The effect of mode of delivery on uncoupling protein-2 levels

Jehan H Sabry, MD(1), Soha A El-Gendy, MD(2), Omima Mohamed Abd El-Haie, MD(2), Abdelfattah Elkhoury(2), Afify E Abd El Latif, MBBCh(3).

Abstract

Background: Uncoupling proteins (UCPs) are carrier proteins located in the mitochondrial inner membrane that disturb the proton gradient by retransporting protons and that inhibit ATP synthesis.

Objective: The aim of our work is to show that a correlation exists between mode of delivery whatever normal vaginal delivery (NVD) or cesarian section (CS) and UCP-2 in humans an increasing UCP-2 levels through normal delivery will protect all organs, and particularly the brain, against oxidative damage and play a role in preventing organ dysfunctions.

Methods: This study was designed as a cross sectional study which was carried out on eighty healthy full term babies delivered by normal vaginal delivery and cesarean section. Studied neonates were classified into two groups: GROUP I included 40 full term healthy babies born with normal vaginal delivery. There were (16 males and 24 females) and GROUP II included 40 full term healthy babies born with cesarean section. There were (24 males and 16 females). Cord blood sample from each newborn was drawn immediately after birth under complete aseptic condition for laboratory investigations. Serum uncoupling protein-2 (UCP-2) was measured using ELISA.

Results: There is statistically highly significant difference between the 2 studied groups regarding Uncoupling protein 2 (UCP2) levels as there is decrease of UCPS in cesarean section compared with the normal vaginal delivery group with a mean (5.848 ± 1.715 ng/mL) & (12.866 ± 5.902 ng/mL) respectively.

Conclusion: This study showed that a correlation exists between mode of delivery and UCP-2 in humans. As UCP-2 is described as playing a significant role in the formation of nerve cells and deficiency of this protein during development of the brain may lead to behavioral problems extending to adulthood, we think that increasing UCP-2 levels through normal delivery will protect all organs, and particularly the brain, against oxidative damage and play a role in preventing organ dysfunctions.

Key Words: Uncoupling protein-2, newborn, normal spontaneous vaginal delivery, cesarean/section
Introduction

Uncoupling proteins (UCPs) are carrier proteins located in the mitochondrial inner membrane that disturb the proton gradient by retransporting protons and that thus inhibit ATP synthesis.\(^{(1)}\)

Mitochondrial uncoupling proteins are members of the larger family of mitochondrial anion carrier proteins (MACP).\(^{(2)}\)

Oxidative phosphorylation reactions occur inside the inner mitochondrial membrane.\(^{(3)}\)

A proton gradient occurs across the inner membrane with the pumping of protons from the matrix to inter-membrane space during electron transfer through the complex and energy in the electrochemical gradient is used in the formation of ATP as protons return to the matrix. This is catalyzed by ATP synthase.\(^{(4)}\)

This electrochemical gradient produces a proton motive and protons return to matrix under the effect of this force.\(^{(3)}\)

This phenomenon stimulates respiration, the system oxidizes more fuel in order to correct the proton gradient, and more protons are pumped. Since oxygen use is accelerated, the energy given off is released as heat, and body temperature rises. UCPs also lead to a decrease in redox potential and in free oxygen radical production.\(^{(5)}\)

Five different UCPs have to date been identified in mammals.\(^{(6)}\)

UCP-1(also known as thermogenin) is found in brown fatty tissue, Uncoupling protein-2 in several tissues, particularly the brain, Uncoupling protein-3 in brown fatty tissue and muscle tissue, and Uncoupling protein-4 (SLC25A27) and Uncoupling protein-5 (SLC25A14, BMCP) in the brain.\(^{(7)}\)

The most important characteristic of UCP-2 is that it is expressed in a very wide area in the brain.\(^{(8)}\)

Various studies report that when stimulated with cellular stress, UCP-2 plays a role in mitochondrial membrane potential, neuronal activity, body weight regulation, the release of reactive oxygen radicals, the prevention of cellular injury, regulation of fatty acid consumption, cell proliferation, the protection of brain cells and synaptogenesis, although its exact physiological role is uncertain.\(^{(8)}\)

One experimental study compared mitochondrial UCP-2 release in rat pups delivered normally or by the surgical route and showed greater UCP-2 release in neurons in the hippocampal region in pups delivered normally and less in those born by the surgical route.\(^{(9)}\)

Aim of the work:

The goal of this study is to show that a correlation exists between mode of delivery whatever normal vaginal delivery (NVD) or cesarean section (CS) and UCP-2 in humans as
increasing UCP-2 levels through normal delivery will protect all organs, and particularly the brain, against oxidative damage and play a role in preventing organ dysfunctions.

**Subjects and Methods**

**Subject**
This study was designed as a cross sectional study which was carried out in The Delivery Unit of Gynecology and Obstetrics Department of Benha University Hospital between (January 2016 and May 2016). All laboratory investigations were carried out in Clinical and Chemical Pathology Department of Benha University Hospital. The study involved eighty healthy full term babies delivered by normal vaginal delivery (no:40) and cesserian section (no:40).

Neonates of Gestional age <37 and >42 weeks, with major congenital malformations, fetal distress, perinatal hypoxia, maternal diseases or complications during pregnancy were eccluded.

**Ethical considerations**

The study was approved by local Ethics Committee of Benha faculty of medicine and informed written consents were taken from parents of the included newborns prior to be involved in the study.

**Method**

Full perinatal history was taken including prenatal, natal & post natal history, with stress on maternal infections during pregnancy or presence of gestional hypertension and premature rupture of memberane (PROM).

Full clinical assetement was carried out to the neonates in form of Vital signs. (Heart rate, respiratory rate, temperature and blood pressure), Anthropometric measurements (weight, length, head circumference), Skin examination, cardiac, abdominal, chest and central nervous system examination.

Apgar score was carried out on neonates after delivery at one minute after birth and again at five minutes.

Laboratory investigations were drawn from cord blood immediately after birth under complete aseptic conditions for hematological investigations inform of (CBC-Blood Gases-Total and Direct bilirubin-Serum Uncoupling protein-2)

**Sample collection:**
Under sterile aseptic techniques 5 ml of cord blood were withdrawn from the baby by the pediatrician: 1ml of blood was transferred on EDTA for CBC and 1 ml was used for ABG after heparnization. The rest of blood sample was centrifugated after clotting for 10 minutes at 3000 rpm in for separation of the serum. Serum was separated, divided into aliquates and kept at -20 °C till analyzed.

**Serum uncoupling protein 2 determination**

This was done using immunoassay kits provided by Wuhan Fine Biological Technology Co., Ltd, china.

✓ **Principle of the test:**

- The kit uses a double-antibody sandwish enzyme-linked immunosorbent assay (ELISA) to assay the level of human uncoupling protein 2(UCP 2) in samples.

- Add uncoupling protein 2(UCP 2) to monoclonal antibody enzyme well which is pre-coated with human uncoupling protein 2(UCP 2) monoclonal antibody, incubation :then add uncoupling protein 2 antibodies labeled with biotin, and combined with streptavidin-HRP to form immune complex

- Then carry out incubation and washing again to remove the uncombined enzyme.

- Then add chromogen solution A, B, the color of liquid changes into the blue, and at the effect of acid, the color finally becomes yellow.

- The chorma of color and concentration of the human substance uncoupling protein 2 of sample were positively correlated.

**Statistical Analysis**

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21.

Numerical data were summarized using means and standard deviations or medians and ranges, Categorical data were summarized as numbers and percentages. Comparisons between the 2 groups with respect to normally distributed numeric variables were done using the t-test.

Non normally distributed numeric variables were compared by Mann-Whitney test.
Spearman Correlation between variables was done, “r” (Spearman correlation coefficient) ranges from +1 to -1. A value of 0 indicates that there is no association between the two variables; a value greater than 0 indicates a positive association; a value less than 0 indicates a negative association.

All p-values are two-sided. P-values < 0.05 were considered significant

Results

The gestational age of the mothers of our studied neonates was about 38 wks ±1, the maternal age was about 27 years ±5, birth weight of the studied groups was about 3.30 kg ±0.26, the mode of delivery of the studied groups was 40 by normal vaginal delivery and 40 by cesarean section, sex was 40 males and 40 females, there were different parity of the mothers with different preinatal history

laboratory investigation include UCP-2 level, ABG (PH-Pco2-Hco3-BE), CBC (HB-HCT-PLT-WBCS), total & direct bilirubin.

| Table (1) Comparison of maternal age, gestational age and birth weight between 2 studied groups. |
|---------------------------------|---------------|---------------|---------------|-------------|---------------|---------------|---------------|-------------|
|                                 | NSVD          | C.S           |               |             |               |             |               |             |
|                                 | Mean ±SD      | Mean ±SD      |               | P value     |               |             |               |             |
| Maternal age (Years)            | 26 ± 5        | 27 ± 5        |               | 0.323       |               |             |               |             |
| Gestational age (Weeks)         | 39 ± 1        | 38 ± 1        |               | <0.001      |               |             |               |             |
| Birth wt. (Kg)                  | 3.296 ± 0.315 | 3.312 ± 0.21  |               | 0.788       |               |             |               |             |

There is no statistically significant difference between the studied groups regarding maternal age & birth weight, while there is statistically highly significant increase in gestational age in normal vaginal delivery group than cesarean section group as shown in table 1

There is no statistically significant difference between the studied groups regarding pco2, base excess, hemoglobin(HB), hematocrit (HCT), platelets count(PLT) and white blood cells count (WBCS).

there is statistically significant increase of total and direct bilirubin of normal vagina delivery group more than cesserian section there is statistically significant decrease of PH and HCO3 of normal vaginal group than cesserian section group as shown in table 5.

| Table (2) comparison of CRP and apgar scoring between the two studied groups |
|---------------------------------|---------------|---------------|---------------|-------------|---------------|---------------|-------------|
|                                 | NSVD          | C.S           |               |             |               |             |             |
|                                 | Median        | Minimum       | Maximum       | Median      | Minimum       | Maximum       | P value     |
| CRP                             | 2             | 0             | 24            | 4           | 0             | 48            | 0.509       |
| Apgar score 1m.                 | 9             | 8             | 10            | 7           | 6             | 9             | <0.001      |
| Apgar score                     | 9             | 8             | 10            | 8           | 6             | 10            | <0.001      |
There is no statistically significant difference between the 2 studied groups regarding CRP, while there is highly statistically significant increase of apagr score at one minute and five minutes in normal vaginal delivery group more than cesarean section group as shown in table 2.

Table (3) Comparison of Uncoupling protein 2 (UCP2) between
The two studied groups.

<table>
<thead>
<tr>
<th>Uncoupling ptn 2 (ng/mL)</th>
<th>NSVD Mean ±SD</th>
<th>C.S Mean ±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.866 5.902</td>
<td>5.848 1.715</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

UCP2 showed highly highly significant decrease in neonates delivered with CS when compared with those delivered with normal vaginal delivery.

Table (4) Correlation between level of uncoupling protein 2 level and other studied parameters.

<table>
<thead>
<tr>
<th>UNCOUPLING protein 2</th>
<th>r</th>
<th>P value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>0.237</td>
<td>0.035</td>
<td>S</td>
</tr>
<tr>
<td>Birth wt. (Kg)</td>
<td>-0.179</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Maternal age (Years)</td>
<td>-0.08</td>
<td>0.48</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar Score 1 m.</td>
<td>0.676</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Apgar score 5 m.</td>
<td>0.677</td>
<td>&lt;0.001</td>
<td>HS</td>
</tr>
<tr>
<td>PH</td>
<td>-0.3</td>
<td>0.007</td>
<td>HS</td>
</tr>
<tr>
<td>ABG PCO2 (mm Hg)</td>
<td>0.026</td>
<td>0.82</td>
<td>NS</td>
</tr>
<tr>
<td>ABG HCO3 (meq/Lt)</td>
<td>-0.179</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>ABG base excess (meq/Lt)</td>
<td>-0.05</td>
<td>0.65</td>
<td>NS</td>
</tr>
<tr>
<td>HB (g/dl)</td>
<td>0.068</td>
<td>0.55</td>
<td>NS</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>0.103</td>
<td>0.36</td>
<td>NS</td>
</tr>
<tr>
<td>PLT</td>
<td>-0.021</td>
<td>0.85</td>
<td>NS</td>
</tr>
<tr>
<td>WBCS</td>
<td>-0.052</td>
<td>0.65</td>
<td>NS</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.023</td>
<td>0.84</td>
<td>NS</td>
</tr>
<tr>
<td>T.bilirubin</td>
<td>0.377</td>
<td>0.001</td>
<td>HS</td>
</tr>
</tbody>
</table>
Correlation study revealed that there is statistically highly significant negative correlation between uncoupling protein 2 level & blood PH, and there is statistically highly significant positive correlation between uncoupling protein 2 and total bilirubin level and apagr score at one and five minutes, while there is statistically significant positive correlation between uncoupling protein 2 level and direct bilirubin level, but there is no statistically significant correlation between uncoupling protein 2 & other values as shown in table 8.

**Fig. (1):** Correlation between uncoupling protein 2 level and apgar score of newborn at one minute.

![Graph showing correlation between uncoupling protein 2 level and Apgar score 1m](image)

**Fig. (2):** Correlation of uncoupling protein 2 levels and Apgar score of newborn at five minutes.

![Graph showing correlation between uncoupling protein 2 levels and Apgar score 5m](image)
Fig. (3): correlation between uncoupling protein 2 level and blood PH.

Fig. (4): Correlation between uncoupling protein 2 level and direct bilirubin
Discussion

The perinatal environment represents a critical period in brain development that determines the adult architecture of the central nervous system and related functions. Mitochondrial uncoupling protein 2 (Ucp2) is an important determinant of fatty acid utilization by adult neurons.\(^{(10)}\)

Ucp2 is a mitochondrial protein and a byproduct of fat metabolism that expressed in many tissues and is involved in scavenging reactive oxygen species. This activity links Ucp2 to multiple physiological functions, including regulation of metabolism and neuronal activity.\(^{(11)}\)

Ucp2 promotes free radical scavenging\(^{(2,12)}\), which is critical for enabling fatty acid beta oxidation in neurons\(^{(10)}\). This mechanism is also important for adult synaptogenesis\(^{(13)}\). Ucp2 is also implicated in protection of adult\(^{(14)}\) as well as developing neurons in a febrile seizure model in rats at a time of breastfeeding\(^{(15)}\).

The most important characteristic of UCP-2 is that it is expressed in a very wide area in the brain\(^{(8)}\). Various studies report that when stimulated with cellular stress, UCP-2 plays a role in mitochondrial membrane potential, neuronal activity, body weight regulation, the release of reactive
oxygen radicals, prevention of cellular injury, regulation of fatty acid consumption, cell proliferation, protection of brain cells and synaptogenesis, although its exact physiological role is uncertain\textsuperscript{(15,16,17)}. An experimental study compared mitochondrial UCP-2 release in rat pups delivered both normally and by surgical route showed greater UCP-2 release in neurons in the hippocampal region in pups delivered normally than in those born by surgical route\textsuperscript{(18)}.

This cross sectional study was conducted at the Delivery Unit of Benha University Hospital to evaluate the correlation between the mode of delivery whatever normal vaginal delivery (NVD) or caesarian section (CS) and the UCP-2 levels in humans.

The study included 80 healthy full term babies, 40 babies were born by normal spontaneous vaginal delivery (NSVD) and 40 were by cesarean/section (C/S). Cord blood specimens collected after delivery were used for measurement of UCP-2 levels.

In the present study, neonates were 40 males and 40 females with mean gestational age of 38 weeks, birth weight of 3.30 kg, and maternal age of 27 years and mean Apgar score of 9. There was no statistically significant difference between the studied groups regarding maternal age & birth weight, while there was a statistically highly significant decrease in gestational age in CS group when compared with VD group.

The difference in gestational age could be attributed to high percentage of elective CS in our study and this comes in agreement with other studies showing that the gestational age was higher (38-40 weeks) in vaginal delivery than (37-38 weeks) in CS\textsuperscript{(19)} and the risks of preterm delivery were higher in CS than vaginal birth\textsuperscript{(20)}.

The maternal age of the both groups was within the normal age of gestation however other studies showed that higher ages over 30 years old were significantly associated with neonatal and maternal outcomes as well as higher CS rates\textsuperscript{(21)}.

In agreement with a recent study the birth weight showed no difference between the studied groups. In that study the mean weight in the two groups, vaginal delivery and non-emergency cesarean section delivery with spinal anesthesia, were 3317±453 grams and 3420±489 grams, respectively, and there was no statistical difference between the two groups (P=0.182)\textsuperscript{(22)}.

Although another study showed that elective cesarean section performed in private hospitals may be associated with low birth weight among full-term infants than VD\textsuperscript{(23)}, and this could be
attributed to cases of breech presentation and repeated cesarean section in this study that was similar to a study of Hannah and colleagues in 2000 \(^{(24)}\).

In the present study, PH and HCO\(_3\) were significantly higher in SC group than in NSVD group while PCO\(_2\) and base deficit showed no difference between the studied groups.

In consistence with our study, **Riley and Johnson, 1993** found that infants born by elective caesarean section have results which are closer to normal adult values (higher pH, Po\(_2\), base excess and bicarbonate, and lower Pco\(_2\)). \(^{(25)}\)

In accordance a study by Loh et al., entitled “Cord blood gas analysis of deliveries”, 153 vaginal delivery cases and 52 cesarean section cases were examined. HCO\(_3\) levels were lower in vaginal delivery than C-section. But the PH level of vaginal delivery was higher than cesarean section and Pco\(_2\) was significantly was significantly lower in NSVD group than CS group. \(^{(26)}\)

In contrast, a study showed that PH level in both deliveries was normal with no significant difference between the studied groups while the PCO\(_2\) was higher in VD than CS. \(^{(22)}\)

In addition, another recent contrast study showed that no significant difference were found regarding to the umbilical cord arterial blood gases. \(^{(1)}\).

The CBC profile in this study showed no significant difference between the studied groups regarding to the HB, HCT, PLT and WBCs.

In accordance, the study carried out by Redzko et al., the mean HB in normal delivery and caesarean section cases were 16.93 ± 2.44 and 16.30 ± 2.17, respectively. The difference between the two values was statistically non-significant. \(^{(27)}\).

A possible explanation could be the small number of neonates delivered by caesarean section \((n = 7)\) included in that study. The absolute number of patients appears to be clinically insignificant and the power of their analysis was not clinically relevant.

Our study results were also in agreement with those of Hematyar and Ekhtiari, 2008, who found no statistically significant differences between the neonates delivered vaginally and caesarean section in the mean values of Hb and Hct, however this study agreed with ours but the levels of HB and Hct were lower than our study and this discrepancy in the results may be because of the
environmental and physiological conditions under which the specimens were obtained, including mode of delivery, the treatment of umbilical vessels (early or late clamping) and the state of physical activity of the baby.\textsuperscript{(28)}

Also many studies found that delivery by caesarean section did not affect the values of MCV, MCH and MCHC.\textsuperscript{(28,29,30)}

In partial accordance, the mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width, lymphocytes and monocytes showed no significant differences in these two groups. In contrast, the Hb, RBC count, Hct, platelets, total leucocyte count, eosinophils and basophils were found to be higher in vaginally born infants than infants delivered by caesarean section ($P < 0.001$).\textsuperscript{(31)}

Another study by Hematyar and Ekhtiari, (2008) showed in contrast results and reported that increased level of Hb at birth is one of the essential iron storage in infants against iron deficiency anemia. Different causes can lead to decreased Hb level at birth; thus, neonates delivered by caesarean section are more likely to be at risk of developing iron deficiency anemia than those delivered by normal vaginal delivery\textsuperscript{(28)}

Also, an in contrast study showed that second-born twins after vaginal delivery have higher Hb levels and more often polycythemia than their co-twin, but not when born by CS.\textsuperscript{(32)}

The total and direct bilirubin were significantly higher in normal vaginal delivery group than CS group.

In the same respect to our results, Chang et al. (2011) reported that bilirubin level was higher among naturally delivered neonates, compared to those born by cesarean section.\textsuperscript{(30)}

In a study done by Garosi et al in (2016) found that the mean total bilirubin level in naturally delivered newborns was higher (17.3±3.5 mg/dl) than in cases born by cesarean section (16.1±3.9 mg/dl); based on t-test results, the difference was statistically significant ($P=0.02$)

Overall, vacuum assisted vaginal delivery, cephalohematoma, and oxytocin induction are considered as risk factors for hyperbilirubinemia and in fact, oxytocin may directly affect bilirubin metabolism.\textsuperscript{(30)}
Moreover, neonates born by cesarean section are more likely to receive supplements, resulting in the reduced severity of jaundice\cite{33,34}.

However, other studies found no significant relationship between mode of delivery and jaundice\cite{35,36,37}.

Similarly, another contrast study by Sharifizade et al. (2012) found no significant association between the severity of jaundice and mode of delivery\cite{38}.

In the present study, there is no statistically significant difference between the 2 studied groups regarding CRP levels.

Many studies have shown alterations of CRP during pregnancy, labor and postpartum in normal conditions and disease\cite{39}.

It was found that the types of delivery (vaginal or cesarean) section did not affect the response of CRP. Also, it was found that the CRP concentrations in cord blood were not affected in acute fetal distress in emergency cesarean section deliveries\cite{40}.

In contrast, the cesarean section babies had significantly lower peak CRP concentrations than did the babies delivered vaginally, which implies that the physical stress on babies during delivery may be related to the magnitude of the increases in CRP\cite{41}.

Another studies showed the same trend of results that CRP concentrations were significantly lower among elective cesarean deliveries and was primarily associated with duration of labor rather than delivery mode\cite{41,42}.

As for the Apgar score, it was statistically higher in VSVD group than CS group at 1 and 5 min.

In a study done by Arikan and colleagues there was an agreement with the previously mentioned results, newborns with the first minute Apgar score below 7 were higher in the cesarean group (p\textless0.05). Fifth minute Apgar scores and umbilical cord pH values were similar\cite{43}.

Also, In a recent study, children born through the CS (mean $\pm$SD =6.83$\pm$1.31) had a significantly lower Apgar score than those in the vaginal delivery group (mean $\pm$SD =7.19$\pm$1.81)\cite{44}.
In addition, it has long been well documented in several studies that CS delivery is more associated with increased fetal complications including reduced Apgar score, respiratory distress syndrome, and neonatal transfer rate (24,45; 46,47).

Consistent with other studies, the risk of birth asphyxia among babies born by CS was higher than those delivered vaginally. In that study, the mean Apgar score in the first minute was reduced among the CS group compared to the vaginal delivery group. (48)

This observation may be due to the nature of CS done for emergency situation. However, consistent with other studies, there was no difference in Apgar score between the two groups in the fifth minute. (49)

The present study showed that there is statistically highly significant difference between the 2 studied groups regarding Uncoupling protein 2 (UCP2) levels as there is decrease of UCPS in cesarean section group compared with the normal vaginal delivery group.

Various studies have shown that neuronal survival is correlated with increased UCP-2 expression, that neurological healing after experimental stroke and traumatic brain injury is better in rats given human UCP-2, and that UCP-2 prevents release of apoptogenic proteins by acting as a cellular reducing signal or by stimulating mitochondrial uncoupling (50,51).

Pregnancy is a physiological condition that increases oxygen requirements and necessitates high energy for numerous bodily functions. This increase in oxygen intake and consumption causes several changes, particularly in terms of oxidants, in the oxidant-antioxidant balance, and results in oxidative stress. This stress rises still further at birth. (52)

The lower levels of UCP2 during CS could be attributed to the lower antioxidants and higher oxidants in cesarean births compared to normal deliveries (53).

Georgeson et al., also stated that mothers and their neonates have been shown to be exposed to greater oxidative stress in cesarean deliveries, and antioxidant mechanisms involved against that stress are insufficient. (54)

In accordance, Julia Simon-Areces et al. reported that vaginal birth, but not C-section, induces strong expression of Ucp2 in cells of the hippocampus, a region of the brain involved in short- and long-term memory. Whether this reduction in Ucp2 expression results in changes in neuronal activity and brain function was not known at that time known. (9)
Also, another study revealed that in mice, vaginal birth induces significantly higher level of Ucp2 mRNA expression in the hippocampus than experimental C-section. That study showed that during the early postnatal period, UCP2 expression promotes neuronal differentiation, axonal outgrowth and synapse formation in the hippocampus.\(^{(55)}\)

As for human studies, only one study investigated the effect of delivery mode on UCP2 levels in which the mean UCP-2 levels were higher 2.34±0.62 (0.82-4.21) ng/mL in the cases born by NSVD than in the cases born by C/S 2.06±0.51 (0.54-3.02) ng/mL. The difference between the groups was significant (p<0.05).\(^{(1)}\)

There was a significantly positive correlation between gestational age, Apgar score, total and direct bilirubin and UCP2 level. Also, the levels of PH were inversely correlated with UCP2 level.

In accordance positive correlation was found between UCP2 and gestational age as UCP2 level was lower in small for gestational age infants\(^{(56)}\)

The correlation between bilirubin and UCP2 could be attributed to that vaginal birth has higher levels of bilirubin that need higher levels of UCP2 as antioxidant.\(^{(30)}\)

UCP2 has been proposed as a regulator of reactive oxygen species production during electron transport in the mitochondrial inner membrane. The mitochondrial respiratory chain is probably the most important source of superoxide and its rate of formation depends on respiratory activity. Also, UCP-2 protein was described as playing a significant role in the formation of nerve cells in the brain and of networks between these, and deficiency of this protein during development of the brain may lead to behavioral problems extending to adulthood, thus normal Apgar score could be related to the UCP2 levels.\(^{(13)}\)

In conclusion, this study and the data from the literature show that birth by NSVD increases UCP-2 levels. As UCP-2 is described as playing a significant role in the formation of nerve cells and deficiency of this protein during development of the brain may lead to behavioral problems extending to adulthood, we think that increasing UCP-2 levels through normal delivery will protect all organs, and particularly the brain, against oxidative damage and play a role in preventing organ dysfunctions.
Recommendations

- We should encourage normal vaginal delivery more than elective cesarean section. As UCP-2 is described as playing a significant role in the formation of nerve cells and deficiency of this protein during development of the brain may lead to behavioral problems extending to adulthood.
- We think that increasing UCP-2 levels through normal delivery will protect all organs, and particularly the brain, against oxidative damage and play a role in preventing organ dysfunctions.

References


37- BOSKABADI H & NAVAEI M. (2011): Relationship between delivery type and jaundice severity among newborns referred to Ghaem Hospital within a 6-year period in Mashhad.


52- Mutlu B, Bas AY, Aksoy N et al., (2012): The effect of maternal number of births on oxidative and antioxidative systems in cord blood. The journal of maternal-fetal & neonatal medicine :
the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 25:802-805.


