Malang, 09 Februari 2022

Kepada Yth.
HRD Stikes Kepanjen
Jl. Trunojoyo No. 16, Krajan, Panggungrejo
Kepanjen, Kabupaten Malang

Perihal : Permohonan Pekerjaan

Dengan Hormat,

Dengan ini saya mengajukan permohonan bekerja sebagai tenaga pengajar dosen.
Yang bertanda tangan dibawah ini:

Nama	: Herlina Puji Angesti
Tempat, Tgl Lahir	: Malang, 17 Maret 1995
Jenis Kelamin	: Perempuan
Agama	: Islam
Status	: Belum Menikah
Alamat	: Woloso RT 22 RW 04 Ds.Gondowangi Kec.Wagir Kab.Malang
Pendidikan Terakhir	: S2-Magister Ilmu Kesehatan Reproduksi

Sebagai bahan pertimbangan, saya lampirkan kelengkapan data diri saya sebagai berikut:

1. Curiculum Vitae
2. Pas Foto Ukuran 3x4
3. Foto Copy KTP
4. Foto Copy Ijazah dan Transkrip Akademik yang Telah Dilegalisir
5. Surat Keterangan Akreditasi Prodi
6. Sertifikat TOEFL
7. Sertifikat Penunjang Berkaitan Keilmuan Kebidanan

Dengan surat permohonan ini, besar harapan saya dapat diterima dan bergabung dengan STIKES KEPANJEN. Atas perhatiannya saya ucapkan terima kasih.

Hormat Saya,

Herlina Puji Angesti STr.Keb., M.Kes

PROVINSI JAWA TIMUR
KABUPATEN MALANG

NIK : 3507215703950002

Nama	: HERLINA PUJIANGESTI	
Tempat/Tgl Lahir	: MALANG, 17-03-1995	
Jenis kelamin	: PEREMPUAN	Gol. Darah : -
Alamat	: DSN WILOSO	
RT/RW	: 022/004	
Kel/Desa	: GONDOWANGI	
Kecamatan	: WAGIR	
Agama	: ISLAM	
Status Perkawinan	: BELUM KAWIN	
Pekerjaan	: PELAJAR/MAHASISWA	
Kewarganegaraan	: WNI	
Berlaku Hingga	: SEUMUR HIDUP	

MALANG
02-03-2018

herlinapujiangesti@gmail.com Gondowangi RT 22/04 Wagir, Malang WhatsApp :085335198668

HERLINA PUJI ANGESTI

MAGISTER KESEHATAN REPRODUKSI

PENGALAMAN

2021-PRESENT

Indonesia Medika
STAFF MEDIS DAN PENGEMBANGAN GCI

- Sebagai Swaber
- Berkontribusi dalam kegiatan KESMAS gratis di Kelurahan Bunulrejo dan Kelurahan Tulusrejo
- Berkontribusi dalam persiapan Launching Aplikasi InMed
- Sebagai Bidan di Garbage Clinical Insurence (GCI) yang menggunakan sampah dalam skema asuransi

2021-PRESENT

Freelancer
ANALISIS DATA DENGAN SPSS dan PLS

- Uji Asumsi Dasar dan Uji Asumsi Klasik
- Uji Instrumen, Uji Deskriptif, dan Uji Perbedaan
- Analisis Data, Analisis Faktor, Analisis Korelasi, dan Analisis Regresi
- Analisis SEM-PLS

2018

PT KAI DAOP 8, ST Kota Baru Malang
TENAGA BANTUAN LUAR

- Sebagai Tenaga Kesehatan yang memberikan layanan kesehatan kepada penumpang KAI

2017

PMB Bidan "Siti Mahmudah"
ASISTEN BIDAN

- Membantu bidan memberikan pelayanan KIA, ANC, INC, PNC, dan KB

GENERAL SKILLS

- **COMMITMENT TO WORK**
- **ADAPTABILITY**
- **ABILITY TO LISTEN**
- **SELF-CONFIDENCE**
- **TIME MANAGEMENT**

PROFIL SAYA

Magister Ilmu Kesehatan Reproduksi dengan pengalaman bekerja sebagai tenaga kesehatan. Memiliki ketertarikan dalam kegiatan penelitian statistika penelitian dan mengajar.

PENDIDIKAN

2019-2021

Magister Ilmu Kesehatan Reproduksi
UNIVERSITAS AIRLANGGA

- IPK 3.71
- Panitia Seminar Kesehatan "Kehamilan dengan Diabetes Mellitus"
- Panitia Kuliah Tamu Online "Child Pregnancy and Woman Empowering"
- Panitia Webinar Nasional "Membangun Generasi Berkualitas untuk Indonesia Emas"
- Tesis - Pengaruh Paparan Stres Selama Kebuntingan Terhadap Perbedaan Ekspresi Akt, Berat Otak Pada *Cerebrum* dan *Cerebellum Mus musculus* Baru Lahir.
- SCOPUS - Comparison of Akt Ekspresion in The Cerebrum and Cerebellum of Newborn Mus musculus Exposed to Physical Stress and Psychological Stress During Pregnancy.

2013-2017

Sarjana Terapan Kebidanan
POLTEKKES KEMENKES MALANG

- IPK 3.77
- Panitia Pengenalan Program Studi Mahasiswa Baru Tahun Ajaran 2014/2015
- Anggota UKM Anti Narkoba
- Skripsi - Pengaruh Pijat Oksitosin Terhadap Jumlah Pengeluaran Darah Pada Kala Empat Persalinan Normal di BPM Ny."C"AMd.Keb

2011-2013

Sekolah Menengah Atas
SMA NEGERI 2 MALANG

- JURUSAN IPA

No Ijazah : 131222021000111

No. 0141980

KEMENTERIAN PENDIDIKAN, KEBUDAYAAN, RISET, DAN TEKNOLOGI

UNIVERSITAS AIRLANGGA

(Pendirian : PP no 57 tahun 1954)

dengan ini menyatakan bahwa :

Herlina Puji Angesti

Nomor Induk Mahasiswa : 011824653008

Lahir di Malang, 17 Maret 1995

telah menyelesaikan pendidikan dengan baik pada

FAKULTAS KEDOKTERAN

PROGRAM MAGISTER

PROGRAM STUDI ILMU KESEHATAN REPRODUKSI

Tanggal Lulus : 21 Juni 2021

karena itu kepadanya diberikan ijazah dan gelar

MAGISTER KESEHATAN (M.Kes.)

beserta segala hak dan kewajiban yang melekat pada gelar tersebut

Diterbitkan di Surabaya pada tanggal, 08 September 2021

PENGESAHAN
Telah diperiksa kebenaranya dan sesuai
15 SEP 2021
Prof. Budi Santoso, dr.,Sp.OG (K)
NIP 196302171989111001

DEKAN

Prof. Dr. Budi Santoso, dr., Sp.OG(K).
NIP. 196302171989111001

REKTOR

Prof. Dr. Moh. Nasih, SE., MT., Ak.
NIP. 196508061992031002

KEMENTERIAN PENDIDIKAN, KEBUDAYAAN, RISET, DAN TEKNOLOGI
UNIVERSITAS AIRLANGGA
(Pendirian : PP. No. 57 Tahun 1954)
FAKULTAS KEDOKTERAN
Jl Mayjen Prof. Dr. Moestopo 47 Surabaya, 60131 Telp. 031-5020251, 031-5030253, Fax. 031-5022472
Laman : http://www.fk.unair.ac.id, Email : dekan@fk.unair.ac.id

TRANSKRIP AKADEMIK

Nomor : 011824653008/001004/01.3/S2/2021

PROGRAM : MAGISTER

PROGRAM STUDI: ILMU KESEHATAN REPRODUKSI

Nama Mahasiswa : Herlina Puji Angesti
NIM : 011824653008
Tempat, tanggal lahir : Malang, 17 Maret 1995
Akreditasi Institusi : A
SK Akreditasi Institusi : 362/SK/BAN-PT/Akred/PT/XII/2018
Asal Perguruan Tinggi : Poltekkes Kemenkes Malang
Asal Program Studi : DIV Kebidanan

Tanggal Terdaftar : 01 Maret 2019
Tanggal Lulus : 21 Juni 2021
Nomor Ijazah : 131222021000111
Gelar Akademik : Magister Kesehatan (M.Kes.)
sks / IPK : 48 / 3.71
Predikat Kelulusan : Sangat Memuaskan

Judul Tesis : PENGARUH PAPARAN STRES SELAMA KEBUNTINGAN TERHADAP PERBEDAAN EKSPRESI AKT, BERAT OTAK PADA CEREBRUM DAN *CEREBELLUM MUS MUSCULUS* BARU LAHIR

Kode	Mata Kuliah	sks	Nilai
BIS604	Biologi Molekuler	2	B
BIS609	Biologi Sel Dan Biomolekul	2	AB
BIR608	Bioreproduksi	2	A
MAS607	Biostatistika	2	B
BIR602	Embriologi	2	A
BIE603	Endokrinologi Reproduksi Wanita	2	A
PHK602	Fisafat Ilmu Dan Bioetik	2	AB
KDX607	Fisiologi Reproduksi	2	A
BIG601	Genetika	2	A
KME614	Kependudukan Dan Epidemiologi	2	A
KDX603	Metode Lab.Fertilitas	2	A

Kode	Mata Kuliah	sks	Nilai
PNK697	Metodologi Penelitian	2	B
BII610	Mikrobiologi Reproduksi Dan Imunologi Reproduksi	2	A
KDK610	Pathologi Reproduksi Pria	2	AB
KDK611	Pathologi Reproduksi Wanita	2	A
PNK699	Penelitian/Karya Akhir/Riset dan Tesis	6	A
KDX602	Pengendalian Fertilitas Dan Infertilitas	2	AB
PNK698	Proposal Akademik	2	A
KDX613	Seksualitas Dan Psiko Pathologi Seks	2	B
KDX605	Spermatologi	2	AB
KDX606	Teknologi Berbantu	2	A

Diterbitkan di Surabaya pada tanggal 08 September 2021
Dekan,

Prof. Dr. Budi Santoso, dr., Sp.OG(K).
NIP. 196302171989111001

Keterangan

Nilai Huruf	Bobot
A	*4*
AB	*3.5*
B	*3*
BC	*2.5*
C	*2*
D	*1*
E	*0*

Kriteria Kelulusan

IPK	Predikat
3 - 3.4	Memuaskan
3.41 - 3.74	Sangat Memuaskan
3.75 - 4	Dengan Pujian

Catatan : Predikat dengan pujian diberikan dengan memperhatikan masa studi maksimum 2 (dua) tahun.

PENGESAHAN
Telah diperiksa kebenarannya dan sesuai dengan aslinya
Surabaya, tgl. 12 OCT 2021
Dekan Fakultas Kedokteran
Universitas Airlangga

Prof. Dr. Budi Santoso, dr., Sp.OG (K)
NIP 19630217 198911 1 001

SURAT KEPUTUSAN
PENGURUS PERKUMPULAN LEMBAGA AKREDITASI MANDIRI
PENDIDIKAN TINGGI KESEHATAN INDONESIA (PERKUMPULAN LAM-PTKes)

Nomor:
0758/LAM-PTKes/Akr/Mag/XII/2020

Tentang

STATUS, NILAI, DAN PERINGKAT AKREDITASI

PROGRAM STUDI MAGISTER ILMU KESEHATAN REPRODUKSI
UNIVERSITAS AIRLANGGA, SURABAYA

Menimbang :

1. Bahwa sesuai dengan Keputusan Menteri Pendidikan dan Kebudayaan Republik Indonesia No. 291/P/2014 tanggal 17 Oktober 2014 tentang Pengakuan Pendirian Lembaga Akreditasi Mandiri Pendidikan Tinggi Kesehatan;
2. Bahwa sesuai dengan Surat No. 46/E.E3/KL/2015 tanggal 2 Februari 2015 Menteri Riset, Teknologi dan Pendidikan Tinggi (Menristek Dikti) tentang operasionalisasi LAM-PTKes untuk mulai melaksanakan akreditasi pada tanggal 1 Maret 2015;
3. Bahwa sesuai dengan Peraturan Pengurus Perkumpulan LAM-PTKes No. 004/PP/09. 2015 tanggal 11 September 2015 tentang Penilaian Akreditasi Program Studi Kesehatan di LAM-PTKes;
4. Bahwa sesuai Surat Keputusan Pengurus no. 32/SK/K/09.2020 pelaksanaan asesmen lapangan dimasa Pandemi Covid-19 untuk Program Studi Kedokteran (semua jenjang), Program Studi Kedokteran Gigi (semua jenjang) dan Program Studi Farmasi (jenjang Sarjana dan Profesi Apoteker) dilakukan secara daring dan dilanjutkan dengan visitasi lapangan.
5. Bahwa status, nilai, dan peringkat akreditasi program studi kesehatan sebagaimana dimaksud di atas, perlu ditetapkan dalam Keputusan Ketua Perkumpulan LAM-PTKes.

Mengingat :

1. Undang-Undang Republik Indonesia No. 20 Tahun 2003 tentang Sistem Pendidikan Nasional;
2. Undang-Undang Republik Indonesia No. 29 Tahun 2004 tentang Praktik Kedokteran;
3. Undang-Undang Republik Indonesia No. 14 Tahun 2005 tentang Guru dan Dosen;
4. Undang-Undang Republik Indonesia No. 36 Tahun 2009 tentang Kesehatan;
5. Undang-Undang Republik Indonesia No. 12 Tahun 2012 tentang Pendidikan Tinggi;
6. Undang-Undang Republik Indonesia No. 20 Tahun 2013 tentang Pendidikan Kedokteran;
7. Undang-Undang Republik Indonesia No. 36 Tahun 2014 tentang Tenaga Kesehatan;
8. Peraturan Pemerintah Republik Indonesia No. 19 Tahun 2005 tentang Standar Nasional Pendidikan, *jo* Peraturan Pemerintah Republik Indonesia No. 32 tahun 2013 tentang Perubahan Atas Peraturan Pemerintah Nomor 19 Tahun 2005 Tentang Standar Nasional Pendidikan, *jo* Peraturan Pemerintah Republik Indonesia No. 13 Tahun 2015 tentang Perubahan Kedua Atas Peraturan Pemerintah Nomor 19 Tahun 2005 Tentang Standar Nasional Pendidikan;

9. Peraturan Pemerintah Republik Indonesia No. 51 Tahun 2009 tentang Pekerjaan Kefarmasian;
10. Peraturan Pemerintah Republik Indonesia No. 4 Tahun 2014 tentang Penyelenggaraan Pendidikan Tinggi dan Pengelolaan Perguruan Tinggi;
11. Peraturan Presiden No. 8 Tahun 2012 tentang Kerangka Kualifikasi Nasional Indonesia;
12. Peraturan Menteri Pendidikan dan Kebudayaan Republik Indonesia No. 3 Tahun 2020 tentang Standar Nasional Pendidikan Tinggi;
13. Peraturan Menteri Pendidikan dan Kebudayaan Republik Indonesia No. 5 Tahun 2020 tentang Akreditasi Program Studi dan Perguruan Tinggi;
14. Keputusan Menteri Hukum dan Hak Asasi Manusia No. AHU - 30.AH.01.07. Tahun 2014 tentang Pengesahan Badan Hukum Perkumpulan LAM-PTKes Indonesia;
15. Keputusan Pengurus Perkumpulan LAM-PTKes No. 32/SK/K/09.2020 tentang Pelaksanaan Asesmen Lapangan di Masa Pandemi Covid-19.

Memperhatikan : Berita Acara Rapat Pleno Majelis Akreditasi No. 013/LAM-PTKes/BA Akr/XII/2020 tanggal 30 Desember 2020

MEMUTUSKAN

Menetapkan : Status, Nilai, dan Peringkat Akreditasi Program Studi Kesehatan.

Pertama : **AKREDITASI PROGRAM STUDI MAGISTER ILMU KESEHATAN REPRODUKSI UNIVERSITAS AIRLANGGA, SURABAYA**

STATUS : TERAKREDITASI
NILAI : 361 (TIGA RATUS ENAM PULUH SATU)
PERINGKAT : A (SANGAT BAIK)

Kedua : Status, nilai, dan peringkat akreditasi dalam Keputusan ini **berlaku selama 1 (Satu) tahun.**

Ketiga : Keputusan ini berlaku selama proses pengelolaan dan penyelenggaraaan program studi memenuhi dan sesuai dengan ketentuan peraturan perundang-undangan yang berlaku.

Keempat : Dengan dikeluarkannya Surat Keputusan ini, maka status, nilai, dan peringkat akreditasi terdahulu dinyatakan tidak berlaku.

Kelima : Keputusan ini berlaku sejak tanggal ditetapkan.

Ditetapkan di : Jakarta

Pada tanggal : 30 Desember 2020

Ketua,

Prof. dr. Usman Chatib Warsa, Sp. MK., PhD

Salinan disampaikan kepada Yth:
1. Menteri Pendidikan dan Kebudayaan
2. Menteri Pendayaan Aparatur Negara dan Reformasi Birokrasi
3. Kepala Badan Kepegawaian Negara
4. Ketua Badan Akreditasi Nasional Perguruan Tinggi
5. Para Koordinator Lembaga Layanan Pendidikan Tinggi Wilayah
6. Badan Pengembangan dan Pemberdayaan Sumber Daya Manusia Kesehatan Kemenkes
7. Rektor/Ketua/Direktur Perguruan Tinggi yang bersangkutan

062111

PUSAT BAHASA DAN MULTIBUDAYA
UNIVERSITAS AIRLANGGA

03210500415

CERTIFICATE

This is to certify that

HERLINA PUJI ANGESTI

011824653008

sat for **English Language Proficiency Test**

on

May 19, 2021

Best Score Obtained :

Subjects	Score
English Listening Section	52
English Structure Section	50
English Reading Section	52
Total Score	513

Valid To : **May 19, 2023**

Surabaya, **May 19, 2021**
Head,

Prof. Diah Ariani Arimbi, S.S., M.A., Ph.D.
NIP. 197004051994032003

UNIVERSITAS AIRLANGGA

FAKULTAS KEDOKTERAN

PROGRAM STUDI ILMU KESEHATAN REPRODUKSI JENJANG MAGISTER

Sertifikat

Diberikan Kepada

Herlina Puji Angesti, S.Tr.Keb

Sebagai

PANITIA

dalam KULIAH TAMU *ONLINE*

dengan tema "*Child Pregnancy and Women Empowering*"

Selasa, 30 Juni 2020, pukul 08.00 - 11.00 WIB

Koordinator Program Studi
Ilmu Kesehatan Reproduksi Jenjang Magister

Dr.Hermanto Tri Joewono, dr. Sp.OG (K)
NIP. 195601281986031009

Ketua Panitia

Dewi Qurotul A'yuni, S.Tr.Keb
NIM. 011924653007

UNIVERSITAS AIRLANGGA

FAKULTAS KEDOKTERAN

PROGRAM STUDI ILMU KESEHATAN REPRODUKSI JENJANG MAGISTER

Sertifikat

Diberikan kepada

Herlina Puji Angesti S.Tr.Keb

Atas partisipasinya sebagai

PANITIA

Seminar Kesehatan

"Kehamilan Dengan Diabetes Mellitus"

Surabaya, 30 November 2019

SK IBI Wilayah Jawa Timur No. 366/SKP/Sek.PDIB/XI/2019

Peserta:	2 SKP IBI	Moderator:	2 SKP IBI
Pembicara:	3 SKP IBI	Panitia:	2 SKP IBI

Mengetahui,

Pengurus Daerah JAWA TIMUR Ikatan Bidan Indonesia

Hj. Lestari, SST., SH., M.Kes
Ketua IBI Provinsi Jawa Timur

UNIVERSITAS AIRLANGGA

Dr. Hermanto Tri Joewono, dr., Sp.OG (K)
Ketua Program Studi

3rd AIRLANGGA WEBINAR CONFERENCE SERIES

MEMBANGUN GENERASI BERKUALITAS UNTUK INDONESIA EMAS

Certificate of Participation

Faculty of Medicine Universitas Airlangga

certifies that

Herlina Puji Angesti S.Tr.Keb

has participated as an organizing committee in the Airlangga Webinar Conference Series titled
Membangun Generasi Berkualitas untuk Indonesia Emas
Webinar, on November 10th 2020
Accredited by IBI: 194/SKP/Sek.PDIB/x/2020
Participant: 2 SKP / Speaker: 3 SKP / Moderator: 2 SKP / Organizing Committee: 2 SKP

Pengurus Daerah JAWA TIMUR Ikatan Bidan Indonesia

Hj. Lestari, SST., SH., M.Kes
Head of IBI Surabaya

Dr. Hermanto Tri Joewono, dr., Sp.OG(K)
Coordinator of Reproductive Health Science Master's Programme Faculty of Medicine, Universitas Airlangga

Sucia Nadila, S.KM
Head of Organizing Committee

ISSN-0973-9122 (Print) • ISSN-0973-9130 (Electronic)

Volume 15 / Number 4 / October-December 2021

Indian Journal of Forensic Medicine & Toxicology

Website: www.ijfmt.com

Official Organ of Indian Association of Medico-Legal Experts (Regd.)

Type of manuscript: Research Article

Comparison of Akt Expression in the Cerebrum and Cerebellum of Newborn *Mus musculus* Exposed to Physical Stress and Psychological Stress During Pregnancy

Herlina Puji Angesti[1], Hermanto Tri Joewono[2], Widjiati[3]

[1]Posgraduate student of Reproductive Health Science, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia, [2]Obyn MFM Consultant, Department of Obstetry and Gynecology, Faculty of Medicine Universitas Airlangga/RSU Dr. Soetomo, Surabaya, Indonesia, [3]Prof. Department of Embriology, Faculty of Veterinary Medicine Universitas Airlangga, Surabaya, Indonesia

Abstract

Introduction: Prenatal stress prevalence is almost half of the population of pregnant women worldwide. Stress will stimulate glucocorticoids which can disrupt the PI3K-Akt cascade. PI3K-Akt deficiency will cause impaired fetal brain growth and development.

Objective: To compare the Akt expression in the cerebrum and cerebellum of newborn *Mus musculus* exposed to physical stress, psychological stress, the combination of psychological and physical stress, and without stress exposure.

Method: This study was experimental laboratory research. Twenty-four female mice were used as samples and divided into four groups: physical stress exposure group, psychological stress exposure group, the combination of psychological and physical stress exposure group, and control group. Akt expression was tested by immunohistochemistry (IHC) staining. Statistical analysis used the One Way Anova and Kruskal Wallis test.

Results: There were significant differences in cerebrum Akt expression ($p = 0.008$) and cerebellum Akt expression ($p = 0.047$) between the control and stress exposure groups.

Conclusion: There were statistically significant decreases in mean Akt expression in the cerebrum and cerebellum of newborn *Mus musculus* exposed to stress during pregnancy.

Keywords: *Stress, Akt, cerebrum, cerebellum, and Mus musculus.*

Introduction

The brain is an organ that controls all body functions. Intelligence, creativity, emotions, and memory are some of the many things regulated in the brain[8]. The brain is a stress adaptation center that triggers a behavioral and physiological response to stress[15]. Stress increases hormone secretion on the hypothalamus-pituitary-adrenal (HPA) axis. After acute experience stress, the HPA hormone axis quickly returns to pre-stress levels, but chronic stress triggers a sustained response that affects mental and physical distress[14].

Corresponding author:
Widjiati
Department of Embriology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya. Indonesia
E-mail: widjiati@fkh.unair.ac.id

Depression and anxiety occurred in pregnancy, with estimated prevalence of 12% for depression and 15.2% for anxiety. Mild to moderate stress has been reported in half of the population of healthy pregnant women worldwide[1]. Prenatal stress increased glucocorticoids (cortisol) that can damage the brain[12].

High concentrations of glucocorticoids (GC) combined with glucocorticoid receptors (GR) will inhibit neurotrophic factor (NTF) signaling expressed by many tissues in the brain, especially in the cerebrum and cerebellum. NTF is known to increase cell survival by activating Akt/protein kinase B signaling[4]. Phosphatidylinositide 3 Kinase (PI3K)-Akt cascade dysfunction has been recognized as a cause of neurodevelopmental and neuropsychiatric diseases, such as autism, epilepsy, brain injury, and developing brain malformations[17].

Objectives

To compare the Akt expression in the cerebrum and cerebellum of newborn *Mus musculus* exposed to physical stress, psychological stress, the combination of psychological and physical stress, and without stress exposure.

Materials and Methods

This research is a study laboratory experiment with post-test only with a control group design. Samples were 24 female mice (*Mus musculus*), 2-2.5 months old, weighing 20-25 grams. The research was conducted in Faculty of Veterinary Medicine Universitas Airlangga, from January to March 2021.

After adaptation for a week, female mice were divided into four groups, which are: the physical stress exposure group (K1), the psychological stress exposure group (K2), the combination of psychological and physical stress exposure group (K3), and control group (K4). Below are some explanations:

1. K1 is the group with forced swimming for 5 minutes every day in a box measuring 50 cm x 30 cm x 25 cm with a water height of 18 cm. Water temperature ranging from 24°C-28°C and room temperature of 20°C-25°C.

2. K2 is the group with noise exposure with sound intensity 90 dB through TrueRTA software and measured by the real-time sound analyzer (TES 1358) given for 1 hour per day.

3. K3 is the combination of K2 and K1. Both types of treatment are given on the same day with noise exposure for 1 hour. 5 minutes after that, forced swimming for 5 minutes.

Stress exposure to K1, K2, and K3 is given simultaneously at 09.00. Stress exposure is given starting from day 6-15 of pregnancy.

At the end of the 16th day of the experiment, mice were anesthetized with ketamine (Ketamine Hydrochloride Pfizer®, New Jersey, USA) and acepromazine (Castran®, Venray, Netherlands). Delivery by sectio caesarea (SC). The newborn mice were sacrificed through neck decapitation, and the brain organs were dissected.

Akt expression was tested by immunohistochemistry (IHC) and analyzed using the Remmele semi-quantitative scoring system. This Immuno Reactive Score (IRS) is a multiplication between immunoreactive cells (A) and the color intensity score of immunoreactive cells (B).

The Shapiro Wilk test was used to determine the data's normality and the Levene test to determine its homogeneity. If the data's distribution and homogeneity were normal ($p > 0.05$), then the One Way Anova test was used, followed by Post Hoc LSD (Least Significant Difference). If the data distribution is not normal, then the Kruskal-Wallis test is used, followed by the Mann-Whitney U test to determine the difference between the two groups with abnormal data distribution. Meanwhile, to determine the difference between the two groups with normal distribution, it is necessary to use the T-test analysis. Data analysis using IBM SPSS Statistics version 26.00 (New York, USA).

Results

The research sample consisted of 24 female mice based on inclusion criteria and randomized into four groups.

The results showed the mean difference between K1, K2, K3, and K4, as shown in Table 1. Cerebrum Akt expression was higher in the control group (K4) than the stress exposure group (K1, K2, and K3).

Table 1. Akt expression in the cerebrum of newborn mice in each group.

	Mean ± SD			
	K1	K2	K3	K4
Akt expression	8,300 ± 0,726	6,616 ± 1,487	5,017 ± 1,038	9,617 ± 3,468

Statistical analysis used the Kruskal-Wallis test with the result p-value = 0.008. That means there was at least one significant difference between the two groups. The data were normally distributed, so the comparison between the two groups was analyzed using the T-test. T-Test showed significant differences between K1 and K2, K1 and K3, and K3 and K4.

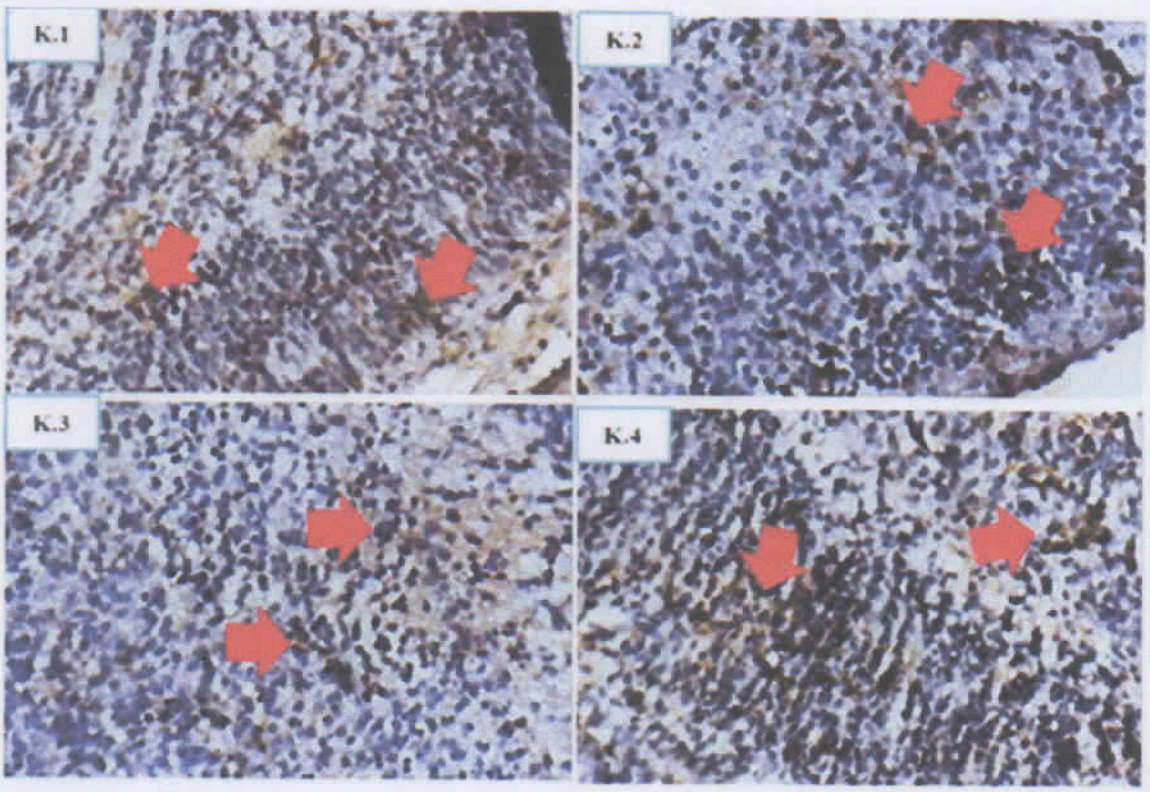

Figure 1. Akt expression (red arrow). Cerebrum Akt expression in the control group (K4) was strongest among the other groups (immunohistochemistry, 400x magnification, Nikon H600L microscope from Nikon Instruments Inc. ™, New York, USA).

Table 2. Akt expression in the cerebellum of newborn mice in each group.

	Mean ± SD			
	K1	K2	K3	K4
Akt expression	9,100 ± 2,767	7,200 ± 3,518	5,467 ± 1,880	9,917 ± 2,549

The results showed the mean difference between K1, K2, K3, and K4, as shown in Table 2. The decrease in Akt expression occurred in the stress exposure group. This Akt expression decrease was in line with the increased stress exposure. Statistical analysis used the One Way Anova test with p-value = 0.047, which means significant differences between groups. Post Hoc LSD test (Least Significant Difference) shows significant differences between K1 and K3 and K3 and K4.

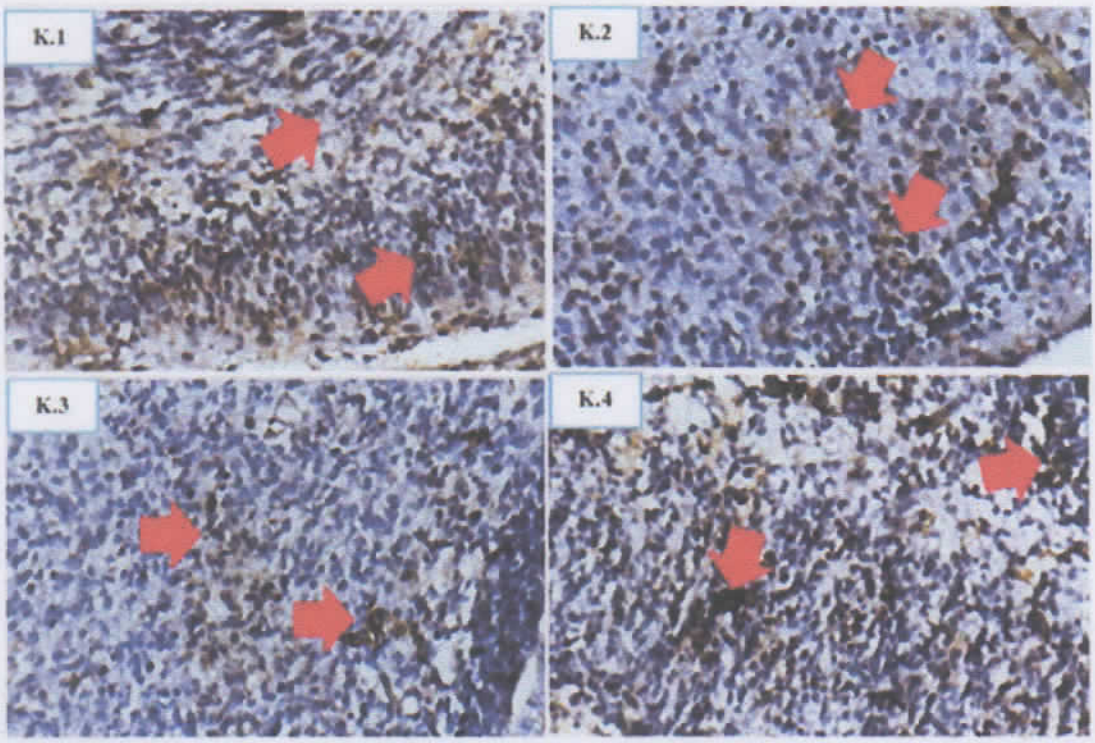

Figure 2. Akt expression (red arrow). Cerebellum Akt expression in the control group (K4) was strongest among the other groups (immunohistochemistry, 400x magnification, Nikon H600L microscope from Nikon Instruments Inc. ™, New York, USA).

Discussion

The results showed that stress exposure during pregnancy decrease Akt expression in the cerebrum and cerebellum newborn mice. Stress during pregnancy causes an increase in placental GC[2]. The fetal HPA axis is very sensitive to excess GC levels that can alter the regulation of HPA function[16]. High GC levels can suppress neurogenesis which endangers cell survival, causing an imbalance in several neurotransmitter systems[10].

The interaction of GC and active GR in adrenocortical cells causes the neurotrophic factor (NTF) signaling pathway to be suppressed. Several proteins have been

classified as NTF: BDNF (Brain-Derived Neurotrophic Factor), IGF-1 (Insulin-Like Growth Factor-1), and GDNF (Glial Cell Line Derived Neurotrophic Factor)[4]. The BDNF system is essential for neural survival and synaptic plasticity in the CNS[13]. BDNF has broad expression in the brain[18]. IGF-1 is an important growth factor in CNS (Central Nervous System) development. In early brain development, IGF-1 has an essential role as an autocrine, proliferative, and prosurvival factor[5]. GDNF activates the PI3K / Akt signaling cascades[4].

NTF plays a role in determining PI3K-Akt regulations. PI3K-Akt signaling activity triggers the catalytic lipid domain of PIP2 to become PIP3[4]. Inactive Akt binds to PIP3 in the plasma membrane, allowing PDK1(Phosphoinositide-Dependent Protein Kinase 1) to access phosphorylate T308 and mTORC2

(Mammalian Target of Rapamycin-2) to phosphorylate S473 as part of the activation of Akt[7].

The Akt signaling pathway has important biological effects on cells, such as increased survival, inhibition of aging, and physiological activity[19]. Akt is a growth factor-induced cell survival mediator and has been shown to suppress apoptotic death in several cell types[9].

The Akt pathways are negatively affected by glucocorticoid exposure[11]. PI3K deficiency causes a significant reduction in brain size during embryogenesis[3]. Many experiments have shown that glucocorticoids can inhibit IGF-1 expression in many tissues and cells[6]. It shows the importance of Akt in brain growth and development[3].

The results showed that Akt expression in the cerebrum and cerebellum was significantly higher in the control group than in the stress exposure group. Akt expression in the cerebrum and cerebellum of newborn mice decreased significantly in line with the stress exposure.

Conclusion

This study concluded that physical and psychological stress exposure during pregnancy could decrease the expression of Akt in the cerebrum and cerebellum of newborn mice.

Conflict of Interest: The authors state that there is no conflict of interest associated with this research.

Source of Funding: The authors have not received specific grants from any funding agency in the public, commercial, or not-for-profit sector.

Ethical Clearance: This study was approved by the

Ethical Committee Faculty of Veterinary Medicine Universitas Airlangga with Number: 2.KE.002.01.2021.

References

1. Bleker LS, Rooij SRD, Roseboom, TJ. Prenatal Psychological Stress Exposure and Neurodevelopment and Health of Children. *Int J Environ Res Public Health*. 2019;16:36-57. doi:103390/ijerph16193657
2. Charil A, Laplante DP, Vaillancourt C, King S. Prenatal stress and brain development Brain. *Research Reviews*. 2010;65:56–79. doi:101016/ jbrainresrev201006002
3. Chen S, Liu Y, Rong X, Li Y, Zhou J, Lu L. Neuroprotektive Role of tthe PI3Kinase/Akt Signaling Pathway in Zebrafish. *Front Endocrinol.* 2017;8:21 doi: 103389/fendo201700021
4. da Silva PGC, Domingues DD, de Carvalho LA, Allodi S, Correa L C. Neurotrophic factors in Parkinson's disease are regulated by exercise: Evidence-based practice. *Journal of the Neurological Sciences*. 2016;363:5–15. http:// dxdoiorg/101016/jjns201602017
5. Dyer AH, Vahdatpour C, Sanfeliu A , Tropea D. The Role Of Insulin-Like Growth Factor 1 (Igf-1) In Brain Development, Maturation And Neuroplasticity. *Neuroscience*. 2016. http:// dxdoiorg/101016/jneuroscience201603056
6. He Z, Zhang J, Huangb H, Yuan C, Zhu C, Magdalou J, Wang, H. Glucocorticoid-activation system mediated glucocorticoid-insulin-like growth factor 1 (GC-IGF1) axis programming alteration of adrenal dysfunction induced by prenatal caffeine exposure. *Toxicology Letters*. 2019;302:7–17. https://doiorg/101016/jtoxlet201812001
7. Hemmings BA, Restuccia DF. PI3K-PKB/

Akt Pathway. *Cold Spring Harb Perspect Biol.* 2012;4:a011189. doi: 101101/cshperspecta011189

8. Hines T. Anatomy of the Brain. *Mayfield Brain and Spine.* 2018. https://mayfieldclinic com/pe-anatbrainhtm
9. Hosoi T, Hyoda K, Okuma Y, Nomura Y, Ozawa K. Akt up- and down-regulation in response to endoplasmic reticulum stress. *Brainresearh.* 2007; 1152: 27 – 31. doi:101016/jbrainres200703052
10. Jauregui-Huerta F, Ruvalcaba-Delgadillo Y, Gonzalez-Castañeda, Garcia-Estrada J, Gonzalez-Perez O, Luquin S. Responses of glial cells to stress and glucocorticoids. *Curr Immunol Rev.* 2010; 6(3) (August): 195–204. doi:102174/157339510791823790
11. Korgun ET, Ozmen A, Unek G, Mendilcioglu I. The Effects of Glucocorticoids on Fetal and Placental Development. *Glucocorticoids–New Recognition of Our Familiar Friend.* 2012. http:// dxdoiorg/105772/50103
12. Mulligan C, D'Errico N, Stees J. Methylation changes at NR3C1 in newborns associate with maternal prenatal stress exposure and newborn birth weight. *Epigenetics.* 2012; 7(8):853-857. doi: 104161/epi21180
13. Numakawa T, Odaka H, Adachi N. Actions of Brain-Derived Neurotrophic Factor and Glucocorticoid Stress in Neurogenesis. *Int J Mol Sci.* 2017;18: 2312. doi:103390/ijms18112312
14. Parker VJ, Douglas AJ. Stress in early pregnancy: maternal neuro-endocrine-immuneresponses and effects. *Journal of Reproductive Immunology.* 2010;85:86–92. doi:101016/jjri200910011
15. Popoli M, Zhen Y, McEen B. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci.* 2013; 13(1): 22–37. doi:101038/nrn3138
16. Waffarn G, Davis EP. Effects of antenatal corticosteroids on the hypothalamicpituitary-adrenocortical axis of the fetus and newborn:experimental findings and clinical considerations. *Am J Obstet Gynecol.* 2012; 207(6): 446-454. doi:101016/jajog201206012
17. Wang L, Zhou K, Fu1 Z, Yu1 D, Huang H, Zang X, et al. Brain Development and Akt Signaling: the Crossroads of Signaling Pathway and Neurodevelopmental Diseases. *J Mol Neurosci .* 2017;61:379–384. doi:101007/s12031-016-0872-y
18. Wurzelmann M, Romeika J, Sun D. Therapeutic potential of brain-derived neurotrophic factor (BDNF) and a small molecular mimics of BDNF for traumatic brain injury. *Neural Regeneration Research.* 2017;12(January): Issue 1. doi: 104103/1673-5374198964
19. Xu F, Na L, Li Y, Chen L. Roles of the PI3K/AKT/ mTOR signaling pathways in neurodegenerative diseases and tumours. *Cell Biosci.* 2020;10:54. https://doiorg/101186/s13578-020-00416-0