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Am J Obstet Gynecol. 2017 Nov;217(5):583.e1-583.e8. doi: 10.1016/j.ajog.2017.05.027. Epub 2017 May 20.



Cell-free DNA, inflammation, and the initiation of spontaneous term labor.

Herrera CA¹, Stoerker J², Carlquist J³, Stoddard GJ⁴, Jackson M⁵, Esplin S⁵, Rose NC⁵.

Author information

Abstract

BACKGROUND: Hypomethylated cell-free **DNA** from senescent placental trophoblasts may be involved in the activation of the inflammatory cascade to initiate **labor**.

OBJECTIVE: To determine the changes in cell-free **DNA** concentrations, the methylation ratio, and inflammatory markers between women in **labor** at term vs women without **labor**.

STUDY DESIGN: In this prospective cohort study, eligible participants carried a nonanomalous singleton **fetus**. Women with major medical comorbidity, preterm **labor**, progesterone use, aneuploidy, infectious disease, vaginal bleeding, abdominal trauma, or invasive procedures during the pregnancy were excluded. Maternal blood samples were collected at 28 weeks, 36 weeks, and at admission for delivery. Total cell-free **DNA** concentration, methylation ratio, and interleukin-6 were analyzed. The primary outcome was the difference in methylation ratio in women with **labor** vs without **labor**. Secondary outcomes included the longitudinal changes in these biomarkers corresponding to **labor** status.

RESULTS: A total of 55 women were included; 20 presented in **labor** on admission and 35 presented without **labor**. Women in **labor** had significantly greater methylation ratio ($P = .001$) and interleukin-6 ($P < .001$) on admission for delivery than women without **labor**. After we controlled for body mass index and maternal age, methylation ratio (adjusted relative risk, 1.38; 95% confidence interval, 1.13 to 1.68) and interleukin-6 (adjusted relative risk, 1.12, 95% confidence interval, 1.07 to 1.17) remained greater in women presenting in **labor**. Total cell-free **DNA** was not significantly different in women with **labor** compared with women without. Longitudinally, total cell-free **DNA** ($P < .001$ in **labor**, $P = .002$ without **labor**) and interleukin-6 ($P < .001$ in **labor**, $P = .01$ without **labor**) increased significantly across gestation in both groups. The methylation ratio increased significantly in women with **labor** from 36 weeks to delivery ($P = .02$).

CONCLUSION: Spontaneous **labor** at term is associated with a greater cell-free **DNA** methylation ratio and interleukin-6 compared with nonlabored controls. As gestation advances, total cell-free **DNA** concentrations and interleukin-6 levels increase. A greater methylation ratio reflects a greater maternal contribution (vs placental) in women with **labor**, likely resulting from greater levels of neutrophils, lymphocytes, and uterine activation proteins at the time of **labor**. Although not significant, women in **labor** had a greater total cell-free **DNA** concentration and thus could

theoretically have more hypomethylated **DNA** available for interaction with the inflammatory cascade. Larger studies are needed to investigate this theory.

Published by Elsevier Inc.

KEYWORDS: IL-6; TLR9; cfDNA; cytokines; signals for **labor**

Comment in

The link between cell-free **DNA**, inflammation and the initiation of spontaneous **labor** at term. [Am J Obstet Gynecol. 2017]

PMID: 28536048 DOI: [10.1016/j.ajog.2017.05.027](https://doi.org/10.1016/j.ajog.2017.05.027)

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances



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