 in the case of fetal acylated ghrelin with maternal acylated ghrelin (β=0.733, p=0.0001) and with the fetal cortisol (β=0.286, p=0.038), the variables have statistically significant correlations with the fetal acylated ghrelin. The adjusted $R^2$ was 0.184 in the case of maternal total ghrelin with maternal glucose (β=-0.467, p = 0.019), the only variable with statistically significant correlation with maternal total ghrelin. There was no independent predictor when the maternal acyl ghrelin or fetal total ghrelin were used as dependent variables.

## 6. Summary of the results and conclusions

Ghrelin was discovered as a hormone related to GH secretion. With advancing gestational age, the placental production of GH is elevated. We found correlation between placental weight and GH levels of neonates. Data available are not consistent: association among circulating total ghrelin and the GH have been reported by some but not by others. It is generally assumed that the GH-releasing activity of ghrelin is dependent on its acylation in serine3. We have not found correlatins between acylated or total ghrelin and GH concentration, which support the hypothesis that ghrelin is not contributing to the high GH concentrations observed during gestation.

However, there was a significant correlation between acylated ghrelin levels of neonates and the placental weight. It is contradictory with Yokota et al, however they examined full-term newborns who were not only of the group of adequate-for-gestational age. It is known, that the ghrelin levels of small-for-gestational age are greater than those of appropriate-for-gestational age infants. Further investigation is need to show the possible relationship between the placenta and the acylation process of ghrelin.

Similarly to others, we didn'n found correlation between maternal and newborn total ghrelin, but we found significant correlation between the fetal and maternal acylated ghrelin levels. It is possible that acylated ghrelin could cross the placenta in human as suggested by Nakahara in rat. The hypothesis that the placenta may play a role in the acylation process is supported in part by the relationship between fetal acylated ghrelin concentration and the placental weight.

In addition to its GH-relasing properties, ghrelin appears to be related to regulation of apetite and glucose metabolism. It is known that ghrelin secretion is increased by fasting and decreased by food intake, glucose and insulin in adults, and there is a negative association between ghrelin and insulin secretion. We also found a negative correlation between total ghrelin and glucose, as well as between total ghrelin and insulin concentrations in the mother's blood only. Farquhar et al. found a similar relationship between cord plasma ghrelin and glucose concentrations. However, in our experiment, the mothers with known gestational diabetes were excluded, in contrast to referred authors, where the prevalence of maternal diabetes was considerable.

Leptin is detectable in cord blood from early in the second trimester and circulating levels of cord blood leptin are positively correlated with birth weight and cord plasma

insulin levels in full-term newborns. These results seem to be inconsistent with our findings, because we have not found any correlation with cord blood leptin. The discrepancy may be explained by gestational age, because more than 98% of leptin secreted by placenta goes to the maternal side, presumably the fetal leptin is being produced by fetal adipose or other tissues. The number of studies have shown that there is a sexual dimorphism in plasma leptin concentrations during the later period of life. During the examination period, the concentration of leptin in the cord blood was very low, and we did not see significant differences between male and female infants.

The multiple regression model shows a relationship between the fetal cortisol and fetal acylated ghrelin concentration. We have measured the maternal and fetal plasma cortisol levels in parallel and the results were consistent with others: the maternal plasma cortisol levels were ten times higher than fetal plasma cortisol and there was a significant linear correlation between them. The limitation of our study is the fact that all mothers received betamethasone. The prenatal betamethasone administration to mothers has been shown to result in similar betamethasone concentrations in maternal and fetal serum. It is known that prenatal maternal betamethasone therapy suppresses the cortisol levels within 1 week of betamethasone treatment, as long as the synthetic glucocorticoid remains in circulation. It is known that synthetic glucocorticoids have genomic potencies several times that of cortisol, this support the hypothesis that there is no close relationship between the efficiency of non-genomic and classical genomic responses of different glucocorticoids. Our results show a positive correlation between fetal cortisol and acylated ghrelin, this suggests the possibility that the cortisol may be involved in the acylation process of ghrelin through a non-genomic action.

Several new findings are reported in the present study. These data provide first evidence that in premature newborns umbilical cord acylated ghrelin concentrations are lower that in maternal blood, and the fetal acylated ghrelin correlate with maternal acylated ghrelin and the fetal cortisol. The physiological role of ghrelin during pregnancy remains to be clarified, buti t may be related to the degree of acylation. The correlation of the fetal acylated ghrelin with the placental weight supports the hypothesis that the placenta may play a role in the acylation process and may be partly affected by cortisol.

## List of publication

The thesis is based in the following publications:

1. Szabó I, Vértes M, Bódis J, **Lányi É**, Sauerhering E: Steroid receptors in human fetal lung Lancet 1980 2 751 IF:9.44

2. Szabó I, **Lányi É**, Vértes M: Human magzati tüdő glükokortikoid receptorai Magyar Nőorvosok Lapja 1986 49 16

3. Szabó I, **Lányi É**, Vértes M, Drozgyik I, Csaba I.: Glucocorticoid receptors in human fetal lung. Problems of the fetal lung maturation and of insufficient lung maturity in the newborn (Ed.: I. Cretti) Vol. I. 170-187 1988

4. Szabó I, **Lányi É,** Szilágyi A, Vértes M, Csaba I: Glucocorticoid receptors in human fetal lung. Gynecology and Endocrinology 1990 4 Suppl.1. 113 IF: 0.43

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6. **Lányi É**, Csernus K, Erhardt É, Tóth K, Urbán B, Lénárd L, Molnár D: Plasma levels of acylated ghrelin during an oral tolerance test in obese children. Journal of Endocrinological Investigation 2007 30(2) 133-137 IF:1.47

7**. Lányi É,** Várnagy Á, Kovács A.K, Cermely T, Szász M, Szabó I: Ghrelin and acyl ghrelin in preterm infants and maternal blood : relationship with endocrine and anthropometric measures. European Journal of Endocrinology 2008 158(1) 27-33 IF:3.14

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1.Szabó I, **Lányi É**, Vértes M, Csaba I: Glucocoricoid and estradiol receptors in human fetal lung. XI. European Congress of Perinatal Medicine Roma 1988

2. Szabó I, **Lányi É**, Vértes M, Drozgyik I, Csaba I : Glucocorticoid And estradiol receptors in human fetal lung. „Problems of the fetal lung maturation and of insufficient lung maturity in the newborn" Symposium Szczecin 1988

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**Cummulative impact factor: 17,7**

Other publications:

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2**. Lányi É**, Székely J, Vértes M: The effect of $PGF_{2alfa}$ treatment on the endometrial oestradiol receptor system. Prostaglandins Leukotrienes and Essential Fatty Acids 1988 31 27-30 $IF_{1988}$:1.10

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7**. Lányi É:** Extended Spectrum Beta-laktamáz (ESBL) termelő Klebsiella izolátumok jelentősége. Gyermekgyógyászat 2005 56 457-460

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