Understanding the Effects of Fetuin-A in Pregnancy

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Human fetuin-A has emerged as a provocative molecule which actions in pregnancy have become the subject of research especially since the last decade. Also known as alpha-2 Heremans-Schmid glycoprotein, fetuin-A is a circulating glycoprotein produced in increased amounts during fetal life by various tissues. Similar fetuin-A concentrations in maternal serum and umbilical cord suggest passive placental transfer of fetuin-A during pregnancy [1]. The concentration of fetuin-A in plasma decreases soon after delivery [2]. In the adult life, it is actively secreted into the blood stream mainly by the liver [3]. Research investigating the effects of fetuin-A in pregnancy has emerged after the following concepts:

- Fetuin-A is a natural regulator of insulin action due to its inhibitory effect on insulin receptor tyrosine kinase activity and autophosphorylation [4,5].
- The gene encoding human fetuin-A resides on the 3q27 region of chromosome 3 which is a susceptibility locus for impaired glucose tolerance, diabetes mellitus, and metabolic syndrome [6-8]. This genetic association has been observed in clinical medicine [9].

Because fetuin-A is a natural inhibitor of insulin receptor activity, several investigators have studied the association of fetuin-A with insulin resistance during pregnancy with conflicting results. In a recent small case-control study, researchers from Austria investigated the role of acute glucose ingestion during standard oral glucose tolerance test on serum fetuin-A levels obtained early in the third trimester in women with gestational diabetes mellitus (GDM) (n=10) and normal controls (n=10) [10]. Fetuin-A correlated only with body mass index but neither showed significant association with insulin sensitivity or insulin and C-peptide levels nor was influenced by glucose tolerance during or after pregnancy. In another case-control study from Hungary involving more subjects (pregnant women with GDM, n=30; normal healthy pregnant, n=104; and non-pregnant controls, n=104), Kalabay and colleagues assessed maternal serum levels of fetuin-A and correlated these levels with indirect parameters of maternal insulin resistance (fasting C peptide and C-peptide/fasting glucose ratio) [11]. They noted that serum levels of fetuin-A were higher in women with GDM and correlated with indirect parameters of insulin resistance.

The genetic association of fetuin-A with metabolic syndrome has been correlated clinically in non pregnant adults [6,12]. Women who present with preeclampsia are at risk of developing metabolic syndrome later in their life [13,14]. Initial attempts to associate fetuin-A with preeclampsia were reported by Shinagawa and Saiotk who found that fetuin-A was more prevalent among urine of women who developed preeclampsia [15]; this association persisted after delivery. Park and colleagues compared maternal serum proteome in women who developed severe preeclampsia (n=8) with normal pregnancies (n=5) [16]; among candidate target proteins, fetuin-A was noted to be elevated in severe preeclampsia cases. Johnstone and collaborators determined the protein expression in highly purified invasive trophoblasts obtained from term placentas of women with preeclampsia (n=5) and controls (n=5) [17]; they found significant increased expression of fetuin-A in trophoblasts from preeclamptic placentas. However, dissimilar results have been published by the group of Molvarec and colleagues [18]: they reported significantly lower levels of fetuin-A in the third trimester in women who developed severe preeclampsia with (n=10) and without (n=20) hemolysis-elevated liver enzymes-low platelets (HELLP) when compared to normotensive controls (n=20). In a subsequent study by the same group [19], women with preeclampsia without HELLP (n=93) presented with significantly lower concentrations of fetuin-A in the third trimester when compared to normotensive controls (n=127). The investigators attributed these findings in correlation to the systemic inflammation that is present in preeclampsia (fetuin-A as a negative inflammatory mediator).

Decreased endovascular trophoblast migration is a common pathologic feature in preeclampsia [20,21]. Recently, our group hypothesized that, analogous to its action on the insulin receptor, fetuin-A inhibits the receptor tyrosine kinase activity of trophoblast growth factors, and as a consequence impairs trophoblast growth and invasion potentially leading to adverse pregnancy outcomes [22]. By treating human primary extravillous trophoblasts with increasing concentrations of fetuin-A, we noted that trophoblast invasion was significantly decreased. Moreover, enhanced invasiveness of extravillous trophoblasts resulting from the addition of various trophoblast growth factors was reversed by elevated concentrations of fetuin-A especially in cells treated with insulin growth factor (IGF)-1 and placental growth factor (PIGF). Exposure to increased concentrations of fetuin-A correlated with a lower expression of tyrosine kinase...
downstream signaling intermediates suggesting that fetuin-A impairs trophoblast cell invasion by inhibiting receptor tyrosine kinase activity of placental growth factors. Interestingly our in vitro effects were observed with fetuin-A concentrations that correlate clinically with metabolic syndrome [12]. We correlated our in vitro findings with a case control study: we compared serum fetuin-A levels among women with preeclampsia (n=111) and healthy pregnant controls (n=95). Women with preeclampsia, especially those with severe disease, had significant elevated serum levels of fetuin-A; this difference remained significant after controlling for diabetes, obesity and chronic hypertension. Our data suggest that increased concentrations of fetuin-A affect trophoblast cell invasiveness and elevated serum concentrations of fetuin-A correlate with preeclampsia.

In summary, limited studies, some of them with a confined number of subjects, have investigated the effects of fetuin-A in pregnancy and its role yet remains to be understood. It appears that increased levels of fetuin-A could be associated with insulin resistance during pregnancy. Also, elevated concentrations of fetuin-A could affect invasive properties of trophoblast cells potentially leading to adverse pregnancy outcomes such as preeclampsia. It is possible that a subset of women who are destined to experience metabolic syndrome later in life present with elevated serum levels of fetuin-A and are susceptible to the development of preeclampsia earlier when they are pregnant.

REFERENCES


