

End of Contract Report

Impact Evaluation of Vitamin A & Beta Carotene Supplementation on Maternal & Neonatal Infections & Prematurity

Prepared by

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Introduction

The Zibuvita Trial was prepared in response to a request for proposals from MotherCare John Snow Incorporated (JSI) in 1995 and was designed to evaluate the effects of low dose vitamin A and beta carotene supplements on the health of women in pregnancy. The level of funding available from MotherCare was not sufficient for both the proposed arms of the trial and support was sort from UNICEF Jakarta for the beta carotene arm of the trial. In the ensuing discussions Dr Roger Shrimpton UNICEF Jakarta urged the primary investigators to consider replacing beta carotene with zinc. This later micro nutrient was proposed because of its established effects on the immune system and the potential for an interaction between vitamin A and zinc on the health of women. Following the provision of additional funds from UNICEF the trial was modified to a factorial design to allow the most efficient use of resources to examine the effects of each micro nutrient supplement and their combined effects on maternal sepsis.

There are 2 main donors for the project MotherCare JSI USA and UNICEF Jakarta. In broad terms funds have been provided by MotherCare for the vitamin A arm of the trial by UNICEF for the zinc arm of the trial. The trial has been conducted in the field area of the Community Health and Nutrition Research Laboratories Medical Faculty Gadjah Mada University. This community health research laboratory is funded by the Indonesian Department of Health through the Third Community Health and Nutrition Loan of the World Bank. This research infrastructure has provided valuable indirect support for the trial.

The research team consists of 3 principal investigators Professor Mohammad Hakimi, Professor Achmad Suryono from the Gadjah Mada University Indonesia and Dr Michael J Dibley from the University of Newcastle Australia and 3 co-investigators, Dr Detty S Nurdiani Professor DR Siti Dawiesah Ismadi from the Gadjah Mada University and Mrs Th Ninuk S H SKM from the Nutrition Academy, Department of Health Yogyakarta. The field team headed by Mr Eko Firdaus and the data management team is headed by Mr Eka Surya.

Research Aims and Hypotheses

The study aims to assess the impact of low dose vitamin A and zinc supplementation during pregnancy on maternal puerperal sepsis neonatal sepsis low birth weight gestational age of the newborn and the zinc vitamin A and hemoglobin status of mother and newborn. The purpose of the interventions is to restore vitamin A and zinc status in the treated mothers in order to assess the role of deficiency of these micronutrients on rates of infection the duration of pregnancy and fetal growth. Changes in maternal vitamin A and zinc status during pregnancy and after delivery will also be examined.

The following **primary hypotheses** will be tested using a randomized placebo-controlled, double masked trial with a factorial design involving four treatment groups a daily dose of 2,400 RE of vitamin A a daily dose of 20 mg of zinc the same daily dose of both zinc and vitamin A or a placebo with no vitamin A or zinc.

The incidence of puerperal sepsis in each of the supplemented groups will be at least 45 percent lower than in that of the placebo group.

The proportion of newborns with low birth weight (<2 500 gms) in each of the supplemented groups will be at least 25 percent lower than in the placebo group.

The following **secondary hypotheses** will also be tested

The proportion of newborns with premature gestational age (< 37 weeks) in the supplemented groups will be at least 30 percent lower than in the placebo group

The incidence of symptoms of neonatal sepsis in the supplemented groups will be at least 25 percent lower than in the placebo group

The zinc and vitamin A status of the mothers after delivery as measured by serum zinc MRDR test serum retinol and breastmilk zinc & retinol will be higher in the supplemented groups than in the placebo group

The zinc & vitamin A status of the newborns as measured by cord blood serum zinc & retinol will be higher in the supplemented groups than in the placebo group

The hemoglobin status of the mothers after delivery will be higher in the supplemented groups than in the placebo group

Aims of End of Contract Report

This "End of Contract" Report of the trial is submitted to provide the donors with information about progress with the trial and the event rates in the study population for the primary hypotheses

Specifically the report aims was to describe the study population and the pregnancy outcomes observed in those women enrolled in the trial who have delivered their infants

Analysis of the effects of each treatment on the key pregnancy outcomes being monitored in the trial will not be performed at this stage and the report will not present micronutrient or hemoglobin status of the mothers and infants

Methods

Experimental Design

The study uses an individually randomized placebo-controlled double-masked trial to assess the impact of low dose vitamin A and zinc supplementation during pregnancy on maternal puerperal sepsis neonatal sepsis low birth weight, gestational age of the newborn and the vitamin A and hemoglobin status of mother and newborn. The factorial design involves four treatments: a daily dose of 2 400 RE of vitamin A, a daily dose of 20 mg of zinc, the same daily dose of both zinc and vitamin A, or a placebo with no vitamin A or zinc. The target of the intervention and the unit of randomization is the mother-infant dyad who are followed through to the sixth week postpartum. The treatments are allocated in blocks (size of blocks remains masked) to ensure balance of treatments across time and residence of study participants. The study population is pregnant women and their newborn infants living in households monitored by the Community Health & Nutrition Research Laboratories Gadjah Mada University in the Purworejo District Central Java Indonesia.

Micronutrient supplements

The vitamin A supplement provides an intake of vitamin A approximately 3 times the RDA for US pregnant women of 800 RE / day and about twice the average observed intake of pregnant women in the US of about 1 200 RE / day (National Academy of Sciences 1990). However, this dose is below the generally accepted safe level of vitamin A intake in pregnancy of 3 000 RE/day over extended periods of time (Underwood 1994). The dose should ensure that vitamin A status can be restored and maintained during pregnancy.

The zinc supplement provides an intake equivalent to the FAO / WHO / ILEA normative requirements for zinc in pregnancy (Gibson, 1994) The dose should ensure that zinc status can be restored and maintained during pregnancy The majority of women in the study are likely to be at least mildly zinc deficient and may have dietary phytate levels sufficient to partially inhibit zinc absorption

Planned sample size

The sample size for the trial was calculated to examine the effects of each micro nutrient supplement It was estimated that 1,241 to 1,324 mothers per micro nutrient supplement group were required assuming 5% α level, 80% power, and minimum detectable differences of 45% for puerperal infection and 25% for low birth weight This sample size had adequate power to examine the effects on prematurity, changes in maternal vitamin A and hemoglobin status, and anthropometry of mother and newborn A final sample size of 1,100 per treatment group was selected resulting in 2,200 per micro nutrient supplement group This sample size was also thought to provide sufficient power to examine any interactions between zinc and vitamin A

Outcomes reported

The following maternal and infant outcomes will be presented in the report

Maternal outcomes

- *Puerperal infection* is a bacterial infection of the genital tract after delivery Since most temperature elevations in the puerperium are caused by pelvic infection, the incidence of fever after childbirth is a reliable index of the incidence of these infections and is used in most community-based studies In clinical settings puerperal fever is defined as "Temperature 38 00C (100 40F) or higher, the temperature to occur on any two days of the first 10 days postpartum, exclusive of the first 24 hours" (Cunningham, MacDonald & Gant, 1989) The following specific indicators of puerperal infection were examined in this report
 - Maternally reported feverishness at least once during the period from day 2 to day 14 postpartum
 - Measured maternal body temperature $\geq 37.5^{\circ}\text{C}$ at least once during the period from day 2 to day 14 postpartum
 - Measured maternal body temperature $\geq 38^{\circ}\text{C}$ at least once during the period from day 2 to day 14 postpartum

These indicators were chosen because of their simplicity and ease of computation from the maternal postpartum data There was insufficient data available to use the classical clinical definition noted above Associated symptoms of infections were also not considered in the report

- *Labour related outcomes* The following maternally reported indicators were examined in this report
 - Labour reported to last more than 1 day
 - Reported prolonged rupture of membranes (if reported time from rupture of membranes to delivery was >120 minutes for parity 1, otherwise >60 minutes)
 - Reported feverishness during labour
 - Reported excessive bleeding during labour or within 2 days of delivery

- ° Reported use of mor than 3 pads for bleeding during labour

Infant outcomes

- *Low birth weight* was a weight < 2 500 grams based on a measurement taken by the birth attendant using standard equipment provided by the research team
- *Pre-term delivery* was identified by
 - duration of pregnancy <259 days of gestation based on date of last menstrual period and date of delivery
 - duration of pregnancy <259 days of gestation based on maternal report of pregnancy duration
- *Abortions* were pregnancies ending with the delivery of a non-living infant and the mother regarded the outcome as either a spontaneous or induced abortion
- *Stillbirths* were pregnancies ending with the delivery of an infant that showed no signs of life and the mother did not identify the outcome as an abortion
- *Early infant deaths* were pregnancies ending with the delivery of an infant showing signs of life but who died on the first day of life

Field Methods

Enrollment and Eligibility Criteria

Supported by the Community Health and Nutrition Research Laboratories and a special household census a surveillance system to monitor for the onset of pregnancy in women of reproductive age was established in about half the subdistricts of Purworejo District or a total of about 17,000 households. Women were excluded from intensive monitoring for pregnancy if they were not married or did not have a life-partner if they were pregnant beyond their first trimester at the time of enrollment, if they were currently using oral contraceptives an IUD injectable contraceptives or Norplant or if there was evidence they were entering the menopausal state. Informed consent for pregnancy monitoring was obtained from the eligible women. The consenting women were visited at home by female interviewers monthly to detect the occurrence of pregnancy. The procedure for the detection of pregnancy was based on recording the date of last menstrual period (LMP) and confirmed with a pregnancy test in the field. Women who were pregnant for no more than 90 days were then invited to participate in the trial using a further consent process.

It took the field team several months to perfect the method to detect pregnancies and the level of enrollment was behind schedule from the beginning of the field work. The main cause of the problem with the field work was insufficient field staff to maintain the monthly visitation. Delayed visits resulted in late detection of pregnancy thus resulting in many women being excluded from the trial. With adequate field staff the approach is an appropriate method for the field detection of pregnancy.

Distribution of interventions and monitoring compliance

Once women were enrolled in the trial there were visited at home to distribute their supplements check compliance with the supplementation and to sort out any problems they were experiencing with the study protocol. Initially these visits took place every fortnight but was reduced to a monthly frequency once the women were comfortable with the supplementation and demonstrated a high level of compliance. The supplements were packaged in plastic strips with sufficient capsules for 2 weeks or 1 month. Unused capsules were returned to the field worker at the following home visit and were counted and recorded to monitor compliance. Women experiencing difficulties with the study protocol were visited by specially

trained field staff for counselling. The women's planned birth attendant was visited during this period to explain the trial and seek her support during the delivery and postpartum period.

Detection of onset of labour

A team of monitors visited the villages and birth attendants of all women who were within 1 month of their expected delivery date. This team alerted the field nurses once a woman in the trial had entered labour. The field team aimed to visit all women within 24 hours of delivery.

Postpartum monitoring

Trained field interviewers visited all study participants on each day following delivery for 14 days to record symptoms and to monitor body temperature. This intensive field monitoring was not implemented with the first 400 deliveries and for these women visits were made only twice a week. This delay in implementing the postpartum protocol has resulted in a differential loss of trial data since some study variables can be validly collected with less frequent visits. It however has resulted in the loss of maternal sepsis outcome data on the first 400 deliveries. At present the postpartum monitoring is proceeding smoothly and there are sufficient field staff to reach all study participants.

Statistical methods

Trial data was analyzed using the statistical packages SPSS and Epi Info Version 6. Baseline characteristics and outcomes will be presented as the proportion of each characteristic or outcome to the total sample or mean \pm SD as appropriate. These simple analytical methods are sufficient to indicate if outcomes of interest presents in the study population with clinically significant magnitude.

Results

Data management

By the end of August 1997 1434 baseline forms (form code ZB), 7622 pregnancy monitoring forms (ZH), 8428 compliance monitoring forms, 633 delivery data forms, 3542 maternal postpartum monitoring forms, 938 maternal anthropometry forms, 4423 infant monitoring forms and 2973 blood sample forms had been collected and entered into the computer. Basic data cleaning has been completed on the data entered but this process will continue until at least the end of the data collection.

Baseline characteristics

The study subjects appear to be representative for Purworejo District by a number of social and demographic characteristics of the respondents (Table 1). The mean age of the respondents was 28.2 years. An unexpected finding was the high proportion of deliveries assisted by midwives (55.0%) in comparison to traditional birth attendants (30.4%). This higher rate of deliveries by trained health personnel may reflect changes in birthing practices following the deployment of village midwives by the Department of Health or it may reflect an unexpected intervention from the conduct of the trial in the community.

Study subjects

By the end of August 1997 a total of 1893 women had enrolled in the trial of whom 633 had

completed their pregnancy with 586 live births 28 abortions 18 stillbirths or early neonatal death and 1 case with missing pregnancy outcome data (Table 2) Also 663 of the women in the trial had enrolled in the sub study to assess changes in micro nutrient status during pregnancy Postpartum maternal outcome data was collected for 288 but postpartum maternal body temperature data was only recorded for 122 women

Pregnancy outcomes

There was evidence of maternal postpartum sepsis in the study population Across all treatment groups 14.9% of women reported being feverish on at least one occasion from day 2 to day 14 postpartum (Table 2)

The mean birth weight of infants from all treatment groups was 3 190 grams (SD \pm 530 grams) However the proportion of infants with birth weight < 2 500 grams was lower than expected at 5.6% (Table 2) The rate of pre-term delivery (gestation < 259 days or 37 weeks) varied depending on which method was used to assess the duration of pregnancy and ranged from 23.9% when based on the date of the last menstrual period versus 12.9% when based on maternal reports of pregnancy duration

Across all treatment groups 13.6% reported labour lasting more than 1 day, 14.0% reported prolonged rupture of membranes and 11.8% reported use of more than 3 pads for bleeding during delivery (Table 2)

Conclusions and Recommendations

Progress of Trial

- The field trial has been able to measure the primary outcomes of interest maternal sepsis birth weight and duration of gestation with adequate reliability The strongest outcome is maternal sepsis and the weakest is duration of gestation
- The loss of maternal sepsis data at the start of the trial although regrettable needs to be viewed from the perspective of a field trial that was aiming to recruitment 4 500 subjects and was attempting to perfect field methods at the start of the trial These field problems have now been solved

Future Trial Activities

- It is essential for the success of the trial that the women already recruited should be followed up according to the trial protocols This would give a sample size of approximately 500 per treatment group or a total of 2 000 trial participants No-cost extension of the trial up to the end of December 1997 is therefore requested
- With remaining field work some outcomes should be dropped where there is evidence the field team is having difficulty collecting the data Examples of data collection that could be dropped include the Carpurro method to assess gestational age morbidity follow up of infants beyond 2 weeks postpartum These changes would allow the field team to focus on the key outcomes especially maternal sepsis

References

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Table 1 Baseline characteristics of respondents by treatment group

Baseline Characteristics		Count	%
Residence (N=1,772)	Urban	72	5.1
	Rural	1329	94.9
Highest level of education (N=1,802)	No schooling	41	2.9
	Primary school	795	56.3
	Junior high school	301	21.3
	Senior high school	231	16.4
	Tertiary education	44	3.1
Number of pregnancies (N=1,812)	One	190	13.3
	Two	554	38.8
	Three	407	28.5
	Four	180	12.6
	Five	54	3.8
	Six or more	43	3.1
Place of delivery for study birth (N=780)	Hospital	71	11.2
	Maternity clinic	91	14.4
	Home	402	63.8
	Other	66	10.5
Birth attendant for study birth (N=769)	Mother herself	32	5.1
	Family member	25	4.0
	TBA*	189	30.4
	Midwife or nurse	342	55.0
	Physician	34	5.5

* Traditional birth attendant

Table 2 Pregnancy outcomes for study population

Pregnancy outcomes	n/N*	Percent
Maternal outcomes related to labour		
Mother reported labour lasting >1 day	81 / 595	13.6
Mother reported prolonged rupture of membranes	84 / 602	14.0
Mother reported feverish during labour	31 / 596	5.2
Reported excessive bleeding during labour or within 2 days of delivery	100 / 596	16.8
Mother reported using > 3 pads for bleeding during labour	70 / 594	11.8
Infant outcomes		
Mother reported pregnancy ended in abortion	28 / 633	4.4
Pregnancy ended in live birth	586 / 604	97.0
Pregnancy ended in still birth	14 / 604	2.3
Pregnancy ended in infant death on first day of life	4 / 604	0.7
Maternally reported duration of pregnancy <259 days	74 / 573†	12.9
Duration of pregnancy based on last menstrual period <259 days	140 / 586	23.9
Birth weight <2 500 grams	29 / 522‡	5.6
Maternal postpartum sepsis		
Mother feverish at least once during 14 days postpartum	43 / 288§	14.9
Maternal temperature >37.5°C at least once during 14 days postpartum	15 / 122§	12.3
Maternal temperature >38.0°C at least once during 14 days postpartum	8 / 122§	6.6

N varies because of missing data. 633 pregnancies were followed up with 28 resulting in abortions, 586 live births, 18 stillbirths or early neonatal deaths and 1 case with missing birth outcome data.

† This question was not asked of mothers with stillbirths or abortions.

‡ Birth weight data not available for 64 live births (10.9%).

§ No postpartum maternal outcome data collected on 298 women and postpartum temperature data only recorded for 122 women.