

# PLASMA ESTRIOL LEVELS IN HIGH-RISK PREGNANCIES AND RESPONSE TO COMPLAMINA THERAPY†

by

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## Introduction

Estriol titre is used as an index of the normal functioning of the foetoplacental unit during pregnancy. A definite titre appears at about 16 weeks of gestation and shows a gradual rise till delivery. Any variation from the normal level indicates dysfunctioning of this unit leading to foetal distress and calls for proper management. Urinary estriol has been used as the guiding factor but it has often provided misleading values. Accordingly, the determination of estriol in plasma is being considered as a more useful guide for the functioning of foetoplacental unit.

In the limited studies reported so far plasma estriol levels have been found to be more reliable. This steroid has been reported to fall in high-risk pregnancies but more studies to substantiate these find-

ings are needed. Accordingly, the present investigation was undertaken to determine the relationship of maternal plasma estriol to foetal distress in different high risk pregnancies and their subsequent management.

## Material and Methods

Subjects for this study were selected from amongst the pregnant women attending the ante-natal clinic or admitted in the obstetrics ward of the Queen Marys Hospital, King George's Medical College, Lucknow from November 1977 to July, 1978. They were between 18 to 40 years of age and with a parity of 0.8. Women showing no abnormal complications were considered as normal pregnant. The abnormal pregnancies were subgrouped into bad obstetrics history, toxæmia, anaemia, post-maturity, twin pregnancy, dysmaturity, syphilitic, rhesus-isoimmunization, placental abnormality and intrauterine death.

Bad obstetrics group included subjects with previous abortions or premature delivery or still birth and in whom the obstetrical future was unknown. The cases with hypertension (B.P. 140/90 or above), oedema, high blood pressure, and albuminuria were included in toxemia group.

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The cases overdue by 10 to 14 days from the expected date of delivery comprised the post-maturity group. Dysmaturity group included cases in whom the size of the foetus was less than the period of amenorrhoea. Twin pregnancy was confirmed by X-ray and later at delivery. The rhesus isoimmunization and syphilitic cases were diagnosed by blood tests; the syphilitic subjects were treated with Penidure LA-12 during pregnancy. The placental abnormality case had a previous recorded history of abnormal placenta.

2-4 ml of blood was drawn and transferred to heparinized tubes. The radioimmunoassay procedure used for the determination of estriol is based on the work of Tulchinisky and Abraham (1971) and Abraham *et al* (1974). This method measures the unconjugated plasma estriol. The anti-estriol used was highly specific and hence chromatography was not required. The lowest sensitivity was 12.5 pg. All the hormones and reagents used in the assay of plasma estriol were procurd in the form of a complete kit from Messrs Pantex, Malibu, California, U.S.A.

The main advantage of this method is its greater sensitivity and needs only 200  $\mu$ l of maternal plasma.

#### Results

The results are presented in Table I. It is evident that in all the cases characterized as high-risk pregnancies the plasma estriol levels were significantly lower than that in the normal pregnant subjects ( $P < 0.01$ ). Even then, most of the subjects delivered normal babies at full term. Some of the cases did deliver prematurely but the babies were normal. The low haemoglobin content (5 gm%) of the mother, too, had no untoward effect on pregnancy outcome. An estriol level of less than 5  $\mu$ g/ml, irrespective of case

status, had an adverse effect on the fetus and all the babies born to such mothers were still born.

The estriol levels did not show any correlation for indications of pregnancy outcome such as caesarean sections and low forceps delivery, etc.

#### Response with Complamina

In eleven cases showing low estriol levels in the third trimester of pregnancy, Complamina (R) Retard (Xantinol Nicotinate; (7-(2 hydroxy-3 (N-2 hydroxyethyl-N-methyl-amino)-prophyl)-1-3-dimethyl-xanthane, pyridine-3-carboxylate) therapy at a dose of 500 mg twice daily for 2 to 12 weeks was given.

The results presented in Table II show significant increase of estriol levels after Complamina treatment. Interestingly, all the cases delivered normal healthy babies at full term.

Here, too, the estriol levels had no relationship with the type of deliveries i.e. normal, caesarean section or low forceps.

#### Discussion

In the high risk pregnancy cases unconjugated (free) plasma estriol levels indicate placental function since it secretes mostly unconjugated estriol which is conjugated and cleared from circulation via the maternal kidney (Stafford and Watson, 1974; Katagiri *et al*, 1976; Macrae and Mohamedally, 1970). Hence the plasma estriol titre during the last trimester of pregnancy is used to monitor foetoplacental function. However, the critical levels of estriol to indicate the foetal stress are not yet well defined. Nevertheless, a titre of less than 4 ng/ml in plasma during the last 6 weeks of pregnancy has generally been accepted as a sign of foetal distress

TABLE I  
Plasma Estriol Levels and Outcome of Delivery in Human High Risk Pregnancy Cases

Groups	Total number of cases	Estriol levels ng/ml Mean $\pm$ S.E.	Outcome of delivery				Still births
			Live born				
			FTND	Premature	LFD	LSCS	
Normal Pregnant	20	14.90 $\pm$ 1.36	16	—	1	3	—
Twin Pregnancy	1	16.16	1	—	—	—	—
Bad Obstetrics History	10	7.32 $\pm$ 1.02	6	1	—	2	1 Fresh
Dysmaturity	7	9.23 $\pm$ 1.16	6	—	1	—	—
Anaemia	6	9.89 $\pm$ 1.04	4	1	—	—	1 Premature Fresh
Syphilitic	5	6.77 $\pm$ 1.52	3	—	—	1	1 Premature Fresh
Postmaturity	5	9.66 $\pm$ 1.50	3	—	—	2	—
Toxemia	3	12.0 $\pm$ 2.84	—	2	1	—	—
Rhesus Isoimmunization	2	6.90 $\pm$ 1.21	2*	—	—	—	—
Heart Disease	1	8.50	—	—	—	1	—
Placental Abnormality	1	7.2	—	—	—	1	—
Intrauterine Death	1	4.3	—	—	—	—	1 Macerated

FTND — Full term normal delivery.

ISCS — Lower segment caesarian section.

LFD — Low forces delivery.

\* One baby died of severe jaundice.

TABLE II  
*Estriol Levels After Complamina Treatment*

Groups	Total number of cases	Mean estriol levels ng/ml		Outcome of delivery			
		Pre-treatment	Post-treatment	FTND	Premature	LFD	LSCS
Dysmaturity	6	7.90	12.78	5	—	1	—
Toxemia	2	6.55	13.33	—	1	1	—
Bad obstetrics history	2	7.65	12.85	2	—	—	—
Placental abnormality	1	4.4	10.0	—	—	—	1

FTND — Full term normal delivery.

LFD — Low forceps delivery.

LSCS — Lower segment caesarian section.

(Tulchinisky and Abraham, 1971; Lindberg *et al*, 1974).

In the present study, too, the cases in whom the estriol level fell below 5 ng/ml had intrauterine death of foetus or delivered premature still born babies.

Interestingly, in a case of Rh-isoimmunization where plasma estriol was less than 6 ng/ml, the baby developed severe jaundice after delivery and died. Such an observation has also been reported earlier (Lindberg *et al*, 1974). These findings indicate that decreasing levels of estriol in the plasma of pregnant mother is a sign of placental dysfunction *vis-a-vis* foetal distress and need immediate corrective therapy.

Complamina is known to enhance perfusion of microcirculation, has been successfully used to stimulate estriol secretion in 4 subjects threatened with eclampsia due to low estriol. All the cases delivered normal babies and there was no side effect of the drug (Berstein and Kessel 1968). These investigators also suggested that Complamina regulates blood supply of placenta and thereby improves its functions.

The present study supports this interesting finding since all the 11 cases of dysmaturity toxemia, bad obstetrics history and placental abnormality with low plasma estriol responded to complamina therapy. The estriol levels rose to near normal and all the subjects delivered healthy babies.

The present study clearly reveals that monitoring of plasma estriol is highly helpful in the management of high risk pregnancy.

We feel that this test should be routinely used in all cases showing clinical signs of foetal stress in the third trimester of pregnancy.

#### Conclusions

Monitoring of plasma estriol titres during late pregnancy is highly helpful in the proper management of high-risk pregnancies. The study highlights that a fall of estriol level below 6 ng/ml at 34-36 weeks of gestation results in still born babies. We found that Complamina is a useful drug for the foetoplacental function since it restores the falling estriol levels to normal and consequently ensures foetal well being.

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