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DYSREGULATION OF MATERNAL SERUM ADIPONECTIN IN PRETERM LABOR

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Abstract

Objective—Intra-amniotic and systemic infection/inflammation have been causally linked to preterm parturition and fetal injury. An emerging theme is that adipose tissue can orchestrate a metabolic response to insults, but also an inflammatory response via the production of adipocytokines, and that these two phenomenon are interrelated. Adiponectin, an insulin-sensitizing, anti-inflammatory adipocytokine, circulates in multimeric complexes including low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers and high-molecular-weight (HMW) isoforms. Each of these complexes can exert differential biological effects. The aim of this study was to determine whether spontaneous preterm labor (PTL) with intact membranes and intra-amniotic infection/inflammation (IAI) is associated with changes in maternal serum circulating adiponectin multimers.

Study design—This cross-sectional study included patients in the following groups: 1) normal pregnant women (n=158); 2) patients with an episode of preterm labor and intact membranes without IAI who delivered at term (n=41); 3) preterm labor without IAI who delivered preterm (n=27); and 4) preterm labor with IAI who delivered preterm (n=36). Serum adiponectin multimers (total, HMW, MMW and LMW) concentrations were determined by ELISA. Non-parametric statistics were used for analyses.

Results—1) Preterm labor leading to preterm delivery or an episode of preterm labor which does not lead to preterm delivery, was associated with a lower median maternal serum concentration of total and HMW adiponectin, a lower median HMW/total adiponectin ratio, and a higher median LMW/total adiponectin ratio than normal pregnancy; 2) among patients with preterm labor, those with IAI had the lowest median concentration of total and HMW adiponectin, as well as the lowest median HMW/total adiponectin ratio; 3) The changes in maternal adiponectin and adiponectin multimers remained significant after adjusting for confounding factors such as maternal age, BMI, gestational age at sampling, and parity.

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Conclusion—1) Preterm labor is characterized by a change in the profile of adiponectin multimers concentrations and their relative isoforms. These changes were observed in patients with an episode of preterm labor not leading to preterm delivery, in patients with intra-amniotic inflammation, or in those without evidence of intra-amniotic inflammation; 2) The changes in adiponectin multimer concentrations reported in preterm labor are different from those previously reported in spontaneous labor at term, suggesting that there is a fundamental difference between preterm labor and labor at term; 3) The findings reported herein, provide the first evidence for the participation of adiponectin multimer in preterm parturition. We propose that adiponectins and adipokines in general provide a mechanism to organize the metabolic demands generated by the process of preterm parturition regardless of the nature of the insult (intra-amniotic inflammation or not).

Keywords

Adiponectin; Adipokines; Pregnancy; High molecular weight (HMW); Medium molecular weight (MMW); Low molecular weight (LMW); Preterm labor; Intra-amniotic infection; Inflammation; Chorioamnionitis; Preterm delivery; Energy Requirements; Energy Expenditure; Preterm Birth; Metabolism; Metaflammation

Introduction

Infection and/or inflammation has been implicated as a mechanism of disease responsible for preterm parturition and fetal injury,[1–12] indeed, infection and/or inflammation are the only pathologic processes for which a firm causal link with preterm parturition has been established and a molecular pathophysiology has been defined.[8;13]

In addition to the unequivocal experimental, epidemiologic and clinical evidence causally linking intra-amniotic infection and/or inflammation (IAI) and preterm parturition,[1–4;6;8;9;13–52] there are several lines of evidence supporting a cause and effect relationship between systemic infection/inflammation and preterm parturition: 1) systemic administration of microbial products to pregnant animals can result in spontaneous preterm labor and preterm birth;[29;53] 2) administration of IL-1, a potent pro-inflammatory cytokine, to pregnant mice induces preterm labor and preterm birth.[54] Furthermore, exposure of these mice to the natural antagonist of IL-1 (IL-1 receptor antagonist) abrogates parturition;[55] 3) extra uterine infection resulting in systemic inflammation such as malaria,[56;57] pyelonephritis,[58–60] pneumonia[61;62] and periodontal disease[63;64] have been associated with preterm birth; and 4) non-infectious chronic inflammatory disorders like systemic lupus erythematosus,[65;66] inflammatory bowel diseases,[67–69] asthma,[70;71] and morbid obesity[72–74] have been associated with preterm parturition.

Adipose tissue has emerged as a highly active endocrine organ[75–77] that can orchestrate a metabolic response to insults, but also an inflammatory response via the production of soluble factors known as adipocytokines. Adipocytokine is a term used to describe cytokines that are produced mainly, but not necessarily exclusively, by adipose tissue. A wide range of highly active molecules are members of the adipocytokine family: Interleukin (IL)-6,[78;79] tumor necrosis factor (TNF)-α,[80] leptin,[81;82] adiponectin,[83–86] resistin,[87–89] visfatin,[90–92] and others.[93;94] Adipocytokines have been implicated in the pathophysiology of inflammatory disorders such as asthma,[95] inflammatory bowel disease,[96] rheumatoid arthritis,[97;98] multiple sclerosis[99;100] and obesity.[101–109] Furthermore, several adipocytokines such as resistin[110;111] and visfatin[51;112;113] have an immunoregulatory effect on the innate immune response. Others, like leptin, have been shown to regulate both the innate[114;115] and the adaptive immune pathways.[116;117] Collectively these finding support an important role for adipocytokines in the regulation of the inflammatory response.

Adiponectin is the most abundant gene *(AMP1)* product of adipose tissue[83;118–120] and has a wide range of biological activities. Indeed, adiponectin has been implicated in the pathophysiology of the metabolic syndrome including insulin resistance,[121–124] atherosclerosis,[125;126] hypertension,[127] and dyslipidemia.[128] In addition to its well-characterized metabolic effects, a solid body of evidence strongly suggests that adiponectin is an important mediator of inflammatory responses. Adiponectin circulates in humans in distinct forms: 1) low-molecular-weight (LMW) trimers; 2) medium-molecular-weight (MMW) hexamers; and 3) high-molecular-weight (HMW) oligomers (12 to 18 subunits).[129;130] These adiponectin multimeric complexes have differential biological effects,[130–133] and it has been proposed that elucidation of the putative physiologic and pathologic role of adiponectin can not be discerned without the investigation of the profile of adiponectin multimer concentrations and their relative distribution.

Recently, we have suggested that intra-amniotic adipocytokines may play a role in the innate immune response against intra-amniotic infection/inflammation.[51;111] However, to date there are no studies about primary adipokines in preterm labor. Thus, the aim of this study was to determine whether there are changes in adiponectin multimers in patients with preterm labor (PTL) with and without IAI.

Materials and methods

Study design and population

A cross-sectional study was designed by searching our clinical database and bank of biological samples, including 262 patients in the following groups: 1) normal pregnant women (n=158); 2) patients with an episode of preterm labor and intact membranes without IAI who delivered at term (n=41); 3) preterm labor without IAI who delivered preterm (<37 weeks gestation) (n=27); and 4) preterm labor with IAI who delivered preterm (n=36).

All women provided written informed consent prior to enrollment and the collection of blood and amniotic fluid. The collection and utilization of blood and amniotic fluid for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital (Chile), the Wayne State University (Detroit, Michigan, USA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (Bethesda, Maryland, USA). Many of these samples have previously been used to study the biology of inflammation, hemostasis, and growth factor concentrations in normal pregnant women and those with pregnancy complications.

Clinical Definitions

Patients were considered to have a normal pregnancy or spontaneous preterm labor as previousely defined.[51;111] Intra-amniotic infection was defined as a positive amniotic fluid culture for micro-organisms. Intra-amniotic inflammation was diagnosed by an amniotic fluid IL-6 concentration ≥2.6 ng/mL.[134]

Amniotic fluid collection

Amniotic fluid samples were obtained by trans-abdominal amniocentesis. Samples of amniotic fluid were cultured for aerobic/anaerobic bacteria and genital mycoplasmas. An amniotic fluid white blood cell (WBC) count, glucose concentration and Gram-stain were also performed shortly after collection as previously described.[135–137]

Maternal serum sample collection and quantitative determination of adiponectin multimeric forms

Maternal blood samples were collected immediately before or after the amniocentesis into vacutainer tubes. Samples were centrifuged and the sera were stored at −80°C until analysis. Sensitive enzyme-linked immunoassays were used to determine the concentrations of adiponectin multimeric forms in maternal serum. Immunoassays were purchased from ALPCO Diagnostics (Salem, NH, USA). The assays were run according to the recommendations of the manufacturer. To detect HMW adiponectin, serum samples were pretreated with a specific protease that selectively digested MMW and LMW adiponectin. We were also able to determine the combined HMW and MMW adiponectin concentrations by pretreating the samples with a protease that specifically digested LMW adiponectin. Maternal serum samples were assayed directly to determine total adiponectin concentrations. Briefly, untreated and pretreated maternal serum samples were incubated in duplicate wells of the micro titer plates, which had been pre-coated with a monoclonal antibody specific for adiponectin. During this incubation any adiponectin present in the standards and untreated or pretreated maternal serum samples was bound by the immobilized antibodies. After repeated washing and aspiration to remove all unbound substances, an enzyme-linked polyclonal antibody specific for adiponectin was added to the wells. Unbound materials were removed with repeated washing and a substrate solution was added to the wells and color developed in proportion to the amount of adiponectin bound in the initial step. The color development was stopped with the addition of an acid solution and the intensity of color was read using a programmable spectrophotometer (SpectraMax M2, Molecular Devices, Sunnyvale, CA, USA). The concentration of adiponectin in untreated and treated maternal serum samples was determined by interpolation from individual standard curves composed of human adiponectin. Total, HMW, and HMW-MMW adiponectin concentrations were derived directly from the assay plates. MMW adiponectin concentrations were obtained by subtracting HMW adiponectin value from the combined HMW-MMW value. Finally, the LMW adiponectin value was computed by subtracting HMW and MMW adiponectin values from the total adiponectin values. The calculated inter- and intra-assay coefficients of variation for adiponectin multimers immunoassays in our laboratory were 2.2% and 4.2%, respectively. The sensitivity was calculated to be 0.04 ng/mL.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Kruskal–Wallis tests with post-hoc analysis by Mann-Whitney U tests were used for comparisons of continuous variables. Multiple linear regression analysis was used to determine which factors were significantly and independently associated with maternal serum adiponectin isoforms as well as their relative distribution (after log transformation). The following parameters were included in the model: maternal age, gestational age at sampling, birth weight, first trimester body mass index (BMI) and the presence of preterm labor. A p value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 14 (SPSS Inc., Chicago, IL, USA).

Results

The demographic and clinical characteristics of women with a normal pregnancy and those with preterm labor are displayed in Table I. There was no significant difference in the median first trimester BMI or parity between the four groups. Women with a normal pregnancy had a lower gestational age at sampling than those with preterm labor without IAI who delivered either at term (p=0.003) or preterm (p<0.001). The median gestational age at sampling did not differ significantly between women with a normal pregnancy and those with preterm labor with IAI (p=0.08). Women with a normal pregnancy had a higher median

maternal age than those with preterm labor without IAI who delivered either at term (p=0.003) or preterm (p=0.01). The median maternal age did not differ significantly between women with a normal pregnancy and those with preterm labor and IAI (p=0.06). Comparison of the demographics and clinical characteristics among patients with preterm labor is presented in Table I.

Total Adiponectin concentrations in preterm labor vs. normal pregnancy

The median maternal serum total adiponectin concentration was lower in patients with preterm labor with IAI than in those with preterm labor without IAI who delivered either preterm (median: 3,076 ng/mL, interquartile range [IQR] 2,082–3,391 vs. 3,411 ng/mL, IQR 2,937–4,586; p=0.01, Figure 1) or at term (4,115 ng/mL, IQR 2,977–5,596; p<0.001, Figure 1). Similarly, patients with preterm labor and IAI had a lower median maternal serum total adiponectin concentration than those with a normal pregnancy (3,076 ng/mL, IQR: 2,082–3,391 vs. 6,551 ng/mL, IQR 4,790–8,635; p<0.001, Figure 1).

The median maternal serum total adiponectin concentration was lower in patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p<0.001 for both comparisons, Figure 1). Among patients with preterm labor without IAI, the median maternal serum total adiponectin did not differ significantly between those who delivered preterm and those who delivered at term (p=0.2).

HMW Adiponectin concentrations in preterm labor vs. normal pregnancy

The median maternal serum HMW adiponectin concentration was lower in patients with preterm labor and IAI than in those with preterm labor without IAI who delivered either preterm (1,372 ng/mL, IQR 756–1,557 vs. 1,783 ng/mL, IQR 928–2,438; p=0.01, Figure 2) or at term (1,936 ng/mL, IQR 1,209–2,827; p<0.001, Figure 2). Similarly, patients with preterm labor and IAI had a lower median HMW adiponectin concentration than those with a normal pregnancy (1,372 ng/mL, IQR 756–1,557 vs. 3,660 ng/mL, IQR 2,444–5,418; p<0.001, Figure 2).

The median maternal serum HMW adiponectin concentration was lower in patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p<0.001 for both comparisons, Figure 2). There was no significant difference in the median maternal serum HMW adiponectin concentration between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.4)

MMW Adiponectin concentrations in preterm labor vs. normal pregnancy

The median maternal serum MMW adiponectin concentration was lower in patients with preterm labor and IAI than in those with preterm labor without IAI who delivered at term (683 ng/mL, IQR 544–9467 vs. 977 ng/mL, IQR 660–1,292; p=0.009, Figure 3) but comparable with those with preterm labor without IAI who delivered preterm (654 ng/mL, IQR 481–745; p=0.13) Patients with preterm labor and IAI had a lower median MMW adiponectin concentration than those with a normal pregnancy (683 ng/mL, IQR 544–9467 vs. 1,437 ng/mL, IQR 965–1,804; p<0.001, Figure 3).

The median maternal serum MMW adiponectin concentration was lower in patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p<0.001 for both comparisons, Figure 3). There was no significant difference in the median maternal serum MMW adiponectin concentration between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.3).

LMW Adiponectin concentrations in preterm labor vs. normal pregnancy

The median maternal serum LMW adiponectin concentration was lower in patients with preterm labor and IAI than in those with preterm labor without IAI who delivered at term (975 ng/mL, IQR 797–1,105 vs. 1,232 ng/mL, IQR 928–1,641; p=0.001, Figure 4) but comparable with those with preterm labor without IAI who delivered preterm (1,071 ng/mL, IQR 612–1,426; p=0.2) Patients with preterm labor and IAI had a lower median LMW adiponectin concentration than those with a normal pregnancy (975 ng/mL, IQR 797–1,105 vs. 1,195 ng/mL, IQR 886–1,672; p<0.001, Figure 4).

The median maternal serum LMW adiponectin concentration did not differ significantly between patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p=0.07 and p=0.98, respectively; Figure 4). Similarly, there was no significant difference in the median maternal serum LMW adiponectin concentration between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.1).

HMW/total adiponectin ratio in preterm labor vs. normal pregnancy

The median maternal HMW/total adiponectin ratio was lower in patients with preterm labor and IAI than in those with preterm labor without IAI who delivered either preterm (0.41, IQR 0.34–0.48 vs. 0.49, IQR 0.36–0.57; p=0.03, Figure 5) or at term (0.44, IQR 0.36–0.52; p=0.04, Figure 5). Similarly, patients with preterm labor and IAI had a lower median HMW/total adiponectin ratio than those with a normal pregnancy (0.41, IQR 0.34–0.48 vs. 0.56, IQR 0.49–0.64; p<0.001, Figure 5).

The median maternal HMW/total adiponectin ratio was lower in patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p<0.001 for both comparisons, Figure 5). There was no significant difference in the median maternal HMW/total total adiponectin ratio between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.46).

MMW/total adiponectin ratio in preterm labor vs. normal pregnancy

The median maternal MMW/total adiponectin ratio did not differ significantly between patients with preterm labor and IAI and those with preterm labor without IAI who delivered either preterm (0.24, IQR 0.20–0.31 vs. 0.26, IQR 0.17–0.29; p=0.8, Figure 6) or at term (0.23, IQR 0.16–0.27; p=0.3, Figure 6). In contrast, patients with preterm labor and IAI had a higher median MMW/total adiponectin ratio than those with a normal pregnancy (0.24, IQR 0.20–0.31vs. 0.22, IQR 0.17–0.26; p=0.01, Figure 6).

The median maternal MMW/total adiponectin ratio did not differ significantly between patients with preterm labor without IAI who delivered either preterm or at term than in those with a normal pregnancy (p=0.1 and p=0.4, respectively; Figure 6). There was no significant difference in the median maternal MMW/total total adiponectin ratio between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.4).

LMW/total adiponectin ratio in preterm labor vs. normal pregnancy

The median maternal LMW/total adiponectin ratio did not differ significantly between patients with preterm labor and IAI than in those with preterm labor without IAI who delivered either preterm (0.32, IQR 0.25–0.37 vs. 0.28, IQR 0.23–0.38; p=0.3, Figure 7) or at term (0.30, IQR 0.20–0.43; p=0.4, Figure 7). In contrast, patients with preterm labor and

IAI had a higher median LMW/total adiponectin ratio than those with a normal pregnancy (0.32, IQR 0.25–0.37 vs. 0.20, IQR 0.13–0.28; p<0.001, Figure 7).

The median maternal LMW/total adiponectin ratio was higher in patients with preterm labor without IAI who delivered either preterm or at term than that of those with a normal pregnancy (p<0.001 for both comparisons, Figure 7). There was no significant difference in the median maternal LMW/total total adiponectin ratio between patients with preterm labor without IAI who delivered preterm and those with preterm labor without IAI who delivered at term (p=0.6).

Multiple regression analysis was employed to examine the relationship between the serum concentrations of adiponectin isoforms and preterm labor while adjusting for maternal age, maternal BMI at the first trimester, gestational age at blood sampling, and birthweight. The final regression model suggested that an episode of preterm labor and first trimester BMI was independently associated with a lower maternal serum total adiponectin (p<0.001 and p=0.005, respectively), and HMW adiponectin concentrations (p<0.001 and p=0.001, respectively), as well as with a lower HMW/total adiponectin ratio (p<0.001 and p=0.008, respectively). In addition, only the presence of preterm labor was independently associated with higher maternal LMW/total adiponectin ratio (p<0.001) compared with normal pregnancies.

Discussion

Principal findings of the study

1) Preterm labor leading to preterm delivery or an episode of preterm labor which does not lead to preterm delivery, was associated with a lower median maternal serum concentration of total and HMW adiponectin, a lower median HMW/total adiponectin ratio, and a higher median LMW/total adiponectin ratio than normal pregnancy; 2) among patients with preterm labor, those with IAI had the lowest median concentration of total and HMW adiponectin, as well as the lowest median HMW/total adiponectin ratio; 3) The changes in adiponectin and adiponectin multimers remained significant after adjusting for confounding factors such as maternal age, BMI, gestational age at sampling, and parity.

Metaflammation - the intricate interface between metabolism and inflammation

An emerging theme in modern biology is that adipose tissue can orchestrate metabolic responses to injury, and also inflammatory responses. The first description of a molecular link between adipose tissue and inflammation was made by Hotamisligil et al.[138] who demonstrated an over-expression of TNF-α, a pro-inflammatory cytokine, in obese rodents. Subsequently, unequivocal experimental, clinical and epidemiological evidence has strongly supported a causal link between adipose tissue and the inflammatory response: 1) adipose tissue is a crucial site for the production of inflammatory mediators such as TNF-α,[139] IL-6,[140] monocyte chemoattractant protein (MCP)-1,[141;142] C-reactive protein (CRP),[143;144] serum amyloid A[145] and plasminogen activator inhibitor-1 (PAI-1);[146] 2) adipocytokines such as resistin,[111;147] visfatin,[51;112;113] and adipsin[148] have been implicated in the regulation of the innate immune responses. Other adipocytokines such as leptin[117;149] and adiponectin[150;151] have been shown to have an effect on both the innate and adaptive limbs of the immune system; 3) knockout mice for IL-6,[152] TNF-α,[153] PAI-1,[154] IL-18,[155] IL-1α,[156] MCP-1,[157] JNK1[158] are often obese or have a metabolic phenotype related to obesity (e.g. insulin resistance or improved insulin sensitivity); 4) adipose tissue in obese individuals is characterized by macrophage infiltration.[159;160] Moreover, adipose tissue-resident macrophages are a source of pro-inflammatory mediators that can regulate the secretory activity of adipocytes;[161] and 5) obese patients have higher circulating pro-

inflammatory and acute phase reactant adipocytokines such as TNF-α,[162] IL-6,[163] and CRP[140] than non-obese individuals. Furthermore, weight loss is associated with low serum CRP,[164;165] IL-6[166] and circulating serum amyloid A.[145]

It is important to note that the classic features of inflammation: *calor* (heat), *dolor* (pain), *rubor*, (redness) *tumor* (swelling) and *function laesa* (impaired function)[167] are not necessarily present in the inflammatory response observed with an increased deposition of fat or adipose tissue. Indeed, the term "Metaflammation"[168] (metabolically triggered inflammation) was coined to note the unique characteristics of the inflammatory response associated with metabolic derangements, such as obesity or insulin resistance. In contrast to the often short-term, adaptive response of "classical" inflammation, which is crucial for tissue repair, metaflammation is chronic, triggered by nutrient surplus and has detrimental long-term effects. Importantly, both processes engage a similar set of molecules and signaling pathways.[161;169] The terms "subclinical," "low-grade," and "chronic" inflammation are being used interchangeably in the context of obesity.

The two major roles of adiponectin: regulation of metabolic responses and/or inflammation

While a large body of evidence supports a causal relationship between obesity and inflammation, the precise mechanisms through which this regulation occurs have not been yet completely characterized. One plausible mechanism involves adipocytokines.[94;151;170;171] Adiponectin is the adipocytokine[83;118–120] that circulates at the highest concentrations.[101;118;172–177] In addition to its well-described role in governing energy homeostasis,[122–124;178;179] adiponectin has anti-inflammatory properties. Several lines of evidence support the immunoregulatory and anti-inflammatory effects of adiponectin: 1) adiponectin suppresses macrophage production of pro-inflammatory cytokines such as TNF-α,[151;180] IFN-γ,[150] and IL-6;[181] 2) adiponectin induces production of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist[150;180;182] by human monocytes, macrophages and dendritic cells; 3) exposure of cultured macrophages to adiponectin results in inhibition of their phagocytic activity in response to stimulation with LPS;[151] 4) the presence of adiponectin in T-cell proliferation assays results in a decreased ability to evoke an allogenic T-cell response;[150] 5) adiponectin inhibits activation of the nuclear transcription factor NF-κB in endothelial cells;[171] 6) adiponectin prevents LPS-induced hepatic injury by inhibiting the synthesis and/or release of TNF-α;[183] 7) adiponectin knockout mice have higher levels of TNF-α mRNA expression in adipose tissue, as well as higher circulating TNF-α concentrations than adiponectin-sufficient mice;[179] 8) alterations in adiponectin concentrations have been reported in the presence of systemic inflammatory conditions such as in the serum of overweight/obese individuals,[84;104;118] those with insulin resistance, [124;178] systemic lupus erythematosus,[184;185] in the intestinal adipose tissue of patients with Crohn's disease,[186;187] and in the synovial fluid[97] and circulation[188] of patients with rheumatoid arthritis.

Adiponectin multimers: a new paradigm for hormonal regulation

Adiponectin undergoes post-translational modifications before its secretion by adipocytes. Distinct multimeric forms include: LMW trimers, MMW hexamers, and HMW oligomers (12 to 18 subunits).[129;130;189] These isoforms have different biological effects, and it has been proposed that the concentrations of each multimeric isoforms, as well as their relative abundance, regulate the pleiotropic effects of adiponectin. This view is supported by the following findings: 1) *in vitro*, HMW and MMW adiponectin induce increased secretion of the pro-inflammatory cytokines, IL-6[190] and IL-8[190;191] by monocytes; 2) in contrast, exposure of monocyte to LMW adiponectin results in increased secretion of the anti-inflammatory cytokine IL-10 [192] and a decreased release of IL-6;[180;181] 3) treatment with

HMW adiponectin, but not with LMW adiponectin, results in a dose dependent reduction in serum glucose concentrations[193] in adiponectin knockout mice; 4) weight reduction,[194] refeeding of patients with anorexia nervosa[177] and treatment with thiazolidineone[193] are characterized by improved insulin resistance and by marked and specific elevation of HMW; and 5) LMW adiponectin activates AMP-activated protein kinase (AMPK),[132] whereas HMW and MMW activate NF-κB.[132] Collectively, these findings suggest a differential biological effect for adiponectin multimeric complexes. Moreover, these reports highlight the importance of evaluating adiponectin multimers and their relative distribution in order to elucidate the role of adiponectin in physiologic and pathologic conditions.

Adipokines, inflammation and human pregnancy

Several lines of evidence suggest that adipokines play an important role in normal pregnancy and in pregnancy complications: 1) normal pregnancy is associated with alterations in circulating adiponectin,[104;107;173–176] resistin,[105] visfatin[109] and other adipocytokines; 2) circulating maternal adiponectin correlates with insulin resistance indices during pregnancy;[77;195–197] 3) gestational diabetes mellitus (GDM) is associated with higher maternal concentrations of leptin,[198] CRP,[197] TNF-α,[199] resistin[200] and visfatin[108;201;202] than non diabetic pregnant women. In addition, patients with GDM have lower concentrations of adiponectin than normal pregnant women;[196;203–207] 4) overweight pregnant women have a lower plasma concentration of adiponectin[104;107] and a higher concentration of leptin[208] than non-obese pregnant women; 5) preeclampsia is associated with higher concentrations of leptin,[209] visfatin,[210] and TNF-α,[211] as well as lower concentrations of resistin[212] and altered maternal circulating adiponectin;[106;213–215] and 6) IAI is associated with higher amniotic fluid concentrations of visfatin[51] and resistin.[111] The aforementioned reports support for a role for adipocytokines in metabolic- and inflammatory phenomenon observed in complications of pregnancy.

Preterm labor is characterized by quantitative and qualitative changes in adiponectin multimers

Preterm labor was associated with low maternal concentrations of total adiponectin, HMW adiponectin, MMW adiponectin, as well as a low HMW/total adiponectin ratio and a high LMW/total adiponectin ratio. Of note, these findings were consistent across all preterm labor groups regardless of preterm delivery or the presence of IAI. To date, there is no data concerning the association between primary adipocytokines (those who are produced primarily by adipose tissue) and preterm labor. We have previously reported higher HMW adiponectin concentrations and higher HMW/total adiponectin ratios in normal pregnant women in labor.[107] Thus, the lower serum concentration of adiponectin multimers in patients with preterm labor may be attributed to the process of preterm parturition, and not labor *per se*. In this regard, term and preterm labor would appear to be different.

Adipocytes control the production of adiponectin multimers. Hence, the findings of the current study indicate that even a single episode of preterm labor which does not result in preterm delivery is associated with changes in the profile of maternal adipocytokines. Similar findings were observed in preterm labor which leads to preterm delivery regardless of the presence or absence of intra-amniotic inflammation/infection. The explanation for the observations reported in this study requires further investigation.

Why is preterm labor a state of dysregulation of adiponectin multimers?

Patients with preterm labor had a significantly lower median maternal serum concentration of total adiponectin than that of women with normal pregnancies. This finding is due to a selective lowering in the serum concentrations of HMW and MMW isoforms (indeed, LMW/total adiponectin ratio was higher). This observation is important because some

metabolic effects of adiponectin, such as the insulin sensitizing effect, are mediated by the HMW isoform.

Whether these changes in serum adiponectin isoforms concentrations are a cause or a consequence of preterm labor cannot be discerned by this study because of its cross-sectional nature. One possibility is that an episode of preterm labor imposes metabolic challenges to both hosts (mother and/or fetus). For example, the mother requires more fuel to maintain increased uterine contractility and the fetus may have its own increased requirements in preparation for birth. The changes in maternal serum adiponectin multimers reported herein favor a state of insulin resistance which enhances the availability of glucose, the major metabolic fuel.

Differences between spontaneous labor at term and preterm labor: why?

Spontaneous labor at term is characterized by higher maternal serum concentrations of the high molecular weight and HMW/total adiponectin ratio.[107] The opposite is the case for preterm labor. What is the explanation for this paradox?

One view of pregnancy is that energy must be employed first to support the growth of the conceptus, and then when the fetus reaches maturity and cannot be sustained in utero by the placenta and/or mother, energy utilization is shifted towards the execution of parturition. In contrast, preterm parturition is the result of a pathologic process which may affect adipose tissue function, directly or indirectly. The response of adipose tissue to such a pathological insult is translated by a change in the concentrations of adiponectin multimers, but such a change is not observed in normal labor because there is no adipose tissue dysfunction in normal labor.

In conclusion, the present study is the first to examine maternal serum adiponectin multimers concentrations in patients with preterm labor. Since adiponectin multimers are exclusively produced by adipocytes, the findings reported herein indicating a change in adiponectin multimers in maternal serum lead us to suggest that a form of adipose tissue dysregulation occurs in preterm labor. This observation is novel because it suggests that adipokines may play a role in preterm parturition, and provides a molecular basis for the excess rate of spontaneous preterm birth in extremely lean and obese patients. The implication of this is that changes in lifestyle and pharmacologic interventions which target adipose tissue may be of value in the prevention of preterm birth, in a subset of patients, and that there may be molecular markers to assist with monitoring response. Further studies are required to test the set of hypotheses that derive from our observations.

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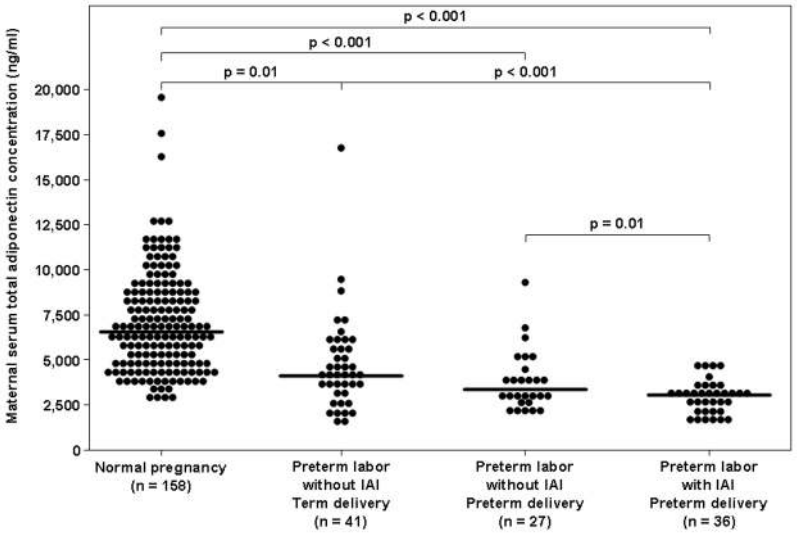

Figure 1. Comparison of the median maternal serum total adiponectin concentrations between women with normal pregnancies and patients with spontaneous PTL

The median maternal serum concentration of total adiponectin was lower in patients with PTL than in those with a normal pregnancy. Among women with PTL, patients with IAI had the lowest median maternal total adiponectin.

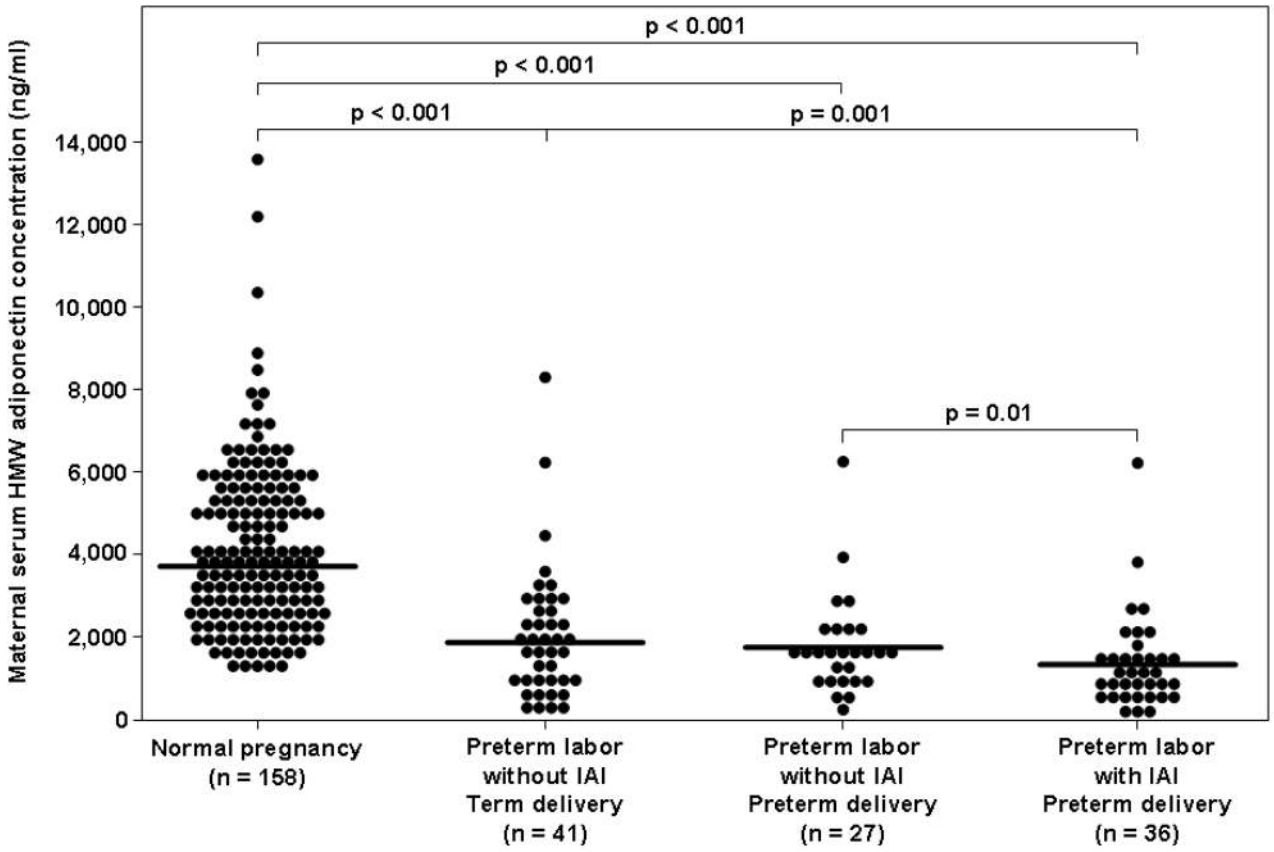

Figure 2. Comparison of the median maternal serum HMW adiponectin concentrations between women with normal pregnancies and patients with spontaneous PTL

The median maternal serum concentration of HMW adiponectin was lower in patients with PTL than in those with a normal pregnancy. Among women with PTL, patients with IAI had the lowest median maternal HMW adiponectin.

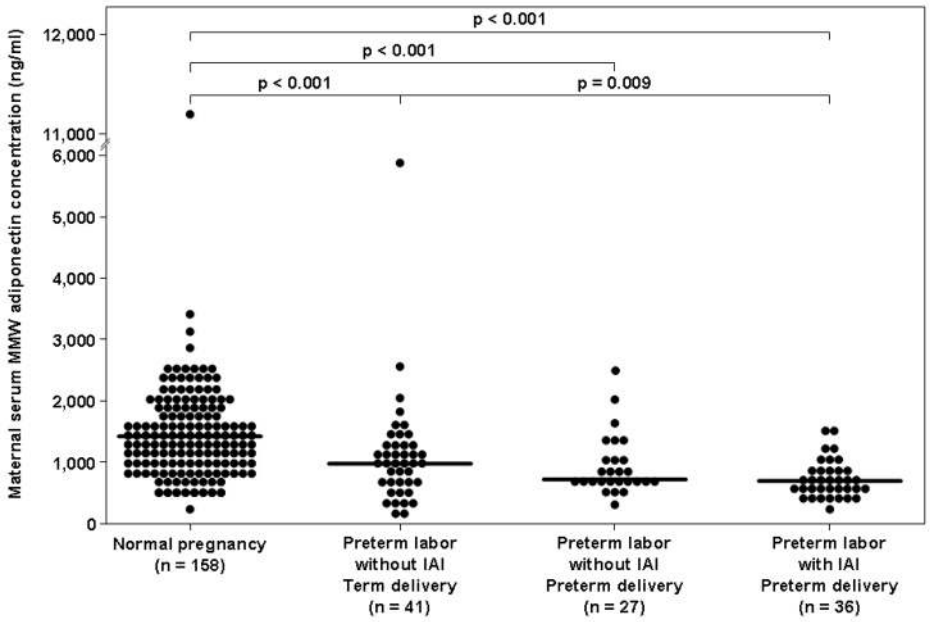

Figure 3. Comparison of the median maternal serum MMW adiponectin concentration between women with normal pregnancies and patients with spontaneous PTL

The median maternal serum concentration of MMW adiponectin was lower in patients with PTL than in those with a normal pregnancy. Among women with PTL, patients with IAI had lower median maternal MMW adiponectin than patients with PTL who delivered at term.

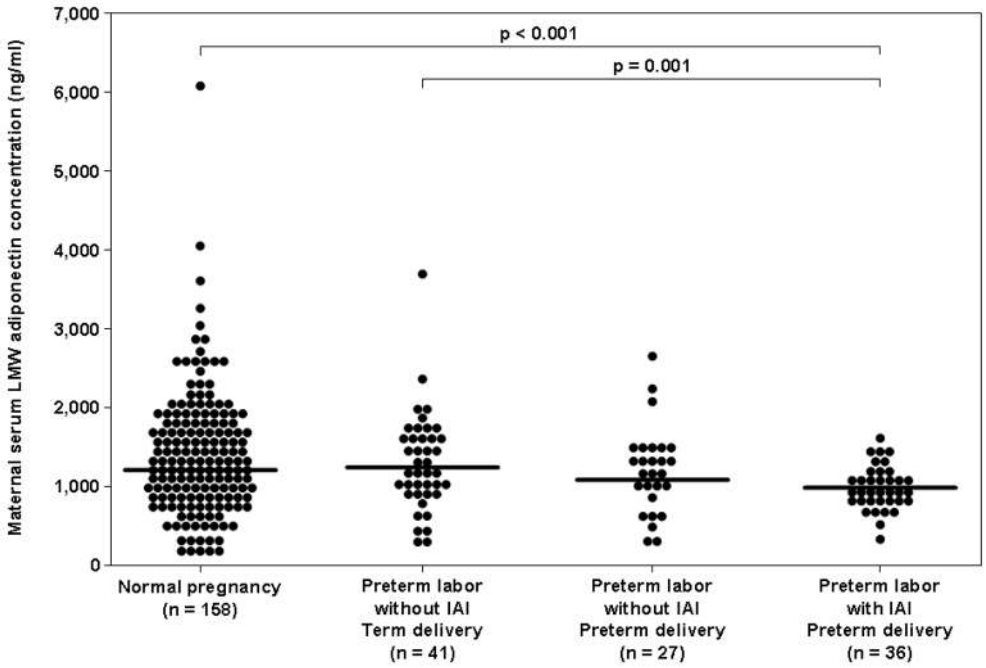

Figure 4. Comparison of the median maternal serum LMW adiponectin concentrations between women with normal pregnancies and patients with spontaneous preterm labor

The median maternal serum concentration of LMW adiponectin was lower in patients with preterm labor and IAI than in those with a normal pregnancy and than that of those with preterm labor who delivered at term.

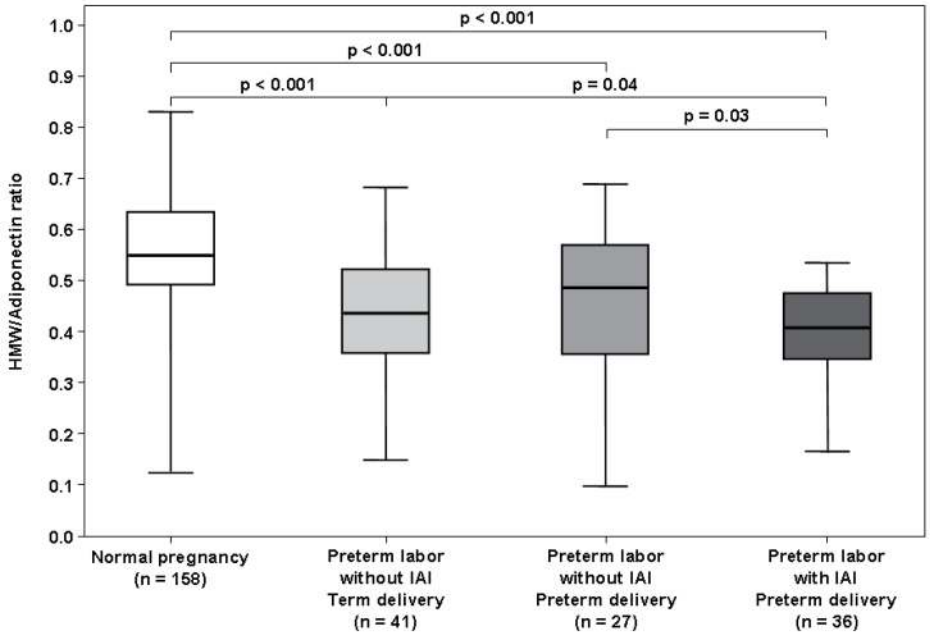

Figure 5. Comparison of the median maternal serum HMW/Total adiponectin ratios between women with normal pregnancies and patients with spontaneous preterm labor

The median maternal serum HMW/Total adiponectin ratio was lower in patients with preterm labor than in those with a normal pregnancy. Among women with preterm labor, patients with IAI had the lowest median maternal HMW/Total adiponectin ratio.

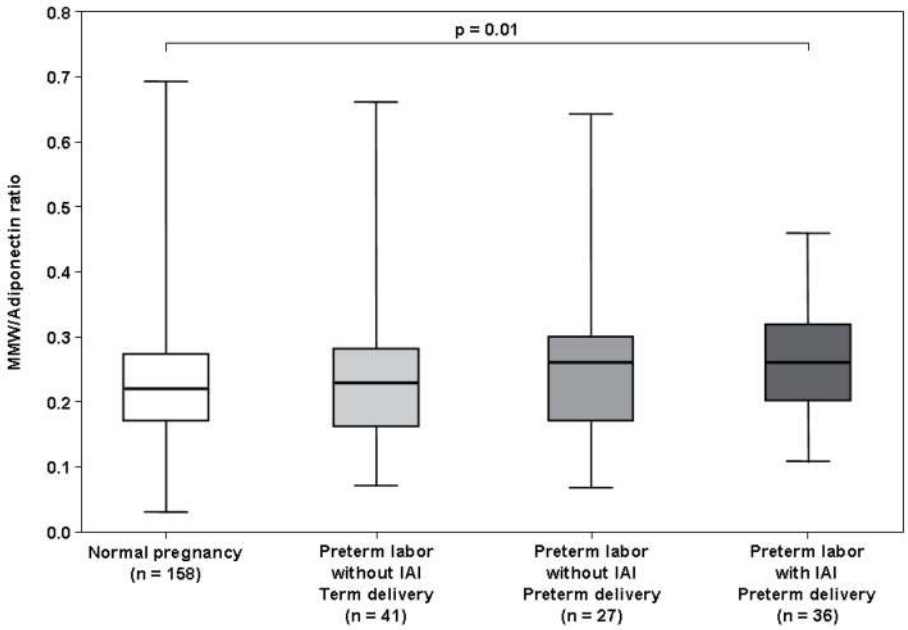

Figure 6. Comparison of the median maternal serum MMW/Total adiponectin ratio between women with normal pregnancies and patients with spontaneous preterm labor

The median maternal serum MMW/Total adiponectin ratio was higher in patients with preterm labor and IAI than in those with a normal pregnancy. The MMW/Total adiponectin ratio did not differ significant among the preterm labor groups.

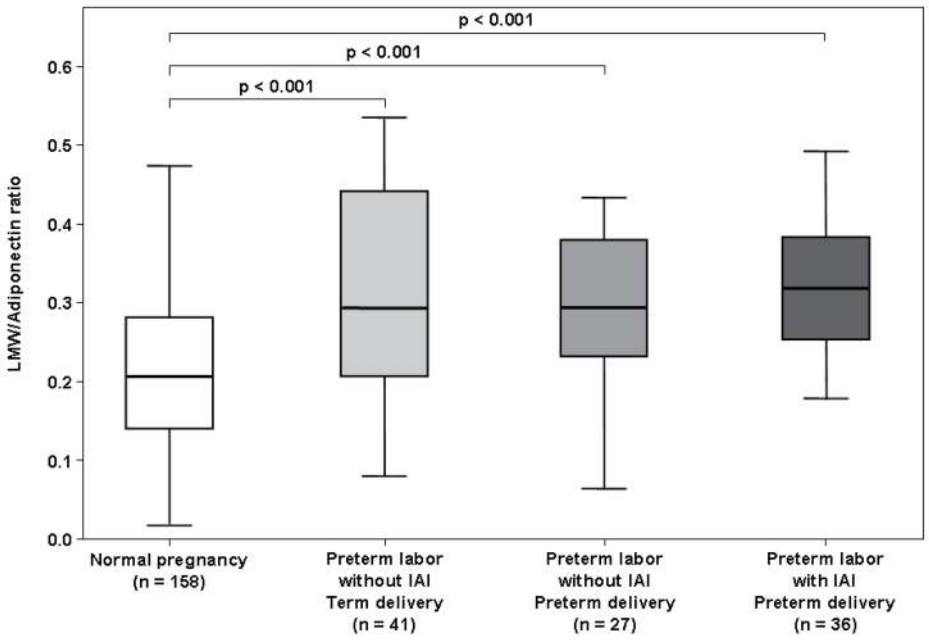

Figure 7. Comparison of the median maternal serum LMW/Total adiponectin ratio between women with normal pregnancies and patients with spontaneous preterm labor

The median maternal serum LMW/Total adiponectin ratio was higher in patients with preterm labor than in those with a normal pregnancy. LMW/Total adiponectin ratio did not differ significant among the preterm labor groups.

Table I

Clinical and demographic characteristics of the study population

	Normal Pregnancy (n=158)	PTL without IAI Term delivery (n=41)	p[1]	PTL without IAI Preterm delivery (n=27)	p[2]	PTL with IAI Preterm delivery (n=36)	p[3]
Maternal age (years)	26 (21–31)	23 (19–27)	NS	22 (20–29)	NS	24 (20–28)	NS
Parity	1 (0–2)	2 (1–2)	NS	2 (1–3)	NS	2 (1–3)	NS
First trimester BMI (kg/m^2)	23.1 (21.3–25.9)	23.6 (20.3–29.2)	NS	25.5 (22.3–29.0)	NS	26.6 (23.4–31.1)	NS
GA at blood sampling (weeks)	27.7 (25.3–29.0)	30.0 (26.1–32.2)	NS	31.0 (28.0–32.9)	<0.01	25.4 (24.3–30.8)	<0.05
GA at delivery (weeks)	40.0 (39.0–40.4)	38.3 (37.3–39.4)	<0.01	34.6 (33.7–35.3)	<0.01	26.3 (24.5–31.0)	<0.01
Birth weight (grams)	3465 (3210–3702)	2903 (2697–3267)	<0.01	1940 (1760–2310)	<0.01	815 (628–1645)	<0.01

p[1]: comparison between preterm labor who delivered at term and preterm labor without IAI

p[2]: comparison between preterm labor who delivered preterm without IAI and preterm labor with IAI

p[3]: comparison between preterm labor who delivered at term and preterm labor with IAI

Values are expressed as median and interquartile (IQR) range; **PTL:** preterm labor; **GA:** gestational age; **BMI:** body mass index; **IAI:** intra-amniotic infection/inflammation **NS:** not significant

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