Evaluation of Circulating Acylated-ghrelin, Leptin, Growth Hormone, IGF-1, IGFBP-1, IGFBP-3 and their Correlation Among Healthy Pregnant Subjects

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Abstract

Propose:
Maternal diabetes, nausea, changes in appetite, blood pressure alteration, anxiety, complication of fetus growth and many other obstacles that happen during pregnancy are related to the changes of circulating hormones. To illuminate the reasons for some of these problems, present work was designed.

Method:
Seventy-seven healthy women aged 22-30 years (Pregnant, n=43, gestational age between 14-18 weeks and 34 matched non-pregnant) participated in this study, according to inclusion criteria. Circulating level of fasting acylated ghrelin, leptin, growth hormone (GH), insulin-like growth factor 1(IGF-1) and its carrier proteins (IGF1BP-1 and IGF1BP-3) were evaluated for all participant, while α-fetoprotein, β-HCG and unconjugated estriol were measured for pregnant subjects, using immunoassay methods.

Results:
Evaluated data shows neither acylated ghrelin nor GH of pregnant group differ from nongravid subjects, whereas their circulating levels of total IGF-1, IGF1BP-1, IGF1BP-3 and leptin increased (P<0.001). Additionally, there were significant (P<0.01) correlations between leptin and BMI (r= 0.46), IGFBP-3 (r= 0.52) or IGFBP-1 (r= -0.34), among pregnant subjects. Significant correlations (P<0.01) were also detected between their α-fetoprotein and IGFBP-1 (r= 0.30) or between IGFBP-1 and IGFBP-3 (r= -0.39).

Conclusion:
Unchanged ghrelin may confirm earlier report that showed increase of ghrelin is the cause of maternal diabetes, while increases of IGF-1 IGF1BP-1, IGF1BP-3 and leptin are necessary to meet the demand of fetus growth. In conclusion, in this study for the first time, we showed many unlooked correlations between different parameters that have role in healthy pregnancy and disturbance of their harmony could be the cause of pregnancy complication or fetal growth that desires further investigation.

Introduction

Pregnancy is one of most important incident in a female life that associates with many psychological and physiological events. Ample of researches have been carried out to determine the reasons for these changes. Although pervious researches have rationalize the reasons for many of these incident, still there are many questions to be answer, especially regarding maternal diabetes mellitus, nausea, changes in appetite, alteration in blood pressure, anxiety, complication about growth of fetus and many other obstacle that happen during pregnancy. Almost all of the complications of pregnancy are related to the changes in the circulating hormones, which are the most important physiological event that occur during this period. Beside alteration in the circulating level of reproductive hormones, leptin, ghrelin and associated hormones such as growth hormone (GH), insulin like growth factors (IGFs), and IGF binding proteins (IGFBPs) are important factors that influence the metabolic of carbohydrate and lipids and consequence in the alteration in appetite, growth of fetus and increase in the body weight of mother (Laursen, Overgaard et al. 2001; Skjaerbaek, Frystyk et al. 2004; Fuglsang, Skjaerbaek et al. 2005).

Active ghrelin (acylated ghrelin) is an endogenous ligand of GH secretagogue receptor and emerged as a pleiotropic modulator of diverse biological functions, including energy homeostasis and role in the reproduction (Fuglsang, Skjaerbaek et al. 2005; Garcia, Lopez et al. 2007; Moshtaghi-Kashanian and Razavi 2009). Only few study looked at circulating level of ghrelin in pregnancy and interesting results were reported (Fuglsang, Skjaerbaek et al. 2005; Palik, Baranyi et al. 2007; Tham, Liu et al. 2009). The only group who study the relationship of GH with ghrelin during pregnancy were Fuglsang and coworkers (Fuglsang, Skjaerbaek et al. 2005) that reported absence of any correlation between these hormones. Leptin, which was identified originally as an
adipocyte-derived protein, was regarded for years as an exclusive regulator of satiety and energy homeostasis (Hauguel-de Mouzon, Lepercq et al. 2006).

A role for leptin in reproductive and pregnancy was later suggested by the findings that plasma levels of leptin during gestation are greater than in nongravid individuals or leptin is synthesized within the feto-placental unit (Hauguel-de Mouzon, Lepercq et al. 2006; Henson and Castracane 2006; Moshtaghi-Kashanian and Razavi 2009). Although leptin has an opposite effect with the action of ghrelin and its increase levels have been reported during pregnancy (Johnstone and Higuchi 2001; Atawi, Warsy et al. 2004; Ittikhar, Khoja et al. 2008), its correlation with ghrelin have not been reported.

In addition, the main mediator of the actions of GH are insulin-like growth factors (IGFs) that constitute a system of peptides that promote mitosis, growth, and organ development by both paracrine and endocrine pathways (Bach, Headey et al. 2005). Under normal circumstances, less than 1% of IGF-1 circulates in the free form and is degraded within a few minutes (Bach, Headey et al. 2005; Lauszus 2007). So that the bioavailability of IGFs in the circulation is modulated by at least six specific IGF-binding proteins (IGFBPs) (Lauszus 2007) and these binding proteins are the main regulator of bioavailable IGFs in the circulation (Ezzat, Duncan et al. 2008). It was shown that IGF-1 and its binding proteins especially binding protein-1 have role in development of diabetes mellitus (Bach, Headey et al. 2005; Ezzat, Duncan et al. 2008). While the majority of IGF-1 is bound to IGFBP-3 that is unable to cross the endothelium, IGFBP-1 is comparative small and has been propose to be the pivotal acute regulator of IGF-1 activity. Furthermore, IGFBP-1 is capable to cross the endothelium and is acutely modulating access of IGF to tissues and cell surface receptors (Ezzat, Duncan et al. 2008). Although IGF-1 and IGFBPs are the main mediator of the actions of GH, scatter researches look into their circulating levels during pregnancy and reported different conclusion depending to their experimental designs (Luthman, Bremme et al. 1991; Langford, Nicolaides et al. 1995; Martina, Kim et al. 1997; Laursen, Overgaard et al. 2001; Skjaeraabek, Frystyk et al. 2004; Qiu, Vadachkoria et al. 2005).

To find out the reasons for complications of pregnancy several researches have been carried out before, while to our knowledge there is not a single published work that considers the interrelation of ghrelin, leptin, GH, IGF-1 and IGFBPs, in healthy pregnant subjects. There should be a harmony between the circulating hormones and other related factors such as IGFBPs during a healthy pregnancy, before linking any complication to fluctuation of GH or related factors. Lack of any published work that illuminates the correlation between GH and related factors in healthy pregnancy made us to design this study to complete previous studies and investigate the potential role of these factors in the complications of pregnancy, especially gestational diabetes mellitus (GDM) and pre-gestational diabetes which are known to pose risks to the mother and developing fetus. For this propose, we evaluate the circulating levels of acylated ghrelin, leptin, GH, IGF-1, and circulating levels of IGFBP-1 and IGFBP-3 among young pregnant mothers and compare their data with age and height matched non-pregnant control group.

Methods

Forty-three young pregnant women (first or second pregnancy) aged between 22-30 years, who had an average height and their gestational age was between 14-18 weeks (table 1) participated in this study. According to the therapeutic gynecologist, the pregnancy was normal, and none of them had any complication during their pregnancy, or previous gastrointestinal surgery and all of them were singleton pregnancy. A triple test including a-fetoprotein, b-HCG, and unconjugated estriol was carried out for all of them to rule out Down syndrome and neural tube defects, using Alpha logical Medical Systems software (UK). A gynecologist as control group recruited 34 non-pregnant women who were in the same range of age and height. This group of participant had a regular menstrual cycle and did not use any medications during last six months. Other inclusion critical that applied to all the participants was a stable weight in the last 3 months, absence of hormonal treatment before, nonsmoker, normal lipid profile, fasting glucose and postprandial glucose (assessed by the laboratory examination before recruited in this study) by therapeutic gynecologist.

Five ml of fasting peripheral blood was collected from each applicant and divided in two tubes. Three ml of blood was collected in plane tube, using the serum for evaluation of hormones and IGFBP-1 and 3, while 2 ml was collected in the anticoagulant (EDTA) tube to use the plasma for measurement of acylated ghrelin. Plasma and sera were separated using routine protocol (an incubation
of 10 minutes in room temperature, and centrifuge at 800 g for 5 minutes). Separated sera and plasmas were kept in -20º C until the time of assessment.

Circulating levels of alpha-fetoprotein and titer of β-HCG were evaluated using automated electro-chemiluminescence method (Roche diagnostic Elecsys 2010 system, USA), while enzyme-linked immunoabsorbent assay (ELISA) was used to evaluate unconjugated estriol (Labor diagnostika nord GmbH & Co. KG, Germany). For evaluation of acylated ghrelin (BioVender Laboratory Medicine Inc., France), leptin (dbc Diagnostic Biochem Inc., Canada), GH (Monobind Inc. USA), IGF-1(Immunodiagnostic system Ltd. UK), IGFBP-1 (Medix Biochemica, Finland) and IGFBP-3 (Biosource, Belgium) we used ELISA kits and followed the protocols provided by the manufactures of kits.

Data were analyzed using SPSS (Version 16.0) PC program. Independent sample T-test was used for comparison of two groups, after checking for normal distribution of data. Determination of correlations was carried out using Pearson’s two-tailed bivariate model. P values less than 0.05 were considered as significant differences.

**Results**

Informative data of all participants are presented in table 1. Although height of pregnant subjects were matched with the control group, body weight and BMI of them were higher (<0.05) than non-pregnant subjects. None of pregnant subjects had any risk of Down syndrome or associated complication (neural tube defects or trisomy 18) , according to the calculated multiple of the median (MoM), analyzed for the values for the triple test (a-fetoprotein, β-HCG, and unconjugated estriol).

They also had a healthy fetus as asses by ultrasonography of nuchal scan (NT), biparietal diameter (BPD) and crown rump length (CRL).

Analysis of evaluated data obtained for the fasting acylated-ghrelin and GH showed pregnancy did not affect the circulating level of these hormones, while values obtained for leptin and IGF-1 were significantly higher among pregnant subjects (P<0.001). Furthermore, pregnant group had significantly (P<0.001) higher circulating IGFBP-1 and IGFBP-3 when their values were compared with the corresponding data obtained for the non-pregnant subjects (table 2).

Statistical analysis of data for the pregnant subjects showed there are positive and significant (P<0.01) correlations between their circulating leptin and BMI (r= 0.46) or leptin and IGFBP-3 (r= 0.52), while there was a negative association (P<0.05) between their leptin and IGFBP-1 (r= -0.34). In addition, positive correlations (P<0.05) were also detected between BMI and IGFBP-3 (r= 0.35), Α-fetoprotein and IGFBP-1 (r= 0.30) of pregnant subjects. Finally, a negative correlation (P<0.01) between IGFBP-1 and IGFBP-3 (r= -0.39) was also detected among pregnant subjects. Among non-pregnant subjects, only significant negative associations (P<0.05) were detected between ghrelin and IGFBP-3 (r= -0.39), or BMI and IGFBP-1 (r= -0.35).

**Discussion**

Our data shows neither acylated ghrelin nor GH of healthy pregnant subjects (gestational age 14-18 weeks) differ from non-pregnant women; whereas their circulating levels of total IGF-1 and its carrier proteins (IGFBP1 and IGFBP3) increases. Additionally, fasting level of leptin also increases among pregnant subjects that significantly correlated with their BMI.

Previously reported data showed an increase in the circulating level of total ghrelin among healthy pregnant subjects (Fuglsang, Skjaerbaek et al. 2005), while Palik and colleagues (Palik, Baranyi et al. 2007) reported a rise in acylated ghrelin during second trimester of gestational diabetic patients. Our data may compare with the recently published work of Tham and coworkers (Tham, Liu et al. 2009) that showed acylated ghrelin decreases during pregnancy, likely because of a decrease in the acylation process. This group also pointed out that desacyl ghrelin increases in gestational diabetic patients, possibly reflecting resistance to the inhibitory effect of insulin on ghrelin secretion (Tham, Liu et al. 2009). Ghrelin has been implicated in the regulation of a large array of endocrine and non-endocrine functions, such as GH secretion, food intake, energy balance, adiposity (Castaneda, Tong et al. 2010; Epelbaum, Bedjaoui et al. 2010; Kageyama, Takenoya et al. 2010), puberty (Mostaghli-Kashanian and Razavi 2009) and fetal development (during different stage of pregnancy) (Nakahara, Nakagawa et al. 2006). Since there are limited data (increase of total or acylated ghrelin reported to be one of the causes of gestational diabetes) it is too early to arbitrator maternal diabetes mellitus with a single ghrelin evaluation and further investigations are necessary to illuminated the role of ghrelin in gestational diabetes. While earlier works
showed a steady increase of GH during pregnancy (Czech, Jeske et al. 1979; Kletzky, Rossman et al. 1985; Zhou, Shi et al. 2001), recently published works indicated diminishes GH throughout pregnancy period (Luthman, Bremme et al. 1991; Fuglsang, Skjaerbaek et al. 2005) that support our data for GH. This discrepancy did arise from the earlier evaluating methods and cross reaction of human placental lactogen with pituitary GH (Luthman, Bremme et al. 1991).

Now it is well documented that during gestational period the placental lactogen that is produced by the syncytiotrophoblast and found predominantly in the maternal circulation, can progressively replaces pituitary GH in the maternal circulation from mid-gestation onwards, peaking towards term (Fuglsang, Skjaerbaek et al. 2005; Fuglsang 2008; McIntyre, Zeck et al. 2009). Furthermore, in normal circumstances, it is circulating level of GH that cause synthesis and release of IGF-1 (predominantly) by the liver. However during gestational period, the gradual increase of circulating placental lactogen that replace mother’s GH, could be the reason for increase in circulating IGF-1 and associated IGFBPs (Takeuchi, Morikawa et al. 1988; Wiesli, Zwimpfer et al. 2006). The increase in placental lactogen may be a cause for the reduction in acylated ghrelin, too. Finally, it is reported that placental lactogen is an important potential regulator of maternal insulin resistance in human pregnancy and the circulating level of it may influence fetal growth as well as modifying carbohydrate metabolism (McIntyre, Zeck et al. 2009). Our presented data regarding IGF-1 is fully supported by the previously reported data (Caufriez, Frankenne et al. 1990; Luthman, Bremme et al. 1991; Skjaerbaek, Frystyk et al. 2004; Wiesli, Zwimpfer et al. 2006; Lauszus 2007; Tennekoon, Pathmaperuma et al. 2007), while opposed by results of Zhou (Zhou, Shi et al. 2001) and coworkers who showed the circulating level of IGF-1 only increases during third trimester. Following increase in the total IGF-1, we also detected increases in both IGFBP-1 and IGFBP-3 that correlate with the earlier published work (Luthman, Bremme et al. 1991; Langford, Nicolaides et al. 1995; Skjaerbaek, Frystyk et al. 2004; Wiesli, Zwimpfer et al. 2006; Tennekoon, Pathmaperuma et al. 2007). It is obvious that during pregnancy, there is a rapid and progressive increase in both maternal and fetal tissue growth and increases in circulating IGFs and associated binding proteins should meet the demand for such growth stimulating factors. Moreover, biologically active form of IGF-1 is the free fraction of it, which comprises less than 1% of the total IGF-1 in the circulation and this fraction is thought to be controlled by rapid alterations in IGFBPs concentrations (Qiu, Vadachkoria et al. 2005). Circulating IGF-1 is probably the most potent anti-catabolic and anabolic hormone in humans and its long-term function may lie primarily in carbohydrate and lipid homeostasis (Qiu, Vadachkoria et al. 2005; Ezzat, Duncan et al. 2008). Since there is structural homology between IGF-1 and insulin, the reduction in circulating IGFBPs may influence insulin production such away to cause gestational diabetes. On the other side, IGFBPs are believed to have direct cellular actions modulating numerous processes including cell growth, differentiation and apoptosis (Ferry, Katz et al. 1999; Firth and Baxter 2002; Mohan and Baylink 2002), distinct from their roles as carrier proteins. For example, IGFBP-1 that has a greater affinity for IGF-1 than it does for its own receptor and modulate the action of IGFs, though it is an endocrine factor that acts in paracrine/autocrine fashion for fetal growth (Fowler, Nicolaides et al. 2000). Increase in the circulating IGFBP-1 inhibits the action of free IGF-1 and reduce the bioavailability IGFs to specific cell membrane receptors (Martina, Kim et al. 1997) so that it can prevent the development of gestational diabetes (Qiu, Vadachkoria et al. 2005). Our evaluated IGFBP-1 for healthy pregnant subjects (that was nearly five time of non-pregnant subject) may confirm the hypothesis of previously reported data (Qiu, Vadachkoria et al. 2005). Furthermore, the majority of circulating IGF-I is bound to IGFBP-3, a large protein forming a complex with IGFs, which is unable to cross the endothelium (Ezzat, Duncan et al. 2008).

This complex not only transporting IGFs, but maintains a circulating reservoir of IGFs and prolonging its half-life (Bhatti, Van Ham et al. 2006). The fact that IGFBP-3 has an inhibitory action on IGF-I bioavailability, brought about a suggestion that increase in IGFBP-3 proteolysis observed during the development of diabetes may in fact represent a compensatory mechanism in an attempt to raise circulating level of IGF-I (Ezzat, Duncan et al. 2008). This hypothesis could support by our data of IGFBP-3 that did rise in healthy pregnant subjects, so that it may prevent gestational diabetes by its rising during pregnancy period.

Similar to previous reported data (Sattar, Greer et al. 1998; Schubring, Englaro et al. 1998; Anim-Nyame, Sooranna et al. 2000; Al-Atawi, Addar et al. 2004; Atawi, Warsy et al. 2004), we also detected an increase in the circulating level of leptin among pregnant subjects. It was reported that serum leptin concentration increases in the first trimester and elevated throughout human pregnancy.
(Hauguel-de Mouzon, Lepercq et al. 2006). Though leptin has direct role in the reproduction (Moshtaghi-Kashanian and Razavi 2009), the increases in the first trimester is before any perceptible rise in body weight, imply that factors other than increased adiposity modulate leptin levels (Henson and Castracane 2006). Furthermore, part of this rise could be the leptin that is produced by the fetal adipose tissue (Yura, Sagawa et al. 1998; Lepercq, Catalano et al. 2007).

Like in non-pregnant women, we shown that leptin levels are significantly correlated to body weight and BMI, while pervious published work reported that its rise correlated to blood pressure too (Buhling, Harder et al. 2005). In addition, in this study for the first time we show that there are positive correlation between circulating leptin and IGFBP-3 and negative association with IGFBP-1. The relationship between leptin and BMI, synthesis and release of IGFBPs, or diastolic blood pressure clearly indicate circulating leptin level or body weight of pregnant subject (BMI) has important role during gestational period. Moreover, the primary function of leptin is to reduce body weight by decreasing the metabolic of carbohydrate or increases the catabolism of lipids, and reduction of appetite (Henson and Castracane 2006). By considering the correlation of leptin and IGFBPs and its role it in regulation of BMI or blood pressure and appetite, measurement of circulating level of leptin may serve as a marker for detecting and monitoring pregnancy complications, including maternal diabetes mellitus, nausea, changes in appetite and hyperphagia.

It is well document that over-rise of circulating a-fetoprotein during pregnancy is a predictor of neural tube defects. Here for the first time we showed positive correlation between a-fetoprotein (that its serum level raises during pregnancy) and IGFBP-1 or negative correlation between circulating levels of IGFBP-1 and IGFBP-3 among healthy pregnant subjects. Since our data is the first report that shows such correlation among healthy pregnant subject, it is too early to achieve a conclusion, but we may suggest that the disturbances of these correlations may be the cause may complications of pregnancy such as Down syndrome and neural tube defects.

Conclusion(s)

In conclusion, in this study for the first time we showed many unlooked correlations between circulating IGFBPs and leptin, or a-fetoprotein and IGFBPs, although our data was limited. These data clearly indicates there should be a harmony in circulating levels of leptin, ghrelin, GH, IGFs, IGFBPs, a-fetoprotein, HCG and steroid hormones, during a healthy pregnancy period and disturbance of this harmony could be the cause of pregnancy complications and fetal growth.

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References


Illustrations

Illustration 1

Table 1: Informative data of participants; Young healthy pregnant women (n=43) that had their first or second pregnancy, and 34 matched age and height Non-pregnant were recruited according to inclusion criteria. Values in brackets represent standard deviation of means.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pregnant Mean (SD)</th>
<th>Non-pregnant Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>26.02 (2.38)</td>
<td>25.41(2.41)</td>
<td>0.27</td>
</tr>
<tr>
<td>Height (meter)</td>
<td>1.63(0.08)</td>
<td>1.64(0.04)</td>
<td>0.53</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.42(12.79)</td>
<td>59.62(6.13)</td>
<td>0.017</td>
</tr>
<tr>
<td>BMI (Kg/M^2)</td>
<td>24.54(4.62)</td>
<td>22.21(2.83)</td>
<td>0.012</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>16.28 (1.48)</td>
<td>None</td>
<td>N</td>
</tr>
<tr>
<td>β-HCG (IU/L)</td>
<td>28576(16704)</td>
<td>Not-determin</td>
<td>N</td>
</tr>
<tr>
<td>AFP (IU/ml)</td>
<td>33.91(16.95)</td>
<td>Not-determin</td>
<td>N</td>
</tr>
<tr>
<td>Free-E3 (ng/ml)</td>
<td>3.10 (1.55)</td>
<td>Not-determin</td>
<td>N</td>
</tr>
</tbody>
</table>
Illustration 2

Table 2: Evaluated parameters for pregnant subjects (n=43) and age and height matched non-pregnant control group. Values in brackets represent standard deviation of means.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Case</th>
<th>Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin (pg/ml)</td>
<td>Pregnant</td>
<td>43.73 (10.87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>44.74 (4.44)</td>
<td>0.62</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>Pregnant</td>
<td>65.18 (26.73)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>17.28 (6.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GH (mIU/ml)</td>
<td>Pregnant</td>
<td>1.83 (2.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>1.76 (1.61)</td>
<td>0.87</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>Pregnant</td>
<td>228.03 (73.42)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>130.84 (18.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGFBP-1 (ng/ml)</td>
<td>Pregnant</td>
<td>138.38 (53.49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>24.65 (21.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>Pregnant</td>
<td>4797.44 (586.74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pregnant</td>
<td>4068.82(422.12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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