Original article

The Effects of Prenatal Yoga for Primagravida with Gen Expression mRNA FKBP5 (FK506-binding Protein 51)

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Abstract

Background: FKBP5 protein plays an important role in determining sensitivity to negative glucocorticoid feedback, a key mechanism for stopping the HPA axis response in stressful episodes.

Methods: The design of this study is a quasi-experimental approach / quasi experimental and one group design pre and post test design with group control. The sample in this study amounted to each group of 12 respondents as control and treatment of yoga.

Results: There was a significant difference ($p = 0.000 <\propto$) on average FKBP5 gene expression in the control group before (7.1 ± 0.59) and after observation (9.43 ± 0.68), meaning that there was an increase in cortisol levels in the control group in the control group before and after observation, while the treatment group showed a significant difference ($p = 0.001 <\propto$), the average expression of FKBP5 gene before being treated (7.52 ± 0.49) and after being treated (6.88 ± 0.54),

Conclusion: There was a significant difference ($p = 0.000 <\propto$) on average FKBP5 gene expression in the control group, which means that prenatal yoga decreased FKBP5 gene expression before and after treatment.

Keywords: *MRNA expression, FKBP5 gene, Yoga, Trimester III*

Introduction

During pregnancy there is a period of physiological, psychological and environmental transition that results in varying degrees of difficulty for women. 1,2 bio-physio-psycho-social changes during pregnancy can cause stress. especially in the third trimester, because in this period is (waiting period) where there is growth and development of the fetus that increases dramatically. Research using ultrasound Doppler flow velocimetry shows high resistance of uterine arteries in women with high anxiety scores in the third trimester[1,2.] Psychological burden on pregnant women is more common in the third trimester of pregnancy than in the first and second trimester, so that in the third trimester mothers need calm and support from their husbands, families and health workers, with the expectation that mothers can face pregnancy and preparation calm labor, without complication[s3,4,5].

When psychological problems arise during pregnancy, a risk assessment of treatment for the mother and fetus must be carried out, because pharmacological therapies such as antidepressants and benzodiazepines are known to cross the placental barrier. Therefore, non-pharmacological therapies must be considered as possible options for pregnant women in an effort to avoid side effects dru[g6]. Some non-pharmacological therapies that can be considered include psychotherapy, massage therapy, yoga, and listening to music. Yoga has sparked a special interest as an alternative therapy, because more and more evidence has to do with the increasing effect of decreasing depressive symptoms and reducing cortisol in some populations7,8

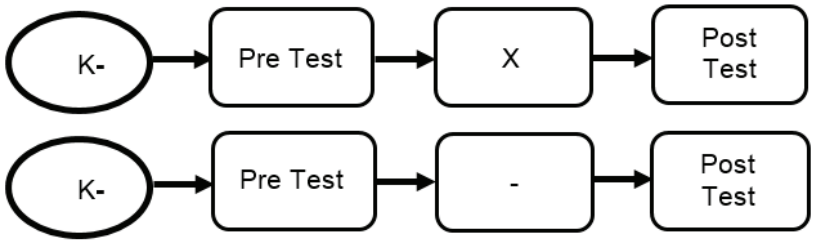
The FKBP5 gene is located on chromosome 6p21.31 and has 13 exons. Overexpression of FKBP5 can reduce the affinity of hormone binding and GR nuclear translocation, thereby reducing GR sensitivity Decreased GR sensitivity can cause interference with negative feedback on the HPA axis and can cause HPA axis dysfunction. Many studies show that the interaction between FKBP5 polymorphisms and childhood trauma is associated with stress-related psychiatric conditions [910,11].

The importance of FKBP5 in GR signaling was initially discovered in New World Monkey which showed an increase in plasma cortisol levels compared to other apes and primates, including humans. In squirrel monkeys for example, free cortisol levels are 50-100 times that of humans but these animals do not show signs of hypercortisolism due to GR resistance in the target organ. It has been found that this GR resistance is partly conferred by overexpression of FKBP5.[12,13].

FKBP5 was chosen in this study because it is based on some evidence. FKBP5 protein plays an important role in determining sensitivity to negative glucocorticoid feedback, a key mechanism for stopping the HPA axis response in stressful episodes[14,15.] Changes in FKBP5 expression or function can increase cortisol load and contribute to allostatic changes in cortisol regulation that occur with repeated stress exposure FKBP5 which is a co-chaperone of heterocomplex GR, part of negative feedback that regulates GR activity. When cortisol binds to GR, FKBP5 is replaced by a positive regulator signaling GR, FKBP4, and the complex is inserted into the nucleus for transcriptional regulation activity. Overexpression of FKBP5 reduces nuclear translocation from the GR complex by isolating it in the cytosol. Interestingly, glucocorticoid exposure increases FKBP5 expression, reduces glucocorticoid negative feedback and allows cortisol to participate in its own regulation [16,17].

Materials and Methods

This study uses quantitative research with quasi experimental / quasi experimental approaches and one group design pre and post test design with group control. The research design can be seen in the research design scheme.



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Ket

K-1	:	Group intervensi
K-2	:	Group control
Pre test	:	Test Conducted before treatment /intervention
X	:	Prenatal Yoga intervention
Post test	:	Test conducted after treatment/ ntervention

The population in this study were all trimester III primigravida. The sample in this study amounted to 24 respondents. The inclusion criteria used as research subjects include the following: Primigravida trimester III (UK> 28 weeks), with a planned pregnancy and willing to become a respondent and sign an informed consent. Ages 20 to 35 years, Normal pregnancy., Fetus alive, single. Criteria for moderate anxiety

Data Analysis

Normality test of sample data with the Shapiro-Wilk test, this test is subject to the FKBP5 content ratio scale data

Result

In the comparison test FKBP5 gene expression in the control group and the treatment group between observations before and after paired sample t test (paired sample t test) was used.

Table 1 Results Of Comparison Tests Before FKBP5 Gene Expression and After Treatment

Group treatment	Before Rerata ± SD	After Rerata ± SD	p-value
Control	7.1±0.59	9.43±0.68	0.000
Treatment Yoga	7.52±0.49	6.88±0.54	0.001

Table 1 shows that there is a significant difference (p = 0,000 <∝) on average FKBP5 gene expression. In other words there is the effect of the treatment of Yoga exercises on the expression of FKBP5 gene in third trimester pregnant women, namely Yoga exercises can reduce FKBP5 gene expression in third trimester pregnant women. So the second minor hypothesis has been proven, that prenatal Yoga exercises affect FKBP5 gene expression in trimester III primigravida.

In the results of the comparative test of FKBP5 gene expression between the control group and the treatment group, the independent sample t test was explained and shown concisely as shown in table 2 below.

Table 2 Test results for comparison of FKBP5 gene expression groups control with the treatment group

Observation	Control Rerata ± SD	Treatment Rerata ± SD	p-value
Before	7.1±0.58	7.52±0.49	0.072
After	9.43±0.68	6.88±0.54	0.000

Table 2 shows that there was no significant difference (p = 0.072> ∝) of average FKBP5 gene expression between the control group (before) (7.1 ± 0.58) and the treatment group (before) (7.52 ± 0.49). This means that FKBP5 gene expression between the control group and the treatment group before observation was the same or there was no significant difference.

Appear in Table 2 shows that there is a significant between non-action and prenatal yoga exercises on FKBP5 gene expression in primigravida trimester III.

Table 3 Correlation test results between variables in groups

Corelasi variable	n	Koefisien korelasi (r)	p-value
Worred with FKBP5	12	0.819	0.001
cortisol with FKBP5	12	0.901	0.000
CRHR1 With FKBP5	12	0.846	0.001

Discussion

Table 1 shows that there was no significant difference (p = 0.072> ∝) on average FKBP5 gene expression at 27-28 weeks gestation between the control group (before) (7.1 ± 0.58) and the treatment group (before) (7.52 ± 0.49) . This means that FKBP5 gene expression between the control group and the treatment group at 27-28

weeks gestation is the same or no significant difference. The results of this study are in line with this study of two European cohorts characterized by both middle-aged and elderly adults using candidate genes and broad genome approaches to identify genes associated with diurnal cortisol secretion and their relationship with depressive symptoms.

The results of the study obtained evidence of the relationship between FKBP5 SNP rs9470080 with salivary cortisol concentration and depressive symptoms. FKBP5 is a co-chaperone of hsp90, which is part of a receptor complex that regulates glucocorticoid receptor sensitivity (GR). The increase in FKBP5 gene expression causes an increase in GR resistance to cortisol, which can cause hypercortisolism[18,19].

The examined the relationship of three HPA glucocorticoid receptor (NR3C1) -related genes, mineralocorticoid receptors (NR3C2), and FK506 binding protein 5 (FKBP5) with suicide in populations in Japan. The results showed that the haplotype in the FKBP5 gene was associated with suicide between the observed suicide group and the control group. FK506 binding protein 5 (FKBP5), which acts as a co-chaperone of GR, is associated with GR sensitivity to cortisol and SNP in the FKBP5 gene has been shown to be associated with depression treatment response and recurrence of depressive episodes) proved that SNP FKBP5 has been associated with depression.

In the literature review, there are several studies related to the FKBP5 gene polymorphism associated with suicide. Among them are analyzing the American population, where it was found that the polymorphism of rs1360780 and rs3800373 in FKBP5 was related to suicide attempts ($p < 0.01$). Likewise, those who analyzed the African population and found that carriers of polymorphism rs3800373 had a high rate of suicide attempts (0.35), compared with patients exposed to life difficulties. On the other hand, there was a significant relationship between the hslotype rs3800373TT and rs1360780TC in FKBP5 with suicidal behavior in the Japanese population ($p < 0.05$ for each haplotype it can be concluded that prenatal yoga decreases FKBP5 gene expression before and after treatment [20, 21].

The study analyzed FKBP5 and glucocorticoid receptor (GR) genes and protein expression in amygdala suicides, without a history of clinical psychiatry and was not treated with anxiolytic or antidepressant drugs and as appropriate. The results showed that FKBP5 and GR gene expression was significantly reduced in AMY (−38% and −48%, respectively) of suicide victims compared with controls. Interestingly, FKBP5 and GR protein expression also decreased significantly (−41% and −42%, respectively) in AMY of suicide victims compared to controls. In line with the research conducted it was proven that no relationship was found between FKBP5 gene polymorphisms and bipolar disorder with psychotic characteristics, such as melancholic depression[22].

Carriers of the rs9470080 genetic variant in the FKBP5 gene have lower cortisol and an increased risk of depressive symptoms compared to non-variant carriers. Observations that FKBP5 rs9470080 carriers are more likely to report clinically relevant depressive symptoms and are also more likely to use antidepressants or antipsychotics further indicate that depressive symptoms are good markers of severe psychiatric disorders [8,16,20]. The results of this study assume that the relationship between FKBP5 variants and depression cannot be explained by cortisol parameters because there is no relationship between cortisol and depressive symptoms, this reflects a lack of power, but can also indicate that other mechanisms besides the regulation of basic cortisol underlie the observed relationship[1,7,9].

FKBP51 levels can reach 13 times higher in Bolivian squirrel lymphocytes compared with humans, which leads to heterocomplex GR and reduced affinity for GC ligands. In humans, evidence for GC resistance mediated by FKBP51 can now be found. High levels of FKBP51 correlate with resistance to GC therapy for asthma. This finding suggests that the genetic variant of FKBP5 might play an important role in the chronic stress response rather than the acute stress response[23].

The increase in FKBP5 activity is also induced by stress hormones such as glucocorticoids, thus affecting the subsequent transcription of the FKBP5 gene and, consequently, GR sensitivity. FKBP5 induction by elevated cortisol levels can lead to regulation of disturbed negative feedback from the HPA axis, thereby extending cortisol levels which increase in response to stressors and thus increase susceptibility to psychiatric illness. Several SNPs in FKBP5 have been identified as interesting, including rs1360780 proven to have functionality. The rs1360780 minor allele has been associated with twice the amount of FKPB5 protein in lymphocytes relative to other genotypes [4,9,16].

In vitro experiments have shown that overexpression of humans FKBP5 also reduces the binding affinity of the hormone and GR nuclear translocation. it makes sense that changes in FKBP5 expression can also affect human GR function in vivo. FKBP5 expression is also induced by steroids, including glucocorticoids as part of an intracellular ultra-short negative feedback loop for GR activity. Increased transcription and translation of FKBP5 after activation of steroid receptors will then reduce the sensitivity of GR[11,13,]

Conclusion

There was a significant difference ($p = 0.000 < \propto$) on average FKBP5 gene expression in the control group before (7.1 ± 0.59) and after observation (9.43 ± 0.68), it could be interpreted to mean an increase in cortisol levels in the control group in the control group before and after observation , it can be concluded that prenatal yoga decreases FKBP5 gene expression before and after treatment.

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Conflict of Interest- None of the authors has competing interests

Ethical Clearance- This research was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University Makassar, (No. 839/ UN4.6.4.5.31//PP36/2019), and all research subjects gave written informed consent.

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