International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: SJIF: 5.995
Available Online at www.journalijcar.org
Volume 6; Issue 11; November 2017; Page No. 7145-7149
DOI: http://dx.doi.org/10.24327/ijcar.2017.7149.1089

Research Article

COGNITION WITH OR WITHOUT IRON SUPPLEMENT IN ANAEMIA DURING PREGNANCY

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A R T I C L E I N F O

Article History:
Received 20th August, 2017
Received in revised form 29th September, 2017
Accepted 30th October, 2017
Published online 28th November, 2017

Key words:
Iron, Cognition, Pregnancy

A B S T R A C T

Back ground: Iron deficiency anaemia among pregnant women is the Global public health problem & may affect cognition. & its prevalence is greater than the prevalence of anemia Objective: To study cognitive functions among pregnant women with iron deficiency anemia (IDA) and to see the effect of elemental Iron Supplementation. **Materials & Methods:** An interventional (Before-After) study was conducted on 30 pregnant volunteers of 20-40 years of age with IDA (hemoglobin 7-10 g/dl, Ferritin < 12 ng/mL) enrolled at 14 weeks of gestation from the antenatal clinic of a tertiary care hospital. Cognitive functions (Mini Mental Status Examination Part I & II, P300) Serum ferritin, and Hemoglobin level were estimated before and after 16 weeks of 120 mg elemental iron therapy. **Results:** levels of Mean Hemoglobin and Serum Ferritin increased significantly ($p<0.001$) after iron therapy as compared to baseline. Cognitive functions as suggested by MMSE scores & P300 showed a statistically significant improvement ($p<0.001$ and $p<0.01$) after iron supplementation & It is significantly correlated with S. ferritin before and after treatment **Conclusion:** There is a significant correlation of Cognitive functions in pregnancy with Iron deficiency as indicated by decreased level of S. ferritin which improves after iron supplementation.

INTRODUCTION

Iron plays a pivotal role in many functions of the body, which include the oxygen transport, production of ATP (the main energy storage and transfer molecule in the cell), nuclear & mitochondrial function, and protection of cells from oxidative damage. (Michael & Richard. 2007). It is also required in normal neurodevelopment through enzymes controlling neurotransmitter synthesis, cell division, neuronal energy metabolism and myelination. (Erikson *et al*. 2001, Beard JL & Connor. 2003). Iron deficiency anemia (IDA), being the most prevalent nutrient deficiency in the World, responsible for fifth of early neonatal mortality and tenth of maternal mortality thus 800,000 deaths including 2.4% of global Disability Adjusted Life Years (DALYs) have been attributed to iron deficiency (Robert.2003). Female population is more prone to develop Iron deficiency anemia &more than 80% female are affected during pregnancy. Estimates from the World Health Organization (WHO) report that from 35%to 75% (56% on average) of pregnant women in developing countries and 18% of women from industrialized countries are anemic. (Nyuke & Letsky.2000, Ogunbode.2003, Ilobachie & Meniru.1990, Massawe.1999 & WHO1993) IDA during pregnancy is associated with poor performance on developmental ratings in infants and lower scores in cognitive function tests among infants. Cognition is a generic term embracing the quality of knowing which includes perceiving, recognizing, conceiving, judging, sensing, reasoning and imaging (Baltimore 1976 & Lozoff *et al*.1986).S tudies are suggestive to have impaired cognitive abilities in IDA even in the absence of overt anemia. IDA among pregnant women in developing countries like India is associated with adverse outcomes including preterm delivery and higher maternal mortality. On an exhaustive literature search, not a single study was found that impart evidence to suggest effect of iron supplementation on cognition during pregnancy and its correlation with serum ferritin. In studies so far Cognition has been assessed by Questionnaire based methods but at present more sensitive and non-invasive methods like the recording of Event Related Potentials (ERPs) instead of questionnaire based neuropsychological methods are available to quantify cognition. With the help of ERPs one can evaluate subtle alterations in central nervous system functions & can better correlate IDA with possible early brain alterations, which would indicate future cognitive defects. (Haliday.1993, Shankar N *et al*. 2000) Hence to see IDA association with cognition before and after Iron supplementation was planned so that corrective measures can be taken for the reduction of illness and disabilities such as cognitive impairment and decreased work capacity on developing infants that would have a strong negative effect on social and economic development in low- and middle-income countries. Therefore this study was designed to explore cognitive functions in

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pregnant women with iron deficiency anemia before and after iron supplementation and its correlation with serum ferritin level.

MATERIALS AND METHODS

Study Design, Sampling*:* An interventional before-after study was conducted in outpatient department of a tertiary care hospital on pregnant women having iron deficiency anemia. We have decided to include 30 participants in this study. This sample size would render at least 80% power and 95% confidence for estimating difference among cognitive function measured via Event related potential (auditory) after Iron supplementation among study subjects.

Participants*:* This study was conducted on pregnant women with iron deficiency anemia who came to outpatient department of a tertiary care hospital. Inclusion criteria were ''Women with singleton pregnancy at 14 weeks having normal presentation, not associated with any other medical or obstetrical complications, Hb level was 7 to 10g per dl and Serum ferritin levels <12 ng per ml. (Alperetal. 2000 & Asif N *et al*.2007) Excluded Participants were those having History of "drug intake in the last 6months like nitro vasodilators or glucocorticoid , history of chronic disease, hematological abnormalities addictions, infectious diseases, poor hearing and very poor vision''

Forty seven iron deficient pregnant women from middle socio economic back ground were screened on the basis of eligibility criterion for recruitment. Informed written consent was also obtained from all participants. Out of 47, 11 participants were excluded primarily because of advanced gestational age & their hemoglobin concentration was >10g/dl. Six participants did not turn up during follow up. So analysis was done on data obtained from 30 Iron deficient pregnant females were enrolled from Antenatal outpatient services on the basis of detailed history, clinical examination, routine laboratory blood & urine tests as per standard protocols.

Procedures*:* Biochemical parameters for Iron status and & cognition were assessed before and after oral Iron supplementation for 16 weeks (160 mg of Ferrous sulphate containing 60 mg of elemental Iron BD for 16 weeks). Coexistence of Helminthic infections causing anemia were excluded by Deworming with Albendazole 400 mg before giving the iron tablets).

Assessment of Iron deficiency Anemia

1. Screening of participants for anemia was done by taking detailed medical history and routine laboratory tests i.e.-Hb, TLC, DLC, Indices (MCV, MCHC, S. iron) and NESTROF test (to exclude Thalassemia), Smear for Malarial parasite, Stool for ova/ cysts, Total proteins & Urine Culture and sensitivity.
2. Blood was centrifuged & serum was analyzed for Serum Ferritin, VitB_{12} and CRP in the Department of Bio-chemistry. Bio-chemical parameters VitB12& Serum Ferritin by Electro Chemi-Luminescence Immunoassay (ECLIA), C- Reactive Protein (CRP by ELISA using commercially available kit) were estimated to exclude Megaloblastic anemia & correlation of stress & inflammation with pregnancy (Asobayire FS *et al.*2001& Vanden Broek2000).

All volunteers were subsequently treated with 60 mg elemental iron twice daily for next 16 weeks after which Serum ferritin, Vitamin B_{12} and CRP levels were again re-evaluated.

Assessment of Cognition

Quantitative assessments of Cognitive functions of participants were conducted by Mini-Mental State Examination (MMSE) and Auditory Event Related Potentials (ERP- P300 examination; EB Neuro machine: Galileo, Italy) before and after completion of oral Iron supplementation for 16 weeks.

Mini Mental State Examinations (MMSE): Participants were asked to fill MMSE questionnaire & their score was calculated. The MMSE is a valid Neuro- psychological test to quantify cognitive function. It provides bedside assessment of a broad array of cognitive functions including orientation, attention, memory, construction and language. MMSE is divided into two sections, the maximum score of part I is 21 & score of part II is 9. The range of MMSE score among Normal Participants is 24 – 30.Below normal range, scores labeled as mild(21-24 points), moderate (10-20 points) &severe (≤9 points) cognitive loss (FolsteinMFetal.1975). Scores decline as age advances and increase with higher educational level.

P300 Event Related Potentials Auditory (AERPs)*:* Event related potentials (ERPs) are distinct class of evoked potentials generated when the subject is selectively attentive to the stimulus. The P300 is a late endogenous positive event related potential, is a measure of cognition occurring approximately 300msecs after the onset of novel stimulus or a stimulus that is perceived as target stimulus among other stimuli means that subject is required to distinguish the rare stimulus (the target) from a group of other frequent stimuli (the non-targets). Assessment of Waveform P300 in Auditory Event Related Potentials of participants was done by using EB Neuro machine (Evoked potential measuring system- Galileo Italy). The Event Potentials (EPs) were recorded as per the guidelines of International Federation of Clinical Neurophysiologists (IFCN) (Michael J.1988).

Statistical Analysis*:* Analysis was done with IBM SPSS 21 Software. Continuous variables presented as mean and standard deviation. Comparison of various mean levels of all parameters before and after study was done by using paired t-test. Correlation coefficient was used to test correlation between improvement in iron deficiency and improvement in cognition. P-value < 0.05 was considered statistically significant.

Ethics*:* Institutional Ethics Committee has approved project and written informed consent of every participant was obtained.

RESULTS

A total of 37 participants were interviewed, advised IFA and were asked to follow up after 16 weeks. Out of 37 participants, 30 turned for follow up.

Table I Baseline parameters at 14 wks of gestation.

Variable	Mean	Standard Deviation
Age (Years)	24.63	3.24
Period of gestation (weeks)	14.2	0.40
Body Mass Index (kg/m2)	22.13	2.27
Hemoglobin (gm/dl)	7.94	0.84
Serum Ferritin (ng/ml)	8.79	2.10
C- Reactive Protein (mg/l)	6.11	2.24

Pregnant women were between 20-40yrs. of age (mean age 24.63 ± 3.24 years). Table 1 shows baseline characteristics of study participants. The baseline parameters serum ferritin, haemoglobin, CRP and Vitamin B_{12} were recorded at 14 weeks gestation as mean age was 14.2 (0.40) having BMI 22.13.

Table 2 shows results of haemoglobin, ferritin, vitamin B12 levels and cognitive parameters (MMSE and AEP) after 16 week ferrous sulphate regimen. A significant increase in serum ferritin 13.66(1.42)ng/ml as compared to the baseline 8.79 (2.39) ng/ml which was statistically significant($p<0.001$).

Table 2 Biochemical parameters depicting iron status and cognition (MMSE& Auditory event potentials) after 16wks of Iron supplementation

Variable	Before Treatment (Mean (SD))	After Treatment (Mean (SD))	Mean Difference with 95% Confidnce Interval	p-value
Haemoglobin	7.94 (0.84)	8.95 (0.88)	1.01 (0.77 to 1.2)	<0.001
Ferritin	8.79 (2.39)	13.66 (1.42)	4.86 (4.32 to 5.41)	<0.001
MMSE (Part-1)	16.83 (1.98)	18.13 (1.07)	1.30 (0.62 to 1.97)	<0.001
MMSE (Part-2)	4.33 (0.92)	5.76 (1.00)	1.43 (0.93 to 1.93)	<0.001
Haemoglobin	7.94 (0.84)	8.95 (0.88)	1.01 (0.77 to 1.2)	<0.001
Ferritin	8.79 (2.39)	13.66 (1.42)	4.86 (4.32 to 5.41)	<0.001
P-300 Latency(msec)				
Fz	327.53 (32.15)	305.26 (46.81)	-22.26 (-37.57 to -6.95)	0.006
Cz	327.53 (32.15	281.66 (56.98)	-35.40 (-56.63 to -14.16)	0.002
Pz	319.46 (34.17)	291.33 (65.13)	-28.13 (-52.45 to -3.80)	0.025
P300-Amplitude (msec)				
Fz	5.13 (1.14)	5.97 (0.78)	0.844 (0.46 to 1.22)	0.001
Cz	6.48 (0.82)	7.25 (0.91)	0.77 (0.544 to 0.99)	<0.001
Pz	6.86 (0.87)	8.31 (1.63)	1.45 (0.95 to 1.96)	0.001

Showing significant improvement in cognition & iron status and after iron supplementation

Table 3 Showing correlation of cognition with serum ferritin

Variable	Correlation Coefficient	p-value
Difference in P-300 Latency		
Fz	-.052	.786
Cz	.010	.958
Pz	.158	.406
Difference in P-300 Amplitude		
Fz	.144	.447
Cz	.010	.958
Pz	.130	.492
Difference in MMSE Part 1	-.148	.436
Difference in MMSE Part 2	-.184	.330

Showing insignificant results because of lower dose and poor bioavailability of oral iron

The increase in hemoglobin (mean Hb before treatment 7.94 ± 0.84 g/dl and after the iron supplementation 8.95 ± 0.88 g/dl,) was also statistical significant as $p<0.001$. Cognition was measured with score of MMSE that got increases significantly from its base line value since mean difference with 95% confidance interval was for part I & II were 1.30(0.62to1.97) & 1.4(0.93to 1.93). Results got further strengthened by observations of p300 latency and amplitude. Improvement in P-300 latency was statistically significant. Similarly P-300 Amplitude scores had shown ($p<0.001$) significant improvement after treatment as shown in table 2 Improvement in cognition indicated by MMSE and evoked potential after treatment for iron deficiency anemia indicates that iron status plays important role in cognition.

DISCUSSION

Cognition has been considered as an abstract & direct property of brain that represents mental functions. Iron deficiency anemia being worldwide problem may affect cognition .Recent study by Beard J.L *et al* suggested a significant influence of iron deficiency anemia's on dynamic properties and functional features of the central nervous system activity.(Beard JL.2003) It was suggested by studies of petranovicet.al that cognitive achievement has been associated with hemoglobin (Hb) and S. Ferritin level in both anemic and non-anemic persons, i.e. higher Hb and S. Ferritin level results in better CNS function (Petrinivac D *et al*.2008).

Pregnancy and the lactation period is a critical nutritional stage for optimal psychomotor and cognitive development & during pregnancy & Serum Ferritin is considered as the gold standard test to determine iron deficiency anemia. IDA during pregnancy may lead to deranged cognitive development in their babies & proper cognitive development among children is must for better world tomorrow. Beard *et al* also suggested the positive correlation of neural functioning and Iron status (Beard J L *et al.* 2005). Few studies suggests that iron supplementation in infants may positively influence children's psychomotor development whereas it does not alter their mental development or behavior controversial Laura E & Murray *et al* suggested to have behavioral problems in children associated with poor iron status in early period of their pregnancy (Laura E *et al*.2007).

Present study is one of the rare useful study seeing association of maternal iron status at the end of first trimester i.e. at 14weeks& cognition before and after Iron supplementation with the help of both neuropsychological (MMSE) and neurophysiologic methods i.e. p300 (Event related potentials). Supplementation for 16 weeks were chosen for 2 reasons. One is to ensure that the female given Iron supplements would be iron repleted at the end of the study& another reason is animal based studies evidence that liver Iron concentrations replenished earlier than brain iron concentrations. (Laura E *et al*.2007).

The recording of long latency event related cerebral evoked potentials had been used as an objective measure of cognitive functions and perception. The detection of an infrequent stimulus in an oddball paradigm is associated with a parieto-central component of an event related potential (P300) & it is able to elicit target related responses in parietal cortex, cingulate, prefrontal superior parietal cortex as suggested with help of functional imaging by David E.J.Linden. 2005 also observed by John Polich *et al* 1995. They discovered that p300

reflect neuro-electrical activity related to cognitive processes, Decrease in latency and increase in Amplitude was considered as improvement in cognitive tasks & we are able to assess attention and memory dysfunction as the amplitude of the P300 is directly related to the novelty of the stimulus while its latency appears to be related to the assessment of the stimulus and of working memory adjustment to it. We have tried to eliminate all the confounders like age, socioeconomic status etc associated with Event related potentials. Facts above also get strengthened by observations of our study as shown in table2 in which latent period ($p<0.05$) and Amplitude ($p<0.001$) that were measured in patients with IDA had a tendency towards significant improvement after iron supplementation of 16 weeks). Similar kind of significant improvement was noticed on the basis of Neuropsychological test i.e. M.M.S.E part I &II after treatment. ($p<0.001$) as shown in table2. Similar kind of responses has been seen by using Detterman's cognitive abilities test and study of Murray Kolb and Beard *et.al* that suggested the iron supplementation not only improves 5–7 folds in cognitive performance but also increases speed in completing the cognitive tasks with improvement in Hb and serum ferritin. Bruner *et al* & Laura etal further strengthened our study by noticing the fact of iron supplementation has improved verbal learning and memory in even non anemic iron de cient adolescent girls. (JohnPolich & Albertkok.1995), Regarding Associations of p300 and MMSE before and after Iron therapy were shown by their correlation with serum ferritin and Hb as shown in table3. Significant improvement in cognition was there before and after iron supplementation of 16 weeks but negative correlation was observed between p300&MMSE with Hb &serum ferritin there would be two reasons for that First is women were given low dosage of iron i.e 160 mg of ferrous sulphate containing 60 mg of elemental iron for 4mths as that could be proven with study done by Fernando E & Ragip A. *et al*.2005 & studies published in pregnancy journal states that either higher doses of oral Iron therapy or intravenous supplementation should be given. Studies of Alhossain A *et al*. 20112 also suggested Intravenous iron supplementation during pregnancy because of poor bioavailability of oral iron than newer highly efficacious iron II & Iron III complexes. Another reason is pregnancy being high demand state dysregulation of hepcidin concentration has been noticed. (A. Khalafallah *et al*. 2010) The mechanism by which iron de ciency alters cognition and behavior in adults is largely unexplored. Possible reasons for iron affecting cognition are as follows(i) abnormalities in neurotransmitter metabolism ii)decreased myelin formation and iii) alterations in brain energy metabolism. So with results described in our study, it is logical to suggest that IDA (Iron deficiency Anemia) has great in uences on cognitive functions and cerebral activity and not only symptomatic improvement is possible with Iron supplementation, it would improve cognition as well as adverse outcomes including preterm delivery and higher maternal mortality.

In conclusion, above study demonstrated that there is a strong association of iron deficiency indicated by serum ferritin levels with cognitive functioning in pregnant females which gets improved with Iron supplementation.

Limitations

1. Cognitive functions can be explored in its domains with larger no of subjects
2. Cognitive functions with intravenous Iron supplementation can be done or proper brain Iron repletion.

Acknowledgement

No grant has been taken, We are extremely thankful to our collegues biochemistry staff and our study subjects because without their dedicated involvement It was impossible to finish our study.

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How to cite this article:

Ritu Dabas *et al* (2017) 'Cognition With or Without Iron Supplement In Anaemia During Pregnancy ', *International Journal of Current Advanced Research,* 06(11), pp. 7145-7149. DOI: http://dx.doi.org/10.24327/ijcar.2017.7149.1089

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