

ROLE OF MATERNAL SERUM ZINC ON FOETAL GROWTH RATE AND ADVERSE PREGNANCY OUTCOMES: A COHORT STUDY

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ABSTRACT:

To compare maternal serum Zinc in each trimester of pregnancy with foetal growth rate and different adverse pregnancy outcomes to derive the critical cutoff in predicting APO. The reported incidences of these outcomes in India are as follows: spontaneous abortion 1.7%, 1% gestational diabetes, and 0.9% of stillbirths. As zinc is important for the preservation of cellular structures, any imbalance in zinc can predispose to infertility, foetal abnormalities, foetal death, and reduced weight or size of infants. So, this study attempts to compare maternal serum zinc between normal healthy pregnancy and the adverse pregnancy outcomes to derive the critical cutoff to justify their supplementation. Ethical approval and CTIRI registration Ethics clearance was obtained from the Institutional Ethics Committee of Kasturba Hospital Manipal IEC:182/2019 on 13/3/19. CTIRI registration - REF/2020/01/030393. Patient/subject (n=1280) recruitment was made after the ethical approval and CTIRI registration. During each trimester-booking visit, leftover fasting serum samples were collected from the biochemistry laboratory, and serum Zn was measured. In first trimester, serum zinc was significantly lower in spontaneous abortion and gestational diabetes mellitus compared to normal delivery. Our study implies zinc supplementation is crucial in early pregnancy to maintain a healthy pregnancy.

KEYWORDS: Pregnancy, zinc, spontaneous abortion, gestational diabetes.

Aim and objective: To compare maternal serum Zinc in each trimester of pregnancy with foetal growth rate and different adverse pregnancy outcomes to derive the critical cutoff in predicting APO.

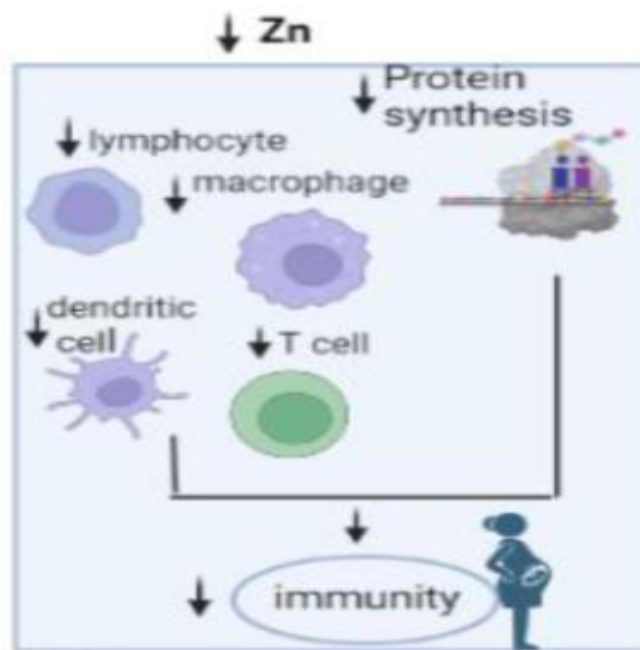
INTRODUCTION

Ten to twenty per cent of reported pregnancies are associated with Adverse pregnancy outcomes (APO). According to WHO data on pregnancy outcomes prevalence estimates in Europe and North America, 15%-30% are due to miscarriage, 0.3%-2.5% stillbirths, 6%-22% Preterm births <37 weeks, 10-14% Low birthweight <2,500g, 30% Small for gestational age, and 1.7%-3.2% neonatal death. The reported incidences of these outcomes in India are as follows: spontaneous abortion 1.7%, 1% gestational diabetes, and 0.9% of stillbirths [1-4]. Of these, 60% are credited to maternal nutritional changes and 40% to the alteration in the placenta and the fetus[5].

As zinc is important for the preservation of cellular structures, any imbalance in zinc, can predispose to infertility, foetal abnormalities, foetal death, and reduced weight or size of infants (figure 1-3) [5,6]. Accordingly, the supplementation of micronutrients is often prescribed during the pregnancy period without a proper validation/guideline regarding dosing/time, duration of supplementation, etc.

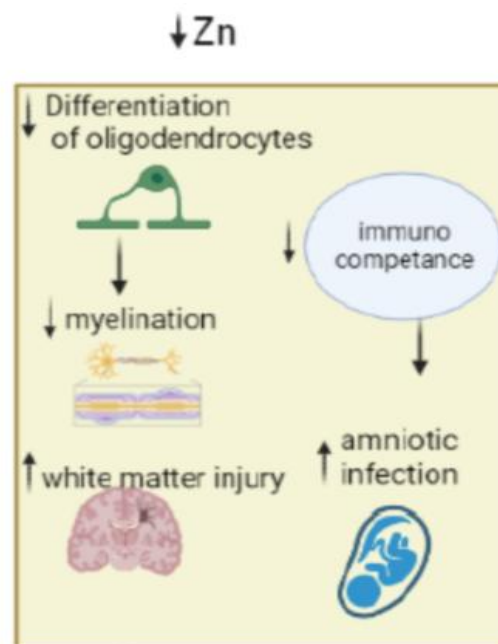
This has led to many unwanted supplementations. Studies have reported complications in pregnancy after unwanted multiple micronutrient supplementation during pregnancy [7,8].

There is a need to identify the exact population needing supplementation to prevent its abuse in each trimester/phase of pregnancy before supplementation can be initiated. So, this study attempts to compare maternal serum zinc between normal healthy pregnancy and the adverse pregnancy outcomes (spontaneous abortion (SA), fetal growth restriction (FGR), preterm birth, gestational diabetes mellitus (GDM)) to derive the critical cutoff to justify their supplementation.



SPONTANEOUS ABORTION

Figure1: Role of zinc in spontaneous abortion



PRETERM BIRTH

Figure 2: Role of zinc in preterm birth

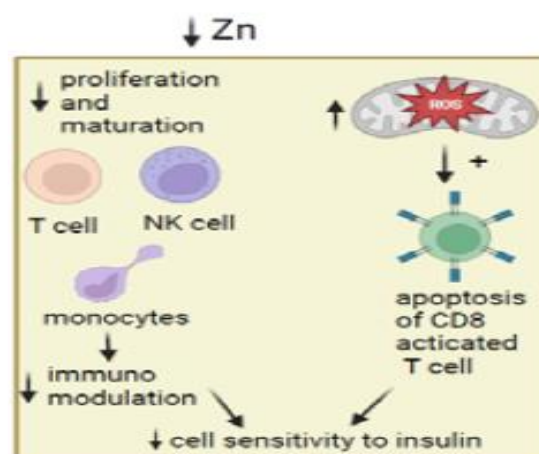


Figure 3: Role of zinc in Gestational diabetes mellitus

MATERIALS AND METHODS:

Inclusion criteria – Pregnant women in the age group of 20-38 years without any thyroid medication or known thyroid illness, coming for regular antenatal checkups.

Exclusion criteria – Patients with chronic hypertension, overt diabetes, IVF pregnancy, multifetal gestation, thyroid cancer/thyroidectomy/any surgery of the thyroid, or pregnancy known with TORCHS infection.

Methodology: Ethical approval and CTRI registration Ethics clearance was obtained from the Institutional Ethics Committee of Kasturba Hospital Manipal IEC:182/2019 on 13/3/19. CTRI registration - REF/2020/01/030393 Patient/subject (n=1280) recruitment was made after the ethical approval and CTRI registration. During each trimester–booking visit, leftover fasting serum samples were collected from the biochemistry laboratory, and serum Zn was measured (figure 4 & table 1). In the next period of gestation, anomaly scan (18- 20 weeks), GDM screening at 24- 28 weeks, and foetal growth parameters (HC, BPD, AC, FL) were measured and charted on the growth chart. Throughout pregnancy, all subjects were observed for onset problems like - spontaneous abortion, GDM, Preterm labor, FGR, IUD/stillbirth, etc as adverse pregnancy outcomes.

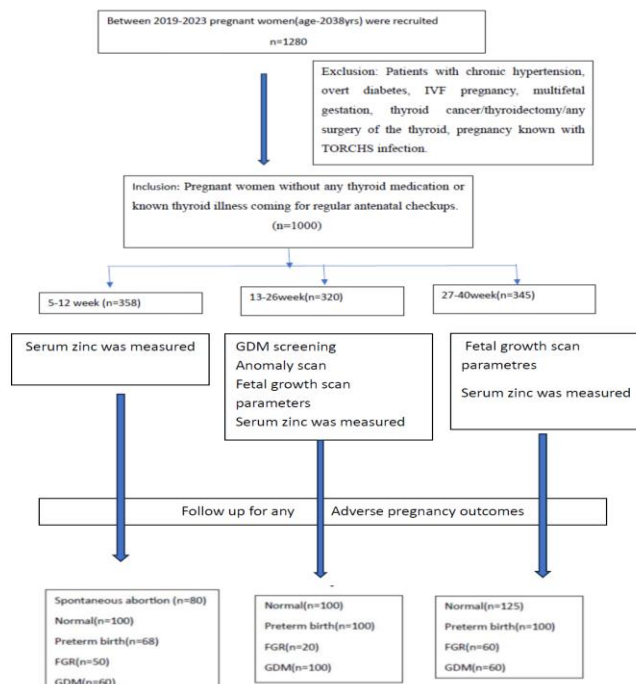


Figure4 : Consort diagram for material and methods

Table1: Analytical methods used for the analysis of Biochemical parameters

S No.	Parameter/ Manufacturer	Method name	Analyser	Normal Range
1	Serum zinc/CORAL DIAGNOSTICS Ltd	Zinc reaction with nitroPAPS	Semi- Autoanalyser	70 - 115 µg/dL

RESULTS:

In our study, participant demographics of first, second and third trimester (figure 5-7). In first trimester (figure 8), serum zinc was significantly lower in spontaneous abortion and gestational diabetes mellitus compared to normal delivery. (Multinomial regression, p -value<0.05, C.I-95%). In third trimester (figure 6), Serum zinc levels were significantly lower in cases of gestational diabetes mellitus. (Multinomial regression, p -value<0.05, C.I-95%). There was no significant association between serum zinc in each trimester with foetal ultrasonography indices (Nuchal translucency, Crown rump length) and foetal growth rate parameters (Head circumference, Biparietal diameter, Abdominal circumferences, Femur length).

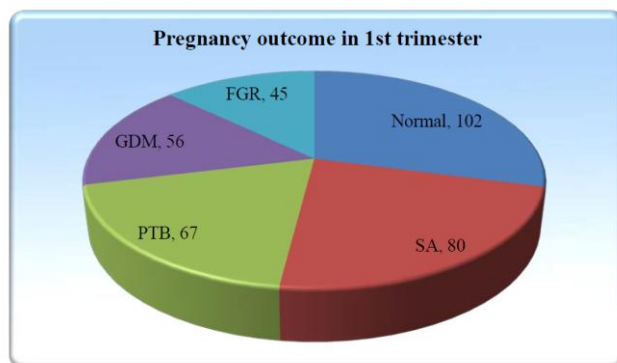


Figure 5: Participant Demographics in first trimester of pregnancy

(SA-Spontaneous abortion PTB-Preterm birth, GDM-Gestational diabetes mellitus, FGR- Fetal growth restriction)

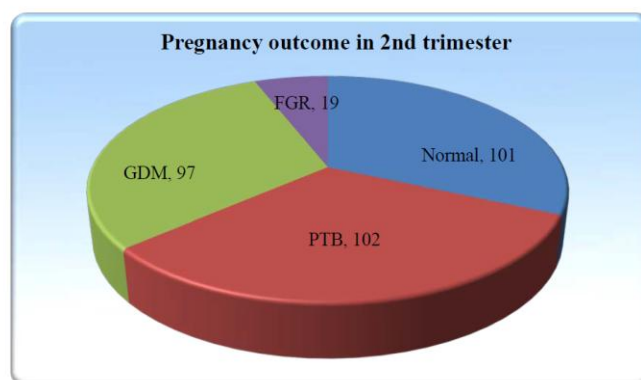


Figure 6: Participant Demographics in second trimester of pregnancy

(SA-Spontaneous abortion PTB-Preterm birth, GDM-Gestational diabetes mellitus, FGR-Fetal growth restriction)

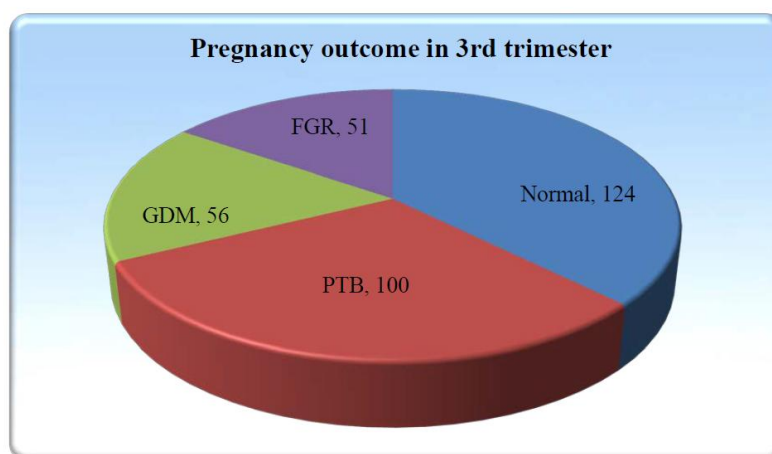


Figure 7: Participant Demographic in third trimester of pregnancy

(SA-Spontaneous abortion PTB-Preterm birth, GDM-Gestational diabetes mellitus, FGR-Fetal growth restriction)

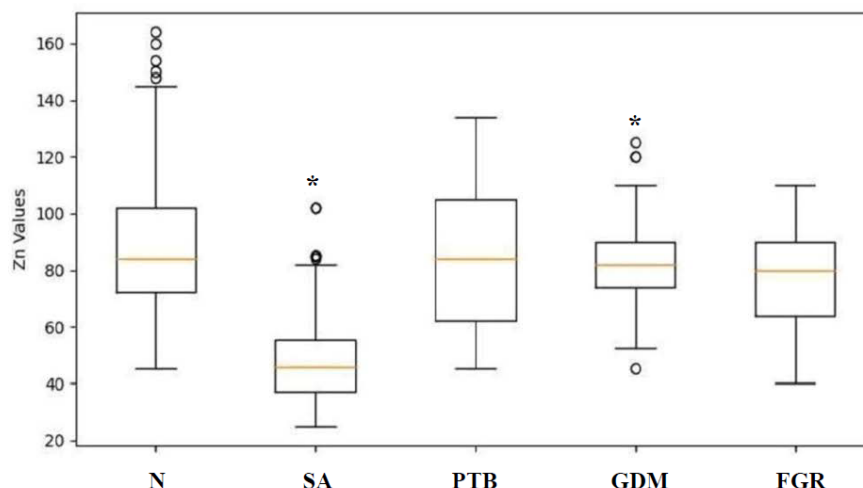


Figure 8: Comparison of maternal serum zinc in first trimester of pregnancy with different adverse pregnancy outcome

**Multinomial regression, p -value<0.05, C.I-95% N-Normal, SA-Spontaneous abortion, PTB-Preterm birth, GDM-Gestational diabetes mellitus FGR-Fetal growth restriction, APO-Adverse pregnancy outcomes.*

Table 2: Cutoff values of serum zinc for predicting different APO in first trimester

APO	Cutoff (mcg/dL)	AUC	PPV	NPV	Sensitivity	1-specificity
Normal	165	0.69	0.54	0.74	0.62	0.4
SA	65.2	0.7	0.44	0.86	0.85	0.54
GDM	64.2	0.61	0.25	0.95	0.91	0.61
PTB	90	0.62	0.38	0.84	0.45	0.21

Table 3: Cutoff values of serum zinc for predicting different APO in third trimester

APO	Cutoff (mcg/dL)	AUC	PPV	NPV	Sensitivity	1-specificity
Normal	112	0.52	0.56	0.58	0.62	0.42
GDM	124	0.67	0.22	0.8	0.7	0.62
PTB	80	0.57	0.41	0.76	0.79	0.62

DISCUSSION:

Studies have shown an association of maternal serum zinc with adverse pregnancy outcomes. However, no studies have measured trimester-wise cutoff values and relative risk for the range of the maternal serum zinc for the prediction of APO. So, this study measured maternal serum zinc in each trimester to establish trimester-wise cut-offs for predicting adverse pregnancy outcomes and foetal ultrasonography indices.

Maternal serum zinc measured at 5-12 weeks < 65.2 mcg/dL was associated with spontaneous abortion (table 2). This is in accordance with many other studies that showed low concentrations of maternal serum zinc can decrease antibody production, affecting maternal and foetal immunity and causing spontaneous abortion (Figure1)[9-14]. Maternal zinc measured at 5-12weeks<64.2mcg/dl and 27-40weeks ≤ 124mcg/dl were associated with GDM (table 2 and 3). This is in accordance with previous studies[15-17].Insulin activity is decreased due to zinc deficiency as it reduces the cell sensitivity to insulin, maturation of T-cells and monocytes, increases oxidative stress, which induces the apoptotic deletion in the CD8+CD25+activated regulatory T cell, immunomodulation is altered and hence leads to gestational diabetes mellitus. Besides, two zinc ions are present in hexamer of Zn-insulin complex and forms other complexes with insulin. Therefore, zinc supplements may benefit glucose homeostasis.

Maternal serum micronutrients did not show any significant association with foetal growth rate parameters (Head circumference, Biparietal diameter, abdominal circumference, Femur length) in any adverse pregnancy outcomes compared to healthy pregnancies. This may be because these indices are very minuscule and altered by a tiny fraction between subjects.

CONCLUSION:

Zinc was significantly lower in the first trimester among spontaneous abortion and Gestational diabetes mellitus. Also, lower maternal serum zinc in the third trimester was observed among GDM cases. Zinc showed good

negative predictive value for SA, GDM and PTB in the first trimester. Our study implies zinc supplementation is crucial in early pregnancy to maintain a healthy pregnancy.

Limitations of the study

We could not estimate the cutoff value for the prediction of FGR as participants had very few FGR cases as adverse pregnancy outcomes.

What does this study add to the clinical work

This study suggests that zinc supplementation is crucial in early pregnancy to maintain healthy pregnancy. Hence, it suggests supplementing the same.

Funding Declaration

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