EFFECT OF POST-PARTUM PLASMA IN RHEUMATOID ARTHRITIS*

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This report is a pilot study to determine the clinical effects of post-partum plasma in rheumatoid arthritis. After 1½ years of unsuccessful efforts to collect post-partum plasma through our obstetrical service on a voluntary basis, a grant of funds from the New York Chapter of the Arthritis and Rheumatism Foundation has made it possible to persuade donors to offer the necessary plasma.

Our observations are derived from a series of eleven patients with active rheumatoid arthritis who were given transfusions of post-partum plasma.

Material

The selection of cases for this report was based on the diagnostic criteria for active rheumatoid arthritis established by the American Rheumatism Association in the "Primer and Handbook for Arthritis Clinics" (Steinbrocker and others, 1949).

The ages of our eleven patients ranged from 29 to 59 years. There were seven females and four males. The average duration of the disease was 4·8 years, varying from 6 months to 15 years. All the patients selected for treatment had previously received physiotherapy and salicylates; five had previously been given Butazolidin, two chrysotherapy, two F alcohol, and three cortisone. Only one of the patients previously given steroid therapy had received any within 3 months of starting plasma.

Methods

The technique described by Granirer (1952) was followed meticulously. The only modification was the use of type-specific plasma, rather than pooled plasma, to obviate the possibility of reactions (Angrist, 1952;

Hsia and others, 1953). Cross-matching was performed before each transfusion as an added precautionary measure.

Venous blood was obtained 12-48 hrs post-partum. All of the post-partum donors were on the obstetrical service of the Lenox Hill Hospital. When indicated, the red cells were returned intravenously to the donor.

The plasma was prepared in our blood bank in the routine manner. For precautionary measures it was deemed necessary to obtain two sterile cultures at 14-day intervals before the plasma was used.

Each patient was observed for a minimum period of 3 weeks, either in the hospital or in the out-patient clinic, before the initiation of our therapy.

The plasma was administered intravenously in doses of 250-275 ml. at weekly intervals for an arbitrarily selected course of 10 weeks.

To determine the clinical effects, a weekly appraisal of each patient was performed by two observers. Evaluation of each patient's progress included the routine assessment of four subjective factors:

- (1) pain,
- (2) stiffness,
- (3) sense of well-being,
- (4) joint tenderness.

Objective evaluation was based on the therapeutic criteria of the American Rheumatism Association (Steinbrocker and others, 1949). Radiographs of the affected joints were repeated when indicated. Temperature, pulse, and weight were recorded routinely.

Certain laboratory studies on each patient were repeated at bi-weekly intervals:

- (1) Complete blood count and haemoglobin,
- (2) Erythrocyte sedimentation rate,
- (3) Total cholesterol and partition,
- (4) Total serum proteins, albumin-globulin ratio, and circulating eosinophil counts.

Rose tests (SCA) were performed both before and after treatment.

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Results

No consistent subjective or objective improvement was noted in any of these patients. Table I gives a summary of our results, including the number of transfusions of post-partum plasma, the stage of the disease, the sedimentation rate before and after therapy, the functional class before and after treatment, and the grade of response.

Eight patients completed the arbitrary course of ten transfusions. One patient obtained moderate subjective and objective benefit after the seventh treatment, but gradually worsened in spite of continuing therapy and an additional transfusion. After the eleventh post-partum plasma, plain blood plasma was introduced for 2 weeks without the patient's knowledge. Her condition continued to deteriorate, and she was started on oral Compound F alcohol and a moderate response soon followed.

In three patients, plasma therapy had to be discontinued after eight and nine transfusions, respectively, because of marked progression of the disease.

Two patients obtained some questionable subjective improvement that was not sustained.

Table II (opposite) shows the results of laboratory studies before and after treatment. There was no change in the level of the haemoglobin or other components of the blood picture. There was no improvement or trend toward restoration to normal in reversed albumin-globulin ratios. Blood sedimentation rates remained elevated and the values of

cholesterol and its fractions were not significantly altered.

Untoward Effects.—Untoward effects were limited to transfusion reactions (Scudder, 1953). These were of three types:

- (1) urticaria,
- (2) rises in temperature,
- (3) chills or chilly sensations with or without a rise in temperature.

Reactions usually developed soon after the transfusions; they were easily controlled by the usual measures, and in the cases of urticaria by anti-histaminics. No instance of homologous serum jaundice has occurred so far, but many of the patients were not out of the potential incubation period at the time of writing.

Controls.—The complete lack of response to the post-partum plasma nullified the need for administering the control plasmas which were originally planned as part of the study.

Discussion

The observation that patients with active rheumatoid arthritis may experience a remission or show decided improvement during pregnancy has been confirmed by many investigators (Alfred-Brown, 1942; Sclater, 1943; Flynn, 1942; Hench, 1938; Holbrook, 1948). Hench (1938) reported a total of 37 cases of pregnancy in 22 patients with rheuma-

TABLE I
RESULTS OF ADMINISTERING POST-PARTUM PLASMA*

Case No.	Total Transfusions	E.S.R.†		Stage of Disease	Class		Grade Response	Comment
		Before Treatment	After Treatment		Before Treatment	After Treatment		
1	10	86	100	3	3	4	IV	Worse
2	11	48	37	2	2	3	IV	Worse. Now improved on Compound F
3	10	80	82	3	3	3	IV	Unchanged
4	10	53	57	2	3	3	IV	Slight subjective improvement
5	9	74	80	4	4	4	IV	Disease progressed. Refused further treatment.
6	10	31	52	2	2	2	IV	Unchanged
7	10	90	82	2	2	2	IV	Unchanged
8	10	42	71	1	3	3	IV	Unchanged
9	8	74	80	1	2	4	IV	Worse
10	8	90	99	3	4	4	IV	Unchanged. Refused further treatment
11	10	43	40	2	2	2	IV	Unchanged

* According to the criteria of the American Rheumatism Association (Steinbrocker and others, 1949).

† Westergren (mm./hr).

TABLE II
ANALYSIS OF LABORATORY STUDIES BEFORE AND AFTER POST-PARTUM PLASMA

Case No.	Hgb (g.)		RBC (millions)		Total Cholesterol (mg./100 ml.)		Albumin (g./100 ml.)		Globulin (g./100 ml.)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	14.2	12	4.7	4.3	185	173	4.4	4.4	2.9	2.6
2	13.1	12.4	4.4	4.2	176	171	3.5	3.7	3.6	3.6
3	10.2	12.1	3.4	4.2	225	219	3.0	3.3	5.7	5.9
4	15.5	13.3	4.7	4.6	235	212	3.8	2.4	4.2	5.4
5	10	10	3.6	3.8	151	137	3.0	3.2	3.3	3.8
6	12	11.9	3.7	4.0	170	192	4.0	4.6	3.3	3.9
7	13	13.8	4.2	4.6	163	180	5.2	5	1.9	2
8	12.6	12.1	4.6	4.7	152	156	2.9	3.7	2.9	3.9
9	12.5	12.8	4.1	4.2	180	170	5.2	5	2.9	2.7
10	10.4	8.4	3.8	3.4	160	146	3.0	4.4	2.5	4.8
11	11.9	13.1	4.2	4.6	161	150	3.5	3.8	3.9	3.9

toid arthritis. There was marked improvement during 34 (91 per cent.) of their pregnancies. Holbrook was able to collect a total of 96 pregnancies in women with active rheumatoid arthritis; eighty (83 per cent.) showed marked improvement or developed a remission during gestation. With this relationship in mind various ingenious methods of reproducing the effects of pregnancy have been devised. It is convenient to divide the methods into two categories:

- (1) Direct influence of pregnancy,
- (2) Indirect effect through products of pregnancy.

Direct Effect.—Pregnancy *per se* has been advised by some as a therapeutic aid (Holbrook, 1948), but needless to say this is not always practicable.

An attempt at producing a state of "pseudo-pregnancy" with massive doses of human chorionic hormone in a patient with rheumatoid arthritis was reported by Archer (1950), but pseudo-pregnancy was not achieved and no clinical benefit resulted.

We were unable to uncover any report in the literature describing the effect upon rheumatoid arthritis in patients developing pseudo-cyesis.

Indirect Effect.—The indirect effect through pregnancy-products is the more practical and is the one with which we are chiefly concerned. The current interest in the use of pregnancy blood and its derivatives was initiated by Barsi in 1941; 6 years later (Barsi, 1947) he reported a study of 28 patients and described beneficial results in 64 per cent., with no change in 36 per cent. of his series. He felt the results were not statistically significant, but was

impressed with the rapidity of improvement and the lasting effects in those patients favourably affected.

Since that time other workers have reported the use of pregnancy blood, post-partum plasma, and placental cord serum.

Table III (overleaf) summarizes ten analytical studies with pregnancy products reported in the literature.

Lucherini and Pala (1951) reported four patients with rheumatoid arthritis given eight transfusions of 300 ml. pregnancy blood. Two patients were unchanged; improvement was reported as moderate in one, and good in another.

Holbrook (1951) noted two or three dramatic results in a series of over one hundred cases treated by pregnancy blood, but discontinued the treatment because there was not enough pregnancy blood available.

Four independent investigators reported varying results with placental cord serum. Tufts and others (1950) reported beneficial results with placental cord serum given in combination with sodium salicylate in eight cases of rheumatoid arthritis.

Aronson and others (1952) and Levy and others (1953) reported favourably on a total series of 47 cases of rheumatoid arthritis treated with placental cord serum, 10 ml. intramuscularly twice weekly. Although no patient gave a Grade I response, 31 (66 per cent.) had a Grade II response.

Spielberg (1953) reported fifteen cases treated with placental blood serum; three achieved a Grade I response, and another three had a Grade II response.

Simson and Bunim (1952) reported a series of

TABLE III
HISTORY OF PREGNANCY PRODUCTS USED IN RHEUMATOID ARTHRITIS

Analytical Investigations		Agent	No. of Cases	Results (Grade Response)*				Authors' Opinion
Author	Date			I	II	III	IV	
Barsi	1947	Pregnancy blood	28					Beneficial results 64 per cent. Rapid and lasting effect No change 36 per cent.
Lucherini and Pala	1951	Pregnancy blood	4					One good improvement One moderate improvement Two unchanged
Tufts and others	1950	Placental cord serum (with Na salicylate)	9					Beneficial
Aronson and others	1952	Placental cord serum	47	0	31 (66%)	10 (21%)	6 (13%)	Very encouraging
Levy and others	1953							
Spielberg	1953	Placental cord serum	15	3 (20%)	3 (20%)	4 (27%)	5 (33%)	Valuable
Simson and Bunim	1952	Placental cord serum	8			2	6	No significant beneficial effect
Granirer	1951	Post-partum plasma	8		8			Remissions in all. Seven additional patients unresponsive to steroids improved with post-partum plasma
Norcross and Lockie	1951	Post-partum plasma	6					No subjective or objective improvement
Neustadt and others (Present study)	1954	Post-partum plasma	11				11	No significant response Four patients worse

* Steinbrocker and others (1949).

eight patients treated with injections of placental serum, in whom no significant beneficial effect was obtained.

Granirer (1951) reported the successful use of post-partum plasma in eight patients with rheumatoid arthritis. In this study he stated that all his patients sustained gradual remissions lasting from 6 weeks to 1½ years. Chemical abnormalities of the blood, such as anaemia and reversal of the albumin/globulin ratio, were restored to normal. However, the blood sedimentation rate did not improve. No beneficial response was obtained when plain plasma was administered to a control group of patients.

Norcross and Lockie (1951) administered 250 ml. post-partum plasma once a week for a period of 12 weeks to six patients with active rheumatoid arthritis. No subjective or objective improvement was obtained.

Bunim (1951) mentioned two patients who failed to respond to sixteen post-partum transfusions, but showed moderate improvement when a steroid compound was administered.

Hsia and others (1953) recently reported the administration of Cohn's Fraction IV prepared from pooled post-partum plasma to a total of sixteen children, seven with rheumatoid arthritis. No beneficial effect on the rheumatoid arthritis was observed, and four out of the sixteen patients treated developed homologous serum hepatitis.

Although our series consists of only eleven patients, for the purposes of a screening study of the effects of post-partum plasma, we feel this material is adequate to reflect at least the trend of responsiveness, since the original report on this subject was based on only eight cases, and no further analysis of results in a larger group has appeared to our knowledge. Moreover, it has been stated by Granirer that improvement usually occurs between the fourth and sixth treatment, and all but one of the patients in this series have received eight or more transfusions of the specific plasma.

Plain Blood and Plasma Transfusions.—Some investigation of the use of normal blood and plasma in the treatment of rheumatoid arthritis has also been pursued. Repeated transfusions of normal blood have been recommended in patients with relatively acute or subacute rheumatoid arthritis. After the transfusions some striking remissions of the disease have been described by some observers (Holbrook, 1951).

Simpson and others (1949) treated forty patients with rheumatoid arthritis with blood transfusions and ten patients with plasma transfusions. An immediate improvement in levels of haemoglobin, haematocrit, and blood sedimentation rate occurred in all patients given whole blood. However, these constituents returned to their previous abnormal

values within 28 days. Patients given plasma showed no improvement in these estimations. The arthritis was reported to be unaffected by the transfusions.

Summary

(1) The clinical and certain haematological and biochemical effects produced by the intravenous administration of 250 ml. post-partum plasma once a week for 8 weeks were observed in a series of eleven patients with active rheumatoid arthritis.

(2) This study has failed to demonstrate any significant responsive trend or any appreciable beneficial effect of post-partum plasma on the symptoms or course of active rheumatoid arthritis.

(3) No significant influence on abnormal blood chemical constituents was observed in any of our group during or after the administration of post-partum plasma.

(4) The administration of post-partum plasma as a therapeutic measure for rheumatoid arthritis in our small series demonstrated no evidence of benefit to justify its further investigation.

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Effet du plasma puerpéral sur l'arthrite rhumatismale

RÉSUMÉ

(1) On observa les effets cliniques et certains effets hématologiques et biochimiques produits par l'administration intraveineuse de 250 cc. de plasma puerpéral une fois par semaine à un groupe de onze malades atteints d'arthrite rhumatismale.

(2) Au cours de cette expérience on ne put déceler aucune tendance à une réponse significative ni aucun effet salubre appréciable du plasma puerpéral sur les symptômes ou l'évolution de l'arthrite rhumatismale active.

(3) Pendant ou après l'administration du plasma puerpéral on n'observe dans aucun cas un effet significatif sur les composants chimiques anormaux du sang.

(4) Dans notre petite série l'administration à titre thérapeutique du plasma puerpéral dans l'arthrite rhumatismale n'offrit aucune indication favorable qui puisse justifier des recherches ultérieures.

Efecto del plasma puerperal sobre la artritis reumatoide

SUMARIO

(1) Se observó los efectos clínicos y algunos efectos hematológicos y bioquímicos consecuentes a la administración endovenosa de 250 cc. de plasma puerperal una vez por semana a un grupo de once enfermos con artritis reumatoide.

(2) No fué posible demostrar en este estudio tendencia alguna a una respuesta significativa ni efecto beneficioso apreciable del plasma puerperal sobre los síntomas o la evolución de la artritis reumatoide activa.

(3) Durante o después de la administración del plasma puerperal en ningún caso se vió un efecto significativo sobre los componentes químicos anormales de la sangre.

(4) En nuestra pequeña serie la administración de plasma puerperal como medida terapéutica en la artritis reumatoide no evidenció ventaja alguna que pudiera justificar investigaciones ulteriores.