A METHOD REVIEW OF PHARMACOLOGICALLY INDUCED HYPERTENSION IN PREGNANT RATS MODEL: N_{Ω}-NITRO-L-ARGININE METHYL ESTER HYDROCHLORIDE (L-NAME)

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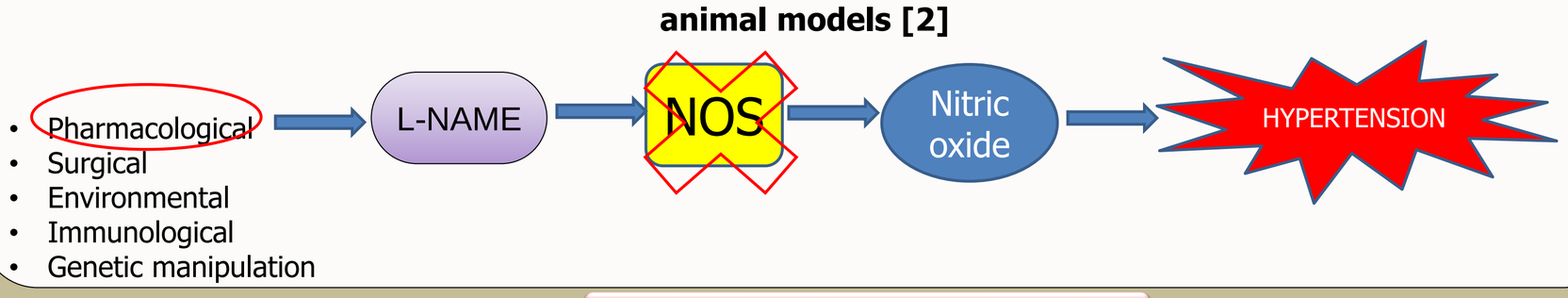
ABSTRACT

Background: Hypertensive disorders of pregnancy contribute a high percentage in maternal and fetal mortality and morbidity. They affect about 8% of pregnancies worldwide. There are various animal models used in the study of pregnancy-associated hypertensive disorders including induction of animals by surgical, environmental, pharmacological, immunological, or genetic manipulation. L-NAME is a drug that has been used to induce hypertension by inhibition of Nitric oxide synthase (NOS). **Purpose**: The objective of this study is to establish hypertension in a pregnant rat model by using L-NAME. **Methodology**: Thirty-two female Sprague-Dawley rats were randomly assigned to four groups (n=8 in each): Control- non-pregnant (C), control-pregnant (P), Non-pregnant-L-NAME (CL) and pregnant-L-NAME (PL). On Day 13 of gestation, the treated groups were given 60mg/kg/day of L-NAME via oral gavage until the day of delivery. A series of blood pressure were measured via pre-warmed tail-cuff method. The number and weight of the litters and total maternal weight gain were recorded. **Result**: Introduction of L-NAME to PL group resulted in an increase of the mean SBP and MAP however, it does not follow the definition of hypertension in pregnancy.
Introduction of L-NAME to CL group resulted in an increase of the mean SBP and MAP which is higher compared to PL group. The mean of maternal weight gain, number of litters and litters' weight were not significant. There were several complications that we observed in the treated groups including one rat had died and some of them experienced temporary neurological deficits such as unilateral upper limb paralysis and bloody eye discharge. **Conclusion**: This method caused maternal morbidity and mortality, but it was relatively safe for the fetus. The pregnancy itself has hypotensive mechanism to protect the fetus. This method used oral gavage as the route of administration could not established hypertension in pregnancy rat model might be due to short-acting of L-NAME. The alternative way is to change the method of administration of L-NAME by giving chronic inhibition of NOS through subcutaneous injection or mixing the drug with drinking water.

BACKGROUND

- Hypertensive disorders of pregnancy remarkably confer a high percentage of maternal and fetal mortality and morbidity [1,3,5].
- Worldwide, they affect about 5-10% of pregnancies [4].

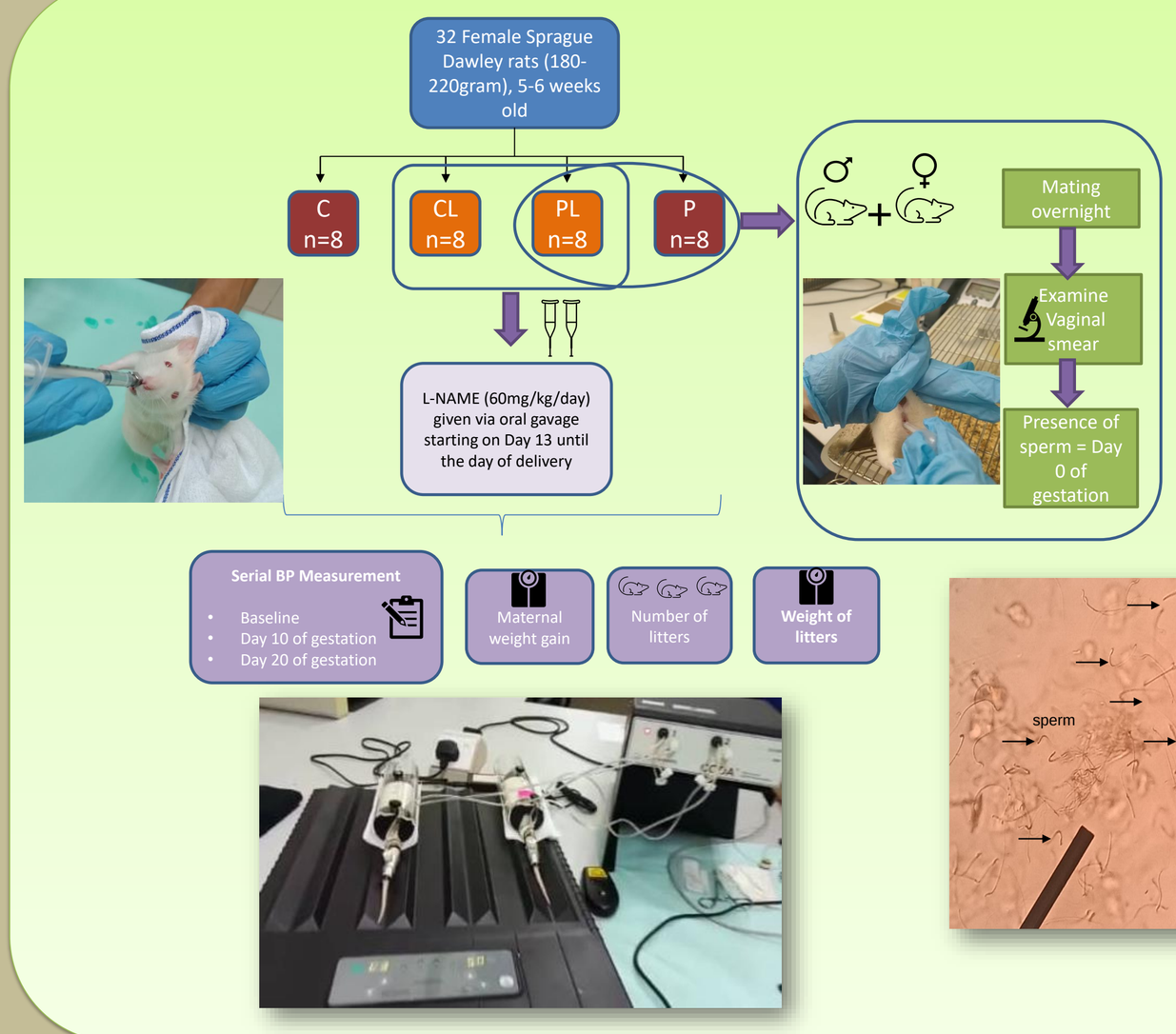
HDP-associated animal models [2]



OBJECTIVE

- The objective of this study is to establish hypertension in a pregnant rat model by using L-NAME

METHODOLOGY



RESULT

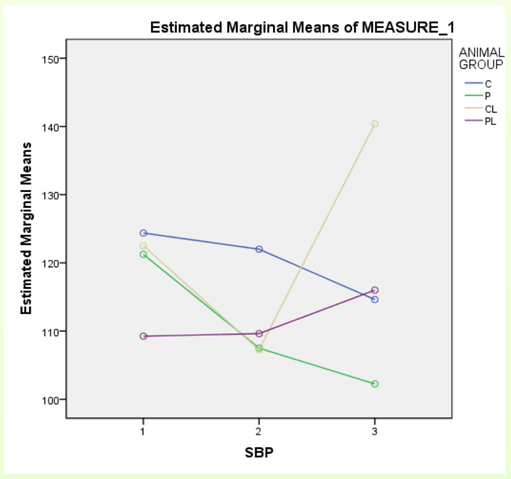


Figure 1: Estimate Marginal Means of systolic blood pressure (SBP) mm Hg

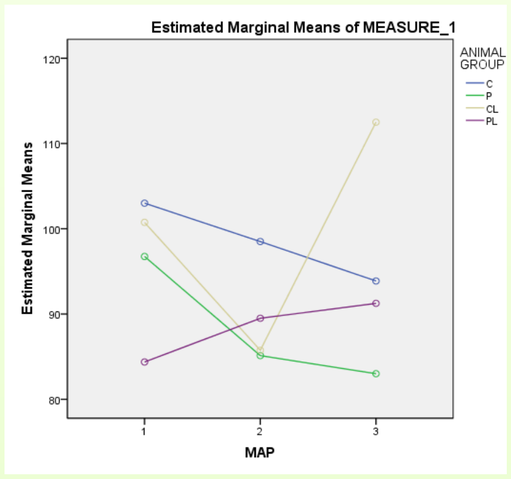


Figure 2: Estimate Marginal Means of mean atrial blood pressure (MAP) mm Hg

	df	Error	F	P value	η_p^2
SBP	2	56	2.78	>0.05	0.090
SBP*Animal Group	6	56	4.45	<0.05	0.323
Animal Group	3	28	4.22	<0.05	0.311
MAP	2	56	2.45	>0.05	0.080
MAP*Animal Group	6	56	3.68	<0.01	0.283
Animal Group	3	28	5.235	<0.01	0.359

C: Control, non-pregnant
P: Control, pregnant
CL: Non-pregnant+ L-NAME
PL: Pregnant + L-NAME

SBP1: Baseline BP
SBP2: D10 of gestation BP
SBP3: D20 of gestation BP

MAP1: Baseline BP
MAP2: D10 of gestation BP
MAP3: D20 of gestation BP

Figure 3: Table summary of one-way repeated measures ANOVA test to compare the effect of L-NAME on SBP and MAP taken at different duration

Animal Group		N	Mean	SD	t	df	P value
Weight gain	P	8	99.0	17.22	0.014	14	0.99
	PL	8	98.9	18.06			
Number of Litters	P	8	8.5	4.34	-0.45	14	0.66
	PL	8	9.25	1.83			
Litters' weight	P	8	39.9	34.03	-1.34	10	0.21
	PL	8	57.5	15.34			

Figure 4 : Table summary of independent sample t-test for equality of means between P and PL group for maternal weight gain, number of litters and litters' weight

DISCUSSION

- Introduction of L-NAME to PL group resulted in an increase of the mean SBP and MAP however, it was not fit into definition of hypertension in pregnancy.
- Introduction of L-NAME to CL group resulted in an increase of the mean SBP and MAP which is higher compared with PL group.
- It might be due to pregnancy itself has hypotensive mechanism to protect maternal and fetal well being.
- L-NAME was administered via oral gavage in which the drug was given one shot at particular time. The mechanism of L-NAME to induce hypertension in pregnancy animal model is by chronic inhibition of NO synthase, so that it requires prolong action throughout the day.
- Oral gavage might be not an ideal route of administration for this purpose.
- The alternative routes are via subcutaneous injection or mixing the drug with drinking water..

REFERENCES

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