Laporan Akhir
IRPA RM7

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Jabatan Fisiologi

Pusat Pengajian Sains Perubatan
USM Caw. Kelantan

End of Project Report

A. Project number: 06 – 02 – 05 - 6021

Project title: To investigate the role of fetoplacental prorenin, rennin EDRF and Endothelins in the Toxaemia of pregnancy.

Project leader: Dr Harbindar Jeet Singh

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B. Summary for MPKSN Report (*For publication in the Annual MPKSN Report, please summarise the project objectives, significant results achieved, research approach and team structure*)

The main objective of the study was to investigate the role of Endothelin-1, EDRF, renin and prorenin in fetoplacental tissues. The precise pathogenesis of pre-eclampsia is still unknown but there is a generally held view that placental hypoperfusion, secondary to some vaso-active substance, may be responsible for this disease entity. Endothelin-1 is a very powerful vasoconstrictor whereas EDRF is a vasodilator. Renin, through activation of the localized renin angiotensin system, may also work as a vasoconstrictor. Prorenin is being considered by some as not only a precursor of renin but, it by itself, as a vasodilator. We hypothesise that there probably exists an imbalance between the various vasodilator and vasoconstrictor substances in the placenta, more in favour of vasoconstrictors. This imbalance may be responsible for the placental vasoconstriction and consequently placental hypoperfusion.

Our observations reveal significantly higher levels of endothelin-1 in fetoplacental tissues from women with pre-eclampsia. We did not find any significant differences in renin activity or renin concentration in the fetoplacental tissues between the two groups. Total renin however was significantly higher in tissues from women with pre-eclampsia. We were unable to measure EDRF in this study and therefore would find it difficult to precisely state the significance of these observations. But in another separate study, we have observed a lowered kallikrien-kinin (KKS)activity in placenta from women with pre-eclampsia. KKS has vasodilator properties. It is possible therefore that EDRF activity may be similarly lowered. Nitric oxide synthetase activity has been observed to be lower in placentae from women with pre-eclampsia.

From our observations it may be concluded, that there exists an abnormality in the expression of endothelin in the placenta and an over production of this peptide may be responsible for some of the vasoconstriction and consequently hypoperfusion of the placenta. The raised prorenin may be a response to this vasoconstriction but its vasodilator response may be blunted. However more studies are needed to identify the cellular sources of these peptides in the placenta before it can be conclusively established that over production of endothelin-1 may indeed be the primary abnormality.

C. **Objectives achievement**

- **Original project objectives** (Please state the specific project objectives as described in Saction II of the Application Form)
  1) To measure renin activity in feto-placental tissues
  2) To measure renin concentration and feto-placental tissues
  3) To measure prorenin cncentration in feto-palcental tissues
  4) To measure endothelin-1 concentration in fetoplacental tissues
  5) To measure EDRF concentration in fetoplacental tissues
  6) Endothelin-1 and EDRF production in HUVEC
- **Objectives Achieved** (Please state the extent to which the project objectives were achieved)

  Objectives 1 – 4 achieved

- **Objectives not achieved** (Please identify the objectives that were not achieved and give reasons)

  Objectives 4 –5 not achieved
  Reason – Insufficient funds approved.

D. **Technology Transfer/Commercialisation Approach** (Please describe the approach planned to transfer/commercialise the results of the project)

Publication of the findings in international journals. It has added another aspect to the possible pathogenesis of pre-eclampsia.

A paper entitled " *Endothelin-1 in feto-placental tissues from normotensive women and women with pre-eclampsia*" has just been accepted for publication in **Acta Obstetricia et Gynecologica Scandinavica**

A second paper entitled '**Total rennin in fetoplacental tissues of normotensive women and women with Pre-eclampsia**" is currently under preparation and shall be submitted for publication to an international journal shortly

E. Benefits of the Project (Please identify the actual benefits ansing from the project as defined in Scetion III of the Application Form for examples of outputs, organisational outcomes and sectoral/national impacts, please refer to Section III of the Guidelines for the Application of R&D Funding under IRPA)

- **Outputs of the project and potential beneficiaries** (Please describe as specifically as possible the outputs achieved and provide an assessment of their significance to users)

Our findings of raised endothelin-1 and total renin levels in the placentae of women with pre-eclampsia suggest of a possible imbalance of vaso-active factors in the placenta. They seem to suggest of an imbalance that is more in favour of vasoconstriction and may be responsible for the placental hypoperfusion which underlies the pathophysiology of preeclampsia. Our observations have certainly highlighted the need to clearly examine the role of vaso-active substances in the placental vasculature. An abnormal expression of vaso-constrictors coud result in placental vascular constriction and consequently hypoperfusion.

This study identifies the possible vaso-constrictors and it is possible endothelin-1 blockers may have a role in the management of pre-eclampsia.

- **Organisational Outcomes** (Please describe as specifically as possible the organisational benefits arising from the project and provide an assessment of their significance)

This study has helped establish our department as another center for the study of hypertension in pregnancy and pre-eclampsia

- **National Impacts** (If known at this point in time, please describe as specifically as possible the potential sectoral/national benefits arising from the project and provide an assessment of their significance

D. Assessment of project Structure

- **Project Team** (Please provide an assessment of how the project team performed and highlight any significant departures from plan in either structure or actual man days utilised

  Overall the project team performed well. The only disappointment was that we were unable to fully carry out all the objectives because of insufficient funds and the distribution of the funds over the three years.

- **Collaborations** (Please describe the nature of collaborations with other research organisation and/or industry)

  None at the moment

G. Assessment of Research Approach (Please highlight the main steps actually performed and indicate any major departure from the planned approach or any major difficulty encountered)

The approach was as planned and there were no departures from it.

H. Assessment of the Project Schedule (Please make any relevant comment regarding the actual duration of the project and highlight any significant variation from plan)

No real variations. The project went on as planned

I. Assessment of Project Costs (Please comment on the appropriateness of the original budget and highlight any major departure from the planned budget)

The budget requested was appropriate for the objectives outlined. However the funds approved were not sufficient to realize all the objectives.

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J. Additional Project Funding Obtained (In case of involvement of other funding sources, please indicate the source and total funding provided)

None

K. Other Remarks (Please include any other comment which you feel is relevant for the evaluation of this project)

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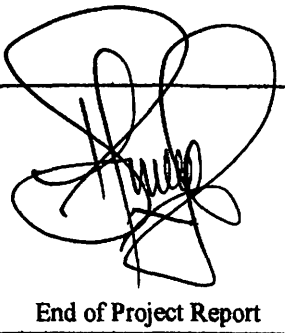
Date : 24/8/2000.

Signature :



Technology Transfer/Commercialisation Approach (*Please describe the approach planned to transfer/ commercialise the results of the project*)

Patent (*Please state full title of the patent by giving the patent number or application number*)

NONE

Publication pertaining to the research finding

(a) Report/Conference Paper

1. ' The distribution of endothelin in feto-placental tissues of women with pregnancy-induced hypertension" 3rd National Conference on Medical Sciences 25 – 26 May 1997, Kota Bharu, Kelantan
2. "Total rennin concentration in fetoplacental tissues from women with pregnancy-induced hypertension" 4th National Conference on Medical Sciences 8-9 June 1998, Kota Bharu Kelantan
3. "Renin in fetoplacental membranes of normotensive pregnant women and women with pre-eclampsia" 4th Congress of the Federation of Asia-Oceania Physiological Societies, 27 Sept - 1Oct 1998, Brisbane Australia
4. Endothelin-1 in feto-placental tissues from Normotensive pregnant women and women with pre-eclampsia. 15th Scientific Meeting of the Malaysia Society of Pharmacology and Physiology 8-9th May 2000, Kota Bharu Kelantan

(b) Journal Publication (*Use only the standard accepted abbreviations for Journal titles. If there are none give full Journal title*)

1. HJ Singh, A Rahman, ET Larmie, A Nila " Endothelin-1 in feto-placental tissues from normotensive pregnant women and women with pre-eclampsia" Acta Obs & Gyn. Scand. (In press)

2. HJ Singh, A Rahman, ET Larmie, A Nila " Prorenin, total renin and renin activity in feto-placental tissues from normotensive pregnant women and women with pre-eclampsia" (Under preparation)

(c) Others:

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- Post Graduates (*Who graduated or who are still participating in the project*)

Student Name & Year of Registration/Nationality	Thesis Title	PhD/MSc	Year of Completion
NONE			

- No. of Research Assistants or Officers funded by the project:

  (a) Research Officers: 1 (one) (b) Research Assistants: None

- Collaboration (*Please describe the nature of collaborations with other research organizations and/or industry*)

  Institutions:

  (a) Local Institutions

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  (b) International Institutions:

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