

Interleukin-6 (IL-6) Levels of Preeclampsia Pregnant Women in Ethnic Bugis, Makassar, Mandar, and Toraja

by Sitti Wahyuni

FILE	ECLAMPSIA_PREGNANT_WOMEN_IN_ETHNIC_BUGIS_MKS_MANDAR_N_TORAJA.PDF (418.29K)	WORD COUNT	3404
TIME SUBMITTED	06-FEB-2021 04:12AM (UTC+0700)	CHARACTER COUNT	17945
SUBMISSION ID	1502640460		



Interleukin-6 (IL-6) Levels of Preeclampsia Pregnant Women in Ethnic Bugis, Makassar, Mandar, and Toraja

Eka Fitri Amir¹, Muh Nasrum Massi², Sitti Wahyuni³, Yuyun Widaningsih⁴, Sharvianti Arifuddin¹

¹Department of Midwifery, Postgraduate School, Hasanudin University, Indonesia; ²Department of Microbiology, Faculty of Medical, Hasanuddin University, Indonesia; ³Department of Parasitology, Faculty of Medical, Hasanuddin University, Indonesia; ⁴Department of Pathology Clinic, Faculty of Medical, Hasanuddin University, Indonesia.

ABSTRACT

Introduction: The imbalance between proinflammatory cytokines impairs the permeability in blood vessels resulting in increased blood pressure. In preeclampsia patients found an increase in IL-6 levels compared to normotensive mothers.

Objective: To determine differences in levels of cytokines IL-6 in pregnant women with preeclampsia and normotension in the Bugis, Makassar, Mandar and Toraja tribes so that it can be used as a marker for the prevention of the continuation of advanced preeclampsia and is used as one of the determinants of early detection.

Methods: This research is a cross-sectional study with a case-control study where respondents were 44 pregnant women with a gestational age over 20 weeks with a diagnosis of preeclampsia and 44 pregnant women over 20 weeks with normotension. The criteria for respondents in this study were not suffering from systemic diseases and were domiciled in the study area which was the Makassar, Bugis, Mandar, and Toraja tribes. Data collected included age, body mass index (BMI), parity, history of preeclampsia, and Tribal Status. Interleukin levels were determined using the Human Interleukin 6 ELISA Kit.

Results: Differences in mean IL-6 levels in the preeclampsia group in four ethnic groups namely Makassar, Bugis, Mandar and Toraja with a significant value of p-value 0.032 ($p < 0.05$) as well as in the normotension group also had differences in IL-6 levels with a p-value of 0.002 ($p < 0.05$). While the difference in IL-6 levels of preeclampsia and normotension in each tribe results in significant differences in Makassar (0.001) and Toraja (0.010).

Conclusion: Differences in serum IL-6 levels in Makassar, Bugis, Mandar, and Toraja ethnic variations must be considered risk factors that influence the incidence of preeclampsia.

Key Words: Interleukin-6, Preeclampsia, Ethnicity, Pregnancy

INTRODUCTION

Preeclampsia is a specific condition in pregnancy that is characterized by endothelial dysfunction and coagulation. The diagnosis of preeclampsia is based on the presence of hypertension and proteinuria at gestational age over 20 weeks.¹ Preeclampsia is classified into preeclampsia and severe preeclampsia based on measurements of blood pressure, proteinuria level, and laboratory results.² Specific signs of preeclampsia (BP >140/90 mmHg and proteinuria >300 mg/24 hours) and sometimes accompanied by other symptoms such as oedema, headache, blurred vision, symptoms of abdominal pain and thrombocytopenia.³

The prevalence of preeclampsia ranges between 2-8% of all pregnancies in the world and makes preeclampsia as one of the causes of high rates of maternal morbidity and mortality in various regions.⁴ Based on the results of the Indonesian Health Demographic Survey (SDKI) data, it was explained that there was an increase in MMR from 228 to 359 maternal deaths per 100,000 live births, mostly caused by bleeding, hypertension in pregnancy (HDK), and infection. But the proportion of HDK including preeclampsia-eclampsia has increased by 25% as the main cause of death in mothers to date.⁵ South Sulawesi Provincial Health Office data from 2016 to 2018 experienced an increase in cases from 163 to 639. West Sulawesi Health Service including Majene General Hospital treated 144

Corresponding Author:

Eka Fitri Amir, Department of Midwifery, Postgraduate School, Hasanuddin University, Indonesia.
Email: amiref18p@student.unhas.ac.id; ekafitriamir@gmail.com

ISSN: 2231-2196 (Print)

ISSN: 0975-5241 (Online)

Received: 18.07.2020

Revised: 11.09.2020

Accepted: 12.10.2020

Published: 14.12.2020

patients with preeclampsia diagnoses, West Sulawesi Health Office released data on Maternal Mortality Rates due to Hypertension in pregnancy including preeclampsia in 13% of all deaths in West Sulawesi.⁶

The imbalance between proinflammatory cytokines such as cytokine IL-6 will support the dysregulation in regulating permeability in blood vessels that can become endothelial dysfunction resulting in increased blood pressure. In preeclampsia, patients found an increase in IL-6 levels compared to normotensive mothers.^{7,8} The prevalence of preeclampsia has developed into a major complication in pregnancy with a different spreading pattern in each region, research conducted to assess the impact of maternal race or ethnicity on the level of preeclampsia in Hawaii, the Philippines, and China states that the Asia Pacific ethnic group as an ethnic group is at high risk of preeclampsia.⁹ Likewise, genetic differences related to the immunity of white, black and Hispanic pregnant women living in Boston and New York. The results of the investigation identified population differences and regional ethnic variations as risk factors for preeclampsia.^{10,11}

Pregnant women of the Bugis, Mandar, Makassar, and Toraja tribes as the largest ethnic group in the South and West Sulawesi Region have not been specifically examined about the risk factors for preeclampsia.

MATERIALS AND METHODS

Research sites

This research was conducted in March-June 2020 and has received ethical approval recommendations by number UH19121049 protocol. The study was conducted in four hospitals and four Puskesmas in South and West Sulawesi, namely the RSPTN Unhas, Jumpandang Baru Health Center and Barabarayya health centre in Makassar, Lasinrang General Hospital and Mattirobulu health centre in Pinrang District, Majene Regional Hospital and Totoli Phealth centre in Majene District and Elim Hospital and Rantepao Health Center in Tana Toraja.

Data types and sources

Data collected from the sample are demographic data (age, education, domicile), obstetric history (parity and preeclampsia history, marital history, history of antenatal care), and medical diagnoses. Data were taken from pregnant women over 20 weeks with a diagnosis of preeclampsia based on the diagnosis of obstetricians and obstetricians in research hospitals and health centres and pregnant women over 20 weeks with normal pregnancy as a control group.

Data collection technique

Data related to demographic data and obstetric history and

ethnic status of the respondents were collected using a questionnaire through direct interviews with respondents and the closest people of the respondent. Meanwhile, for blood sampling, researchers were assisted by laboratory personnel in hospitals and puskesmas where the study was conducted. The collected samples were then centrifuged and stored in the refrigerator at 4 ° C. After all samples were filled, serum interleukin-6 levels were examined using a Magnesium Assay Kit at the University Medical Research Center Laboratory (HUM-RC).

RESULTS

The data shows that the age and parity characteristics between the group of preeclampsia mothers and the group of normotensive mothers have almost the same characteristics. While the body mass index characteristics there are differences in the characteristics of pregnant women with preeclampsia and normotension (Table 1).

Table 1: Demographic Characteristics of Respondents

Characteristics	Preeclampsia (n = 40)	Normotension (n = 40)	p value
Age n (%)			
Risky	7 (46.7)	8 (53.3)	0.500 *
No risk	37 (50.7)	36 (49.3)	
Parity n (%)			
Primigravida	14 (51.9)	13 (48.1)	0.500 *
Multigravida	30 (49.2)	31 (50.8)	
BMI n (%)			
Less	0 (0)	1 (100)	0.005 *
Normal	8 (30.8)	18 (69.2)	
Over	21 (48.8)	22 (51.2)	
Obesity	15 (83.3)	3 (16.7)	

* chi-square

The results of the average analysis of serum IL-6 levels from the four ethnic groups of preeclampsia pregnant women showed different mean levels in each ethnic group and the Makassar ethnic group showed the highest value of 144.54 pg/ml while the ethnic group with the average serum IL-6 level the lowest was in the Mandar ethnicity which was 93.86 pg/ml, the difference in the average IL-6 levels of maternal serum in preeclampsia had a significant value ($P < 0.05$) (Table 2).

The results of the average analysis of serum IL-6 levels from the four ethnicities of normotensive pregnant women showed different mean levels in each ethnic group with a P-value ($P < 0.05$), and in the Makassar ethnic group the highest value was 81.91 pg/ml while the group ethnicity with the lowest

average serum IL-6 level in the Toraja ethnic group, which is 55.52 pg/ml (Table 3).

Table 2: IL-6 levels in pregnant women in the Bugis, Makassar, Mandar and Toraja tribes who have preeclampsia (n = 44)

Tribes	IL-6 levels (Pg / ml) Mean ± SD	p-value *	Sig. **
Makassar	144.54 ± 60.60	0.032	±0.077
Bugis	98.90 ± 21.65		±0.337
Mandar	93.86 ± 17.18		±0.185
Toraja	111.7 ± 68.4		±0.049

* Kruskal-Wallis test; ** Shapiro-Wilk normality test

Table 3: IL-6 levels in pregnant women in the Bugis, Makassar, Mandar and Toraja tribes that are normotensive (n = 44)

Tribes	IL-6 levels (Pg/ml) Mean ± SD	p-value *	Sig. **
Makassar	81.91 ± 38.38	0.002	±0.026
Bugis	81.92 ± 20.87		±0.337
Mandar	67.28 ± 17.80		±0.185
Toraja	55.52 ± 23.01		±0.594

* Kruskal-Wallis test; ** Shapiro-Wilk normality test

Two tribes have a mean serum IL-6 level which is significantly different in the preeclampsia and normotension groups, namely the Makassar ethnic group (P and Toraja ethnicity while the Bugis and Mandar ethnic groups do not have a significant difference in IL-6 level, however the mean IL-6 level 6 serums in all ethnic groups showed higher levels of IL-6 in the group of pregnant women with preeclampsia (Table 4).

Table 4: Differences in IL-6 levels between preeclampsia pregnant women and normotensive pregnant women in the Bugis, Makassar, Mandar, and Toraja tribes (n = 88).

Tribes	Preeclampsia status	IL-6 levels		p-value *
		Mean rank	Sum of rank (Pg/ml)	
Makassar	Preeclampsia	15.91	175.00	0.001
	Normotension	7.09	78.00	
Bugis	Preeclampsia	12.82	141.00	0.365
	Normotension	10.18	112.00	
Mandar	Preeclampsia	14.00	154.00	0.076
	Normotension	9.00	99.00	
Toraja	Preeclampsia	15.00	165.00	0.010
	Normotension	8.00	88.00	

* Mann-Whitney test

DISCUSSION

Based on statistical tests in table show that age, parity, and history of preeclampsia did not differ significantly in both normal pregnancy and pregnancy with preeclampsia with (p> 0.05). Meanwhile, body mass index has a significant difference in the group of preeclampsia pregnant women and normotensive pregnant women (p<0.05), overweight pregnant women, and more obesity in the group of preeclampsia mothers.

The main finding in this study is the level of Interleukin-6 (IL-6) serum of pregnant women with preeclampsia having average serum (144.54 pg/ml) in the Makassar tribe, (98.90 pg/ml) in the Bugis tribe, (93.86 pg/ml) in Mandar rate, (111.7 pg/ml) in Toraja rates that differed significantly from the p-value of 0.032. while the mean serum IL-6 levels in normotensive mothers by ethnic groups differed significantly at 81.91 pg/ml in the Makassar tribe, 81.92 pg/ml in the Bugis tribe, 67.28 pg/ml in the Mandar tribe, 55.52 pg/ml in the Toraja tribe. this is in line with studies which state that mean serum IL-6 levels are lower in the normotensive maternal group compared with serum IL-6 levels in mothers who have preeclampsia. Other studies also mention that in patients with preeclampsia found increased levels of IL-6 compared to normotensive mothers.

The imbalance between proinflammatory cytokines such as cytokines IL-6 will support the dysregulation in regulating permeability in blood vessels that can become endothelial dysfunction resulting in increased blood pressure. Among the markers of increased inflammation in preeclampsia is the presence of a concentration of serum IL-6 levels.

More specific findings in this study found differences in serum IL-6 levels of preeclampsia pregnant women and normotensive based on ethnic groups, namely in the Makassar ethnic group having a p-value of 0.001, in the Bugis ethnicity P-value 0.367, in the Mandar ethnicity P-Value 0.076 and in the ethnic group Toraja p-value 0.010. The Bugis and Mandar ethnic groups statistically (p>0.05) did not have differences in levels between preeclampsia and normotensive pregnant women but had a high average IL-6 level of 141.00 pg/ml compared to the normotension group of 112.00 pg/ml, as well as in the Mandar ethnicity with an average of 154.00 pg. ml in the preeclampsia group and 99.00 pg/ml in the normotension group. While the Makassar da Toraja ethnic group had significantly different levels of IL-6 (p-value <0.05).

Inflammation in pregnancy can be explained by the factor of the placenta suffering from ischemic injury or reperfusion which leads to the theory of endothelial dysfunction, acute and chronic inflammation is a response to inflammation designed to send leukocytes to the area of inflammation. Arriving in the area of inflammation, leukocytes clean up

every microbe that invades the process of decomposition of ischemic tissue, if inflammation lasts longer then there will be characteristic signs such as induction of lymphocytes and macrophages accompanied by a proliferation of blood vessels delivered by leukocytes especially monocytes.^{14,15} If it continues, tissue damage occurs due to the release of enzymes, chemical mediators, toxic oxygen by leukocytes. Inflammatory events illustrate that proinflammatory cytokines have increased, giving rise to clinical signs of PE such as hypertension, proteinuria, edema and micro-thrombotic angiopathy.¹⁶

Proinflammatory cytokines are associated with defects in the invasion of placental cytotrophoblasts. In the placental implantation process, there are imperfections in the remodeling of the spiral arteries, where the enlargement of the arteries only reaches 40% of the increase in diameter should be in pregnant women. This situation causes a reduction in local perfusion to the placenta which then forms cytotoxic factors resulting from the ischemia.¹⁷

The ethnic variations studied are in one region on the island of Sulawesi, namely ethnic Makassar, Bugis, Mandar, and Toraja which are the majority ethnic groups that inhabit the regions of South and West Sulawesi. In this study found differences in IL-6 levels based on differences in ethnic variations. The average serum IL-6 levels of Makassar, Bugis, Mandar, and Toraja ethnicities are higher compared to mothers with Normotency in Makassar, Bugis, Mandar, and Toraja ethnic groups.^{12,13,18}

Some studies report that the prevalence rate of preeclampsia is different for each ethnicity, a study illustrates that preeclampsia is not experienced by all ethnic groups, it is reported that ethnic minority groups have a higher risk than the white race.¹⁸ A retrospective study in the Pacific islands states that native Hawaiian subgroups have a higher prevalence of preeclampsia compared to the population of the Chinese population.¹⁹

Differences in serum IL-6 levels in pregnant women with preeclampsia and pregnant women. Normotency by ethnic group was reported by several researchers who stated that individuals with certain cytokine levels had a higher risk of developing diseases related to blood vessel function.²⁰ A retrospective study of preeclampsia pregnant women in the Negev found that the incidence of preeclampsia is closely related to seasonality, culture and genetic factors²¹ and differences in serum cytokine levels that have different allele frequencies between different populations.¹¹ However, more in-depth studies are needed regarding the presence of serum IL-6 in a particular population or ethnicity so that it becomes a marker of disease risk among ethnic groups.^{20,21}

CONCLUSION

Differences in serum IL-6 levels in ethnic variations in Makassar, Bugis, Mandar, and Toraja should be considered risk factors that influence the incidence of preeclampsia and become one of the determinants of early detection as a marker of prevention of preeclampsia protection in the advanced stages.

ACKNOWLEDGEMNET

The authors are also grateful to authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Funding: None

Conflict of Interest: None

REFERENCES

1. Bartsch E, Medcalf KE, Park AL, Ray JG, Al-Rubaie ZTA, Askie LM, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: Systematic review and meta-analysis of large cohort studies. *BMJ* 2016;353:1–10.
2. Cornelius DC. Preeclampsia: From inflammation to immunoregulation. *Clin Med Insights Blood Disord*. 2018;11:1179545X17752325.
3. Didion SP. Cellular and oxidative mechanisms associated with interleukin-6 signaling in the vasculature. *Int J Mol Sci* 2017;18(12):25634.
4. Gathiram P, Moodley J. Pre-eclampsia: Its pathogenesis and pathophysiology. *Cardiovasc J Afr* 2016;27(2):71–8.
5. Kemenkes. *Kemenkes RI Tahun 2015-2017*. 2019;(Idl):2017–9.
6. Dimkes. *Profil Dinas Kesehatan Sulawesi Barat*. 2018; (Maternal Mortality Rate).
7. Marca B, Brewer J, Wallace K. IL-6-induced pathophysiology during pre-eclampsia: Potential therapeutic role for magnesium sulfate? *Int J Interf Cytokine Mediat Res* 2011;3(1):59–64.
8. Kenny LC, Kell DB. Immunological Tolerance Pregnancy, And Preeclampsia: The Role Of Semen Microbes and The Father. *Front Med* 2017; 4: 239.
9. Nagakawa K, Lim E, Harvey S, Miyamura J, Juarez DT. Racial/ethnic disparities in the association between preeclampsia risk factor and preeclampsia among women residing in Hawaii. *Physiol Behav* 2017;176(10):139–48.
10. Liu B, Li Y, Yao Y, Li H, Liang H, Xin M, et al. Polymorphisms of the IL27 gene in a Chinese Han population complicated with pre-eclampsia. *Sci Rep* 2016;6:1–6.
11. Nguyen DP, Genc M, Vardhana S, Babula O, Onderdonk A, Witkin SS. Ethnic differences of polymorphisms in cytokine and innate immune system genes in pregnant women. *Obstet Gynecol* 2004;104(2):293–300.
12. Geldenhuys J, Rossouw TM, Lombaard HA, Ehlers MM, Kock MM. Disruption in the regulation of immune responses in the placental subtype of preeclampsia. *Front Immunol* 2018; 9:1659.
13. Fisher SJ. Why is placental abnormal in preeclampsia? *Am J Obstet Gynecol* 2015 Oct;213(4 Suppl):S115–22.
14. Saito S, Sakai M. Th1/Th2 balance in preeclampsia. *J Reprod Immunol* 2003;59(2):161–73.

15. Valencia-Ortega J, Zárata A, Saucedo R, Hernández-Valencia M, Cruz JG, Puello E. Placental Proinflammatory State and Maternal Endothelial Dysfunction in Preeclampsia. *Gynecol Obstet Invest* 2019;84(1):12–9.
16. Taylor BD, Tang G, Ness RB, Olsen J, Hougard DM, Skogstrand K, et al. Mid-pregnancy circulating immune biomarkers in women with preeclampsia and normotensive controls. *Physiol Behav* 2017;176(3):139–48.
17. Lockwood CJ, Yen CF, Basar M, Kayisli UA, Martel M, Buhimschi I, et al. Preeclampsia-related inflammatory cytokines regulate interleukin-6 expression in human decidual cells. *Am J Pathol* 2008;172(6):1571–9.
18. Whincup PH, Gilg JA, Papacosta O, Seymour C, Miller GJ, Alberti KGMM, et al. Early evidence of ethnic differences in cardiovascular risk: Cross-sectional comparison of British South Asian and white children. *Br Med J* 2002;324(7338):635–8.
19. Webster LM, Gill C, Seed PT, Bramham K, Wiesender C, Nelson-Piercy C, et al. Chronic hypertension in pregnancy: Impact of ethnicity and superimposed preeclampsia on placental, endothelial, and renal biomarkers. *Am J Physiol - Regul Integr Comp Physiol*. 2018;315(1): R36-R47,
20. Gan GG, Subramaniam R, Lian LH, Nadarajan VS. Ethnic variation in interleukin-6 -174 (G/C) polymorphism in the Malaysian population. *Balk J Med Genet* 2013;16(2):53–8.
21. Shental O, Friger M, Sheiner E. Ethnic differences in the monthly variation of preeclampsia among Bedouin and Jewish parturients in the Negev. *Hypertens Pregnancy* 2010;29(3):342–9.

Interleukin-6 (IL-6) Levels of Preeclampsia Pregnant Women in Ethnic Bugis, Makassar, Mandar, and Toraja

ORIGINALITY REPORT

%23
SIMILARITY INDEX

%11
INTERNET SOURCES

%15
PUBLICATIONS

%11
STUDENT PAPERS

PRIMARY SOURCES

- 1** Chandra Ariani Saputri, Isharyah Sunarno, Andi Nilawati Usman, Aryadi Arsyad, Irfan Idris. "Serum magnesium levels in normal pregnant women, severe preeclampsia, and severe preeclampsia with complications; a consideration for early supplementation?", *Enfermería Clínica*, 2020
Publication **%6**
- 2** Submitted to Universitas Hasanuddin
Student Paper **%3**
- 3** ijcrr.com
Internet Source **%2**
- 4** www.ijcrr.com
Internet Source **%2**
- 5** archive.org
Internet Source **%1**
- 6** Q. Chen, M. Zhao, F. Guo, Y.X. Yin, J.P. Xiao, P.R. Stone, L.W. Chamley. "The reduction of **%1**

circulating levels of IL-6 in pregnant women with preeclampsia by magnesium sulphate and nifedipine: In vitro evidence for potential mechanisms", Placenta, 2015

Publication

7 Submitted to CVC Nigeria Consortium % 1
Student Paper

8 e-journal.poltekkesjogja.ac.id % 1
Internet Source

9 belitungraya.org <% 1
Internet Source

10 T Fujioka. "Effect of methylprednisolone on the kinetics of cytokines and liver function of regenerating liver in rats", Hepatology Research, 2001 <% 1
Publication

11 Babbette LaMarca. "IL-6-induced pathophysiology during pre-eclampsia: potential therapeutic role for magnesium sulfate?", International Journal of Interferon, Cytokine and Mediator Research, 2011 <% 1
Publication

12 Submitted to Aspen University <% 1
Student Paper

13 link.springer.com <% 1
Internet Source

14

www.reproductivemedicine.com

Internet Source

<% 1

15

jurnal.unissula.ac.id

Internet Source

<% 1

16

repositorio.unicamp.br

Internet Source

<% 1

17

Lorenz Rieger. "Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia - a prospective observational study", *Reproductive Biology and Endocrinology*, 2009

Publication

<% 1

18

watermark.silverchair.com

Internet Source

<% 1

19

www.spandidos-publications.com

Internet Source

<% 1

20

Guilhermo Justino Mundim, Marina Carvalho Paschoini, Edward Araujo Júnior, Fabricio Da Silva Costa et al. "Assessment of angiogenesis modulators in pregnant women with pre-eclampsia: a case–control study", *Archives of Gynecology and Obstetrics*, 2015

Publication

<% 1

21

www.frontiersin.org

Internet Source

<% 1

22

Efthymios N Deliargyris, Ronald J Raymond, Theoharis C Theoharides, William S Boucher, David A Tate, Gregory J Dehmer. "Sites of interleukin-6 release in patients with acute coronary syndromes and in patients with congestive heart failure", *The American Journal of Cardiology*, 2000

Publication

<% 1

23

"Motivational and Satisfaction Level Among Medical Teachers in India: A Questionnaire Based Survey", *International Journal of Current Research and Review*, 2017

Publication

<% 1

24

Q Chen. "The role of autocrine TGF β 1 in endothelial cell activation induced by phagocytosis of necrotic trophoblasts: A possible role in the pathogenesis of preeclampsia", *The Journal of Pathology*, 2010

Publication

<% 1

25

Stoop, Dominic, Miriam Baumgarten, Patrick Haentjens, Nikolaos P Polyzos, Michel De Vos, Greta Verheyen, Michel Camus, and Paul Devroey. "Obstetric outcome in donor oocyte pregnancies: a matched-pair analysis", *Reproductive Biology and Endocrinology*, 2012.

Publication

<% 1

26

Lene S. Knudsen, Ib J. Christensen, Tine

Lottenburger, Mads N. Svendsen et al. "Pre-analytical and biological variability in circulating interleukin 6 in healthy subjects and patients with rheumatoid arthritis", Biomarkers, 2008

Publication

<% 1

EXCLUDE QUOTES ON

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE MATCHES < 5 WORDS