Comparative Study Using Progesterone and Gynipral - Hexoprenaline Sulphate, with Effects in Postpone Preterm Birth

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The prevalence of preterm delivery is rising over time. Preterm delivery is a major cause of mortality in infants. In this study, we aimed to compare the frequency of psychological disorders among women with preterm delivery versus term delivery. In this study, psychological disorders in 25 women, who experienced preterm delivery (gestational age of less than 37 weeks) and in 25 women who had term delivery were examined, using Profile of Affective Distress (PAD) and Symptom Checklist-90 questionnaire (SCL-90). Women, who experienced preterm delivery were treated with progesterone from gestational age 24 and Gynipral - Hexoprenaline Sulphate ($C_{22}H_{30}N_2O_{10}S$), 48 hours before birth. The mean age of the participants was 26.26 for women with term delivery and 28.96 in preterm-delivery. The mean (PAD questionnaire) of the participants in the preterm delivery group being higher than that of the term delivery group, indicating a relevant tendency for the women in the first group to experience a strong affective disorder. The mean score of Symptom checklist-90 questionnaire (SCL-90) in women with term delivery was 49.16 (AS = 12.19) and 92.32 (AS = 29.71) in women with preterm delivery ($p < 0.001$). The results reveal statistically significant differences in the short-term emotional reactions between the two groups of participants. Psychological disorders were higher in women with preterm delivery compared to those with term delivery.

Keywords: progesterone, hexoprenaline sulphate - $C_{22}H_{30}N_2O_{10}S$, PDA, SCL-90, preterm delivery

Preterm labor is defined as regular uterine contractions, which result in changes in cervical length before 37 weeks of pregnancy [1]. An estimated 15 million preterm births occur each year worldwide. Preterm delivery is an important cause of mortality in infants, with the frequency of 5 - 11% [2-5]. A worldwide study reported a rising trend in preterm birth during the past decades [3]. Complications of preterm birth can cause permanent disability in the survivors [2]. On the other hand, increased rate of preterm delivery poses a significant economic burden on the society [3]. Pregnancy affects mothers physically and mentally [6-10]. These women exhibit symptoms such as: lack of concentration, disappointment, schizophrenic reactions, memory loss, affective psychosis, loss of interest in activities, dramatic changes in personality or lack of motivation [11-13].

The prevalence of perinatal major and minor depression is up to 20% [12, 13]. Compared to the physical aspect, fewer studies have evaluated the psychological aspect of women before preterm delivery.

Gynipral - Hexoprenaline Sulphate, 4-[2-[6-[[2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]amino]hexylamino]-1-hydroxyethyl]benzene-1,2-diol sulphate, is used to stop the tract between 22 and 37 weeks of pregnancy in patients without medical or obstetrical contraindications on tocolysis [14, 15].

The duration of treatment should not exceed 48 hours, as the data show that the main effect of tocolysis treatment is the delivery delay of up to 48 hours; in randomized controlled trials no statistically significant effects on perinatal mortality or morbidity were observed. This delay can be used to administer glucocorticoids or to implement other measures known to improve perinatal health [16].

Gynipral should be given as soon as possible after the diagnosis of premature labor has been established and after the patient has been evaluated to eliminate any contraindications on the use of hexoprenaline. The examination should include an adequate assessment of cardiovascular status of patients with continuous ECG monitoring during treatment [17-19].

Progesterone - $C_{21}H_{30}O_2$, (8S,9S,10R,13S,14S,17S)-17-acetyl-10,13-dimethyl 1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-3-one, can also be administered in order to prevent the preterm birth. Therapeutic Progesterone is a synthetic form of the endogenous hormone progesterone [20]. Progesterone binds to the progesterone receptor, resulting in dissociation of heat shock proteins, receptor phosphorylation, and transcription activation through direct or indirect interaction with transcription factors. This agent exerts inhibitory effects on estrogens by decreasing the number of estrogen receptors and increasing its metabolism to inactive

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metabolites. Progesterone induces secretory changes in the endometrium, decreases uterine contractility during pregnancy, and maintains pregnancy [18, 19].

Other agents used to delay premature uterine activity include magnesium sulphate, beta-mimetics, oxytocin antagonists, calcium channel inhibitors, and adrenergic beta-receptor agonists.

Experimental part

Patients and methods

In this cross-sectional study, 25 women with term delivery (m = 26.26; *AS* = 4.45) and 25 women with spontaneous preterm delivery (gestational age of less than 37 weeks), (m = 28.96; *AS* = 3.33), who referred to Odobescu Obstetrics and Gynecology Hospital (2017-2018), Timisoara were recruited. All subjects are of Romanian nationality, aged 15-35 years (m = 27.61; *AS* = 4.13). The prevalence of psychological disorders was compared between the two groups. All participants provided a written informed consent. We provided an informed consent about the aims to the participants. The data file remained anonymous, and the identity of the participants was protected. Our study was done in accordance with the Ethical Committee regulations, guidelines and in accordance to some published models [21-23]. The symptom checklist-90 (SCL-90) questionnaire has 90 items and nine subscales that measure depression, anxiety, phobic anxiety, somatization, obsessive-compulsive, hostility, interpersonal sensitivity, paranoid ideation, and psychoticism. Score rating is based on a five-point scale and evaluates the individual mental status during the last week (0 = none, 1 = a little, 2 = to some extent, 3 = much, 4 = very much) (Blacker, 2000). Scores on each of the nine subscales, which are less than 2.5, represent the absence of a disorder; scores from 2.5 to 3.0 represent the presence of a disorder; and scores higher than 3.0 represent the presence of a serious disorder. Total scores from 90 to 200 represent a significant mental health problem and a need to visit a psychiatrist, and scores more than 200 represent a serious mental health problem, including psychotic and mood disorders.

Profile of Affective Distress (PDA) includes the following scales: functional negative emotions - sadness/depression; dysfunctional negative emotional - sadness/depression; functional negative emotions - worry/anxiety; dysfunctional negative emotions - worry/anxiety; functional negative emotion sadness/depression, worry/anxiety; dysfunctional negative emotions - sadness/depression, worry/anxiety; and positive emotions [24].

Women, who experienced preterm delivery, were treated with progesterone, $C_{21}H_{30}O_2$, from gestational age 24 and Gynipral - Hexoprenaline Sulphate, $C_{22}H_{30}N_2O_{10}S$ (fig. 1), 48 h before birth [15, 18].

Gynipral - Hexoprenaline Sulphate ($C_{22}H_{30}N_2O_{10}S$) was administered in order to prevent and especially to postpone pretherm delivery. This postpone of pretherm delivery can be utilized in order to have time to administer glucocorticoids and surfactants and to implement other known measures in order to ameliorate the perinatal health. Gynipral - Hexoprenaline Sulphate, ($C_{22}H_{30}N_2O_{10}S$), being a tocolytic agent, belonging to the drugs, that prevents the preterm labor and immature birth by suppressing uterine contractions (tocolysis), was administered [14, 15, 25-28].

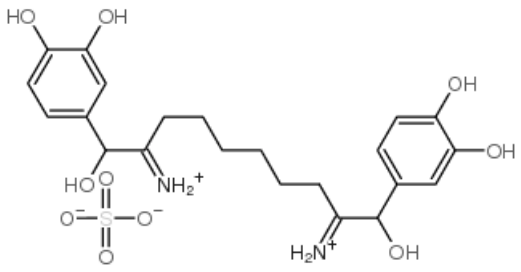

Fig. 1. Structural formula of hexoprenaline sulphate (Molecular Weight: 514.546)

According to the existing protocols Gynipral - Hexoprenaline Sulphate - $C_{22}H_{30}N_2O_{10}S$ must be administered respecting the following information:

Pharmaceutical treatment

Acute tocolysis

The usual dose is 10 μg Gynipral - Hexoprenaline Sulphate, ($C_{22}H_{30}N_2O_{10}S$), 1 ampoule x 2mL, administered by intravenous injection. Subsequently, if necessary, Gynipral is given as an intravenous infusion at a rate of 0.3 μg/min.

Intense tocolysis

Treatment is started with 10 μg Gynipral - Hexoprenaline Sulphate, ($C_{22}H_{30}N_2O_{10}S$), 1 ampoule x 2mL, intravenously administered, slowly, in bolus and continued with Gynipral as an intravenous infusion at the rate of 0.3 μg/min. Alternatively, Gynipral can be given as an intravenous infusion at a rate of 0.3 μg/min without a bolus injection [14, 15].

Long term tocolysis

Gynipral - Hexoprenaline Sulphate ($C_{22}H_{30}N_2O_{10}S$) is recommended to be given as a continuous infusion at a rate of 0.075μg/min [15].

Progesterone ($C_{21}H_{30}O_2$), was administered to prevent the preterm birth [15, 18, 19].

Statistical analysis

All analyses were carried out using SPSS software (version 17.0, Chicago, IL, USA). Mean (m) and standard deviation (SD) were used to describe numerical variables. Independent t-test was utilized to compare the quantitative outcomes between the two groups. The reported p values, $p = 0.000$, $p < 0.001$, $p < 0.05$ were considered as statistically significant.

Results and discussions

We studied 50 women: 25 women with spontaneous term delivery and 25 with preterm delivery, women in the second group were treated with progesterone ($C_{21}H_{30}O_2$) from gestational age 24 and Gynipral - Hexoprenaline Sulphate ($C_{22}H_{30}N_2O_{10}S$), 48 hours before birth. The mean age of women with term delivery was 26.26 (*AS* = 4.45) and 28.96 (*AS* = 3.33) for women with preterm delivery.

Statistical analysis of data revealed a statistically significant difference between the two groups in terms of affective distress for all measured scales ($p = 0.000$; $p < 0.001$). The mean of the participants in the preterm delivery group being higher than that of the term delivery group, indicating a relevant tendency for the women in the first group to experience a strong affective disorder (table 1).

The mean score of SCL-90 in women with term delivery was 49.16 (AS = 12.19) and 92.32 (AS = 29.71) in women with preterm delivery. The mean scores for subscales anxiety, interpersonal sensitivity, hostility and depression, were 2.5 or less in the two groups, but it was significantly higher in the preterm delivery group (P value < 0.03).

Mental health disorders were only observed in preterm delivery group (table 2).

From the analysis of the results obtained after completing the PAD-questionnaire, it is observed that the level of general affective distress and the level of scales for the

Variable	N	Mean		SD		
		Term delivery	Preterm delivery	Term delivery	Preterm delivery	student t Test, t(58)
PDA	25	106.86	222.86	16.19	51.91	**-11.683***
Functional negative emotion depression	25	6.33	13.96	2.08	3.718	**-9.802***
Dysfunctional negative emotion depression	25	9.00	26.40	1.43	8.33	**-11.266***
Functional negative emotion anxiety	25	8.33	24.76	2.66	4.68	**-16.704***
Dysfunctional negative emotion anxiety	25	7.66	24.86	2.39	4.73	**-17.737***
Functional negative emotion depression/anxiety	25	17.33	46.43	4.86	9.95	**-14.290***
Dysfunctional negative emotion depression/anxiety	25	16.66	51.23	3.83	9.41	**-18.261***
Positive emotions	25	44.00	50.00	3.80	6.39	**-4.416***

*** p < 0.001 (p = 0.000)**

Table 1
MEAN SCORE, STANDARD DEVIATIONS AND STUDENT t-TEST FOR PDA SCALES

	Delivery	Mean	SD	p Value
Somatization	Term	71.7	25.3	0.085
	Preterm	75.2	28.3	
Obsessive compulsive	Term	23.61	9.71	0.064
	Preterm	26.42	10.32	
Interpersonal sensitivity	Term	0.5383	0.51719	< 0.001
	Preterm	0.9633	0.61671	
Depression	Term	0.7333	0.50107	< 0.001
	Preterm	1.1150	0.63535	
Anxiety	Term	0.5683	0.43628	0.03
	Preterm	1.0167	0.64733	
Hostility	Term	0.6550	0.49143	< 0.001
	Preterm	1.0517	0.59674	
Phobic anxiety	Term	65.01	23.60	0.762
	Preterm	66.71	26.07	
Paranoid ideation	Term	38.03	21.70	0.075
	Preterm	45.11	25.01	
Psychosis	Term	21.70	8.31	0.083
	Preterm	25.35	13.33	

Table 2
MEAN SCORE AND STANDARD DEVIATIONS OF SCL-90 IN THE TWO GROUPS

evaluation of functional negative emotions, dysfunctional negative emotions sadness/depression, worry/anxiety is significantly lower in women with term delivery, they present low intensity distress, compared to a higher level ($p < 0.001$) in women with preterm delivery, experiencing functional/dysfunctional negative emotions with higher frequency and intensity. On the other hand, the level of positive emotions is also significantly higher in term delivery compared to those with term delivery ($p < 0.001$) [29-31].

Women with preterm labors had significantly higher scores, in this study, in the anxiety, interpersonal sensitivity, hostility and depression subscales of the SCL-90 questionnaire. Several studies examined the occurrence of psychological disorders as a result of childbirth and found that the frequency increases when a premature birth occurs [31-34].

These findings suggest that by reducing stress and psychological distress and through improving social support, it may be possible to enhance the quality of life of these patients [35-43].

Conclusions

The results reveal statistically significant differences in the short-term emotional reactions between the two groups of participants. Although the term of birth was extended by treatment with progesterone ($C_{21}H_{30}O_2$) and Gynipral - Hexoprenaline Sulphate ($C_{22}H_{30}N_2O_{10}S$), psychological disorders were higher in women with preterm delivery at any level compared to those with term delivery.

Therefore, to prevent adverse outcomes, special care should be provided to those women with psychological disorders.

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Manuscript received: 16.11.2017