

# THE INFLUENCE OF PROGESTERONE TREATMENT ON THE COURSE AND OUTCOME OF PREGNANCIES FOLLOWING SUTURE OF THE CERVIX FOR CERVICAL INCOMPETENCE

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## SUMMARY

In this work, we have been studying the effects of Progesterone treatment on the outcome of pregnancy and its influence on the newborn, in a group of women who have undergone cerclage as a treatment of cervical insufficiency, in comparison with a group of women who have had cerclage and have not been treated with Progesterone.

The results may be summarized as follows:

1) Preventive Progesterone treatment after cerclage does not influence abortion rate, but reduces significantly the hospitalization due to threatened abortion (uterine contractions).

2) In the group treated with Progesterone, lower newborn birth weight and Apgar score were observed.

(\*) The Study was done as a partial fulfillment of the requirements for obtaining the Degree of Doctor of Medicine in the Medical School of the Hebrew University in Jerusalem. The Study was performed in the Department of Obstetrics & Gynecology, Rivkah Sieff Hospital, Safed, Israel.

## INTRODUCTION

The problem of abortion following suture of the cervix in pregnant women is a matter of much thought and controversy. Still there is discussion in medical literature as to if and why suture of the cervix causes uterine contraction. The constant question the gynecologist today asks himself is whether or not to give medications in order to alleviate contractions. There is controversy regarding this subject. There are medical centers in Israel and abroad in which progesterone is given in order to prevent uterine contraction (<sup>1, 2, 3, 4</sup>). As in many other fields in medicine, in this case also progesterone is given as "preventive medicine". The progesterone was isolated and its composition was made known by Butenandt, Cobler and Westphal (<sup>5</sup>) in 1934. The progesterone is decomposed and pregnandiol is released through the urine (<sup>6</sup>). The main question that motivated us to make this study is: whether or not there is an indication for treatment which will prevent contractions after cervical suture.

## MATERIAL AND METHODS

30 women with a clear diagnosis of cervical incompetence were studied. They were hospitalized one day before suture of the cervix was scheduled. The following progesterone treatment was performed:

1) 1 gm of 17 alfa hydroxyprogesterone caproate (Proluton Depot \*\*) was given one day before the cervical suture was performed, and later, after suture, 500 mg per day was given for a period of 4 days.

2) On being discharged from the hospital, the women were instructed to inject 500 mg twice a week for an average period of 15 weeks.

The diagnosis of cervical incompetence and the indication for the cerclage were done according to one or more of the three following criteria:

1) Hysterosalpingography was diagnostic to cervical incompetence.

2) Gynecological check-up, not in pregnancy, to prove opening of the cervix according to the Hegar Test No. 8, when proof of cervical incompetence is when Hegar No. 8 passes lightly (<sup>1, 4</sup>).

\*\* Proluton Depot, Shering.

3 - a) A spontaneous abortion that began with rupture of the membranes in the 2nd trimester of pregnancy.

b) Artificial abortion in the 1st month or 2nd month when in the follow-up of the 2nd pregnancy, opening of the cervix was found.

A control group of 30 women diagnosed as suffering from cervical incompetence according to the above criteria, for which suture of the cervix was performed in 1975 and 1976 in the Obstetric and Gynecological Department in Safed was established. Women with cervical or uterine malformations were not taken into account.

In the control group, 4 of the women were sutured according to the Shirodkar procedure<sup>(7)</sup> and 26 women according to the McDonald procedure<sup>(8)</sup>, whereas, in the Study group, 29 women were sutured according to the McDonald procedure and only 1 woman according to the Shirodkar procedure. Before cerclage, the women underwent laboratory analysis of glucose, urea, blood count, ECG and urine analysis for culture. The suture was done under general anesthesia during the 12th and 16th week of pregnancy, both in the control and study groups. The suture was done only after the fetal heartbeats were heard, while using a Doppler or by performing B-Scan by Ultra-Sound waves<sup>(1)</sup>. All the women were hospitalized one day before suture; they were allowed to get out of bed the day after suture and were discharged from the hospital 3 days later. The women were invited for follow-up in the High-Risk Pregnancy Clinic of the Hospital and stayed in follow-up until the end of pregnancy. In most of the women, the suture was effectively taken out in the 28th week of the pregnancy, unless the woman had an early delivery, premature rupture of membranes or abortion. 2 women from the study group and 4 women from the control group later came voluntarily to have the suture taken out. All women delivered their babies in the hospital. In all the statistical calculations T Student test parameter, the Fisher Test  $F = \frac{(S_1)^2}{(S_2)^2}$  were used. The P test was performed also.

## RESULTS

The first aim was to check if the control group (i.e. women who underwent cervical suture without progesterone treatment) was identical in results to the study group (i.e. women who received the progesterone treatment), from the point of view of the data findings.

Table No. 1 shows that the age of the women in the control group, which fluctuated between 19 and 38 years had an average of 28.13 years, compared with the women in the study group, where age was between 19 and 38 years, averaging 27.70. The statistical test proves that the 2 groups are identical according to Student and Fisher tests: from the point of view of the age of marriage, the number of years varied in the control group between 1-18, averaging 8 years; and in the study group moved between 1-19 years, averaging 7.52 years. Statistical tests have also shown the identity on the groups. In the control group, the number of children was between 0-3, averaging 1.53, whereas in the study group, the number of children was between 0-4, averaging 1.60. The Student and Fisher Tests also prove the identity of the 2 groups. In a comparison of the number of births of the two groups: in the control group the number was between 0-3, averaging 1.53, and in the study group between 0-5, averaging 1.38.

Another datum that is learnt is the number of artificial abortions before the cervical suture. In the control group, the number varied from 0-2, an average of 0.60 to each woman. In the study group, the number varied between 0-12, with an average of 1.70 to each woman. (The average was influenced by the fact that one patient had 12 artificial abortions). The number of natural abortions was compared between the 2 groups in order to prove their identity. In the control group, the number varied from 0-4, where the average was 1.87 to each woman. In the study group, the number varied between 0-4 with an average of 1.33 to each woman.

If we sum up the number of abortions, we will find that the average in the control group is 2.47 and in the study group, 2.98. From these results we conclude that the 2 groups are identical in comparison, with the exclusion of one factor,

Table 1. — *Comparison between different data of the two groups.*

Data	Control group - 30 cases		Study group - 30 cases		Statistical parameters	
	Mean ±	S=Standard deviation	Mean ±	S=Standard deviation	T	F
Women-age . . . . .	28.13	5.80	27.70	5.36	0.30	1.17
Marriage (years) . . . . .	8	5.49	7.52	4.83	0.42	1.25
No. of children . . . . .	1.53	1.11	1.60	1.25	0.23	1.27
No. of deliveries . . . . .	1.53	1.11	1.87	1.38	1.05	1.55
Week of gestation at cerclage .	14.63	2.83	15.47	4.43	0.87	2.45
Length of cervix (cm) . . . .	1.40	0.45	1.40	0.48	0.00	1.14
Opening of cervix (cm) . . . .	0.67	0.70	0.87	0.69	1.12	1.03
No. of artificial abortions . . .	0.60	0.65	1.17	2.39	1.26	13.52
No. of spontaneous abortions .	1.87	0.89	1.33	1.32	1.16	2.20
Total abortions . . . . .	2.47	2.16	2.50	2.98	0.045	1.90

$P < 0.001$  to items 1, 2, 3, 4, 6, 7 data of F parameter.

$0.001 < P < 0.01$  to items 5, 9, 10 data of F parameter.

$P > 0.05$  to items 8 data of F parameter.

$P < 0.001$  to all items of T parameter.

i.e. the number of artificial abortions, for which the imbalance in ratio was explained.

All the results prove the identity of the 2 groups as the statistical parameters do not exceed 2, which means that in 95% the groups are identical. The above-mentioned data indicate the statistical identity of the 2 groups. We can now compare the different data findings of the pregnancies in which cervical suture was performed.

The first data findings deal with the week of pregnancy in which cervical suture was performed: in the control group, the number of weeks of pregnancy were 9-20, averaging 14.63; in the study

group, the weeks of pregnancy were 10-29, averaging 15.47. Another datum used to prove the identity of the 2 groups was the length of the cervix at the time of suture: in the control group the length of the cervix ranges between 1 cm and 2 cm, averaging 1.40 cm; whereas in the study group the length of the cervix was 1-2 cm, averaging 1.40 cm, i.e. the 2 groups are identical in that datum.

The opening of the cervix at the time of suture was another datum compared: in the control group, the opening moved between 0-1.5 cm; in the study group 0-2 cm. Therefore this datum also indicated the identity of the 2 groups. After discussing and proving the identity of

Table 2. — *Days and diagnosis of hospitalization in the two groups.*

Groups	Case No.	%	Week of hospitalization	Diagnosis of hospitalization	No. days of hosp.	Total No. of days
Control group	1		36	Contraction and lower abdominal pain	8	
	2		34	»	6	
	3	16.66	19	»	6	36
	4		20	»	9	
	5		24	»	7	
Study	1	3.33	13	Threatened abortion	49	49

Table 3. — *Comparison between the abortions of the two groups and the week of cervical suture.*

	Control group (4 cases)					Study group (4 cases)				
Women No. . . . .	1	2	3	4	mean	1	2	3	4	mean
Week of cerclage . . .	13	11	10	13	11.25	16	16	12	14	14.5
Week of abortion . . .	21	16	20	22	19.75	23	21	20	21	20.25

the 2 groups in accordance with ten different data, history and physical, we come to the analysis of the results of the influence of progesterone treatment.

The general dosage of the progesterone given to each woman moved between 3.5 gm to 24.5 gm, where the average is 11.4 gm for one woman. We analysed the influence of 1) days of hospitalization during pregnancy, 2) outcome of pregnancy, 3) the neonate at the time of delivery, 4) the influence of giving progesterone treatment on the hospitalization during pregnancy.

Table No. 2 indicates the total number of days of hospitalization during pregnancy and the reasons therefore. In the control group, out of 30 women, we hospitalized 5 (16.66%), due to contractions and lower abdominal pains. The week of hospitalization varied from the 19th week to the 36th week pregnancy. Following symptomatic treatment of the pains, they disappeared and the women were discharged; the number of days of hospitalization varied between 6-9 days and the total sum of hospitalization days was 36 days. In contrast with the study group, where 1 woman (3.33%) was hospitalized in the 13th week, a week after suture, and was included in the group of high-risk pregnancies. The woman was given progesterone treatment in a dosage of

15 mg per day during 49 days of hospitalization. The statistical comparison test revealed  $0.01 < P < 0.05$  and the influence of progesterone treatment on the course of pregnancy. Table No. 3 indicates that in the control group there were 4 abortions, 13.33% of all women in the weeks 21, 16, 20 and 22, an average of 19.75 weeks. In the study group there were 4 abortions, 13.33% of all the women in the weeks 23, 21, 20, 21, an average of 20.25 weeks. These abortions were recognized by ruptured membranes, bleeding and pains in the lower abdomen. The weeks when suture was done in the 4 women of the control group were 13, 11, 10, 13, averaging 11.25 weeks, when the average weeks in the whole control group were 14.63 weeks. The week of suture in the 4 women in the study group were 16, 16, 12, 14, averaging 14.5 weeks, when the average of the whole study group is 15.47 weeks. The 4 women that aborted in the study group received progesterone treatment in average dosages of 4.625 gm; 7 out of 26 women who delivered (26.92%) in the study group received an average dosage of 5.71 gm per woman of progesterone. The women that aborted in each group are identical, from the point of view of data findings, to the rest of the women who didn't abort.

Table 4. — *Comparison of Apgar score and babies weight at delivery.*

	Control group (26 cases)		Study group (26 cases)		Statistical parameters	
Outcome	Mean $\pm$	S.D.	Mean $\pm$	S.D.	T	F
Weight (gm) . .	3113	497.7	2789	854	1.66	2.83
Apgar score . .	9.69	0.89	8.73	1.70	2.46	3.65

The influence of progesterone treatment on the neonates: in table No. 4 a comparison was made by the Apgar and the weight of the neonates between the control group and the study group. The weight of the neonates in the control group varied between 2200 gm - 4400 gm, averaging 3113 gm. The weight of the neonates in the study group varied between 990 gm - 4060 gm, averaging 2789 gm. The Apgar score was 6-10 in the control group with a mean of 9.69 while in the study group it was 3-10, averaging 8.73.

## DISCUSSION

The abortion rate following cervical suture is still a problem of much thought and controversy among gynecologists all over the world. There are many reasons for uterine contraction after and due to cerclage. The main controversy is whether or not to treat women after cerclage with tocolytics.

In many medical centers, progesterone is still given in order to inhibit uterine contractions (<sup>1, 2, 3, 4</sup>). The main question which we did ask ourselves in starting this work was if there is a rationale to prevent uterine contraction, following cerclage, by progesterone treatment, supposing that it prevents contraction (<sup>2, 9, 10</sup>). From the results, we can say that 16.66% of untreated women need hospitalization because of uterine contractions and lower abdominal pains, in comparisons to 3.33% of the treated group.

The delivery rate in both groups was 86.66% (26 women), which means that the surgical procedure only (cerclage) as a treatment for cervical incompetence was enough. This fact proves that the hor-

monal treatment failed to prevent abortions (<sup>11</sup>). Similar results of surgical treatment only, without the addition of hormones, were obtained also by Lash (<sup>12</sup>) with 86% of success, Wren (<sup>13</sup>) 88%, Shirodkar (<sup>7</sup>) 85.7% and Naver (<sup>11</sup>) with 92% of success following cerclage only. Gaus (<sup>4</sup>) obtained 84.4% of success with the combination of surgical and hormonal treatment (progesterone acetate together with ethynil estradiol), while Weingold, using hydroxyprogesterone caproate, obtained 74.6% of success rate.

In conclusion, we think that the progesterone treatment for prevention of abortion is unnecessary. It was found that the neonates of the treated group were less in weight. It may be that this finding is important, but the group was too small for such a conclusion.

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