

## Effect of Substitution Therapy on the Birth Weight of Newborns, Postpartum Adaptation, Trophism and Course of the Neonatal Abstinence Syndrome

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### Abstract

**Aim:** Evaluation of the effect of substitution therapy on the birth weight of the newborn, its postpartum adaptation and course of the neonatal abstinence syndrome.

**Patients and methods:** We studied heroin-addicted women and women undergoing methadone and buprenorphine substitution. During the 3 years we concentrated on 47 heroin-addicted women and 60 women under substitution for prenatal screening, labour and delivery.

**Results:** Birth weight of newborns was lowest in the group of heroin-addicted women as compared to the group receiving substitution with buprenorphine  $p < 0.01$  and to the group of methadone-substituted patients  $p < 0.05$ . The highest number of changes in the placenta was exhibited by heroin users, both when compared to methadone users ( $p < 0.01$ ) and buprenorphine users ( $p < 0.001$ ). The highest statistically significant number of newborns with IUGR symptoms were born to heroin-addicted women. The lowest Apgar score was recorded in all three evaluations in the group of buprenorphine users and the highest in methadone-substituted women.

**Conclusions:** Substitution therapy provides pregnant women with the possibility of social stabilization and adequate prenatal care. With regard to the fact that methadone substitution protracts the newborn's abstinence syndrome, attention has been recently focused on substitution with buprenorphine that seems to be from this viewpoint a more considerate option.

**Keywords:** Addicted women; Buprenorphine; Iugr; Metadone; Pregnancy; Substitution

### Introduction

The lifestyle of heroin-addicted women is rather disorganized and their prenatal care during pregnancy usually insufficient. They visit the prenatal centre only sporadically (1-6 times during the whole period of pregnancy), about 50% of them come to the hospital only upon the onset of contractions or after the discharge of amniotic fluid. Heroin passes through the placenta to the fetal tissues within 1 hour after the application. There is no unambiguous evidence that the increased incidence of congenital developmental defects and reduction of the length of gestation could be ascribed only to opiates. Degradation of the drug in the maternal organism is associated with its degradation in the fetus which results in an increased risk of distress and death of the fetus [1]. Drug level fluctuations in heroin users, similarly as recurring abstinence syndrome, cause changes in the placenta and development of the placental insufficiency. These changes are manifested in the microscopic image of the placenta in the form of an increased incidence of intervillous and perivillous microfibrin deposits, increased vascularization of villi, an increased number of proliferations of trophoblastic buds and nuclear nodules. Due to the placental insufficiency, the fetuses are born with intrauterine growth retardation. Therefore it is recommendable to perform during each visit of the pregnant woman in the prenatal centre ultrasound biometry of the fetus, to check the amniotic fluid volume and condition of the placenta, and starting from the third trimester, also measuring of the flow rate in the umbilical artery.

Newborns may exhibit clinically significant levels of drugs in the serum for another several hours or days after the birth and the organism is completely detoxified long after discharge of the child from the maternity hospital.

Various drugs, particularly those with an inhibitory effect on CNS, are known for causing the newborn's physical dependence which is

manifested by the so called neonatal abstinence syndrome (NAS). Most often NAS develops after exposure to opiates 24-48 hours after the birth. In case of methadone it may develop up to 2-4 weeks after the birth because the drug degrades from the deposits in the organism of the fetus gradually. The neonatal abstinence syndrome occurs in 60-90% newborns. The symptoms may persist for 3-4 months after the birth. Up to 70% of newborns with NAS have symptoms of CNS irritability that may progress into convulsions, 50% of them have symptoms of tachypnea, apnoic pauses, feeding problems [2,3]. Diagnosis of the abstinence syndrome includes identification of specific symptoms of behaviour and the function of the vegetative nervous system that may be manifested as disturbances of the gastrointestinal (GIT) and respiratory tract (RT) or central nervous system (CNS).

In the mid-seventies, Finnegan developed a scoring system of the neonatal abstinence syndrome in babies exposed in the prenatal period to heroin or methadone. This scoring system may be successfully applied for identification of symptoms of abnormal behaviour in the newborns. It is the best developed and most frequently used method of NAS scoring in terms of the central nervous system, gastrointestinal tract, respiratory and vasomotor disturbances. It screens 21 NAS symptoms and evaluates them using 1 to 5 scoring. The Finnegan

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scoring system is used for evaluation of degradation mainly of opiates, but also of other drugs. In case of suspected abstinence symptoms, the newborn is observed and monitored every 4 hours. If the score is 8 and more, scoring continues every 2 hours. Neonatal abstinence syndrome is diagnosed if the score is 8 and more in three consecutive readings. NAS treatment is a supporting and pharmacological therapy. Newborns with the history of their mothers' drug abuse should be monitored more frequently and if necessary transferred to the intensive care unit. They require thermoneutral environment, prevention of excessive noise and lighting, and minimal manipulation. Pharmacological NAS treatment after narcotics begins with opiate and morphine preparations. There is no consensus concerning the treatment of the neonatal abstinence syndrome with methadone. Some authors present numerous schemes of its administration while others strongly reject it and strictly contraindicate administration of methadone in the neonatal period. At our Department, methadone is not used in the newborns for the NAS treatment. We use Phenobarbital in case of the opiate NAS as the medication of the second choice or we administer it in combination with opiate preparations.

## Methods

This prospective study was carried out in the period of 2008-2010. Included in the study were heroin-addicted pregnant women and pregnant women undergoing methadone and buprenorphine substitution therapy. During the 3 years we concentrated on 47 heroin-addicted women and 60 women under substitution therapy for prenatal screening. Of this number, 36 pregnant women were methadone-substituted and 24 buprenorphine-substituted. All the pregnant women were followed up in the prenatal centre for high-risk patients of the Department of Gynecology and Obstetrics of the Teaching Hospital and 2<sup>nd</sup> Medical Faculty of Charles University in Prague. All women were screened for duration of pregnancy, birth weight of the newborn, weight loss by 3<sup>rd</sup> day after the birth, presence of changes in the placenta and IUGR, Apgar score at 1<sup>st</sup>, 5<sup>th</sup> and 10<sup>th</sup> minute of life, pH, neonatal abstinence syndrome evaluated by the Finnegan scoring system, duration of the NAS treatment. All enrolled women signed the informed consent and the study design was approved by hospital ethical committee.

Individual groups were compared using the Kruskal-Wallis ANOVA test. Correlation of dichotomic variables was evaluated by means of loglinear models. Calculations were done by means of NCSS 2002 statistical software (Number Cruncher Statistical Systems, Kaysville, UT, USA). Comparison of changes in Apgar score was completed using the repeated measures ANOVA consisting of Drug as the between-factor, subject-factor, Time as the within-factor and Drug × Time interaction. Respecting strongly non-constant variance and asymmetric distribution in the dependent variable, this was transformed by a power transformation to approximate Gaussian data distribution and homoscedasticity. For a graphical demonstration the transformed means with their upper and lower limits of 95% confidence intervals were re-transformed to original scale.

Statistical software Statgraphics Plus from Manugistics (Rockville, MD, USA) was used for evaluation of repeated measures ANOVA model.

We monitored the effect of substitution therapy using two different preparations on duration of pregnancy, birth weight, the newborn's early postpartum adaptation, development of IUGR and placental changes, NAS development, its severity and duration of its necessary therapy. The two groups (methadone and buprenorphine) were

compared with the heroin-addicted pregnant women and with each other.

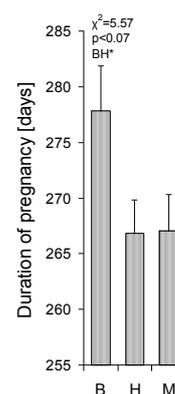
The aim of study was to determine which substitution therapy is more profitable for the course of pregnancy and of NAS.

## Results

In terms of duration of the pregnancy, no statistically significant difference was found when comparing heroin-addicted women and the buprenorphine- or methadone-substituted women (Figure 1).

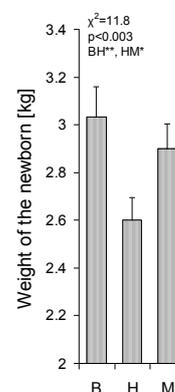
Birth weight of newborns was statistically significantly lowest in the group of heroin-addicted women as compared to the group receiving substitution with buprenorphine  $p < 0.01$  and as compared to the group of methadone-substituted patients  $p < 0.05$  (Figure 2). Physiological weight loss by 3<sup>rd</sup> day after the birth was higher in methadone- ( $p < 0.01$ ) and buprenorphine- ( $p < 0.05$ ) substituted women as compared with heroin users (Figure 3).

When monitoring changes in the placenta in terms of increased incidence of intervillous and perivillous microfibrin deposits, increased vascularization of villi, an increased number of proliferations of trophoblastic buds and nuclear nodules, the statistically highest number of changes was exhibited by heroin users, both when compared



Comparison between heroin-addicted women and the buprenorphine- or methadone-substituted women.

**Figure 1:** Duration of pregnancy (days).



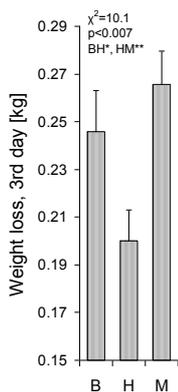
Birth weight of newborns – comparison between heroin-addictive women and the buprenorphine-substituted women ( $p < 0.01$ ) or methadone-substituted women ( $p < 0.05$ )

**Figure 2:** Birth weight of newborns.

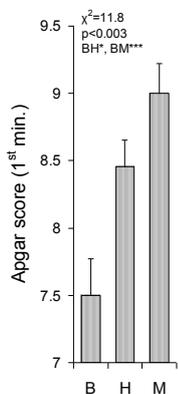
to methadone users ( $p < 0.01$ ) and buprenorphine users ( $p < 0.001$ ). Comparison of the two groups receiving substitution therapy showed statistically significantly more changes in the placenta of methadone-substituted women ( $p < 0.001$ ) (Table 1). Changes in the placenta are associated with the development of a chronic placental insufficiency that may result in IUGR. The highest statistically significant number of newborns with IUGR symptoms were born to heroin-addicted women, namely when compared to the group of methadone users  $p < 0.001$  and to buprenorphine users  $p < 0.05$ . No statistically significant difference between the groups under substitution therapy was found in the incidence of hypertrophic newborns (Table 1) (Figure 3).

Early postpartum adaptation of newborns was evaluated at 1<sup>st</sup>, 5<sup>th</sup> and 10<sup>th</sup> minute of their life using the Apgar score and pH of umbilical cord blood. The lowest Apgar score was recorded in all three evaluations in the group of buprenorphine users and the highest in methadone-substituted women (Figures 4-7). Examination of pH of umbilical cord blood did not reveal any statistically significant differences between individual groups (Figure 8, 9).

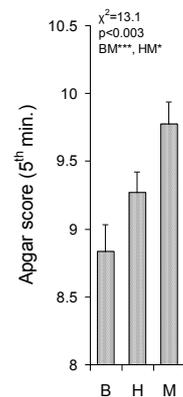
After the birth, the newborns were monitored for the onset of abstinence symptoms and its severity was evaluated using the Finnegan scoring system. The most severe manifestation of the abstinence syndrome was recorded in newborns of methadone-substituted



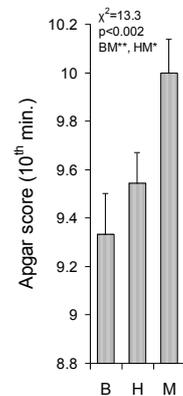
Weight loss by 3<sup>rd</sup> day after the birth - methadone- ( $p < 0, 01$ ) and buprenorphine- ( $p < 0, 05$ ) substituted women in comparison to heroin users  
**Figure 3:** Weigh loss by 3<sup>rd</sup> day postpartum.



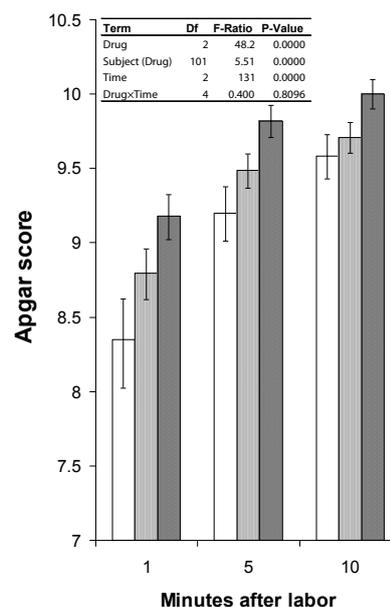
The lowest Apgar score - in the group of buprenorphine users and the highest - in methadone-substituted women  
**Figure 4:** Apgar score at 1<sup>st</sup> minute of life.



The lowest Apgar score - in the group of buprenorphine users and the highest - in methadone-substituted women  
**Figure 5:** Apgar score at 5<sup>th</sup> minute of life.



The lowest Apgar score - in the group of buprenorphine users and the highest - in methadone-substituted women  
**Figure 6:** Apgar score at 10<sup>th</sup> minute of life.



**Figure 7:** Apgar score – development in time.

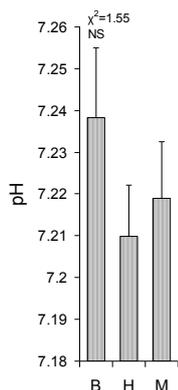
	All		B-H		B-M		H-M	
	X <sup>2</sup>	p-value						
IUGR	15,23	0,0005	5,76	0,0164	0,90	0,3430	14,20	0,0002
Changes in the placenta	33,55	0,0000	33,55	0,0000	12,25	0,0005	6,76	0,0093

Table 1: Changes in the placenta and IUGR.

women, namely on a high significance level as compared to groups of buprenorphine-substituted women and heroin-addicted women ( $p < 0.001$ ). The longest treatment was required by the abstinence syndrome of newborns of methadone-substituted women (Figure 10) as compared both to the buprenorphine-substituted group and the group of heroin-addicted women ( $p < 0.001$ ).

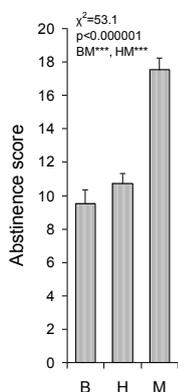
## Discussion

According to some data in the literature, up to 50% of drug-addicted women deliver their babies preterm [4,5]. Our experience corresponds rather to those studies with preterm delivery ranging between 23-29.4% [6,7]. We have not encountered overdue deliveries or hypertrophic fetuses. Duration of pregnancy in heroin-addicted and methadone-substituted women was almost the same (g.w. 38+1 and g.w. 38+2), while in buprenorphine-substituted women the duration



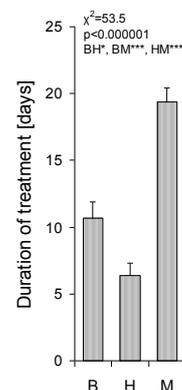
pH of umbilical cord blood – no statistically significant differences between individual groups

Figure 8: pH of the umbilical cord blood.



Severity of NAS – comparison methadone-substituted women to the group of buprenorphine-substituted women and heroin-addicted women ( $p < 0.001$ ). No statistically significant differences between buprenorphine-substituted women and heroin-addicted women

Figure 9: Abstinence syndrome of the newborn (Finnegan scoring system).



The length of treatment of the abstinence syndrome of newborns - methadone-substituted women compared to the buprenorphine-substituted group and the group of heroin-addicted women ( $p < 0.001$ ).

Figure 10: Duration of neonatal abstinence syndrome treatment.

of pregnancy was on average g.w. 39+4, i.e. pregnancy in these women was by more than one week longer. However, the difference was not in our total group of patients statistically significant. In the group of buprenorphine-substituted women, there was also the highest frequency of caesarean sections (33.3%) which may be to a certain extent connected with a higher share of overdue and induced deliveries in this subgroup.

Changes in the placenta, reduced placental perfusion, malnutrition of the mother as well as the direct effect of drugs have an impact on the birth weight of the newborns [5]. In our group, the statistically significantly lowest birth weight was recorded in newborns of heroin-addicted women, with the average birth weight of 2600 g, in the group of buprenorphine users the average birth weight was 3050 g and in the group of methadone users 2900 g. Experiments on animals have demonstrated that administration of heroin directly to the rabbit fetuses reduces their weight [8]. The highest weight loss by 3<sup>rd</sup> day after the birth was recorded in newborns of methadone-substituted women. This may be ascribed to a slower postpartum adaptation of these newborns and distress in the form of a severe neonatal abstinence syndrome.

Changes in the placenta of opioid users are caused both by drug level fluctuations and recurring abstinence syndrome. In our group of patients, we have recorded apart from increased incidence of intervillous and perivillous microfibrin deposits, increased vascularization of villi, also signs of proliferation, deposits of fibrin exsudation on the surface of the chorionic villi, umbilical artery thrombosis, symptoms of funiculitis, umbilical phlebitis, chorioamnionitis. If highly severe, we can consider finding of the anomaly of umbilical arteries with only one artery in place which results in the development of placental insufficiency and IUGR. Therefore in the third trimester, every 14 days we measure biometrics of the fetus, amniotic fluid volume and the flow rate in the umbilical artery. Our evaluation revealed the highest number of changes in the placenta in heroin-addicted women, when comparing

the two groups of women receiving substitution therapy, there were more changes found in the placenta of methadone users. Accordingly, the majority of newborns with IUGR were born to heroin-addicted women. No statistically significant difference in terms of the number of newborns with IUGR was found when comparing the two groups of women under substitution therapy.

The set of symptoms developing in newborns after exposure to opiates for 24-48 hours after the birth is called the Neonatal Abstinence Syndrome (NAS). We have evaluated NAS using the Finnegan scoring system which is due to its simplicity and promptness of the evaluation of the newborn's condition and is the most frequently used method in the clinical practice [2,9]. For treatment we used opium tincture, and only in a few cases phenobarbital. There is no consensus as concerns the treatment of the neonatal abstinence syndrome with methadone. Some authors present numerous schemes of its administration while others strongly reject it and strictly contraindicate administration of methadone in the neonatal period. At our department, methadone is not used in the newborns for the NAS treatment. The most severe NAS was recorded in newborns of methadone-substituted women. These newborns also required the longest treatment which is connected with gradual release of methadone from the newborn's tissues [3,7].

## Conclusion

Substitution therapy provides pregnant women with the possibility of social stabilization and adequate prenatal care. At the same time it eliminates drug level fluctuations in the organism, development of abstinence syndrome in pregnant women, subsequent changes in the placenta and development of placental insufficiency resulting in the

development of IUGR. The higher the substitution dose administered to the mother, the more marked are the newborn's abstinence symptoms. With regard to the fact that methadone substitution protracts the newborn's abstinence syndrome, attention has been recently focused on substitution with buprenorphine that seems to be from this viewpoint a more considerate option.

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