

Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department

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Abstract

OBJECTIVE: The aim of the study was to evaluate the effect of substitution therapy in heroin addicted pregnant women on the course of pregnancy, perinatal outcomes and course of the neonatal abstinence syndrome.

DESIGN OF THE STUDY: A five-year randomised prospective comparative study
METHODS: The study was carried out in the period of 2002–2007. The group of patients included 147 i.v. heroin-addicted pregnant women. All of them were outpatients of our Perinatal Care Unit. Their daily dose of heroin was approximately 1g. Later, 30 women were disqualified from the study for breaking the randomised criteria engagement. The substitution therapy in women who agreed to undergo it, started during the I. trimester of pregnancy. Finally, 47 heroin, 32 methadone and 38 buprenorphine addicted women were enrolled in the study. Birthweight of newborns was compared with the national birthweight tables. Severity and duration of neonatal abstinence syndrome (NAS) were evaluated by Finnegan's score scale.

RESULTS: None of the women delivered before the end of 34th gestational week. We did not encounter any perinatal death or developmental defect. The lowest birthweight, the highest number of newborns with IUGR and the most numerous placental changes were found in the group of heroin-addicted women. The differences compared to the two groups receiving substitution therapy were statistically significant ($p < 0.05$). The severity and course of NAS were the most severe ($p < 0.001$) in newborns of women from the methadone group.

CONCLUSION: Comparison of the groups of outpatients is in many ways questionable because of the restricted possibility of the patients' control. The lifestyle of addicted women has the same impact as the drug use alone. This is probably the main reason for differences in some of the monitored parameters between individual groups. Based on our results we can state that substitution therapy provides pregnant women with the possibility of social stabilization and adequate prenatal care. Substitution therapy decreases the street heroin consumption. Methadone notably protracts the newborn's abstinence syndrome. With regard to this fact, attention has been recently focused on substitution with buprenorphine that seems to be from this viewpoint a more considerate option.

Abbreviations and units

NAS – neonate abstinence syndrome
IUGR – intrauterine growth restriction
IGA – international grant agency
s.c. – cesarean section
CTG – cardiotocograph
AFI – amniotic fluid index
All used units are from The International System of Units

INTRODUCTION

Soon after the “velvet revolution” in 1989, the Czech Republic quickly switched from a transit to final destination country for drugs. However, the drug scene there differs from that in the western countries. Nowhere else in the world is the use of pervitine as the stimulation drug so widely spread as in the Czech Republic. Pervitine accounts for 70% share of the total number of i.v. users of illicit drugs. In the Czech Republic, opiate addicts represent the second most numerous group of drug addicts dependent on the so called “hard” drugs. They account for almost one third of the total number of all drug addicts and almost always they are dependent on heroin. Very popular is also smoking of marijuana where in the age group of 15–34 year olds the Czech Republic ranks as the first country in Europe. During the last 3 years the numbers of users of illicit drugs have stagnated with a slight departure from the so called “hard drugs”. The only exception is cocaine that has been so far less affordable due to high prices, however with the growing standard of life its consumption slightly increases. The number of troubleshooting drug addicts in the Czech Republic is estimated at 30 000. Identical pattern of the use of drugs can be seen in drug-addicted pregnant women, with almost the same percentage share. Annually, 100–150 women dependent on the so called “hard drugs” deliver a baby in the Czech Republic [13].

In our study we focused on heroin-addicted pregnant women. Opiate addiction offers certain possibilities of substitution treatment. The aim of the study was to evaluate the effect of substitution therapy on the

course of pregnancy, perinatal outcomes and course of the neonatal abstinence syndrome (NAS).

The lifestyle of heroin-addicted women is highly disorganized and their prenatal care during pregnancy usually insufficient or non-existing. Heroin passes through the placenta to the fetal tissues within 1 hour after the application and cumulates in the amniotic fluid, causing the fetus' addiction. Degradation of the drug in the maternal organism differs from that in the fetus. Due to immaturity of tissues, detoxification abilities of the fetus are highly limited. Thus, pharmacokinetics of drugs in the fetus differs considerably from that of the mother. In general, the risk of intrauterine distress and death of the fetus is increasing [6]. Drug level fluctuations in heroin users, similarly as the recurring abstinence syndrome, cause changes in the placenta and resulting in 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. Progressive placental insufficiency subsequently causes intrauterine growth retardation (IUGR) of the fetus [12].

The condition of the fetus is further complicated by the fact that often the mother's addiction is not limited to heroin only and is a multi-drug addiction. In addition, the mother is almost always dependent on nicotine.

Opiates induce physical dependence relatively quickly. In the newborn, it is manifested by the so called **neonatal abstinence syndrome** (NAS). NAS develops 24–48 hours after the birth. The neonatal abstinence syndrome occurs in 60–90% of newborns. It is manifested by a variety of symptoms of disturbances of the central nervous system, gastrointestinal and respiratory tracts and of the vegetative nervous system. Up to 70% of newborns with NAS have symptoms of CNS disturbances manifested by increased irritability that may culminate in attacks of generalized convulsions, 50% of children have symptoms of tachypnea, apnoic pauses, feeding difficulties [3,5,9,10].

In the mid-seventies, Finnegan developed a scoring system of the neonatal abstinence syndrome. It is one of the best developed and most frequently used methods of NAS scoring. It screens 21 NAS symptoms and evaluates them using 1 to 5 scoring.

Methadone substitution was legally introduced in the Czech Republic in 1997. Inclusion of pregnant women who are interested in this therapy is preferred. However, due to the fact that the pregnant must attend the methadone centre on a daily basis to get their dose and, consequently, are under continuous control, it is relatively difficult to convince them to participate in this form of substitution. A certain role is played also by the fact that pregnant drug-addicts are quite well informed about the effect of methadone on the course of NAS. Inclusion in the methadone programme is more successful in case of women from higher social strata.

Due to better financial conditions they can afford a higher quality and purer heroin, so develop tolerance more quickly and have to increase the daily dose. Consequently, methadone substitution is in the end their only chance. No wonder that the necessary daily substitution dose of methadone is high and reaches 80mg/24 h and even more. Reduction of methadone doses or conversion to total abstinence are quite rare.

Since 2002, we have been using **buprenorphine** (Subutex®) substitution therapy to treat opiate addiction in pregnant women. Inclusion of women in this type of substitution is relatively successful. A maximum daily dose of 8mg of buprenorphine can substitute the dose of 1g of heroin. As compared to methadone, in part of the pregnant women the daily dose of buprenorphine applied during their pregnancy can be successfully reduced.

METHODS

This prospective study was carried out in the period between October 2002 and October 2007. During 5 years we succeeded to concentrate 47 heroin-addicts and 70 women undergoing substitution therapy for the study. Of this number, 32 pregnant women were methadone-substituted and 38 buprenorphine-substituted. For the sake of validity of the indicators compared, we included in the study only the women whose daily dose of heroin was approximately 1g. In women under substitution therapy, their substitution daily dose had to correspond to this amount of heroin, i.e. approximately 80 mg of methadone and 8mg of buprenorphine. All the pregnant women were followed up in the outpatient department of the Perinatal Care Unit of 2nd Medical Faculty of Charles University in Prague and the Teaching Hospital Motol. All of them signed the Informed Consent with participation in the study. The study was approved by local ethic committee and supported by IGA of Ministry of Health..

The biggest problem in the outpatient follow-up was to eliminate or reduce as much as possible the effect of other negative factors associated with the lifestyle of drug-addicts that might distort comparison of results of individual groups. In spite of this, we attempted to determine randomisation criteria. Criteria for inclusion of the pregnant women in the study are listed in Table 1.

Inclusion in the group was conditioned by participation in one of the substitution programmes by 12th week of pregnancy and observance of the substitution rules. At each visit to the Perinatal Care Unit, all women underwent a simple saline drug test. Due to a positive finding, 15 buprenorphine-substituted women, 14 heroin addicts and 1 methadone-substituted woman were gradually excluded from the study. Comparison of individual groups is shown in Table 2.

All women were screened for duration of pregnancy, birthweight of the newborn, the newborn's weight loss by 3rd day after the birth, onset of the neonatal ab-

Table 1: Inclusion criteria

Age up to 30 years
Dependence on i.v. applied opiates for 3-5 years
HIV negative
BWR negative
Absence of active B and C hepatitis
Negative history of tromboembolism
Primigravidity or second gravidity with uneventful course of the preceding pregnancy
Absence of a any other chronic disease
Smokers up to 10 cigarettes a day
Dg. of the current pregnancy in I. trimester
Absence of another addictive substance
At least 5 visits to the Perinatal Care Unit

stinence syndrome evaluated by the Finnegan scoring system and the period of its treatment. Placentas of all women were sent to histological examination.

RESULTS

No statistically significant differences were found in the comparison of all the three groups in terms of duration of pregnancy. Severe prematurity was encountered in none of the groups, all neonates were delivered after the completed 34th gestational week. Fourteen women in the heroin group (29.8%), 10 women in the buprenorphine group (26.3%) and 7 women in the methadone group (21.8%) delivered prematurely prior to the completed 37th gestational week. Comparison of the birthweight of newborns revealed a statistically significantly lower birthweight in heroin-addicted women as compared to both groups of women under substitution. However, of greater importance is the finding that in heroin-addicted women there was a statistically significantly higher share of newborns with birthweight below 10th percentil of the national birthweight tables.

Placental changes mentioned in the introduction were manifested most markedly and at the same time most frequently found in the placenta of women in the heroin group. Differences shown by the comparison with the groups of buprenorphine- and methadone-substituted women are statistically significant ($p < 0.001$ and 0.01 , respectively).

Delivery in all the followed-up groups was in absolute majority uneventful. Incidence of caesarean section in all groups was very low: 8.5% in the heroin group, 6.3% in the methadone group and 7.9% in the buprenorphine group. Dystocia, breech presentation and the imminent intrapartum hypoxia of the fetus were the only indications for termination of the delivery by s.c. and their incidence was equally distributed between individual groups. In two cases of pregnant women from the heroin group and in once case from the group of buprenorphine group we terminated the delivery by outlet forceps due to the protracted 2nd stage of labour.

Table 2: Comparison of characteristics of individual subgroups

	Heroin (n= 47)		Buprenorphine (n= 38)		Methadone (n= 32)		Fisher exact test p level 0.05
	mean (range)	SD	mean (range)	SD	Mean (range)	SD	
age	26.6 (22-29)	4.2	25.4 (23-28)	4.3	26.8 (23- 29)	3.9	N.S.
duration of addiction (years)	4.2 (3-5)	1.3	3.9 (3-5)	1.4	4.4 (4-5)	1.1	N.S.
parity	1.3	1	1.2	1	1.3	0.9	N.S.
No. of visits in Perinatal Care Unit	5.8 (5-7)	2.2	6.4 (5-7)	2.1	7.2 (5-10)	2.9	H-B - N.S. H-M - 0.04 B-M - 0.08

Legend: H-B – heroin- buprenorphin; H-M – heroin-methadone; B-M- buprenorphine-methadone, SD – standard deviation

Figure No.1: Onset of NAS symptoms and duration of its treatment in individual groups.
Legend: axis y – % of newborns, axis x – duration of treatment (days); squares indicate the buprenorphine group(B), triangles the heroin group(H) and lozenges the methadone group (M).
Statistical signification:
B-M – $p < 0.000001$;
H-M – $p < 0.000001$;
B-H – N.S.

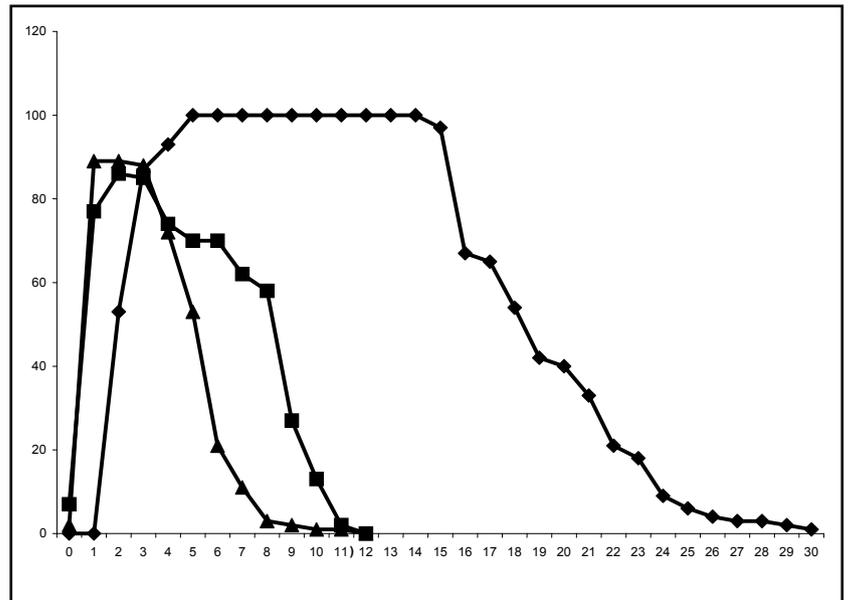


Figure No.2: Degree of NAS severity determined by Finnegan scoring
Legend:
Statistical signification:
B-H – N.S.;
B-M – $p < 0,000001$;
H-M – $p < 0,000001$

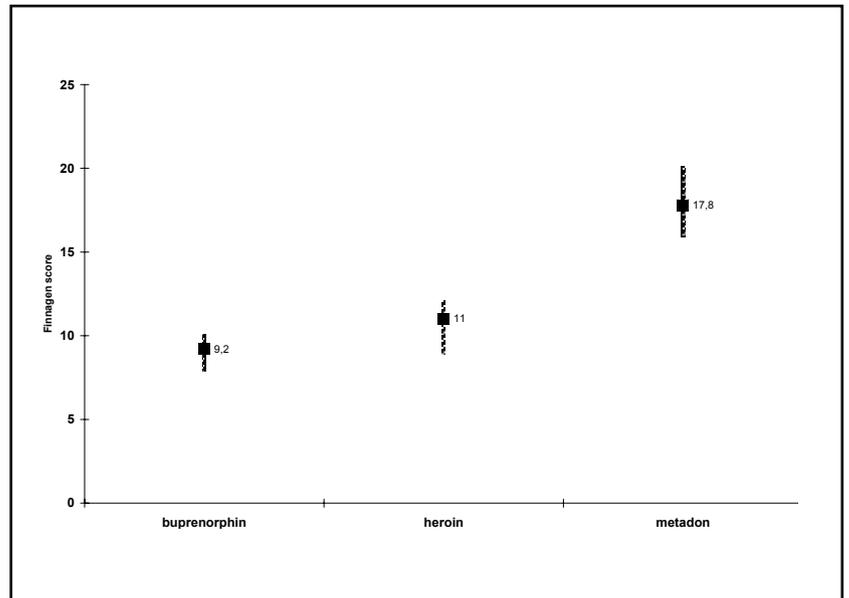


Table 3: Comparison of selected perinatalogical indicators

	heroin	(n=47)	buprenorphine	(n=38)	methadone	(32)	p value p level < 0.05
	mean/No./ %	SD	mean/No./ %	SD	mean/No./ %	SD	
duration of pregnancy (days)	260 (238–282)	28	270 (241–285)	26	261 (238–279)	25	H-B 0.0623 B-M 0.0725 H-M – N.S.
premature labours > 34.g.w.	14 (29.8%)		10 (26.8%)		7 (21.8%)		H-B 0.0836 B-M 0.0638 H-M 0.045
premature labours < 34.g.w.	0		0		0		
birthweight (g)	2601 (1650–3210)	506	3050 (1820–3730)	485	2900 (1730–3690)	656	H-B –0.003 B-M –0.128 H-M –0.007
IUGR	13(27.7%)		4 (10.5%)		3(9.3%)		H-B –0.016 B-M –0.343 H-M –0.007
severe placental changes	18(38.3%)		6 (15.8%)		6 (18.8%)		H-B –0.000 B-M –0.198 H-M –0.002
ph umbilical vein	7.22 (7.19–7.34)		7.24 (7.21–7.4)		7.21 (7.18–7.32)		N.S.
Apgar score 1.5.10 minutes	8.9/ 9.5/ 9.8		8.4/ 9.3/9.7		8.7/9.3.9.6		N.S.
caesarean rate	4 (8.5%)		3 (7.9%)		2 (6.2%)		N.S.
weight loss 3rd day (g)	196 (180–231)	28	248 (198–256)	33	269 (220–286)	32	H-B –0.042 B-M –0.102 H-M –0.007

Legend: H-B – heroin-buprenorphine, B-M – buprenorphine-heroin, H-M heroin-methadone; No.– number of cases; SD – standard deviation

Typical of deliveries in all groups were accentuated emotional manifestations of the women. As the main cause of these manifestations we consider a generally low pain tolerance. For this reason we used successfully epidural analgesia in 73% of deliveries.

After the birth, the condition of newborns was evaluated by determination of the Apgar score at 1st, 5th and 10th minute of life and umbilical Astrup. Comparison of all groups did not show any statistically significant differences.

Body weight curves of newborns were evaluated on 3rd postpartal day. The highest weight loss of newborns was recorded in the group of methadone-substituted women. The results are shown in Table 3.

Symptoms of the developing NAS were evaluated by Finnegan scoring at 6 hour intervals. In cases where the scoring was 8 and more, the intervals of evaluation of NAS severity were reduced to 4 hours. Opium tincture was used to assuage NAS. Its dosage was adjusted to the severity of NAS manifestation. In children born to women from the heroin group, NAS developed within 24–48 hours after the birth in 89%, in newborns from the buprenorphine group NAS was manifested within 24–48 hours in 86%. The remaining newborns exhibited no evident NAS symptoms. In babies born to women from the methadone group the symptoms of NAS oc-

curred in 100% of cases. As compared to the former groups, onset of the NAS symptoms in this group was delayed, in 53% of newborns NAS was recorded after 48 hours and in 34% after 72 hours. In 13% of cases the symptoms were manifested 96 hours after the birth. Statistically significant differences were found in examination of the degree of NAS severity and duration of the newborn's treatment. The most severe manifestations were revealed in babies born to women from the methadone group. Corresponding to this was also duration of the necessary treatment. In both cases statistical analysis proved high significance in the comparison with the group of newborns in the buprenorphine and heroin groups ($p < 0.000001$). The results are shown in Figure 1 and 2.

DISCUSSION

Preterm deliveries in opiate-addicted women account according to some older studies [3] for up to 50%. The results of our study support the opinion [1,10] that the incidence of preterm deliveries in these women is substantially lower (21.8–29.8%) and that as a rule they are not the case of severe prematurity. However, it has to be taken into account that we studied a relatively strictly selected group of drug-addicted patients. Duration of

pregnancy in heroin-addicted and methadone-substituted women in our group was almost identical (37+1 and 37+2, respectively), in buprenorphine-substituted women it was 38+4. Thus, pregnancy in the latter group was longer by more than one week. However this difference was not statistically significant in terms of the whole group. Incidence of surgically terminated pregnancies was low in all groups, significantly lower than in the other population of pregnant women.

Direct effect of drugs, the almost always present nicotine, lifestyle and malnutrition of drug-addicts are factors contributing to the development of placental changes leading to restriction of placental perfusion and negative impact on the birthweight of the newborns [2,9]. In our group, the statistically significantly lowest birthweight was recorded in newborns of heroin-addicted women, with the median of 2600 g, in the group of buprenorphine users the median birthweight 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 [2,9]. A similar effect is assumed also in case of application of buprenorphine and methadone. Differences in the birthweight of newborns have to be therefore explained also by another mechanism.

One of the factors contributing to a faster development of changes in the placenta is drug serum level fluctuations in the pregnant's organism. From this viewpoint, a regular administration of a drug is more favourable for the development of the birthweight curve, as was confirmed also by the results our study. Intra-uterine monitoring of the fetus by determination of a modified biophysical profile (CTG + AFI + biometrics of the fetus) if necessary in combination with Doppler flowmetrics especially in the course of III. trimester of pregnancy we consider very suitable for early detection of the symptoms of IUGR. It was not surprising that our evaluation revealed the highest number of changes in the placentas in heroin-addicted women who presumably used the drug at different intervals, the drug was of varying quality and their lifestyle was most disorganized. Accordingly, the majority of newborns with IUGR were born to these women [2,9].

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 the most frequently method used in the clinical practice [3]. For treatment of the newborns we used opium tincture, and only in a few cases of very severe NAS, phenobarbital as a concomitant therapy [3,6]. There is no consensus as concerns the treatment of NAS 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. In the Czech Republic, the use of methadone for the NAS treatment is not currently allowed.

The most severe NAS we recorded in agreement with our expectation in newborns of methadone-substitut-

ed women. These newborns also required the longest treatment which may be explained by gradual release of methadone from the newborn's tissues [1]. Rather surprising was a relatively early onset of NAS after the birth (48–96 hours) in this group of newborns. In the newborns from the heroin and buprenorphine groups, NAS was manifested in about 90% within 24 hours. NAS symptoms were least manifested in the newborns from the buprenorphine group, on average with Finnegan score of 9. Treatment of NAS required on average 11 days. In the newborns from the heroin group NAS was more severe, on average with score of 11. However, the treatment was shorter and took on average one week.

Loss of weight by 3rd day after the birth was the highest in children born to methadone-substituted women. This result may be explained by a slower postpartal adaptation of these newborns affected by the growing stress caused by the development of a severe form of NAS [1,10].

In general, inclusion of a drug-addict in the substitution programme requires a change in her lifestyle. This particularly applies to the methadone substitution. Resocialization in this type of substitution is the most successful as compared to other forms. Prenatal care usually improves and after the birth children are in most cases entrusted to their mothers' care. The negative aspect is the high degree of NAS. The higher the substitution dose administered to the mother, the more marked the newborn's abstinence symptoms [1], this is why attention has been recently focused on substitution with buprenorphine that seems to be from this viewpoint a more considerate option. However, the checking regime in buprenorphine substitution is not so strict as compared to the methadone programme. It does not require of the addict to make substantial changes of her high-risk behaviour, and therefore we often encounter undesirable phenomena associated with this form of substitution, such as abuse of buprenorphine, its illicit sale or i.v. application. Visits to the prenatal centre are irregular and as a result, prenatal care rarely improves. In spite of all problems, buprenorphine substitution compensate for the use of heroin which is especially in case of "street drugs" a highly desirable phenomenon. The course of pregnancy is usually uneventful. In most cases, NAS is only moderate with the symptoms relatively quickly subsiding [4,8].

Although drug addicted women represent in the Czech Republic a marginal problem in terms of obstetrics, this issue has to be properly addressed. We attempted to compare differences in the effect of a daily dose of 1g of heroin and a corresponding dose of substitution drugs, i.e. buprenorphine and methadone, on the course of pregnancy, development of the fetus and the course of the neonatal abstinence syndrome in outpatients of our Perinatal Care Unit.

Substitution as one of the form of help provided to opiate-addicts offers pregnant women the possibility of social stabilization, resulting among other things in

improvement of prenatal care. Substitution eliminates drug level fluctuations in the organism and development of abstinence syndrome in pregnant women. We consider a stable level of drug a lesser evil for the developing fetus even at the cost of development of addiction. Detoxification and subsequent abstinence is recommended only in the course of I. trimester, but our experience in this respect is highly negative. The same applies to psychosocial support in case of outpatients, where we have not achieved any significant success, either [11]. We have not practically recorded any case of full abstinence of the pregnant.

Substitution is a small and rather uncertain step towards abstinence. Despite the above mentioned negatives, it may be recommended with regard to the course of pregnancy and the final outcome of children born to the opiate-addicts. Very positive in this respect is the high percentage of children that can be entrusted to their mothers' care. Financial costs spent by the state on the subsequent social control and assistance provided to these risk-associated families are significantly lower as compared to those required by institutional care of children.

Statistics

Individual groups were compared using the Kruskal-Wallis ANOVA test. The relation between the binary variables was evaluated by means of the Fisher test. The relation between data of other categories was evaluated on the basis of the χ^2 -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).

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