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A COMPARATIVE STUDY OF SERUM BETA HUMAN CHORIONIC GONADOTROPHIN AND OCULAR CHANGES IN PREGNANCY INDUCED HYPERTENSION IN SECOND TRIMESTER OF PREGNANCY

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ABSTRACT

Background: Hypertension disorder of pregnancy affects up to 8% of all gestations. Pregnancy induced Hypertension is defined as hypertension that develops for first time in pregnancy after 20 weeks of gestation. Pathophysiological placental abnormalities are seen consistently by increasing secretion of hormone HCG. Most ocular changes in pregnancy are harmless. For example, 14% of pregnant women need a new eyeglass prescription. Some changes, however, are serious, such as retinal effects of hypertension, which can be a sign of pre-eclampsia. **METHOD** The present study was being conducted on 50 healthy pregnant controls and 50 clinically established pregnancy induced hypertensive subjects. Serum hCG was measured and Fundoscopy for retinal changes was done. For analyzing the Data, Statistical software SYSTAT version 12 was used. The results were revealed in mean ±standard deviation. Comparisons of cases and control groups were done by applying Z test. Student's t-test at 5% ($p=0.05$) and 1% (0.01) level of significance was used for correlation. **RESULTS**: Serum βHCG was significantly higher ($t=18.14$; $p<0.01$) in pregnancy induced hypertensive subjects as compared with healthy pregnant control subjects.40% to 100% of pregnant women with high blood pressure have retinal changes whose severity is correlated with the severity of pre-eclampsia or eclampsia. **CONCLUSION:** Abnormally high serum β HCG in PIH Subjects is a dreaded complication of pregnancy. Serum β HCG should be included in routine investigation. Most ocular diseases can be treated with the usual drugs in pregnant women and Recommendations about drug treatment should be checked against current information that can be found on the embryotox.de and reprotox.de websites

KEYWORDS: Pregnancy induced hypertension, βhCG, Funduscopy, hyperplacentosis.

INTRODUCTION

Pregnancy is a physiological process but needs strict monitoring throughout gestational period to circumvent perilous complications like pregnancy induced hypertension (PIH), gestational diabetes etc. Pregnancy induced hypertension is defined as blood pressure ≥140/90 on two occasions, atleast 6 hours apart and proteinuria of ≥300mg/24 hours or ≥ 1+dipstick after 20 weeks of gestation in previous normotensive women **(1)**.

Pregnancy induced hypertension (PIH) is the most common medical complication of pregnancy, whose incidence has continued to increase worldwide. It is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually **(2, 3)** and risk is very high in Indian women **(4)**. WHO estimates that one woman die every minute due to the complications of hypertensive disorders of pregnancy (HDP) **(5)**. Pregnancy induced hypertension is a disease influencing 5-10% of all pregnancies and PIH is identified in 3.9% of all pregnancies **(6)**. Recently, multiple hypothesis have been postulated to understand the complex etiopathogenesis which

includes placental ischemia, altered endothelial cell function, possibly secondary to altered lipid metabolism, immune maladaptation and genetic imprinting **(7)**. PIH is considered to be a trophoblastic disorder and the supporting evidence comes from the fact that these patients may suffer from either hyperplacentosis or an abnormal placentation **(8)**.

In PIH, there is mid-trimester surge of βHCG due to overwhelming secretory response of the immunologically modified trophoblast **(9)**. Also, there is 2-3 times rise in serum triglyceride concentration which are likely to get accumulated in the uterine spiral arteries contributing to endothelial activation and damage **(10)**. Hypoxic placental damage caused by hypertensive disorders results in reactive hyperplasia of the cytotrophoblastic cells and thereby increasing secretion of hormone HCG **(11)**.

Human chorionic gonadotrophin (HCG), pregnancy hormone is a glycoprotein with biological activity similar to luteininzing hormone (LH). It is secreted by syntiotrophoblasts and cytotrophoblasts before 5 weeks and later produced exclusively by syntiotrophoblasts.It was discovered by Zondek in the year 1930.

It is comprised of 2 dissimilar subunits - α and β subunits containing 92 and 145 amino acids. Both subunits are held together by electrostatic and hydrophobic forces. An amino acid sequence of α subunit is identical to FSH (follicle stimulating hormone), LH and TSH (thyroid stimulating hormone). The terminal 30 amino acid sequence of β subunit is unique to hCG. Molecular weight: 36000 Daltons. Secreted by trophoblasts; before 5 weeks, syncytiotrophoblasts and cytotrophoblasts produce hCG; later produced exclusively by syncytiotrophoblasts. Intact hCG is released by exocytosis. hCG acts via plasma membrane LH-hCG receptors. Plasma half-life: 36 hours.

hCG exists in multiple forms due to enzymatic degradation and modification during synthesis and processing.

i. Intact hCG
ii. Hyperglycosylated hCG
iii. Nicked hCG
iv. Free subunits.

Regulation of synthesis

Gonadotrophin Releasing Hormone (GnRH), activity stimulates hCG secretion.

Endorphin and inhibin inhibits secretion of GnRH and hCG.

Clearance

Renal clearance accounts for 30% of hCG clearance. Remaining is likely cleared by metabolism in liver.

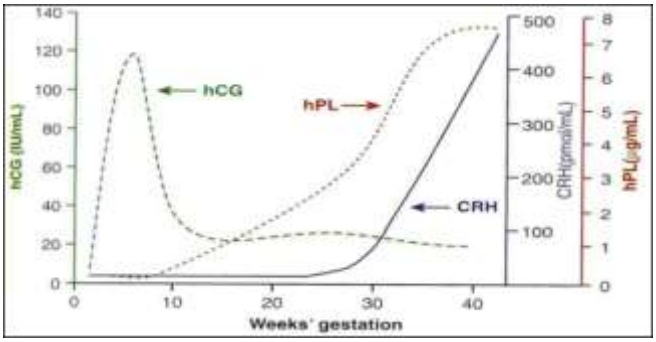
hCG concentration in serum

hCG is detected in serum as early as 7 to 9 days after LH surge. Levels of hCG increases rapidly in early pregnancy doubling every 2 days. Levels peak at 8-10 weeks reaching 100000 mIU/ml. This is followed by relatively sharp decrease beginning at 12 weeks and reaches a nadir by 20 weeks and maintains at these lower levels throughout the remainder of pregnancy. Levels disappear 2 weeks after delivery. hCG levels are raised in Multifoetal gestation, Foetus with Down' syndrome, Gestational trophoblastic disease, whereas hCG levels are lowered in Ectopic pregnancy, Impending miscarriage.

Functions of hCG

1. Supports corpus luteum of pregnancy till placenta takes over.
2. Stimulates foetal Leydig cells to produce testosterone.
3. Promotes secretion of relaxin by corpus luteum (in vivo).
4. May promote uterine muscle relaxation and vasodilatation.

Fig. 1: Serum hCG levels throughout normal pregnancy



Numerous different assays for quantitative estimation of hCG have been developed that differ in methodology (radio-immunoassay, enzyme immunoassay, fluorescent immunoassay), sensitivity and specificity.

hCG in preeclampsia

As placenta is the primary source for hCG production, measurement of plasma hCG levels has proven to be

effective screening tool for pregnancies with altered placental mass or function. The physiological increase in oxygen tension between 10 and 12 weeks gestation determines a decrease of TGF β and allows the trophoblast to differentiate into a more invasive type. In preeclamptic placenta, TGF β level remains high and the trophoblast is arrested at an immature state while its invasiveness is reduced. Since trophoblastic abnormalities play a central role in the development of preeclampsia, these hormones are elevated in maternal serum long before overt preeclampsia is diagnosed and have been proposed as early predictive markers of preeclampsia. Patient with overt preeclampsia in the 2nd trimester have increased maternal serum hCG levels. Some advocate that hCG secretion may be increased as a consequence of abnormal placental invasion or placental immaturity. It may also be linked to the trophoblast response to hypoxia with the development of a hypersecretory state **(12)**.

Most ocular changes in pregnancy are harmless. For example, 14% of pregnant women need a new eyeglass prescription. Some changes, however, are serious, such as retinal effects of hypertension, which can be a sign of pre-eclampsia. Ocular changes may give rise to uncertainty about the administration of ophthalmological drugs or the optimal method of childbirth.

Visual impairment and other ocular changes are rare in pregnancy. They arise in at most 15% of pregnant women and are usually harmless, but are nonetheless a cause of concern among the women who have them and their non-ophthalmologist treating physicians.

The few available epidemiologic studies of ocular changes in pregnancy have mainly concerned retinopathies **(1)** and refractive changes **(2)**. Nearly all pregnant women have reactive changes of the retinal vessels (e1); clearly visible changes arise only in the setting of hypertension, pre-eclampsia, or eclampsia. One in six pregnant women experiences a change in the tear film or eyeglass prescription.

Despite extensive research, the onset of hypertension during pregnancy has proven difficult to predict. Hence this study aims to compare and correlate serum βHCG and ocular changes during 13-26 weeks of pregnancy to investigate the clinical utility of maternal serum βHCG as predictors for PIH in early second trimester.

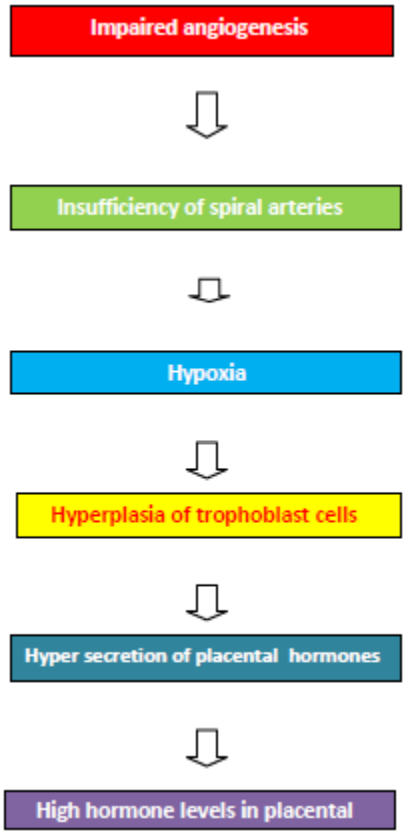


Fig. 2: Proposed hypothesis for raised hCG in preeclampsia

MATERIAL AND METHODS

This study was designed to evaluate all pregnant women between the gestational age of 13-26 weeks who were normotensive and non-proteinuric in first trimester for rise in βHCG and ocular changes.

Depending on the results of clinical examinations and biochemical investigations, all the selected subjects as per study population will be divided into the following groups:

GROUP 1: Healthy pregnant females

GROUP 2: Pregnancy Induced Hypertension females.

Inclusion Criteria

Those with known gestational age of second trimester are selected in this study, irrespective of parity.

Exclusion Criteria

Women with hypertension diagnosed before 20 weeks of gestation (before pregnancy), Women with multiple pregnancy, Pregnant women with diabetes mellitus, Ultrasonography proved congenital mal formations, Women with Liver and Renal failure are excluded.

After taking informed consent, all the subjects were screened for inclusion and exclusion criteria.

COLLECTION AND ANALYSIS OF BLOOD SAMPLES

Taking written consent from all the subjects before taking the samples. After an overnight fast 10-12 hours, about 10ml venous sample was drawn under aseptic conditions from median cubital vein and transferred in a plain vial and the sample was allowed to clot. The serum was separated from the clotted sample by centrifugation at 3000rpm for 10 minutes and the following biochemical parameters were estimated from the separated serum.

ETHICS

The study was approved by the Institutional Ethics Committee of S.N. Medical College, Jodhpur.

BIOCHEMICAL ANALYSIS

Following biochemical parameter was analysed by commercially available reagents and kits. The procedure given in the manuals accompanying the kits was strictly followed:

Serum Beta Human Chorionic Gonadotropin Method

Enzyme Linked Fluorescent Assay Method **(13)**.

Principle

The assay principle combines an enzyme immunoassay sandwich method with a final fluorescent detection (ELFA).

The sample is taken and transferred into the well containing alkaline-phosphatase labelled anti-hCG antibody. The antigen binds to the antibodies coated on the SPR and to the conjugate forming a sandwich. Thus, the remaining free sites are saturated by cycling the conjugate in the fifth well of the strip in and out of the SPR. Unbound components are eliminated during the washing steps.

During the final detection step, the substrate (4-Methyl- umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4–Methyl–umbelliferone), the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample.At the end of the assay, results are automatically calculated by the instrument in relation to calibration curve stored in memory, and then printed out.

Calculation

Once the assay was completed, results were analyzed automatically by the computer. Results were calculated automatically by the instrument in relation to the calibration curve stored in memory (4-parameter logistic model) and the concentrations were expressed in mI.

Table 1: Reference Value

Week of amenarrhoea	Mean (mIU/mL)	Limits (mIU/mL)
4-5	7400	1500-23000
5-6	32800	3400-135300
6-7	52000	10500-161000
7-8	74000	18000-209000
8-9	100000	37500-219000
9-10	105000	42800-218000
10-11	96000	33700-218700
11-12	75300	21800-193200
12-13	66700	20300-166100
13-14	65900	15400-190000
2^{nd} trimester (14-26)	26150	2800-176100
3^{rd} trimester (26-39)	27200	2800-144400

1) Men : <3 mIU/mL
2) Women
- Cyclic women : <4 mIU/mL
- Menopausal women : <13 mIU/mL
- Pregnant women :

Range

The measurement range of the VIDAS HCG kit is: 2-1500 mIU/ml

OCULAR ANALYSIS

Fundus copy should be performed before pregnancy and once per trimester. For high-risk patients, more frequent follow-up examinations are recommended, in the second and third trimesters.

RESULT

Table 2 shows Mean ± SD levels of β hCG of PIH subjects (65298 ± 10221.2) as compared with healthy pregnant controls (26063 ± 11376.4). In the same way, Table 3 illustrates statistical analysis of β hCG with t-value **(18.14)** and were significantly high ($p < 0.01$) in PIH subjects when compared with healthy pregnant controls. Table 4 shows the comparison of Serum βHCG among various studies which support our study.

Table 5 shows Physiological and Pathological Ocular changes during second trimester of pregnancy. However, Fig.3 illustrates the graph of Mean β hCG of subjects studied.

DISCUSSION

The present study was being conducted on 50 healthy pregnant controls and 50 clinically established pregnancy induced hypertensive subjects attending Ante Natal Clinic. The results were compared with age matched healthy pregnant control subjects. The aim of this study was to find out the correlation of serum β hCG levels during 13-26 weeks of pregnancy as predictors for PIH and ocular changes in second trimester of pregnancy.

A comparative study of various anthropometric and biochemical parameters, of all the subjects were carried out. As serum βHCG levels occupied our principle interest, their inconsistency in the pregnancy induced hypertensive subjects in relation to healthy pregnant controls are summarized table 2&3.

All structures in and around the eye can undergo change during and after pregnancy. The most important changes are listed in table 5. The frequency of each type of change is indicated in the table and in the text whenever such information is available.

Biochemical parameters

Serum beta human chorionic gonadotropins

The mean serum βHCG of healthy pregnant control subjects and pregnancy induced hypertensive subjects in the present study was 2606 ± 11376.4 mIU /ml and 65298 ± 10221.2 mIU /ml respectively. (Table: 2) Serum βHCG was significantly higher ($t=18.14; p<0.01$) in pregnancy induced hypertensive subjects as compared with healthy pregnant control subjects. (Table: 3)

Singh A et al (2016) observed that serum βHCG was statistically significantly higher in pregnancy induced hypertensive subjects (41500 ± 14000 mIU /ml) as compared to healthy pregnant control subjects (22500 ± 4500 mIU /ml). Here, the increased βHCG secretion is due to abnormal placental invasion or placental immaturity **(14)**. Also it may be due to abnormal trophoblastic response to hypoxia and subsequent development of a hypersecretory state **(7)**.

In similar study, **Nandini et al (2014) concluded** that the serum βHCG level was significantly high in women developing PIH (65315 ± 10237 mIU /ml) than healthy pregnant control subjects (26088 ± 11391 mIU /ml) with $p<0.001$(15).

In concordance to our study, **Mallick MP et al (2014)** observed that serum βHCG level was significantly high ($p<0.001$) in women developing PIH than healthy pregnant control subjects **(16)**.

G Kaur et al (2012) found that higher levels of βHCG are associated with increased severity of PIH ($P<0.01$). In his study, he found the sensitivity (90.91%), specificity (97.44%) and positive predictive value (83.33%). Hence, concluded that serum βHCG estimation at mid trimester is a good predictor of PIH**(17)**.

Meena D et al (2011) observed that mean serum βHCG level was significantly high (16130.2 mIU/ml) with a significant positive correlation ($p<0.001$)(18). Vidyabati RK et al (2010) observed that the serum βHCG level increased very significantly ($p<0.001$). Hence, it is a very good non-invasive predictor of PIH**(19)**.

Ocular Parameters

40% to 100% of pregnant women with high blood pressure develop retinal vascular changes, visual symptoms are reported in 25-50%. Visual symptoms include blurred vision, photopsia, scotomata, diplopia, corneal odema, visual field defects and blindness may worse with increased severity of disease **(20, 21)**. Mechanisms for these changes include hormonal changes, endothelial damage, hypoperfusion ischemia and edema, and associated vascular disease. Pre-existing retinal changes worsen during pregnancy in 55% of cases.

Pregnancy induced dry-eye syndrome, contact lens intolerance, decreased IOP due to increased aqueous outflow, decreased episcleral venous pressure, decreased scleral rigidity and generalized acidosis during pregnancy, usually decrease post-partum or with the usual drugs **(22, 23)**.

CONCLUSION

To conclude, the present study gives us an idea that abnormally high serum β HCG in PIH Subjects is a dreaded complication of pregnancy. There has been a constant endeavor to identify the risk involved in pregnancy and if possible, its prediction. If prediction is possible, prevention will follow naturally.

The present study indicates an increased risk of PIH in elderly gravida with elevated serum β HCG in second trimester (13-26 wks). As yet there is no practical, acceptable and reliable screening test for PIH. Serum β HCG seems to be good and early predictors for the development of PIH and should be included in routine investigation in second trimester of pregnancy.

Pregnant women and nursing mothers can undergo most types of ophthalmological examination and treatment. Recommendations about drug treatment should be checked against current information that can be found on the embryotox.de and reprotox.de websites.

The study needs to be more comprehensive with large samples collection in larger population for further evaluation and deep research in this field.

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TABLES

Table: 2

Mean β hCG (mIU/ml) of subjects studied

S.N.	Group Studied	β Hcg Mean ± SD
1.	Healthy pregnant Control	26063 ± 11376.4
2.	PIH Subjects	65298 ± 10221.2

Table: 3

Statistical analysis of β hCG among the Group studied

S.N.	Statistical analysis	Group compared
		Non PIH v/s PIH
1	t- value	18.14
2	p – value	<0.01
3	Statistical significance	Highly Significant

Table: 4

Comparison of Serum βHCG among various studies

	Present Study	Singh A etal (2016)	Nandini etal (2014)	MallickM P etal (2014)	Kaur G etal 2012)	Meena D etal (2011)
Mean±SD (mIU /ml)	65298± 10221.2	41500± 14000	65315± 10237	41833.33 ±19.25	----	16130.2
p- value	<0.01	0.0001	<0.001	<0.0004	<0.01	<0.001
Significance	Highly significant	Significant	Highly significant	Highly significant	Significant	Significant

Table :5

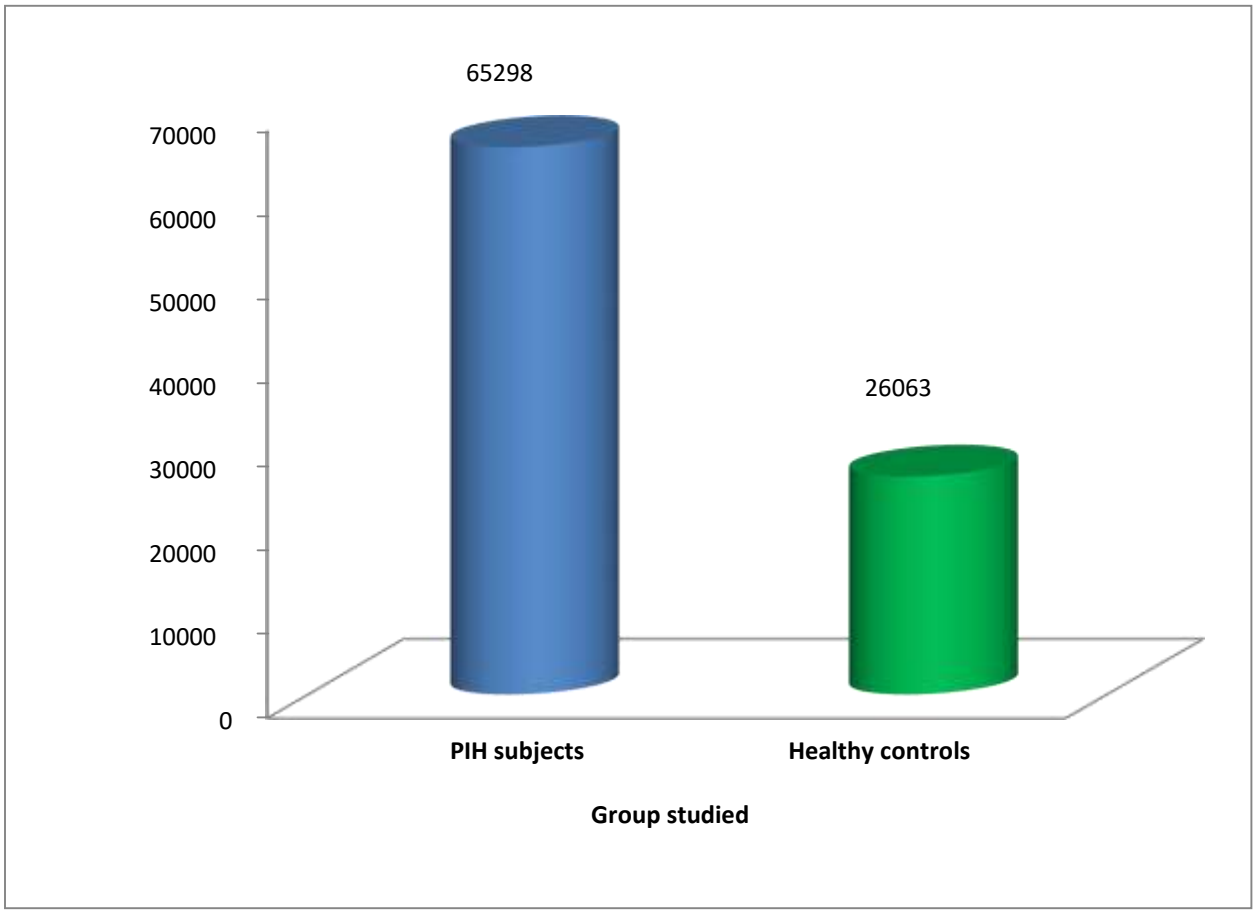
Ocular changes during second trimester of pregnancy

Structure	Physiological/innocuous	Pathological
General	**Lowering of intraocular pressure**	
Lid	Chloasma (5%—703) (4, e2, e3)	• Ptosis (few case reports) (6) • Horner's syndrome (0.4%–2.5%) (e5) • Facial nerve palsy (0.045%) (7)
Conjunctiva	Hyposphagma (10%) (e4)	• Vasospasm in pre-eclampsia
Cornea	• Reduced sensitivity • Krukenberg's spindles (3%) (5) • Increased thickness (14%) (2) • Altered refractive strength • Altered composition of tear fluid (14%) (2)	
Lens	Increased thickness, refractive change (14%) (2)	
Retina		• Worsening of diabetic retinopathy (as high as 55%, ·depending on findings before pregnancy) (1) • Vascular changes in pre-eclampsia (40%–100%) (10, e1) • Serous retinal detachment (0.005%) (10) • Central serous chorioretinopathy (0.008%) (7) Growth of melanomas
Optic nerve /optic pathway	Enlargement of pituitary gland	• Ischemic optic neuropathy in eclampsia • Cortical blindness in eclampsia (0.06%) (12) • Papilledema
Orbit		• Growth of hemangiomas • Carotid-cavernous fistula

GRAPHS

Fig. :3

Mean β hCG (mIU/ml) of subjects studied



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