MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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THE MIRVIE RNA PLATFORM FOR EARLY DETECTION OF PRE-ECLAMPSIA

Keywords: obstetric, hypertension in pregnancy, pregnancy complication, liquid biopsy, pre-eclampsia, MIRVIE RNA platform

SUMMARY OF TECHNOLOGY

The Mirvie Pre-eclampsia Test using Mirvie RNA platform is designed for early identification of pre-eclampsia before any clinical presentation or symptoms occur. It was developed by a company named Mirvie located in California.[1]

The Mirvie RNA platform combines analysis of thousands of RNA messages from the fetus, the placenta and the mother, using machine learning. Analysing plasma cell-free RNA (cfRNA) from a single blood drawn will reveal RNA messages indicating pregnancy changes in fetal growth and maternal physiological changes. The platform is claimed to be able to predict complications earlier based on the underlying biology of each pregnancy.[1,2]

Immediately after plasma sample was taken, it must be stored on dry ice at –80 °C until further processing. Total circulating nucleic acid was extracted from plasma ranging in volume from ~215 µl to 1 ml, using a column-based commercially available extraction kit. Following extraction, cfDNA was digested and the remaining cfRNA was purified. Each of the sample were then analysed using PCR with reverse transcription (RT–qPCR) to assess the relative amount of cfRNA extracted. The threshold cycle (Ct) values from each RNA sample was then measured. The Ct values for an endogenous housekeeping gene were also measured. Subsequently, the cfRNA libraries were prepared. Samples were quantified and paired-end sequencing was performed. Reads were processed following a similar protocol. Briefly, raw sequencing reads were trimmed and mapped. After removing duplicates, gene counts were generated by the platform.[2]

There were four genes identified and used for the platform modelling; which were found to be most significantly associated with pre-eclampsia or placental development. The genes were Claudin 7 (CLDN7), pregnancy-associated plasma protein 2 (PAPPA2), transducin-like enhancer protein 6 (TLE6) and fatty acid-binding protein 1 (FABP1).[2]

Pregnancy-associated plasma protein 2 (PAPPA2) is expressed in the placenta specifically in trophoblast cells. It has previously been linked to the development of

pre-eclampsia and has been associated with inhibition of trophoblast migration, invasion and tube formation. Claudin 7 (CLDN7) is involved in tight cell junction formation and blastocyst implantation; in healthy pregnancies, expression of CLDN7 is reduced in response to oestrogen at the time of implantation. Similarly, transducin-like enhancer protein 6 (TLE6) has also been linked to preimplantation and early embryonic lethality. Fatty acid-binding protein 1 (FABP1) was first purified from human cytotrophoblasts and is known to be highly expressed in the fetal liver; it is critical for fatty acid uptake and transport and is upregulated threefold when cytotrophoblasts differentiate to syncytiotrophoblasts at implantation.[2]

The Mirvie RNA platform for early detection of pre-eclampsia has received Breakthrough Device Designation from the U.S. Food and Drug Administration (FDA) on the 3rd May 2022.[3] Additionally, the Mirvie RNA platform were also studied for early preterm birth cases.[3]

INNOVATIVENESS

Novel, completely new	/
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

Hypertensive disorders of pregnancy (HDP) encompass chronic hypertension, gestational hypertension, pre-eclampsia/eclampsia, and pre-eclampsia superimposed on chronic hypertension. The incidence of HDP increased from 16.30 million [95 % UI 13.56 to 19.42 million] to 18.08 million (95 % UI 15.26 to 21.11 million) globally, with a total increase of 10.92 % from 1990 to 2019. The number of deaths due to HDPs was approximately 27.83 thousand (95 % UI 24.30 to 27.83 thousand) in 2019, with a 30.05 % (95 % UI 28.92–32.71 %) decrease from 1990 to 2019.[4]

Pre-eclampsia per se affects approximately 4% of pregnancies in the United States. It is the second leading cause of maternal mortality worldwide and may lead to serious maternal complications, including stroke, eclampsia, and organ failure. Adverse perinatal outcomes for the fetus and newborn include intrauterine growth restriction, low birth weight, and stillbirth. Many of the complications associated with pre-eclampsia lead to early induction of labour or caesarean delivery and subsequent preterm birth.[5]

In Malaysia, pregnancy-induced hypertension with significant proteinuria is the third leading cause of death (6.8%) among pregnant mother in 2020.[6]

It is generally accepted that the onset of a new episode of hypertension during pregnancy (with persistent diastolic blood pressure >90 mm Hg) with the occurrence of substantial proteinuria (>0.3 g/24 h) can be used as criteria for identifying pre-eclampsia. Although pathophysiological changes (e.g. inadequate placentation) exist from very early stages of the pregnancy, hypertension and proteinuria usually become apparent in the second half of pregnancy and are present in 2%–8% of all pregnancies overall.[7] Its hallmark features are high blood pressure (hypertension) and endothelial dysfunction, leading to widespread end-organ injury. This includes the liver, blood, kidneys, brain and placenta.[8]

There are several identified risk factors and predeterminants of pre-eclampsia. These include nulliparity, multi-gestation pregnancy, advanced maternal age greater than 35 years old, in-vitro fertilisation or other forms of assisted reproductive technology, maternal comorbidities (chronic hypertension, chronic kidney disease, diabetes mellitus, thrombophilia, obstructive sleep apnea, obesity with pre-pregnancy body mass index greater than 30), family history, history of placental abruption or pre-eclampsia in a previous pregnancy, or intrauterine fetal growth restriction.[9]

CURRENT OPTIONS FOR PATIENTS

According to the US Preventive Services Task Force recommendation, screening for pre-eclampsia in pregnant women with blood pressure measurements must be done throughout pregnancy.[5]

Several guidelines exist to stratify risk of pre-eclampsia based on pregnancy factors and maternal characteristics such as the National Institute for Health and Care Excellence (NICE) and American College of Obstetricians and Gynecologists (ACOG) guidelines.[8] Maternal and pregnancy characteristics with existing medical conditions are classified as high or moderate risk factors. Recognition of women at risk of pre-eclampsia for commencement of prophylaxis were also highlighted in Malaysian Clinical Practice Guidelines entitled Management of Hypertension.[10] The advantages for this method are the assessment of clinical factors are readily attainable, applicable to all women at the first visit particularly to determine who might benefit from low-dose aspirin for preterm pre-eclampsia prophylaxis and it does not require specific blood-testing or Doppler ultrasonography at no additional cost.[8] However, its sensitivity is about 41% for pre-term pre-eclampsia and it performs worse for all pre-eclampsia.[8]

A new first-trimester screening algorithm has been developed and validated using maternal risk factor with combination of mean arterial blood pressure, uterine artery resistance measured by Doppler ultrasound, and levels of circulating Placental Growth Factor (PlGF). This method achieves higher sensitivity (~82%) for preterm preeclampsia, however the disadvantage for this method is the additional cost for

blood testing for PlGF and an expertise for ultrasonography to determine maternal uterine artery resistance. The implementation of this method has not been universal.[8]

Another screening method using biomarkers such as soluble fms-like tyrosine kinase 1 (sFlt-1) and PlGF; has been introduced which selectively offered when diagnosis is uncertain or the clinical picture is ambiguous for example those with borderline hypertension, or non-specific symptoms (such as headache) or for women with persistently high blood pressure, who have not met the diagnostic criteria for pre-eclampsia (no strong evidence of other organ involvement).[8]

Soluble FMS-like tyrosine kinase 1 and PlGF are anti- and pro-angiogenic factors (respectively) significantly deranged in pre-eclampsia. The Prediction of Short-Term Outcome in Pregnant Women with Suspected Pre-eclampsia Study (PROGNOSIS) showed that a sFlt-1:PlGF ratio of 38 or lower can accurately rule out the likelihood of developing pre-eclampsia over the next week, with 99.3%, negative predictive value, among women at less than 37 weeks. This test has the potential to reduce admissions for blood pressure monitoring, as it can confidently exclude the likelihood of having pre-eclampsia. As such, it has been translated to clinical practice in some centres. Conversely an sFlt-1:PlGF ratio >38 is only modestly accurate in predicting who will develop pre-eclampsia, with positive predictive value of 36.7% for pre-eclampsia within four weeks, and sensitivity of 66.2%.[8]

Placental Growth Factor (PlGF) alone has also been evaluated to triage care in women with suspected preterm pre-eclampsia. Besides having a very high negative predictive value it has also been shown to predict pre-eclampsia requiring delivery within two weeks with greater accuracy than other commonly used clinical tests (blood pressure, urate, alanine transaminase (a liver function test), and proteinuria24). Specifically, PlGF <100pg/ml in women presenting with suspected pre-eclampsia at <35 weeks' gestation, performed with 96% sensitivity and 98% negative predictive value in predicting whether pre-eclampsia will occur over the next two weeks. Although recent data demonstrates that PlGF alters with gestational age, and thus a blanket definition of screen positive with PlGF <100pg/ml may pick up numerous false positives.[8]

Certain literature emphasized on early detection of pre-eclampsia based on all three main points which focused on a detailed medical history, the collection of biophysical parameters such as blood pressure, arterial stiffness, and Doppler examination of maternal blood vessels, and the determination of biochemical parameters, which can give clues to impaired placental function.[11]

At present, there is no available reliable and cost-effective single screening test for pre-eclampsia which can be recommended for use in most developing countries. The traditional approach to identify the group at high risk for pre-eclapsia that would benefit from prophylactic use of aspirin is based on risk factors from maternal demographic characteristics and medical history, can identify only about 40% of preterm

pre-eclampsia, at a false-positive rate (FPR) of 10%.[12] Although some studies on uterine artery Doppler studies and first-trimester maternal serum markers for early detection of preeclampsia have shown promise. There is not enough evidence to suggest their routine use in clinical practice, more so in resource poor settings.[13].

The aim for the early diagnosis of pre-eclampsia is to start a preventive therapy by administration of 100 mg acetylsalicylic acid (ASA or aspirin) before 16 weeks of pregnancy which has been proven to reduce risk for severe pre-eclampsia.[11]

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on Mirvie Pre-eclampsia Test in early detection of Pre-eclampsia.

There was only one retrievable published scientific evidence on the Mirvie Pre-eclampsia Test using Mirvie RNA platform.

Efficacy

A case-control study recruited singleton pregnancy from two independent cohorts with 72 cases of pre-eclampsia and 452 non-cases which included 31 controls with chronic hypertension and 19 controls with gestational hypertension. Both cohorts included spontaneous preterm birth samples along with the normotensive term samples. The control population thus includes normotensive, chronic hypertensive, gestational hypertensive and spontaneous preterm deliveries, this design was selected to make the control population reflective of a broader population. Samples were collected from eight different biobank selected from LIFECODES (a prospective pregnancy biorepository that has been recruiting pregnant women in the greater Boston since 2006) and POUCH Study Cohort (The Pregnancy Outcomes and Community Health Study cohort which enrolled 3,019 pregnant women at 16-27 weeks' gestation from 1998 to 2004 from 52 clinics in five Michigan communities). The aim of the study is to evaluate the ability of cell-free RNA (cfRNA) signatures in asymptomatic maternal blood which was taken during second trimester to predict the development of pre-eclampsia. Maternal blood taken on average at 14.5 weeks before delivery.[2] The learning curve for the platform was cross-validated and analysed with logistic regression gene features and the study had identified seven genes ($p < 0.005$) relevant to pre-eclampsia or placental development which were CLDN7, PAPPA2, SNORD14A, PLEKHH1, MAGEA10, TLE6 and FABP1. Based on four selected genes (PAPPA2, CLDN7, TLE6 and FABP1) features, a logistic regression model in a leave-one-out cross-validation set-up was used to estimate the probability of pre-eclampsia.

Confidence intervals for area under the curves (AUCs), sensitivity, specificity and positive predictive value (PPV) were all measured and calculated via bootstrapping.

Figure 1. Features and model performance for prediction of pre-eclampsia

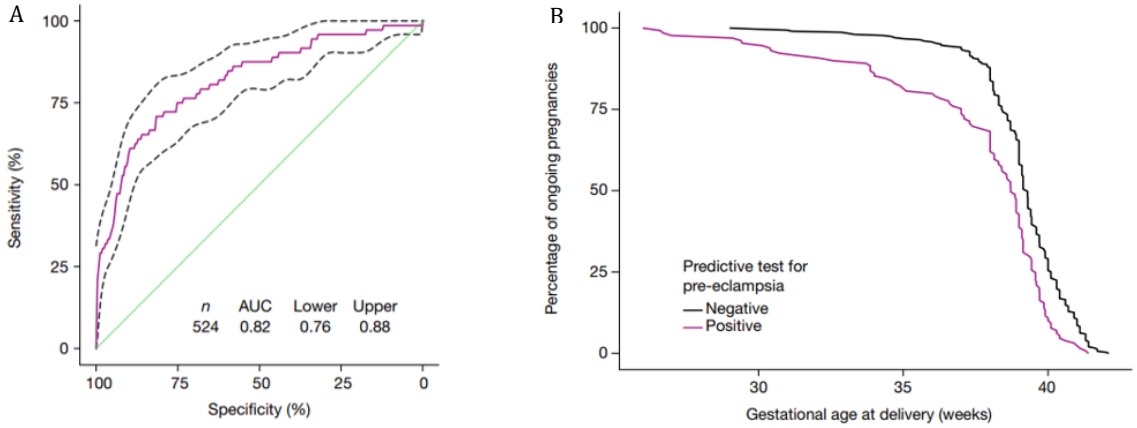

Figure 1 (A) Receiver operating characteristic curve (mean and 95% confidence interval) for the logistic regression model for pre-eclampsia (n = 524). **(B)** Kaplan–Meier curves of deliveries in test-positive and test-negative populations (n = 439), excluding spontaneous preterm deliveries.

The result calculated from the model had shown that the AUC for the model was 0.82 (95% confidence interval, ±0.06). At a sensitivity of 75%, the cfRNA model achieved a positive predictive value (PPV) of 32.3% given a prevalence of pre-eclampsia of 13.7% in their study. It was claimed to be superior to prediction by clinical factors which only achieved a PPV of 4.4%.[2] Subanalysis for non-case group consisted of both normotensive women (n = 263) and women with chronic (n = 31) or gestational (n = 19) hypertension showed that genes identified through comparison of the groups with chronic or gestational hypertension with the normotensive group showed no overlap with genes significant for pre-eclampsia ($p < 0.05$), signifying that the signal for pre-eclampsia is specific to hypertension driven by a placental disorder and the signature is independent of signals associated with chronic hypertension.[2]

b. Cost

There was no retrievable evidence on the cost or cost-effectiveness study of Mirvie Pre-eclampsia Test or Mirvie RNA platform. Comparatively, the price of other screening methods for pre-eclampsia are tabulated in Table 1.

Table 1: Gross comparison of cost for screening methods for Pre-eclampsia.

Screening methods	Cost	Remark
Maternal risk factor	The cost only implies to frequent antenatal visit for blood pressure check-ups and re-assessment.	Public hosp: subsidised by government. Out-of-pocket patient: average 200MYR per visit[14]
US Doppler of uterine artery	The cost of an ultrasound in most cities ranges from about USD110 to 370[15] or ranges	-

	from RM 514.90 to 1732.00; 1USD = 4.68MYR)	
sFlt-1:PlGF ratio	USD 40 per patient (RM 187.25; 1USD = 4.68MYR)[16]	-
Placental Growth Factor alone	2,925.00 Rs (~RM 166.37; 1 Rs = 0.057MYR)[17]	-

c. Societal/ethical

There was no retrievable evidence on societal or ethical issue on Mirvie Pre-eclampsia Test.

d. Safety

There was no retrievable evidence on safety of Mirvie Pre-eclampsia Test. Majority of possible adverse effect could result from venipuncture for the maternal blood sampling and possible of blood-borne disease to the phlebotomist or healthcare provider in handling the sample.

CONCLUSIONS

In conclusion, very limited evidence has shown that Mirvie Pre-eclampsia Test has the potential to be used as standalone molecular predictor for early detection of pre-eclampsia among pregnant mothers. Although the idea of predicting pre-eclampsia by using single blood test is fascinating, however further research with better study design together with cost-effectiveness study are recommended before it is being used in the population.

EVIDENCE

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