Apelin and Difference in Cesarean Section and Normal Vaginal Delivery

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Abstract

Objective: Delivery is an inflammatory process and Apelin, has a vital role in pro-inflammatory process and uterine contractility. Therefore, this article studied maternal serum apelin-36 before and after cesarean (C/S) and natural vaginal delivery (NVD).

Material and Methods: In this study, 166 pregnant, 18-40 years old, were studied during weeks 28-32 of pregnancy until after delivery. They all meet inclusion criteria. To do so, the first blood sample was taken from the participants within third trimester. Twenty-three of these women had to upped elective cesarean and considered as the case group. Then, from the participants who had vaginal delivery, twenty-two were made homogenous concerning demographic characteristics with case group and selected as the control group and the second blood sample in the first 24 h after delivery. Blood samples were measured by means of ELIZA. Data were analyzed by SPSS16.

Results: Maternal Apelin-36 concentration in the third trimester of the pregnancy and the first 24 h after delivery were [82.16 ± 99.40 (NML)], and [86.49 ± 23.769 (NM/L)] in the C/S group and [101.5 ± 105.65 (NM/L)] and [84.9 ± 63.64 (NM/L)] in the NVD group. A significant difference was seen in NVD group before delivery, compared to after delivery (P=0.029). Furthermore, a statically significant difference was seen in Apelin-36 difference before and after delivery in the NVD group, compared to its difference in the C/S group (P=0.005). A positive relationship was seen between Apelin-36 concentrations after delivery and during labor (P<0.05).

Conclusion: The results indicated that this hormone difference level was more in the NVD group, compared to the C/S group. Furthermore, a positive relation was seen during labor.

Keywords
Apelin-36; Delivery type; Labor duration; Natural delivery; Cesarian

Introduction

Vaginal delivery is a preferred way of delivery for most of women, although some specific clinical setting may lead to cesarean delivery [1]. The evidences, obtained from cervix, myometrium, choioamnion membrane and amniotic cavity, in labor time confirm that delivery is an inflammatory process [2-4]. On the other hand, role of Apelin as a pro-inflammatory mediator has been already demonstrated [4-8].

Apelin is a recently discovered bioactive product of Adipokine which is functionally similar to angiotensin-1 coupled receptor (GPCR) [9,10]. Existence of Apelin and its receptor in various tissues of human and mice such as hypothalamus, anterior pituitary, endothelial vessels, heart, lungs, stomach, kidney, mammalian glands, thyroid, ovaries, colon mucus, pancreas, adipose tissue, liver and muscles reveals the widespread role of this hormone [8,10-18]. Furthermore, sex steroids, insulin, TNFα (Tumor Necrosis-Factor Alpha) and growth hormone, CRH (Corticotrophin-Releasing Hormone), AVP (Arginine Vasopressin) are also up-regulated by this novel hormone in human and mice [12,18-22]. Moreover, Lim et al. [23] in Australia, indicated the precise positions of the Apelin and its receptors in placenta and fetal membrane among the pregnant women during spontaneous term and preterm deliveries [23]. At pregnancy; Apelin expression increases in the first trimester of the normal pregnancy then the expression reduces [24]. Apelin expression increases in the first trimester of a normal pregnancy, and then, it reduces. On the other hand, Apelin inhibits spontaneous or induced uterine contractility by oxytocin through its effect on the uterine myometrium [25].

A theory of anti-inflammatory, anti-stress and anti-contraction role of Apelin and its variation during pregnancy has been recently presented. However, a key limitation in this area is that it has not been yet tested on delivery type of pregnant women. In the present study, we tested the hypothesis that there may be an association between the change of Apelin-36 before and after cesarean and natural delivery.

Materials and Methods

This is a nested case-control study conducted on 166 pregnant women of 18-40 years within 28-32 weeks of gestational age referring to the prenatal clinic of Mahdiyeh Hospital of Tehran for the prenatal care, they all meet inclusion criteria. To do so, the first blood sample was taken from the participants within 28-32 weeks of gestational age. Twenty-three of these women had to upped elective cesarean (CS) (cesarean section, individuals with cesarean indications such as breech, macrosomia, repeated cesarean section, etc. that had not experienced labor pain in their recent pregnancy) and considered as the case group. Then, from the participants who had vaginal delivery, twenty-two were made homogenous concerning demographic characteristics (including age, husband’s and mother’s occupation and education, family income, gravidity, parity, and abortion) with case group and selected as the control group. Eventually, the second blood sample in the first 24 h after delivery.

Sampling

The process was clearly explained to each individual and a written consent was obtained. The blood samples were collected according to abovementioned and transferred to the laboratory on the same day to measure serum apelin-36 levels.

They were assessed during active phase for the delivery time and labor duration.

Inclusion criteria were age of 18-40 years, singleton pregnancy, and being Iranian.
**Exclusion criteria** were mental health problems, systemic diseases such as lupus, diabetes mellitus, etc., use of tobacco and alcohol, any pregnancy complications (gestational diabetes, pre-eclampsia etc.), emergency cesarean section and taking any medications except for pregnancy supplements.

**Analytic procedure**

All blood samples were transferred to laboratory on the same day. Then, they were collected and plasma separation done in Gland laboratory. To do so, the plasma was separated and measured by Human apelin-36 Elisa Kit 96 tests Zell Bio, prepared by the exclusive agency (Padgin Medicine Company).

**Instrumentation**

Data collection tools to assess concentrations of maternal serum apelin-36 level, both in the vaginal delivery and the cesarean groups, were routine questionnaire of prenatal care, prepared by Iranian Ministry of Health, observation of clinical examinations, LMP (Last Menstrual Period) , used for calculating EDC (Estimated Date of Confinement), usual laboratory tests of pregnancy period, blood sampling tools (5 ml syringes, alcohol pads, gloves, Garo), and the test tube containing anti-protease.

Inclusion criteria were age of 18-40 years, singleton pregnancy, and being Iranian in the cesarean delivery group (individuals with cesarean indications such as breech, macrosomia, repeated cesarean sections, etc. that had not experienced labor pain in their recent pregnancy).

Exclusion criteria were mental health problems, systemic diseases such as lupus, diabetes mellitus, etc., an emergency cesarean section, taking any medications except for pregnancy supplements, tobacco and alcohol users, and any pregnancy complications (gestational diabetes, pre-eclampsia etc.).

**Statistical analysis**

The collected data were encoded and analyzed by statistical software of SPSS-16. Statistical comparison between two groups were analyzed by T-test, Mann-Whitney. Significance level was considered software of SPSS-16. Statistical comparison between two groups were analyzed by T-test, Mann-Whitney. Significance level was considered as P-value <0.05.

**Results**

Results showed that the concentration of maternal serum Apelin-36 were (101.5 ± 105.65 nm/l) and (84.9 ± 63.64 nm/l) and (82.16 ± 99.40 nm/l), (86.49 ± 23.76 nm/l) in the cesarean group in the third trimester of pregnancy and the first 24 hours after delivery in the vaginal delivery group.

Paired T-test showed a statistically significant decrease in average serum Apelin-36 level in the NVD group (P= 0.029) while there was no difference in the C/S group (P=0.325) (Table 1). Deferential decrease in level of Apelin in NVD group was 16% (P= 0.029).

According to statistical analyses, performed by Mann-Whitney test, there was no relationship between the Apelin-36 concentrations in C/S group, compared to the NVD group at the third trimester of pregnancy and also in the first 24 h after delivery (P= 0.870), (P= 0.236) (Tables 1 and 2).

Furthermore, a statistically significant relationship was seen in Apelin-36 difference before and after delivery in the NVD group and its difference in the C/S group (p=0.005) (Tables 1 and 2).

There was a significant positive relationship between this hormone and length of all phases of delivery (P=0.019), (P=0.005), (P=0.019) (Table 3).

**Discussion**

Our results showed a statistically significant decrease in NVD group (P=0.029). This finding is in agreement with the results of Malamits-puchner et al. (2007) indicating down-regulation of Apelin as soon as possible after birth that could be due to separation of placental [26].

Apelin play a role in a number of physiological and pathological processes. Apelin physiologic expression in inflammation through

**Table 1:** Relation between mother’s serum Apelin-36 level (Nm/L) before and 24 h after delivery in normal vaginal (NVD) and cesarean section (C/S) delivery groups (N=45).

<table>
<thead>
<tr>
<th>Delivery type</th>
<th>Third trimester of pregnancy</th>
<th>The first 24 hours after delivery</th>
<th>Statistical Paired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/S (n=23)</td>
<td>82.16 ± 99.40</td>
<td>86.49 ± 23.76</td>
<td>P=0.325</td>
</tr>
<tr>
<td>NVD (n=22)</td>
<td>101.5 ± 105.65</td>
<td>84.9 ± 93.64</td>
<td>P=0.029</td>
</tr>
</tbody>
</table>

Note: Comparison of the serum Apelin-36 level, after delivery and at the third trimester, using the paired T-test.

**Table 2:** Relation between mother’s serum Apelin-36 level (Nm/L) in the third trimester of pregnancy, the first 24 h after delivery, and its changes with delivery type in NVD and C/S (N=45).

<table>
<thead>
<tr>
<th>Delivery type</th>
<th>Third trimester of pregnancy</th>
<th>The first 24 h after delivery</th>
<th>Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/S (n=23)</td>
<td>82.16 ± 99.40</td>
<td>86.49 ± 23.76</td>
<td>-4.32 ± 19.60</td>
</tr>
<tr>
<td>NVD (n=22)</td>
<td>101.5 ± 105.65</td>
<td>84.9 ± 93.64</td>
<td>16.62 ± 32.34</td>
</tr>
<tr>
<td>Test</td>
<td>Mann-Whitney</td>
<td>Mann-Whitney</td>
<td>Independent T-test</td>
</tr>
<tr>
<td>P-value</td>
<td>0.870</td>
<td>0.263</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Note: *Difference of Apelin-36 at the third trimester of delivery and after delivery

The Mann-Whitney test was used to determine the relationship between mother’s serum Apelin-36 level at the third trimester and the first 24 h after delivery and difference of changes based on delivery type.
The latter study by Lim et al. [23] is not totally consistent with the role of placenta in decreasing level of Apelin. According to this study, there was no effect of preterm and term spontaneous labors on Apelin and its receptor expression in placenta, but a significantly lower expression of Apelin was seen in fetal membrane. This study also clearly proved the anti-inflammatory role of Apelin before labor as well as Apelin’s regulatory role at regulation of proinflammatory cytokines and prostaglandins in amnion so it may suggest that apelin play a role in the rupture of fetal membrane. Consequently, the likelihood of Apelin ran placental transfer suggested by them on the grounds of a positive correlation between maternal and foetal plasma apelin concentration [23]. Unfortunately, there is insufficient data on the regulation and role of Apelin in human gestational tissues.

Another significant result, mentioned before, was that the hormone difference concentration was more in NVD group, compared to C/S group (p=0.005).

Malamits et al. (2007), with a study on 40 mothers, admittedly, reported no association between Apelin and parity or mode of delivery but they found apelin probable role in intrauterine development by demonstrating more plasma Apelin concentrations in full-term fetuses than neonates and their mothers. This is the only study that is not in line with our study [26].

As above-mentioned, Apelin is endogenous ligand for the APJ receptor [10] and widely expressed in various tissues such as heart, brain, pancreas, and blood vessel, placenta and it is involved in lots of physiological functions [28-31]. According to the role of Apelin in food intake, fluids balance, obesity, diabetes mellitus and metabolic syndrome [19,32,33].

It could be deemed as Apelin’s similar role in controlling energy homeostasis and deposition of adipose tissue in utero. Relatively, higher Apelin concentrations in obese participants compared to lean controls and Apelin up-regulation of in states of hyperinsulinemia and inflammatory have both been reported [34-36].

This result may show that the women with C/S are more susceptible to these dire consequences. As there is no study in this regard, more studies are suggested in this field. It was the researchers’ main propose to draw the readers’ attention to the difference in this hormone level in C/S group, compared to NVD. Unfortunately, due to financial problems in the purchase of Apelin-36 kit, researchers were not able to work on more samples in this regard. We suggest further studies with more samples and follow ups in order to investigate this women’s metabolic status.

The last significant result was a significant positive relationship between this hormone and length of all phases of delivery (P=0.019), (P=0.005), (P=0.019).

The results of our study are consistent with Hehir et al. [25] who reported that Apelin inhibits contraction process during labor among obese women and ultimately increases the number of cesarean deliveries [25]. The present study is totally in line with Apelin physiologic function. It inhibits magnocellular and parvocellular oxytocin autocrine and paracrine method and prevents oxytocin release and uterine muscle contraction [34]. Studies on virgin female and male mice revealed that Apelin is colonized with neurophysin (the protein that causes transfer of oxytocin and vasopressin from SON and PVN into posterior pituitary) [37,38].

### Conclusion

Based on the research, already carried out, decreased level of Apelin-36 in NVD can be useful for natural vaginal delivery trend, and also, a high difference in the level of this hormone in NVD may be a protective factor. Moreover, a positive relationship was seen in labor length that may show the important inhibitory effect of Apelin on uterine contractility. Regarding the widespread effects of Apelin on physiology and pathophysiology of pregnancy and human body, as well as its importance and role in metabolic syndrome and obesity, this study suggests conducting more studies in this regard.

### Acknowledgment

The present paper is derived from a master’s degree midwifery thesis. Hereby, the authors appreciate the honorable research deputy of Tarbiat Modares University for their cooperation. We also appreciate the chairperson of Glanads research center of Shahid Beheshti University, Dr. Fahime Ramezan, the chief, Dr. Hedayat, and the Dr. Kazem Nejad for statistical help, and the staff of Tehran Mahdieh hospital who helped the authors.

### References


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**Table 3:** Relation between mother’s serum Apelin-36 level (Nm/L) at third trimester of pregnancy, the first 24 h after deliver with labor duration (N=22).

<table>
<thead>
<tr>
<th>Duration of labor phase 1</th>
<th>Duration of labor phase 2</th>
<th>Duration of labor phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>r=0.301</td>
<td>r=0.260</td>
<td>r= 0.367</td>
</tr>
<tr>
<td>P=0.185</td>
<td>P=0.255</td>
<td>P=0.102</td>
</tr>
<tr>
<td>Apelin-36 at the third 24 h after delivery</td>
<td>r= 0.505</td>
<td>r=0.507</td>
</tr>
<tr>
<td>P=0.005</td>
<td>P=0.019</td>
<td>P=0.019</td>
</tr>
</tbody>
</table>

Note: Spearman Correlation test was used to determine the relationship between mother’s serum Apelin-36 level (Nm/L) at third trimester of pregnancy and the first 24 h after deliver.

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