



## Original article

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## THE INFLUENCE OF PRENATAL STRESS ON NEUROBEHAVIORAL DEVELOPMENT OF FETUS AND CHILD

### SUMMARY

The aim of the paper was to prove the influence of prenatal stress on neurobehavioral development of fetus and child. The investigation was conducted in 2006 by polling the parents of children born during the bombardment of the Federal Republic of Yugoslavia in 1999. On children's regular enrolment into the first grade of elementary school, the parents were to give yes/no answers to the questions about behavior and the existence of behavioral problems during development. The investigation included 685 children divided into four groups by date of birth, so that each group was in different period of development during the bombardment. The first group comprised children whose mothers were not exposed to the bombardment during their pregnancy, that is, the children had already been born. The second group included children whose mothers' pregnancy ranged between the 29<sup>th</sup> and 40<sup>th</sup> week of gestation during the bombardment. The third group comprised children whose intrauterine development was in the range between the 13<sup>th</sup> and 40<sup>th</sup> week of gestation during the bombardment, while the fourth group included children whose intrauterine development during the bombardment was from the moment of conception to the 13<sup>th</sup> week of gestation. The data were statistically processed and presented graphically using the SPSS software package. In the group of children born before the bombardment, there is statistically significantly greater number of hyperactive, aggressive and disobedient children compared to the group of children born during the bombardment (II), in which, statistically significantly, the existence of sensibility, insecurity and crying, accompanied by attacks of fear at night and speech disorders is more frequent. In the children born in 1999 after the bombardment (III and IV), there are no clear differences in the frequency of extroverted (aggressive) and introverted (submissive) behavior. The quality of life in the FR of Yugoslavia before and after the bombardment can be compared to the quality of life of people living in communities where life, because of social and political insecurity, comes down to constant "fighting for survival". The period of bombardment from March 24 to June 9, 1999 was also marked with additional biological insecurity and "escapes" into shelters. The pattern of behavior of children in stressful situations, on the principle "fight or escape", corresponds to behavior of their mothers in the last trimester of pregnancy.

**Key words:** prenatal, stress, neurobehavioral, development, adaptation

## INTRODUCTION

The life quality of an individual depends on social circumstances on the whole, as well as its personal psychic, social and health status. It reflects personal satisfaction with everyday life, meaning without unpleasant emotions, which does not only depend on material well-being. As unpleasant emotions are at the basis of "stress", they stand for a mechanism which links stress and life quality. Due to the accumulation phenomenon, even minor unpleasant situations which last more than six months lead to "stress". However, when such events are extremely unpleasant, especially if they occur in the development period, stress diminishes the quality of entire life, even when its effects last shorter (1).

In the last decade of the XX<sup>th</sup> century, life quality of the great part of the population in the FR of Yugoslavia was similar to the one of all socially and ethnically jeopardized people worldwide (independence, segregation, poverty, economic collapse, increased crime rate, living in the violent neighborhood, etc.). Especially, the time of NATO aggression on the FR of Yugoslavia in 1999 and uncertainty of a three-month-long bombardment are characterized by intensive psychosocial stress of the entire population. After the war effects have ceased and shortlasting "victory" euphoria, life quickly resumed its previous course, already determined by social and political instability (2).

To confirm the opinion that great misfortunes are caused by human activities, it is not necessary to perform psychophysiological studies and provide exact biological proofs. There are many findings about their influence on people, especially sensitive population categories. Therefore, no one should doubt that all pregnant women were exposed to in-tensive "stress" during the bombardment of the FR of Yugoslavia (3).

Typically, stress is followed by recognizable clinical presentation: change in blood pressure, body temperature and heart rate, urine excretion, concentration of blood, lymphocytes and polymorphonuclear leukocytes, capillary permeability, glucose level in blood, alkaline reservoir, level of chlorine and sodium in blood etc. Depending on numerous factors, there develop various patterns of psychic reactions, neuroendocrine, immunological and other processes (4).

According to up-to-date investigations, emotional reactions result from functional co-effects of three anatomic-physiological levels: hypothalamus, limbic system, and neocortex of the telencephalon. Frontal regions of the cortex in humans perform adaptation of emotional reactions through the mechanism evaluating stressful situations. This evaluation mechanism situated in the

cortex of the telencephalon is associated with emotions in the limbic system as well as additional stimulus for secretion. The basic patterns of behavior and active conflicting in stressful situations on the principle of "fight or escape" are programmed by pleasant or unpleasant emotions on the principle of "reward or punishment". Stressful reactions always produce only unpleasant emotions, which are at the same time a punishment for bad outcome, contributing thus to formation of new patterns of behavior. Pleasant emotions stand for a reward for overcoming the crisis and appear after successful solving the problem by active behavior, which explains how the pattern is better remembered (5).

Learning, which establishes and modifies the patterns of behavior, is, therefore, not just a conscious cognitive process. It is also influenced by the contents of the unconscious. It exists in the situations of classic pavlovian instrumental conditioning. It is affected by social and cultural factors and is life-long. The largest number of learned reactions originates from the early childhood, and there are more and more proofs that we start learning before birth. Early traumatic experiences affect both chemistry and anatomy of the brain. Therefore, the time of learning is of crucial importance for the brain development. In other words, the degree of psychological development of an individual at the moment of facing stress determines the kind and severity of consequences on psychic health (6).

The examinations of pregnant women coming from the population suffering for poverty and racial/ethnic segregation have showed that the life quality of previous generations has been associated with a negative pregnancy outcome. Similar studies have also pointed that long-term psychosocial stressors before pregnancy can condition or "set afire" a stressful reaction during pregnancy. Psychophysiological studies have showed overstressed physiological responses to new stressors in these pregnant women (7).

It has been proved that low social status of a pregnant woman, by the mechanisms of psychosocial stress to which she is exposed, increases the frequency of depression and bad habits associated with bad pregnancy outcome (8).

Besides influencing an immediate pregnancy outcome, psychosocial status of a pregnant woman can also play a certain role in modification of neurobehavioral fetus development. After introduction of ultrasound into obstetric practice, many doctors have ascertained that there is a clear connection between current mood of a pregnant woman and behavior of a fetus. Visualization of fetus behavior with regard to a mother's emotional state has started investigations

on this kind of connection and behavior of a neonate, the so-called psychoneonatology. Though some doubts about the mechanisms remain, the results actually support the hypothesis about the intrauterine behavior programming through the interaction between mother, placenta and hormones (9).

It has been proved that the changes in the level of adrenaline, plasma epinephrine and hydrocorticosteroids, which follow hyperventilation, tachycardia and many other effects of a mother's being upset, can also be registered in a fetus. Various mechanisms of their influence function in different phases of fetus development and are to be investigated in the future. It is supposed that in vulnerable development periods, the stress of a mother can permanently change the reactivity between hypo-thalamic-pituitary-adrenaline (HPA) axis and sympathetic-adreno-medullary (SAM) system and influence the development of limbic system and prefrontal cortex, which stand for anatomic substrate of emotional reactions (10).

However, this functional system remains plastic the entire life, so that it is shaped and reshaped by various environment stressors, modeling the basic reaction pattern, obtained by birth. According to some authors, an adopted child can entirely form a new pattern of behavior in stressful situations, different from the one inherited from biological mother (11).

## AIMS

We have made the working hypothesis: that life quality of a pregnant woman (determined by exposure to psychosocial stressors during great misfortunes and/or social/political instability) is characterized by different consequences on neurobehavioral fetal development, with long-term influence on a child's behavior. In other words, the models in postnatal life cannot significantly change the pattern of behavior inherited by birth (up to the age of seven), which shapes the life quality of a mother and her response to stress after the 29<sup>th</sup> week of gestation.

The aim of the paper was to prove that the basic pattern of behavior of a child at the age of seven was prenatally shaped according to mother's behavior in the period from 29<sup>th</sup> to 40<sup>th</sup> week of gestation.

## MATERIAL AND METHODS

The influence of prenatal stress on neurobehavioral fetal development was estimated by comparing the frequency of anxiety disorders and characteristic patterns of behavior in children born in Leskovac in 1999 before, during and after the

bombardment of the FR of Yugoslavia. The investigation was conducted in 2006 by polling the parents in the Pediatric Health Center, when children were regularly tested for enrolling in the first grade of elementary school. The study comprised 685 children, divided into four groups: the children born before the bombardment (from January 1 to March 23), during bombardment (from March 24 to June 30), and two groups of children born after bombardment (from July 1 to September 30 and from October 1 to December 31). In the first group, the mothers were not exposed to the bombardment because their children had already been born. The second group included mothers whose pregnancy ranged from 29<sup>th</sup> to 40<sup>th</sup> week of gestation during the bombardment. In the third group, pregnancy ranged from 13<sup>th</sup> to 40<sup>th</sup> week of gestation, and in the fourth group the range was from conception to 13<sup>th</sup> week of gestation.

As an instrument of polling, a specially designed questionnaire was used, in which the parents had to choose from given answers. The questionnaire was anonymous. As indicators of development disorders, there were: speech disorders, nocturnal urination, disobedience, tics, indecent words, hyperactivity, fears, nocturnal fear, withdrawing into loneliness, thumb-sucking, nail biting, losing consciousness, cramps, clumsiness and being accidentprone, weak appetite, overeating, aggression towards peers, frequent telling lies, aggression towards adults, being concerned, destroying things and toys, drawing attention to itself, blaming others, insecurity, being apt to crying, repeating words or movements, frequent masturbation, stubbornness, irritability, autism, age unadjusted behavior, encopresis.

We were witnesses that "fight" at the time of isolation and sanctions imposed against our country were replaced by "escape" into shelters during the bombardment. The consequences on psychic health of children born that year were estimated seven years later by defining them and comparing the frequency of their features, which characterize these two patterns of behavior. The parameters which characterize the pattern of "fight" and domination in stressful situations are the following: hyperactivity, disobedience, aggression, destroying toys, and telling indecent words. The pattern of "escape or avoidance" is characterized by submissive insecurity, shyness, loneliness, nocturnal fears, speech disorders, irritability, being apt to crying.

The data were statistically processed and graphically presented by using SPSS software package.

RESULTS

After analyzing the results, we concluded that in children born in Leskovac in 1999 the frequency of all variables examined was statistically significant,  $p < 0,001$ , (Table 1).

Table 1. Statistical presentation and frequency of anxiety disorders in total for all four groups

Examined variables	Hi square	Ss	P	Yes	No
Speech disorders	118.577	1	.000	200	485
Nocturnal urination	384.188	1	.000	86	599
Disobedience	230.086	1	.000	144	541
Tics – sudden unwilling movements	630.145	1	.000	14	671
Indecent words	276.241	1	.000	125	560
Hyperactivity and restlessness	4.101	1	.043	316	369
Fears –no nocturnal fears	94.927	1	.000	215	470
Nocturnal fear – sudden screaming, crying	506.454	1	.000	48	637
Withdrawing into loneliness	592.364	1	.000	24	661
Thumb sucking, nail biting	273.707	1	.000	126	559
Losing consciousness and cramps	661.210	1	.000	6	679
Clumsiness, being accident prone	584.947	1	.000	26	659
Weak appetite – nutrition disorders	271.184	1	.000	127	558
Overeating	503.020	1	.000	49	636
Aggression towards peers	278.787	1	.000	124	561
Frequent telling lies	559.359	1	.000	33	652
Aggression towards adults	369.356	1	.000	91	594
Being concerned	566.612	1	.000	31	654
Destroying things and toys	343.394	1	.000	100	585
Drawing attention to itself	67.482	1	.000	235	450
Blaming others	420.977	1	.000	74	611
Insecurity, timidity	289.088	1	.000	120	565
Repeating words or movements	645.584	1	.000	10	675
Frequent masturbation	633.987	1	.000	13	672
Stubbornness	15.488	1	.000	291	394
Irritability, being apt to crying	244.206	1	.000	138	574
Talking to itself	509.899	1	.000	47	638
Acting as a younger child	527.301	1	.000	42	643
Encopresis	372.299	1	.000	90	595

Though the differences in groups were not significant, the frequency of variables examined was a bit higher in children whose mothers' pregnancy during the bombardment was above 13 weeks of gestation. (Figure 1 and Table 2.).

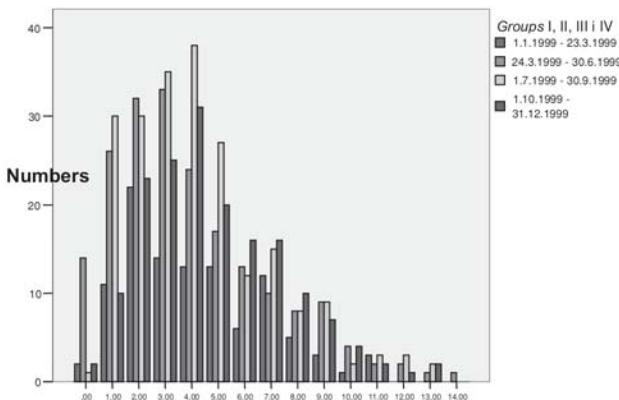


Figure 1. The sum of all examined variables by groups

Table 2. Percentage of variables' frequency by groups

		Groups by date of birth				Total
		1.1.1999 - 23.3.1999	24.3.1999 - 30.6.1999	1.7.1999 - 30.9.1999	1.10.1999 - 31.12.1999	
Total	Number of examinees in the group	105	196	215	169	685
	% within a total number of variables	15,3%	28,6%	31,4%	24,7%	100,0%

Statistical significance in groups was not proved, ( $p < 0.133$ ). (Table 3).

Table 3. Statistically significant differences in the frequency of variables

	Value	Ss	p
Pearson Chi-Square	52.277(a)	42	.133
Likelihood Ratio	52.770	42	.123
Linear-by-Linear Association	4.861	1	.027

The sum of features indicating submissive behavior (more timidity and less aggression) (Table 4) in children whose mothers were exposed to bombardment in the last trimester of pregnancy is statistically more frequent,  $p < 0.05$  (Table 5), compared to the group of children born before the bombardment (Figure 2).

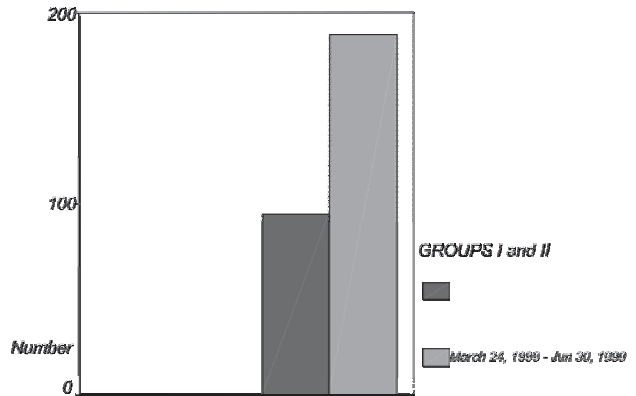


Figure 2. The sum of features indicating submissive behavior in groups I and II

Very high frequency of development problems in children born in 1999 can be associated with the influence of long-term social and economic crises during the '90s. Being highly expressed, partly, the occurrence is the consequence of the examination methodology. When parents have the role of observers and those who estimate, there is a risk of subjective idealization and catastrophic presentation of certain patterns of children's behavior.

However, the examination of correlations among groups was reliable, so that results indicate high specifics and undoubted significance of differences in some features among children born before and during the bombardment. Namely, when



the examined features were summed and qualified as a part of a certain pattern of behavior in reaction to stress (on the principle "fight or escape"), it was shown that the children born during the bombardment were more characterized by submissive behavior. The frequency of children apt to crying, irritable, shy, insecure and, generally, children not inclined to social interaction was increased, while statistically the number of hyperactive, disobedient, indecent and aggressive children was decreased. Therefore, the expectedly increased number of scared mothers during the bombardment which occurred in the last trimester of their pregnancy permanently programmed the submissive behavior of the offspring even in less important life events. High frequency of speech disorders, which is also expressed in the group of children born during the bombardment, is in favor of conclusion about increased anxiety.

Regarding the frequency of all examined variables in group III, there is a possibility that in children born immediately after the bombardment there is a weak, but possible, postponed influence of PTSD mothers being in the early stage of pregnancy during the bombardment (12).

That postnatal influence of mothers and other models did not change the basic pattern of behavior obtained by birth is proved by a considerably large number of children with the opposite pattern of behavior, born immediately before the bombardment. Those children belong to the same generation, so that they grew up and developed along with the children born during the bombardment in the same conditions of the outside world. What is different is only the influence of their mothers as the environment in the period before birth.

## DISCUSSION

Individual differences in psychoneuroendocrine functions play a significant role in someone's behavior. The development model presented in introduction means that these individual differences develop progressively in the interaction between genetic influences, the influence of mother as the environment on fetus and the influence of environment on a newborn and grown up individual. It is considered that previous experiences have long-term and, frequently, permanent consequences when compared to those occurring later in life, whose effects can be transient.

Numerous researches performed on humans and experiments on primates confirm that mother as the environment during pregnancy, by effects of prenatal stress, considerably changes the processes

of fetal neurological development connected with recognition, memory and adaptation to stress. When the total results of experiments performed on animals and studies on humans are surveyed, one can see that, generally in all mammals, the stability of the environment in which a pregnant female lives shapes the behavior of the offspring, their endocrine status and distribution of androgenic and estrogenic receptors in specific parts of the brain.

Retrospective studies performed on humans suggest that chronic psychosocial maternal stress during pregnancy (with elevated levels of CRH, ACTH and cortisol in plasma) increases the possibility of slower development and frequency of developmental disorders in children's behavior. In the adulthood, it can be associated with frequent appearance of schizophrenia, left-handedness or dislaterality with abnormalities of brain morphology. These damages can occur only under the influence of neuroendocrine system, which mediates the influence of psychosocial stress of the mother on the brain development in fetal stage. Excessive CRH and other hormones, such as cortisol and ment-enkefalin, which pass through the placenta, are also associated with damages in a usual fetal reaction to stimulation, after birth with difficulties in temperament of a newborn. Excessive quantity of CRH and cortisol cause damages to fetal brain through changed activities of neurotransmitters, creating predisposition towards disorders of attention and depression. Disorders can be the consequence of these hormones' effects on their receptors in the fetal limbic system (13-20).

There are various neuroendocrine mechanisms which mediate the influence of the social environment, but the key role is given to mother's steroids. In that case, the HPA axis of the fetus need not always be involved and, possibly, in some cases of stress, the involvement of its SAM system is also important. Finally, the changes in their activity influence together the limbic system, where the basic pattern of emotional reaction to stress is shaped: timidity or aggression, that is, learned helplessness or active behavior. Accordingly, dominant or submissive behavior later in life, besides the nature of stressor or evaluation of reality, depends both on the pattern of emotional reactions and reactivity of HPA axis and SAM system inherited by birth (21-28).

The association of the variables examined, prenatal stress and behavioral development of children presented in our study should point to general life quality of a pregnant woman. Based on experiments on animals (primates), studies on humans, whose life was exposed to psychosocial stress, such results are unexpected. We think that they are in favor of hypothesis, stressed by many

authors, that life quality of the mother is very important in modification of fetal neuroendocrine system.

The fact that prenatal stress consequently manifests through various forms of development (primarily anxiety disorders in offspring) should be equally important to an obstetrician during the follow-up of pregnancy, as well as any other agent harmful to fetus. The results indicate that researches should be broadened to various other aspects of development of children born during the bombardment e.g. through the manifestation of sexual orientation, disposition towards certain diseases, shortening of average life span etc.

However, it is necessary to pursue further investigations to understand in which way and to which extent accumulative burden of psychosocial stressors affects women, their reproductive health, and therewith their offspring. Such investigations are quite scarce in number, especially when recent and current wars are concerned. Probably, there is a small number of states affected with war which can undertake such investigation. Mostly, miscarriages, length of pregnancy and perinatal outcome after wars have been investigated so far (29-31).

In Israel, the influence of prenatal stress on the appearance of schizophrenia in children whose

mothers were exposed to bombardment during the Gulf War was investigated, but its increased frequency was not proved (32).

PTSD was proved by measuring the level of cortisol in saliva in babies whose mothers were exposed to the attack of the WTC (33,34).

## CONCLUSION

The long-term influence of the antenatal maternal stress is of key importance for neurobehavioral fetal development, and usually, later in life, is associated with anxiety of a child. This fact justifies the implementation of the program for stress diminishing and social support of a pregnant woman.

By feeling helpless during the bombardment, the majority of pregnant women affected the formation of submissive attitude in their children when reacting to every day life problems, which we registered in our investigation seven years later.

The dominant pattern of behavior in stressful situations is shaped before birth, according to behavior of the mother in the last trimester of pregnancy.

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## UTICAJ PRENATALNOG STRESA NA NEUROBIHEJVORALNI RAZVOJ FETUSA I DETETA

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### SAŽETAK

**Cilj rada bio je dokazati uticaj prenatalnog stresa na neurobihevioralni razvoj fetusa i deteta. Ispitivanje je sprovedeno 2006. godine anketiranjem roditelja one dece koja su rođena u godini bombardovanja Jugoslavije 1999. Prilikom njihovog redovnog upisa u prvi razred osnovne škole roditelji su odgovarali sa da ili ne na pitanja o ponašanju i postojanju bihevioralnih problema u razvojnom periodu. Studija uključuje ukupno 685 dece razvrstane u četiri grupe, po datumu rođenja, tako da je svaka grupa tokom bombardovanja bila u različitom periodu razvoja. U prvoj grupi su deca majki koje u trudnoći nisu bile izložene bombardovanju, odnosno već su bila rođena. U drugoj grupi su ona čije su majke u vreme bombardovanja bile od 29 do 40 nedelja gestacije (NG). U trećoj grupi su deca čiji je intrauterini razvoj u periodu bombardovanja bio u rasponu od 13 do 40 NG i u četvrtoj od začeca do 13 NG. Podaci su statistički obrađeni i prikazani grafički korišćenjem kompjuterskog programa SPSS. U grupi dece rođene pre bombardovanja (I) ima statistički značajno veći broj hiperaktivne, agresivne i neposlušne dece u odnosu na grupu rođenu tokom bombardovanja (II), u kojoj je statistički značajno češća pojava osetljivosti, nesigurnosti i plačljivosti sa napadima noćnog straha i govornim poremećajima. Kod**

dece rođene 1999. godine, posle bombardovanja (III i IV), nema jasnih razlika u učestalosti ekstravertnog (agresivnog) i intravertnog (submisivnog) ponašanja. Kvalitet života u SR Jugoslaviji pre i posle bombardovanja može se porediti sa kvalitetom života ljudi u zajednicama, koje su u svakodnevnoj „borbi“ preživljavanja zbog socijalne i političke nesigurnosti. Period bombardovanja od 24. marta do 9. juna obeležen je dodatnom biološkom ugroženošću i „bekstvom“ u skloništa. Obrazac ponašanja dece u stresnim situacijama, po principu „bekstvo ili borba“, odgovara ponašanju njihovih majki u poslednjem trimestru trudnoće.

*Ključne reči:* prenatalni stres, neurobihejvioralni razvoj, adaptacija