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Original Article

Physiology Section

Trimester Specific Effect of Pregnancy on Maternal Cognitive Function using Critical Flicker Fusion Frequency: A Cross-sectional Study

J ROSHNI[1], S ANU[2], M RAMJI[3]

ABSTRACT

Introduction: Critical Flicker Fusion Frequency (CFFF) measures cognitive function by detecting the threshold at which flickering light appears steady. This threshold reflects neural processing and cortical arousal, making it useful for diagnosing conditions like Alzheimer's and schizophrenia. During pregnancy, hormonal fluctuations can cause cognitive symptoms ("pregnancy brain"). Monitoring cognition ensures safety, productivity, and early detection of complications like pre-eclampsia. Despite importance, CFFF research during pregnancy is limited, especially across trimesters.

Aim: To find out objective cognitive changes in various trimesters of pregnancy using CFFF in primigravid women and compare with non pregnant women.

Materials and Methods: The present observational cross-sectional study was conducted from October 2023 to March 2024 in the Department of Physiology of Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India. The study involved 155 primigravid women in various trimesters and 50 non pregnant women in the age group of 21-25 years. The subjects were categorised into three groups. Group A- 1st trimester group with Gestational Age (GA) between 0-13 weeks, Group B - 2nd trimester group with GA between 14-27 weeks, Group C- 3rd trimester with GA between 28-40 weeks. CFFF was measured in all these groups and the association was analysed. CFFF was measured with CFF M1 model instrument (Mavom Labs, Bangalore) using Netra software. Data were statistically analysed by using Chi-square test.

Results: The study included 53 pregnant primigravid women in the 1st trimester, 51 in the 2nd trimester, 51 in the 3rd trimester, and 50 non pregnant samples of similar age, marital status and with the average husband's income of ₹42,261.29 with significant variability (SD=₹28,048.74). A significant decrease in CFFF values were observed in 1st (p-value <0.001) and 3rd (p-value <0.001) trimesters in pregnant women when compared to non pregnant individuals. The 2nd trimester showed a significant increase in CFFF (p-value <0.001).

Conclusion: The CFFF measurements could provide a useful tool for identifying individuals at risk of more severe cognitive decline or sensory processing difficulties during pregancy and take appropriate measures.

Keywords: Flicker fusion rate, Gestation, Gravida, Mental processing

INTRODUCTION

The CFFF is the rate at which successively presented light stimuli appear to be steady and continuous [1]. CFFF depends on the speed of information processing, concentration, alertness and measures visio temporal resolution. CFFF assesses central nervous system activity and cortical arousal and has been used as a diagnostic tool in disorders like Alzheimer's disease, multiple sclerosis and schizophrenia [1]. Higher CFFF rate indicates greater cortical function and finer cognition [2]. Cognition represents the ability to acquire, store, manipulate and retrieve information. CFFF as a method to assess cognitive functions is objective, simple, quick, low cost and is resistant to the learning effect [3].

Pregnancy is characterised by the most drastic hormonal fluctuations women experience during their reproductive lives [4]. During pregnancy, levels of hormones such as estradiol and progesterone increase by up to 30 and 70 fold, respectively, along with an increase in cortisol and prolactin level in comparison to non pregnant levels [5]. During pregnancy, a considerable number of women experience some degree of cognitive change. The symptoms most frequently reported by women during these reproductive periods are forgetfulness and memory disturbances, poor concentration, increased absentmindedness, and difficulty reading. Cognition was measured using various questionnaires and tools including Edinburg postnasal depression scale, Wecshler adult intelligence scale, rey auditory and verbal learning test and Tower of London [5,6]. Fluctuations in hormonal levels during pregnancy modulated specific cognitive abilities [5]. General cognition, memory, and executive functioning were reduced during gestation, especially during the third trimester [6]. The CFFF has the advantage of being an objective tool, quick, easy to perform and language, education-independent when compared with other tools.

In a 2011 study conducted on pregnant women, subjective deficits in cognition was observed while using standardised questionnaires, whereas no objective deficits in cognition were observed in laboratory tests [4]. This is in condradiction to the results of a study done on healthy pregnant women and non pregnant women using CFFF where no cognitive impairment was noted in all three timester women when compared with the control [7]. There was a decline in CFFF in pre-eclamptic women due to defective endothelial lining [7]. But up to this point, it is unclear if pregnancy in its various trimesters affects CFFF in any way. Hence, the aim of the present study was to find out using CFFF, cognitive changes in various trimesters of pregnancy in primigravid women. After categorising the primigavid women as 1st trimester, 2nd trimester, 3rd trimester groups based on their GA, CFFF was measured and each trimester CFFF values were compared with non pregnant women to detect trimester specific cognitive changes.

MATERIALS AND METHODS

The present observational cross-sectional study was carried out in the Department of Physiology of Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India, from the months of October 2023 to march 2024 after obtaining Institutional Ethical Committee Clearance (IEC No: VMCIEC/068/2023). The study subjects were taken only with explicit informed consent and were given the option to back out with no penalty.

Inclusion criteria: Willing primigravid women of age between 21 and 25 years in various trimesters were included. Age matched non pregnant, healthy, nulliparous women with regular menstrual cycle and without hormonal contraceptive use was included as control.

Exclusion criteria: Both primigravid and control women with any visual problems found on routine ophthalmic examination, psychiatric illness assed using Brief Psychiatric Rating Scale (score less than 31 was taken), sleep disturbances assessed using Pittsberg Sleep Quality Index (score less than 6), on anti-depressant medications, current use of hormonal preparations, chronic medical or neurological disorders, metabolic disorders, hormonal disorders or any neurological disease were excluded from the study [8,9].

Sample size selection: A total of 205 (155 primigravid women and 50 non pregnant women) subjects were enrolled in the study by convenient sampling. The pregnant and non pregnant women who visited the hospital between October and March 2023 and who had given voluntary consent for the study were chosen.

- primagravid women who were in 1st trimester were 53
- primagravid women who were in 2nd trimester were 51
- primagravid women who were in 3rd trimester were 51
- there were 50 non pregnant women

Study Procedure

The subjects were involved in the study after getting their informed voluntary consent. Demographic data including age, marital and socioeconomic status, education, husband income and working status of the women were collected and matched. Last Menstrual Period (LMP) and Expected Delivery Date (EDD) were collected from the pregnant subjects. Enrollment was restricted to primigravid women. In multigravid women fatigue levels may be more pronounced as they must also take care of their older children at home. GA was calculated and based on that; the subjects were categorised into three groups. First trimester group with GA between 0-13 weeks, second trimester group with GA between 14-27 weeks, third trimester with GA between 28-40 weeks. The cognitive changes in various trimesters were then analysed using CFFF.

CFFF was estimated using an in house-built LED based CFF M1 model instrument which was precalibrated and checked for its performance (Mavom lab, Bengaluru) [10]. A value between 35-40 Hz was considered as normal [11]. The subjects were instructed about the procedure following which CFFF was measured. The CFFF test was carried out in dimly lit room with the subject sitting 80 cm away from the module and a 40 W bulb fixed behind the subject. A series of red-light stimuli at different frequencies against a white background ranging from 12 to 120 Hz was presented. The red light was presented against a white background. The subject was asked to focus on the flicker continuously. The frequency of the flicker was slowly and steadily increased from 12 Hz until the subject reports that the flickering of light stopped and perceived as steady or fused light. Mean value of three ascending measures from low to high frequency was collected. Similarly, the mean value of three descending measures from high to low frequency was collected for analysis. The subject has to report when the light started flickering. CFFF was always measured between 10-11 am to avoid diurnal variation, as the value decreases consistently throughout the day [9]. A CFFF value of more than 39 Hz was considered normal and was taken as cut-off value for the study.

STATISTICAL ANALYSIS

Results were analysed using Statistical Package for the Social Sciences (SPSS) software version 22. Statistical tests used were descriptive statistics and Chi-square test. The p-value less than 0.05 were taken as cut-off for statistical significance.

RESULTS

The table shows the average age is approximately 22.42 years with a standard deviation of 1.16 years, and the average husband's income is ₹42,261.29 with significant variability (SD=₹28,048.74). Most individuals fall into the upper-lower (27.1%) and upper-middle (25.2%) socioeconomic status categories. In terms of education, a majority have completed schooling (72.3%) while 11.6% hold a degree. Employment status reveals that 49.7% are private employees, 21.3% are housewives, and 17.4% are government employees. Regarding the visiting period, January sees the highest number of visits (23.87%), followed by November (19.35%) [Table/Fig-1].

The study includes 53 samples in the 1st trimester, 51 in the 2nd trimester, 51 in the 3rd trimester, and 50 non pregnant samples, totalling 155 samples across the three trimesters.

Variables		Total cases	1st trimester (53)	2nd trimester (51)	3rd trimester (51)	Non pregnant (50)
Age (Mean±SD)		22.42±1.16	22.21±1.18	22.37±1.07	22.69±1.17	22.45±1.12
Husband income (Mean±SD)		42261.29±28048.74	41386.79±35867.89	44686.27±23875.92	40745.09±28048.75	42700.32±29000.12
Variables	**Category**	**Total N (%) cases**	**1st trimester (53)**	**2nd trimester (51)**	**3rd trimester (51)**	**Non pregnant (50)**
Socio economic status	Lower	29 (18.7%)	1 (1.9%)	14 (27.5%)	14 (27.5%)	5 (10%)
	Lower-middle	35 (22.6%)	16 (30.2%)	9 (17.6%)	10 (19.6%)	11 (22%)
	Lower-upper	3 (1.9%)	3 (5.7%)	0 (0%)	0	2 (4%)
	Upper	7 (4.5%)	3 (5.7%)	2 (3.9%)	2 (3.9%)	3 (6%)
	Upper-lower	42 (27.1%)	12 (22.6%)	15 (29.4%)	15 (29.4%)	12 (24%)
	Upper-middle	39 (25.2%)	18 (34.0%)	11 (21.6%)	10 (19.6%)	17 (34%)
Education	Degree	18 (11.6%)	18 (34.0%)	0 (0%)	0 (0%)	6 (12%)
	Illiterate	15 (9.7%)	1 (1.9%)	7 (13.7%)	7 (13.7%)	4 (8%)
	Master degree	10 (6.5%)	2 (5.7%)	5 (9.8%)	3 (5.9%)	5 (10%)
	Schooling	112 (72.3%)	31 (58.5%)	39 (76.5%)	42 (82.4%)	35 (70%)
Occupation	Govt. Employed	27 (17.4%)	18 (34.0%)	4 (7.8%)	5 (9.8%)	6 (12%)
	Housewife	33 (21.3%)	15 (28.3%)	12 (23.5%)	6 (11.8%)	10 (20%)
	Private employee	77 (49.7%)	15 (28.3%)	27 (52.9%)	35 (68.6%)	27 (54%)
	Self employed	18 (11.6%)	5 (9.4%)	8 (15.7%)	5 (9.8%)	7 (14%)

Visiting period	December	22 (14.19%)	8 (36.63%)	7 (31.82%)	7 (31.82%)	8 (16%)
	February	22 (14.19%)	8 (36.63%)	7 (31.82%)	7 (31.82%)	7 (14%)
	January	37 (23.87%)	13 (35.14%)	12 (32.43%)	12 (32.43%)	12 (24%)
	March	22 (14.19%)	8 (36.63%)	7 (31.82%)	7 (31.82%)	6 (12%)
	November	30 (19.35%)	10 (33.33%)	10 (33.33%)	10 (33.33%)	9 (18%)
	October	22 (14.19%)	8 (36.63%)	7 (31.82%)	7 (31.82%)	8 (16%)

[Table/Fig-1]: Demographic and socioeconomic characteristics.

[Table/Fig-2] explains the average GA significantly increases across the trimesters, starting from approximately 45.38 days in the 1st trimester, rising to about 154.59 days in the 2nd trimester, and reaching approximately 242.41 days in the 3rd trimester. The combined average GA across all trimesters is around 146.14 days. For the Trimester CFFF measurements, the averages are approximately 36.09 in the 1st trimester, 40.52 in the 2nd trimester, and 32.21 in the 3rd trimester, with an overall average of 36.27 across all trimesters. In comparison, the non pregnant group's CFFF value averages around 40.23. This data highlights the natural progression and variability in GA and trimester measurements during pregnancy, with the non pregnant group's CFFF.

of differences these differences are not statistically significant. This suggests that the variables being compared across the three trimesters do not show significant changes over time.

DISCUSSION

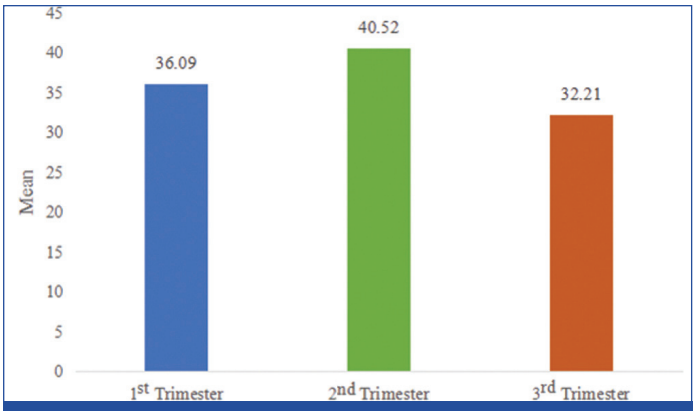
The present analysis revealed that pregnant women in 1st and 3rd trimester exhibited lower CFFF values compared to non pregnant controls [Table/Fig-2]. This decline in CFFF is statistically significant ($p<0.001$) and aligns with well-documented cognitive challenges experienced by many women during pregnancy, such as memory lapses, difficulties concentrating, and heightened absentmindedness assessed using brief psychiatric rating scale.

Variable	1st trimester (N=53)	2nd trimester (N=51)	3rd trimester (N=51)	Overall (N=155)	Non pregnant (N=50)	p-value
Gestational Age (GA) in days	45.38±10.01	154.59±0.57	242.41±18.00	146.14±82.69	-	<0.001
Mean CFFF value in Hz±SD	36.09±1.76	40.52±1.99	32.21±2.15	36.27±3.91	40.23±1.61	<0.001

[Table/Fig-2]: Association of Gestational Age (GA) and trimester specific mean CFFF values across study groups and control.
*Chi-square test
*p-value less than 0.05 is significant

The p-values are all highly significant ($p<0.0001$), indicating that pregnancy is associated with a significant reduction in CFFF when compared to non pregnant individuals. The 2nd trimester has the highest CFFF value (40.52), compared to the 1st trimester (36.09) and the 3rd trimester (32.21), suggesting improved cognition during the 2nd trimester. The Chi-square value of 310.0 and a p-value of <0.001 indicate statistically significant differences between the trimesters.

In pregnant groups, the 1st and 3rd trimesters show lower CFFF values, while the 2nd trimester shows significant improvement in CFFF [Table/Fig-3]. This suggests that pregnancy, especially in the early and late stages, is associated with a reduction in CFFF, with a potential improvement during mid-pregnancy shows that the mean CFFF value increases from the 1st trimester (36.09) to the 2nd trimester (40.52) but decreases in the 3rd trimester (32.21)



[Table/Fig-3]: Mean CFFF values (Hz) across pregnancy trimesters.

The comparative analysis [Table/Fig-4] of the three trimesters shows that there are no statistically significant differences between any of the trimesters (p-values >0.05). The t-tests indicate the magnitude

Variables	1st trimester vs 2nd trimester	2nd trimester vs 3rd trimester	3rd trimester vs 1st trimester
T test	2.47	0.06	2.83
p-value	0.12	0.81	0.09

[Table/Fig-4]: Comparative analysis of trimester differences.

The present study results coincides with the results of previous studies which showed a subjective decline in cognition in pregnant women, measured using various scales and questionnaires [Table/Fig-5] [4-7,12]. A hospital based cross sectional study (1991) on primigravid women showed a decline in implicit memory across all trimesters. A decrease in brain size especially hippocampal volume was observed in 3 dimentional MRI during pregnancy and immediate postpartum period in a 2002 prospective study done on 9 healthy pregnant women. This reduction was more in the 3rd trimester. The brain size reversed back to normal within six months after delivery [13]. In a longitudinal study (2012) done on 55 pregnant women using mood and sleep questionnaires, decreased scores in verbal recall and processing was observed in late pregnancy and postpartum period [5]. Similarly in a 2018 meta-analysis, which involved 20 studies general cognitive and executive functioning were found to be reduced in all trimesters of pregnancy when compared with non pregnant women, particularly more in the third trimester [6]. This was substantiated by poor explicit memory observed in pregnant women. Primiparous rather than multiparous women demonstrated a strong decline in implicit memory [14]. The cognitive problems are more in women with unplanned pregnancy, rural residence and religiosity [12]. The results of the present study were in contradiction to a previous study done on assessing cognition using CFFF in pregnant, non pregnant and pre-eclamptic women. No significant changes were observed between pregnant and non pregnant women [7]. There was also no trimester specific change in cognition. Also in a prospective cohort study (2010) done on 76 pregnant women, there was no significant reduction in cognition [15].

In this study, the 1st and 3rd trimester pregnant women showed lower CFFF values than non pregnant women. This result differs from a study done to measure trimester specific cognitive changes in pregnant women, where a decline in immediate and delayed recall memory was observed only in the 3rd trimester pregnancy and this decline was also not antributed to anxiety, insomnia and physical changes during pregnancy [16]. It could be due to more pronounced decrease in the brain gray matter volume in 3rd trimester pregnancy along with decrease memory [6]. But according to a 2022 study done on third trimester pregnant women, the cognitive decline

Author [Ref. no.]	Place/year of study	Type of study	Number of pregnant and non pregnant women	Outcome
Cuttler C et al., [4]	Columbia/2011	Cross-sectional study	61 pregnant in various trimesters and 24 non pregnant women	Pregnancy related subjective deficits observed using questionnaires. No objective deficits using lab tests. Trimester specific effect not seen.
Henry JF and Sherwin BB [5]	Canada/2012	Longitudinal study	55 pregnant in Late pregnancy and postpartum and 21 non pregnant women (mean age 31.4 years)	Mood and sleep questionnaires-Decreased scores in verbal recall and processing. Trimester specific effect not seen.
Maier M et al., [7]	Germany/2017	Case control observational study	25 non pregnant women, 75 uncomplicated pregnant women in 1st, 2nd and 3rd trimester	No significant differences in CFFF measurements observed in 1st , 2nd, and 3rd trimester.
Davies SJ et al., [6]	Melbourne/2018	Meta-analysis	709 pregnant women and 521 non pregnant women	Memory and executive functioning (P=0.036) significantly reduced during the third trimester of pregnancy.
Kassaw C et al., [12]	Ethiopia/2022	Hospital based cross-sectional study	415 pregnant women	In women >26-year-old, unplanned pregnancy and of rural residence, significant cognitive impairment observed using mini mental state examination (p-value <0.05) Trimester specific effect not seen.
Present study	India/2024	Observational cross-sectional study	155 pregnant primigravid women and 50 non pregnant women	A significant decline (p<0.001) in CFFF was observed in 1st and 3rd trimesters with increased value in 2nd trimester when compared with non pregnant women.

[Table/Fig-5]: Analysis of studies done on pregnant women for assessing cognition [4-7,12].

was attributed to lower sleep quality due to sleep fragmentation in 3rd trimester. Disturbed sleep affects working memory consolidation [17]. The physiological changes of pregnancy, particularly the surge in progesterone and estradiol, likely contribute to this decline. Both hormones are known to influence cognitive and sensory processing, which may account for the observed reduction in CFFF, especially in the early and late stages of pregnancy [5]. Interestingly, the second trimester displayed a relatively higher CFFF values, as reflected in the descriptive statistics and the bar diagram. This period, often referred to as the "honeymoon phase" of pregnancy, may be characterised by a stabilisation of hormone levels or the body's adaptation to pregnancy, leading to a reduction in cognitive and sensory symptoms. However, the first and third trimesters demonstrated greater variability in CFFF, which was indicative of the considerable physiological demands during these periods. This suggests a potential recovery in cognitive function during the second trimester.

The consistently normal CFFF values observed in non pregnant controls across all time points reinforce the notion that pregnancy imposes an additional burden on cognitive and sensory processing. The marked differences in CFFF between pregnant and non pregnant women (p<0.001) suggest that the hormonal and metabolic demands of pregnancy may directly impact cortical arousal and information processing speed, as evidenced by the lower CFFF values in pregnant women. The observed reduction in CFFF, particularly during the first and third trimesters, may have important clinical implications for maternal health. Cognitive complaints are common during pregnancy, and CFFF measurements could provide a useful tool for identifying individuals at risk of more severe cognitive decline or sensory processing difficulties.

Limitation(s)

Despite its valuable insights, this study was not without limitations. The sample size, while sufficient, could be expanded to enhance the generalisability of the findings. Additionally, the focus on multigravid women was excluded.

CONCLUSION(S)

This study demonstrates that pregnancy, particularly during the first and third trimesters, is associated with a significant decline in CFFF, reflecting reduced sensory and cognitive processing capabilities. The second trimester, however, appears to offer a brief period of cognitive recovery, as evidenced by improved CFFF values. Future research could incorporate longitudinal studies to track CFFF changes across pregnancy and the postpartum period. Moreover, while CFFF is a reliable measure of cognitive and sensory processing, integrating additional cognitive assessments would provide a more comprehensive understanding of how pregnancy impacts cognition.

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PARTICULARS OF CONTRIBUTORS:
1. CRMI, Department of Physiology, Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India.
2. Professor and Head, Department of Physiology, Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India.
3. Statistician, Department of Community Medicine, Velammal Medical College Hospital and Research Institute, Madurai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
S Anu,
Professor and Head, Department of Physiology, Velammal Medical College Hospital, Anuppanadi, Ring Road, Madurai-625009, Tamil Nadu, India.
E-mail: anu.sengottaiyan@gmail.com

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