

Results of Psychohormonal Prevention of Premature Deliveries

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Introduction

Since the early sixties, synthetic ACTH has been successfully used for the prevention of abortions and premature deliveries^{8,10,15}. For example, 93% of women with hypothalamic postpregnancy syndrome delivered healthy children compared with only a 30% success rate during previous pregnancies^{7,12}. Also the mortality due to the respiratory distress syndrome has been reduced, as well as obstetrical hemorrhages and hypothalamic postpregnancy syndromes^{1,5,16-19}. However, in some cases of neuroendocrinological gestosis, psychoprophylaxis alone can be significant^{7,22}.

The purpose of this prospective study was clinical evaluation of enzyme monitoring in psychohormonal prevention of premature deliveries.

Material and Methods

140 pregnant women (group I) and 60 pregnant women after infertility treatment (groupe II) received synthetic ACTH-Depot during their threatened pregnancy following the failure psychoprophylaxis alone. They were given 0.5 mg of ACTH-Depot (Cortrosyn-Depot, Synacthen-Depot) every other day with a total of three injections¹⁵. The course and outcome of these pregnancies were compared with 300 pregnant women without need of psychological and hormonal therapy (control group).

Blood oxytocinase and isooxytocinase levels were chemically determined using L-cystin-di-beta-naphtylamide as substrate^{13,24}, which was described and verified in our previous studies¹⁻⁴. The results of these enzymatic measurements are indicated in international units (I. U.- μ mol/1/min) in all of the tables. Statistical analysis was done by level of confidence p less than 0.05 using a computer programme.

Table 1 contains anamnestic data for the above groups. Women in the control group (C), when compared with treated women (T) in group I and II were statistically younger, 2.4 and 1.9 years respectively ($t = 4.6$; $t = 3.1$; $p < 0.001$). Women in the control group had on average 1.3 times less pregnancies ($t = 11.5$; $p < 0.001$) and 0.6 less labors ($t = 6.4$; $p < 0.001$) and 5 times less abortions ($t = 10.5$; $p < 0.001$) than group I but women group II had 4.5 times more abortions ($t = 8.4$; $p < 0.001$) and 5 times less children ($t = 3.8$; $p < 0.001$), as well as 0.3 less labors ($t = 2.7$; $p < 0.05$) and 0.4 more pregnancies ($t = 2.7$; $p < 0.05$) than the control group.

Table 1. Material (mean \pm SD)

Group	Control	Treated I	Treated II
N	300	140	60
Age (years)	27.3 \pm 4.9	29.7 \pm 5.3	29.8 \pm 4.1
Pregnancies	1.8 \pm 1.0	3.1 \pm 1.3	2.2 \pm 1.2
Labors	1.6 \pm 0.8	2.2 \pm 1.1	1.3 \pm 0.7
Abortions	0.2 \pm 0.5	1.0 \pm 1.1	0.9 \pm 0.9
Children	0.5 \pm 0.8	0.7 \pm 0.8	0.1 \pm 0.3

SD: Standard deviation; N: Number

In the control group in general there were 240 past pregnancies in which 150 children had been born, which makes 62.5%, whereas in group I, of 294 pregnancies, 98 children had been born, which makes only 33.3%. Corresponding data of group II were: 72 pregnancies and 6 children (8.3%).

Results

Table 2 shows the modes of terminating pregnancy. No differences were found between the frequencies of spontaneous, oxytocin induced or cesarean deliveries, when comparison was made between the control group and group I. However, the duration of pregnancy in group I was statistically significantly shorter by 2.6 weeks ($t = 6.5$; $p < 0.001$), weight of the newborns was significantly lower by 560 g ($t = 6.8$; $p < 0.001$), length was shorter by 4.1 cm ($t = 6.7$; $p < 0.001$) and difference in the apgar score ($t = 4.0$; $p < 0.001$) were seen. The number of stillborns in group I was 10 (7%), compared with none in the control group. Similarly, as in the anamnestic data (Table 1), results for group II were different. Spontaneous deliveries were half as frequent ($\chi^2 = 37.7$; $p < 0.0019$ and oxytocin infusion and caesarian sections more frequent (respectively $\chi^2 = 15.3$; $p < 0.001$; $\chi^2 = 7.0$; $p < 0.01$). However, in this group no differences were found in apgar scores, weight or length of newborns when compared with control group values in spite of a statistically significant shorter gestation age ($t = 7.3$; $p < 0.001$).

Table 3 shows statistically significant increasing values of oxytocinase and Table 4 of isooxytocinase, with decreasing weeks before delivery. Comparing the results shows that in treated women already 13–16 weeks before delivery the values of oxytocinase and four weeks later isooxytocinase are lower than in the

Table 2. Labor (mean±SD or %)

Group N	Control 300 (100%)	Treated I 140 (100%)	Treated II 60 (100%)
Spontaneous onset	234 (78%)	116 (83%)	24 (40%)
Oxytocin infusion	106 (35%)	46 (33%)	38 (63%)
Cesarean section	64 (21%)	35 (25%)	23 (38%)
Gestation (weeks)	40.1±1.5	37.5±4.6	38.6±1.2
Newborns			
Weight (g)	3440±480	2880±910	3280±600
Length (cm)	54.7±3.0	50.6±7.1	53.3±3.4
Apgar scores	9.7±0.6	9.0±2.0	9.8±0.4

SD: Standard deviation; N: Number

Table 3. Oxytocinase values (mean±SD) before labor in control and treatment groups

Weeks to labour	0	1-2	3-4	5-8	9-12	13-16	17-20
Group (N)							
Control	8.2±1.2 (120)	8.3±0.9 (502)	7.8±0.9 (245)	6.1±2.0 (296)	4.1±1.6 (244)	2.8±1.2 (135)	2.1±1.1 (94)
t	8.3***	15.3***	16.9***	10.3***	4.0***	2.4*	NS
I	5.5±2.1 (48)	5.6±2.3 (181)	4.7±1.8 (108)	4.2±2.0 (199)	3.5±1.5 (193)	2.5±0.8 (142)	2.0±0.5 (85)
II	6.5±1.5 (15)	6.5±1.9 (70)	5.8±2.2 (33)	4.5±1.6 (49)	3.1±1.2 (40)	2.2±1.3 (49)	1.7±0.6 (39)
t	4.2***	7.8***	5.1***	5.3***	3.8***	2.8***	2.1*

(N): Number of enzyme measurements; NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

control group. This is in agreement with our earlier published results. Table 5 shows the use of ACTH-Depot in appropriate weeks before delivery. However, only in women of group I was the duration of pregnancy inversely proportional to the gestation age at which the ACTH therapy was begun. The 2.6 weeks difference between 0 and 17-20 weeks before labor is statistically significant ($t = 5.0$; $p < 0.001$). In the control group, the mean duration of pregnancy was in the range of 39.9 to 40.5 weeks and in group II of 37.7 to 38.4 weeks.

There are anamnestic and parturitional differences between the two treatment groups. That it is why further comparative analysis of materials was concerning only group I. First of all it did not differ from the control group in the method of terminating pregnancy. In Table 6 these two groups are compared according to their methods of onset of labor: spontaneous or induced. In this comparison no statistical difference in the subgroups was found between mothers age, gestation or weight and length of newborns. Only stillborns were twice as frequent in the subgroup of induced labor in comparison with spontaneous

Table 4. Isooxytocinase values (mean±SD) before labor in control and treatment groups

Weeks to labour	0	1-2	3-4	5-8	9-12	13-16	17-20
Group (N)							
Control	6.1±1.3 (36)	6.3±1.7 (111)	6.1±2.0 (64)	4.7±1.3 (88)	3.6±1.2 (87)	2.9±1.0 (46)	2.1±0.6 (39)
t	4.2***	8.3***	7.2***	7.3***	NS	NS	NS
I	4.0±1.0 (8)	4.1±1.5 (59)	3.6±1.3 (44)	3.0±1.2 (54)	3.4±1.3 (55)	2.5±0.7 (32)	2.3±0.5 (15)
II	5.6±1.4 (15)	5.5±1.6 (70)	5.0±1.7 (33)	4.1±1.2 (48)	2.9±0.8 (10)	2.4±1.0 (48)	2.0±0.4 (38)
t	NS	3.1**	2.7**	2.6*	NS	2.4*	NS

(N): Number of enzyme measurements; NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

Table 5. Duration of pregnancy in weeks (mean±SD) in relation to the beginning of ACTH therapy before labor

Weeks to labor	Control	Treated I	Treated II
0	40.3±1.5 (98)	36.7±4.6 (48) t = 5.2***	38.4±1.3 (15) t = 4.6***
1-2	40.2±1.5 (444)	37.1±4.0 (181) t = 10.1***	38.4±2.2 (70) t = 6.6***
3-4	39.9±1.9 (221)	37.0±3.6 (108) t = 7.8***	38.3±2.7 (33) t = 3.3**
5-8	39.8±1.4 (260)	37.2±3.6 (199) t = 9.6***	38.3±2.6 (49) t = 3.9***
9-12	40.0±1.5 (207)	39.2±5.6 (193) NS	37.7±3.6 (40) t = 4.0***
13-16	39.9±1.5 (101)	39.5±2.1 (142) NS	38.2±2.3 (119) t = 6.2***
17-20	40.5±0.8 (60)	40.2±1.8 (85) NS	38.0±3.4 (39) t = 4.5***

SD: Standard deviation; (N): Number of enzyme measurements

NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

labor in the treated group and gestation was shorter in the control group with spontaneous onset of labor ($t = 4.3$; $p < 0.001$) than in the induced one.

In the treatment group I 24 cases (17.7%) were premature deliveries and in subsequent weeks from 37 to 42 there was the following sequence of deliveries: 32, 31, 24, 15, 11, 3, opposite to the control group: 12, 17, 40, 97, 85, 35.

Table 7 shows values of oxytocinase and Table 8 values of isooxytocinase in calendar weeks of pregnancy in group I and control. Tables 9 and 10 show values according to biological age of pregnancy.

Table 6. Comparison of subgroups with spontaneous and induced labors (mean±SD)

Group	Control		Treated I	
	Spontaneous	Induced	Spontaneous	Induced
Onset of labor N	233	67	116	24
Mothers age (years)	27.1±4.9	27.9±4.9	29.3±5.1	31.5±5.8
Gestation (weeks)	39.9±1.5	40.7±1.3	37.3±4.5	38.7±4.8
Newborns				
Weight (kg)	3.43±0.48	3.49±0.41	2.84±0.92	3.08±0.85
Length (cm)	54.7±2.8	54.6±3.5	50.4±7.1	51.3±7.1
Stillborns (N)	0	0	7 (6%)	3 (12%)

SD: Standard deviation; N: Number

Table 7. Oxytocinase values (mean±SD) and calendar age of pregnancies with spontaneous or induced onset of labor

Group	Spontaneous onset		Induced onset		Spontaneous vs induced	
	Control	Treated I	Control	Treated I	C/C	T I/T I
Weeks						
> 40	8.4±1.4 (20)	7.6±2.7 (7)	8.0±1.7 (47)	5.8±1.6 (12)	NS	NS
40–37	8.6±1.9 (344)	6.8±1.9 (105)	7.9±1.4 (184)	6.2±2.1 (42)	4.4***	NS
36–33	6.9±2.1 (259)	5.1±1.8 (164)	5.8±2.0 (43)	4.2±1.4 (27)	3.2**	2.5*
32–29	4.8±0.9 (214)	3.9±1.5 (204)	4.3±1.1 (12)	3.5±1.1 (21)	NS	NS
28–25	3.4±0.7 (121)	2.7±0.8 (194)	3.2±0.9 (11)	2.7±0.6 (19)	NS	NS
24–21	2.5±0.6 (70)	2.1±0.6 (110)	2.0±0.6 (10)	2.1±0.7 (19)	2.4*	NS

(N): Number of enzyme measurements; NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

The above analysis of table 7–10 shows that there is a statistically significant increase in oxytocinase measured in weekly groups in the range from 21–24 to 37–40 scale calendar weeks in the subgroups with the spontaneous or induced labor. Analogous results are obtained with isooxytocinase in both subgroups with spontaneous labor but only in control subgroup with induced labor. Isooxytocinase in induced labors in the treated subgroup does not show sequential increases.

When considering biological age of pregnancy, we may conclude that oxytocinase shows statistically significant increases between weekly intervals from 17–20 until the last week before delivery in subgroups with spontaneous and induced

Table 8. Isoxytocinase values (mean±SD) and calendar age of pregnancies with spontaneous or induced onset of labor

Group	Spontaneous onset		Induced onset		Spontaneous vs induced	
	Control	Treated I	Control	Treated I	C/C	TI/TI
Weeks	t		t		t	t
40-37	6.5±1.6 (35)	5.5±1.3 (19)	5.6±0.7 (26)	2.6±0.2 (4)	2.6*	4.2***
36-33	5.6±1.3 (51)	4.2±1.4 (49)	4.3±0.6 (13)	2.5±0.3 (9)	2.5*	3.6***
32-29	4.1±1.1 (45)	3.4±1.1 (88)	4.0±0.6 (3)	2.1±0.3 (4)	NS	2.3*
28-25	3.3±0.9 (24)	2.6±0.7 (58)	2.6±0.0 (2)	2.5±0.3 (6)	NS	NS
24-21	2.0±0.3 (7)	2.4±0.5 (19)	- (0)	1.5±0.1 (3)	-	3.0**

(N): Number of enzyme measurements; NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

Table 9. Oxytocinase values (mean±SD) and biological age of pregnancies with spontaneous or induced onset of labor

Group	Spontaneous onset		Induced onset		Spontaneous vs induced	
	Control	Treated I	Control	Treated I	C/C	TI/TI
Weeks	t		t		t	t
0	8.6±1.7 (52)	5.3±2.1 (33)	7.8±0.7 (46)	6.0±2.2 (15)	2.8**	NS
1-2	8.6±1.9 (275)	5.1±2.4 (144)	8.0±1.4 (169)	6.1±1.9 (37)	3.5***	2.7**
3-4	7.9±2.1 (175)	4.7±1.7 (97)	7.4±3.9 (46)	4.7±2.0 (10)	NS	NS
5-8	6.2±2.3 (218)	4.3±2.4 (173)	5.6±1.9 (36)	4.2±1.2 (26)	NS	NS
9-12	4.3±0.9 (203)	3.5±1.5 (172)	3.7±1.6 (4)	3.2±1.0 (19)	NS	NS
13-16	3.1±0.9 (88)	2.5±0.8 (125)	2.8±0.6 (13)	2.7±0.6 (17)	NS	NS
17-20	2.3±0.7 (53)	2.1±0.5 (67)	1.6±0.6 (7)	2.0±0.5 (18)	2.5*	NS

(N): Number of enzyme measurements; NS: No significance

Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

t: Student's test values between control and group I or II

Table 10. Isoxytocinase values (mean±SD) and biological age of pregnancies with spontaneous or induced onset of labor

Group	Spontaneous onset		Induced onset		Spontaneous vs induced	
	Control	Treated I	Control	Treated I	C/C	TI/TI
Weeks	t		t		t	t
0	5.6±2.0 (10)	4.0±1.0 (8)	5.0±1.9 (4)	–	NS	–
1–2	6.2±1.2 (332)	4.2±1.5 (55)	5.6±0.6 (20)	2.6±0.2 (4)	2.2*	2.1*
3–4	7.0±1.8 (25)	3.7±1.4 (39)	5.1±0.5 (15)	2.7±0.2 (4)	3.9***	NS
5–8	4.9±0.9 (41)	3.1±1.3 (49)	3.9±0.8 (11)	2.3±0.5 (5)	3.3**	NS
9–12	3.6±2.0 (49)	3.5±1.3 (49)	4.4±0.0 (1)	2.0±0.4 (4)	–	2.1*
13–16	2.9±1.0 (10)	2.5±0.7 (28)	2.6±0.0 (2)	2.1±0.3 (4)	–	NS
17–20	2.1±0.2 (5)	2.4±0.4 (15)	– (0)	2.0±0.7 (5)	–	NS

(N): Number of enzyme measurements; NS: No significance
 Statistically significant: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
 t: Student's test values between control and group I or II

deliveries. But, in subgroups with induced labor the increase stopped in control group 3–4 weeks and in treatment one 15–18 weeks, before labor.

Isoxytocinase shows significant interweekly increases until the 3–4 weeks before labor in control and treatment groups. In control group within induced labor this increase is seen until the last week. However, in the treatment group with induced labor, the enzyme does not show an increase even 17–20 weeks prior to delivery.

In summary, the lack of interweekly increases of both enzymes in the scale calendar weeks does not allow us to predict the necessity for induction of labor in healthy women, with the exception of the treatment group which shows a lack in increase of isooxytocinase. However, according to biological age of gestation, a lack of significant increase of oxytocinase one month prior to labor in healthy women and up to 2 months in treated women indicates the necessity for induction of labor in these groups.

A more useful indicator than oxytocinase is isooxytocinase which in healthy and treated women reaches plateau levels one month before spontaneous labor. However, in the cases of necessary induction of labor in treated women, no increase of isooxytocinase is observed even 5 months prior to delivery. This is in contrast to healthy women, where an increase is shown up to the last week. We can reach a conclusion about the eventual need for induction of labor based upon the observed weekly intervals of increasing isooxytocinase.

Comparing spontaneous labor to induced labor in the control group, the oxytocinase level is statistically significantly more elevated in calendar weeks ranging from 21–24 to 37–40 ($t = 2.4$; $p < 0.05$, $t = 4.4$; $p < 0.001$) and in biological age of gestation from 5–8 weeks to labor. The opposite is seen in the treatment group from 1–2 weeks to labor. In analogical comparison, the isooxytocinase level is more elevated in calendar scale from 33–36 to 37–40 weeks in the control group and 4 weeks earlier in treatment group. Taking into consideration the biological age, the enzyme increases significantly from 5–8 weeks to labor in control group and also 4 weeks earlier in case of treatment.

Conclusion

In the studied material of 140 women in group I, there were 10 stillborns (7%) which is analogous to previous studies¹⁸. The monitoring of treated women during pregnancy allows us to determine several weeks before term of delivery, the duration and final course of the pregnancy. In our opinion it constitutes also the bases of psychoprophylaxis.

In contrast to previous studies comprising patients only with hypothalamic syndromes^{7–12,15} these observations were carried out on 140 general hospitalized women with threatened abortions or premature deliveries. The finding of 82% of births occurring within the biological norm indicates the great utility of enzymatic monitoring of pregnancy.

The conclusions are fully supported by studying the profiles of oxytocinemia during the pregnancies of healthy women²⁰ and those treated with ACTH²³, in relation to natural or instrumental labors and the necessity of oxytocin application.

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