CLINICAL TRIAL WITH XANTINOL NICOTINATE (COMPLAMINA) IN HIGH RISK PREGNANCY

by

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SUMMARY

Xantinol nicotinate (Complamina) is known to enhance perfusion of nutritive micro-circulation, decreases the peripheral vascular resistance, venous pressure, hypercoagulation state and has been successfully used to improve placental circulation. In view of these observations the present study was undertaken to evaluated its effect on larger number of subjects of high risk pregnancy and to note its effect on birth weight of the babies in toxaemia of pregnancy.

Introduction

High-risk pregnancy defined by Schneider (1971) as "any gestation in which prospects of optimal outcome for either mother or child is reduced". High perinatal loss in risk pregnancy has focused world wide attention in this area and considerable research is going on to reduce the sequalae of faetal loss in such cases. A large number of bio-physiological and bio-chemical methods for assessment of placental function have been developed and claimed to show a positive correlation with the welfare of faetus in utero.

In all high-risk pregnancies inadequate placental circulation is the basic pathological feature leading to poor placental function. Howle *et al* (1971) investigated extensively the coagulation changes in normal and toxaemia pregnancy and found evidence of intravascular coagulation with micro-angiopathic changes. Reid *et al* (1971) suggested that in pregnancy toxaemia early changes consistent with hypercoagulation state may be discernible prior to haemorrhagic state which if recognised may be treated prior to the development of generalised fibrin deposition.

Material and Methods

One hundred sixty-two cases were selected for the present study from the women attending Antenatal Clinics and Maternity wards of Queen Mary's Hospital, K.G. Medical College, Lucknow. The

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study was conducted in third trimester of pregnancy, between January 1978 to April 1981. They belonged to the age group of 18-35 years and parity 0-7. These cases were divided into three groups.

I. Control Group — 54 cases

No Complamina drug was given in this group and these cases were again subdivided into following groups.

(a) Normal pregnancy	10 cases
(b) Bad Obstetric history	10 cases
(c) Dysmaturity	7 cases
(d) Pregnnacy with anaemia	6 cases
(e) Postmaturity	5 cases
(f) Pre-eclamptic toxaemia	3 cases
(g) Rhesus isoimmunization	2 cases
(h) Pregnancy with heart disease	1 case
(i) Twins	1 case

II. *Study Group* — 40 cases

Forty women received complamina retard tablets in last trimester of pregnancy. These cases were further subdivided into following groups.

(a) Normal pregnancy	5 cases
(b) Dysmaturity	9 cases
(c) Pregnancy with anaemia	7 cases
(d) Pregnancy with bad Obstetric history	7 cases
(e) Pregnancy with toxaemia	5 cases
(f) Rhesus isoimmunization	3 cases
(g) Pregnancy with heart disease	2 cases
(h) Twins	1 case
(i) Postmaturity	1 case

III. *Toxaemia Group* — 68 cases

In 68 pregnancy with toxaemia cases effect of the drug was seen on birth weight of the babies. These cases were divided into two sub-groups.

(A) Pregnancy with toxaemia received only conventional treatment (rest, sedation, diuretics and antihypertentive drugs). No complamina drug was given in this group, taken as control group. 34 cases

(B) Pregnancy with toxaemia women received complamina retard tablets alongwith conventional therapy 34 cases

In all women routine investigations were done. In toxaemia cases systolic blood pressure ranged from 140-190 and diastolic pressure varied from 90-124 mm. of Hg. Fundus examination and blood urea estimation were carried out in toxaemia group. Complamina Retard Tablets were given in the dosages of 1 tablet (500 mg.) twice daily for 2-8 weeks. Estriol estimations were done serially by Radioimmunoassay (Tulchinsky and Abraham, 1971 and Abraham *et al* 1974) in groups I and II. Hormones and reagents used in the assay of plasma estriol were procurred in the form of a complete kit from Messers. Pantex, Malibu, California, U.S.A.

Observations and Results

Data of 162 subjects were analysed. Table I depicts.

Estriol levels between 28-43 weeks gestation. The levels were 3.64-6.6 ng/ml and showed progressive rise to 9.39 ng/ml at 36 weeks and 14.52 ng/ml. at 40 weeks of gestation. In complamina supplemented women estriol level ranged between 4.47-9.42 ng/ml at 28-34 weeks and it rose to 15.4 ng/ml. at 36 weeks and 24.93 ng/ml at 40 weeks of gestation. It shows that complamina therapy resulted in an elevation of plasma estriol at all times interval

TABLE I

Plasma Estriol Level in Normal Pregnant Women

Groups	No. of cases	Estriol level (ng/ml) Mean + SE				
		Gestation weeks			Birth weight (kg)	Placental weight (gm)
		28-34	35-36	37-40		
Normal pregnancy without complamina therapy	19	6.61 ±0.894	9.39 ±0.774	14.52 ±1.093	2.72 ±0.078	496 ±8.628
Normal pregnancy with complamina therapy	5	9.42 ±3.16	15.41 ±2.87	24.93 ±2.75	2.86 ±0.092	535 ±14.60

as compared to normal pregnant controls where no drug was given.

It is evident from Table II that initial low level of estriol levels were seen in high-risk pregnancy cases except in Rhesus isoimmunization where it was high as compared to the control levels. This might be due to hyperplacentosis. After one week treatment with complamina retard tablets, estriol levels started rising in all the cases and this rise was more marked in dysmaturity, bad obstetric history, twins, pregnancy with toxaemia and Rhesus isoimmunization groups.

TABLE II

Plasma Estriol Level in High Risk Pregnancy Cases

Group	No. of cases	Estriol levels (ng/ml) Mean + SE				
		Gestation weeks			Birth weight (kg)	Placental weight (gm)
		Before drug therapy	Complamina treated group			
		28-34	35-36	37-40		
Dysmaturity	9	6.41 ±2.51	7.76 ±1.86	23.06 ±3.22	2.22 ±0.128	433.33 ±20.4
Anaemia	7	9.34 ±2.044	11.89 ±2.459	11.28 ±2.774	2.80 ±0.16	508.57 ±20.75
BOH	7	4.96 ±0.91	9.84 ±4.47	12.58 ±3.55	2.96 ±0.06	560 ±67.82
Pregnancy with toxaemia	5	6.66 ±1.45	10.05 ±1.06	13.05 ±1.87	2.72 ±0.39	572 ±29.89
Rhesus isoimmunization	3	12.60	21.95	34.64	3.11	580
Pregnancy with heart disease	2	9.11	11.26 ±9.08	—	3.0	575
Postmaturity	1	—	—	9.29	3.4	500
Twins	1	9.36	13.70	23.90	2.3 2.2	780

A comparative analysis of estriol levels, (Table III) shows that there was definite rise of estriol levels in drug treated cases and this rise was statistically significant is normal pregnancy, B.O.H. Dysmaturity and Rhesus isoimmunization subjects.

Outcome of pregnancy was compared in Table IV. There were 3 still births in control series (one each in BOH, pregnancy with anaemia and heart disease), Estriol levels were less than 5 ng/ml in all 3 cases. Five cases delivered prematurely, of these, 1 who had low estriol level 2.3 ng/ml at 28 weeks, rose to 4.41 ng./ml at 34 weeks gestation. This woman delivered prematurely and baby died of respiratory distress syndrome. Four remaining babies were survived.

In drug treated group there were 2 still births in BOH group. One women admitted with absent foetal heart sound showed estriol level of 1.14 ng/ml at 28-34 weeks and in another subject estriol level was 4.08 ng/ml. In both cases estriol level failed to rise after drug therapy and resulted into premature macerated still births. Two cases had premature delivery (one each in pregnancy with anaemia and toxaemia group). In both cases estriol level declined but the babies survived.

Effect on Birth Weight

Since the number of cases were less in groups I and II, 68 subjects having pre-eclamptic toxaemia were taken to evaluate the effect of drug on birth weight of these babies.

Various factors like age, parity, height, weight and socio-economic status influence the birth weight (Datta, 1969, Pachauri, 1970; Srivastava, *et al* 1971 and Ahuja and Khanna 1974). Keeping these factors in view, cases were grouped with special reference to the factors common to all groups.

The mean birth weight of infants, born after complamina therapy was 3.18 kg., while in the control group it was 2.63 kg. The difference between the two groups was 550 gm. which was found to be statistically significant. Infants born to primiparas in complamina supplemented group

TABLE III

Comparative Analysis of Plasma Oestriol Levels in Control and Study Group

Group	Control group (no drug given)		Study group (complamina supplemented group)	
	No. of cases (54)	Mean oestriol levels ng/ml (mean ± SE)	No. of cases (40)	Mean oestriol levels ng/ml (mean ± SE)
Normal pregnancy	19	14.52 ± 1.093	5	24.93 ± 2.75
BOH	10	7.32 ± 1.02	7	12.58 ± 3.55
Dysmaturity	7	9.23 ± 1.16	9	23.06 ± 3.22
Pregnancy with anaemia	6	9.89 ± 1.04	7	11.28 ± 2.77
Pregnancy with toxaemia	3	12.0 ± 2.84	5	13.05 ± 1.87
Rhesus isoimmunization	2	6.90 ± 1.21	3	34.64 ± 2.00
Pregnancy with heart disease	1	8.50	2	11.26 ± 3.08
Postmaturity	5	9.66 ± 1.50	1	9.29
Twins	1	16.66	1	23.90

TABLE IV

Outcome of Pregnancy in Control and Study Group

Group	Control group (no drug)						Study group (complamina supplementation)					
	No. of cases	FTND	Pre ND	LFD	LSCS	SB	No. of cases	FTND	Pre ND	LFD	LSCS	SB
Normal pregnancy	10	13	1 (died RDS)	5	—	—	5	4	—	1	—	—
BOH	10	6	1	—	2	—	7	4	1	—	—	2
Dysmaturity	7	6	—	1	—	—	9	8	—	1	—	—
Pregnancy with anaemia	6	4	1	—	1	1	7	4	1	1	1	—
Pregnancy with toxaemia	3	—	2	1	—	—	5	3	1	1	—	—
Rhesus isoimmunisation	2	2 (1 died jaundice)	—	—	—	—	3	1	—	—	2	—
Pregnancy with heart disease	1	—	—	—	—	—	2	2	—	—	—	—
Postmaturity	5	3	—	—	2	—	1	1	—	—	—	—
Twins	1	1	—	—	—	—	1	1	—	—	—	—
Total	54	34	5	7	4	3	40	28	3	4	3	2

FTND — Full Term normal Delivery, Pre-ND—Premature Normal Delivery, IFD—Low Forceps Delivery, LSCS—Lower Segment Caesarean Section, SB—Still Birth.

were considerably heavier and difference between control and drug treated group was 660 gm. In multipara the difference in birth weight in control and complamina group was 440 gm.

Xantinol Nicotinate (Complamina) therapy to normal pregnant subjects during later stages of pregnancy resulted in increased plasma estriol levels than the control cases of similar gestational age.

TABLE V

Birth Weight of Infants in Control and Complamina Supplemented Group

Parity	Control Group (PET with conventional therapy)		Complamina Supplemented group		Different weight (gm.)
	Total No. of cases	Mean birth weight (kg.)	Total No. of cases	Mean birth weight (kg.)	
Primipara	20	2.57 ± 0.268 t = P<.001*	20	3.23 ± 0.505	660
Multipara	14	2.70 ± 0.570 t = P<.05**	14	3.14 ± 0.491	440
Average	34	2.63 ± 0.39 t = P<.001*	34	3.18 ± 0.50	550

* Significant at 1% level.
** Mildly significant.

Discussion

Studies of Simmer *et al* (1964) and Levitz (1966) have demonstrated that foetus synthesizes the steroidal precursors which later undergo transformation to estrogens in the placenta. The placenta is thus responsible for the final synthesis of large amount of estriol formed during normal human pregnancy. Hydroxylated steriod intermediates formed mainly by foetal adrenals are metabolised by the syncytial trophoblastic cells of the placenta. Metabolism of estriol consists of an extensive conjugation process without major alteration in the basic steroid molecule. Besides deposition in the mucoceum (Kinsella *et al* 1956 and Diczfalusy *et al* 1959) transfer to the maternal compartment appears to be the principal mechanism by which the foetoplacental unit disposes off estriol and its conjugates as reported by Levitz *et al* (1966).

Complamina has been shown to have trophic effects on the overall pharmacokineties of vascular system. Ryan (1959) has shown that complamina improved cerebral circulation by increasing glucose permeation and better oxygen utilization. Similar effects on the highly vascular bed of the placenta might be anticipated and could result in increased plasma estriol levels in subjects receiving complamina retard therapy.

Bergstein and Kessel (1968) used complamina (2000 mg/day) in pregnant women threatened with eclampsia in last trimester for 7 days. Estriol and pregnanediol were below normal before drug therapy but the level rose after commencing treatment. They concluded that complamina corrects inadequate blood supply of the placenta and definitely improves placental function. In the present study also low plasma estriol levels in high-risk pregnancies started rising after a week of

drug supplementation and almost came to normal after two weeks of therapy. This rise was more marked in pregnancy with dysmaturity, BOH twins, pregnancy with toxaemia and Rhesus isoimmunization groups. There was improve outcome of pregnancy and mean birth weight in drug treated group as compared to control group due to improve foetoplacental function and foetal nutrition.

Conclusions

The following conclusions were drawn from this study:

1. Monitoring of plasma estriol titre during late pregnancy is of great help in the proper management of high-risk pregnancies and a fall of estriol level below 5.0 ng/ml. at 34-36 weeks of gestation results in still born babies.

2. This study highlights that Xantinol nicotinate (Complamina Retard) supplementation during third trimester in high-risk pregnancy women, especially in toxaemia group improves the foetoplacental function and there by it improves the foetal nutrition leading to increased birth weight of babies and had no deletarious affect on the babies born following drug therapy.

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