

Impact case study (REF3b)

Institution: King's College London
Unit of Assessment: 3B – Pharmacy and Nutritional Sciences
Title of case study: Accurate diagnosis of pre-eclampsia in both hospital and rural clinic settings
<p>1. Summary of the impact</p> <p>Pre-eclampsia is a major contributor to death and disability in pregnancy. Diagnosis, based on accurate blood pressure (BP)/proteinuria determination, is limited by measurement errors and being late features of the disease. In collaboration with industry, King's College London (KCL) researchers have developed an inexpensive, accurate, simple BP device suitable for rural clinics. This device allows intervention to reduce mortality/morbidity and is currently being rolled out in a Gates Foundation project in Africa and Asia. KCL researchers have also helped the company Alere Inc. with the development of a diagnostically accurate test of placental growth factor (PIGF) in women with suspected pre-eclampsia: Alere Triage[®] PIGF. This demonstrates high sensitivity, superior to current tests, and following commercialisation is being adopted internationally. Their work is additionally reflected in guidelines of international standards for BP device accuracy.</p>
<p>2. Underpinning research</p> <p>Annually up to 20% of the 130 million pregnant women worldwide will be affected by a hypertensive disorder. These make a major contribution to maternal mortality and morbidity and are the leading cause of iatrogenic preterm delivery, resulting in perinatal deaths or anything from short-term to life-long morbidity for the infant. Prediction and prevention of pre-eclampsia remain a major goal. For nearly two decades, King's College London (KCL) researchers, including Prof Andrew Shennan (1997-present, Professor of Obstetrics), Prof Lucilla Poston (1987-present, Tommy's Campaign Professor of Maternal & Fetal Health) and Dr Lucy Chappell (2006-present, Clinical Senior Lecturer) have worked on a programme of characterising accurate blood pressure (BP) measurement and biomarkers for identification of pregnant women.</p> <p>KCL researchers develop ways to accurately measure BP in rural settings</p> <p>Pre-eclampsia is a frequently asymptomatic condition with far reaching consequences for maternal and fetal health. Manually inflated BP devices can be inaccurate as the oscillations generated by a deflating cuff can be inconsistent and unreliable for an accurate algorithm. Work at KCL identified that the oscillations generated in pregnancy, and particularly in pre-eclampsia, further confound the issue (1,2). KCL research has sought to control these issues and move monitoring of pre-eclampsia from a predominantly clinic setting to including self-monitoring at home by testing devices accurate enough to be used in both settings (3,4).</p> <p>This work has been channelled into refining and testing similar low-cost, easy to use antenatal BP equipment in clinics and antenatal outreach posts in rural settings in low-income countries where both equipment and/or expertise to do this are lacking. KCL researchers have worked with a number of companies (Omron, Microlife, Nesei) to find solutions to implementation in such settings. Research demonstrated a systematic under-recording of BP and allowed correction factors to be implemented. Initial validation determined how much to correct systematic errors and alter the pressure transducers readings to mimic the gold standard of Korotkoff sounds taken simultaneously by two blinded trained observers. By introducing a fixed rate deflation valve, the quality of the oscillogram could be improved sufficiently to increase accuracy to acceptable standards, in spite of the manual initiation and deflation control required on low cost devices (5). As such, by repeated testing in pregnancy and pre-eclampsia following KCL-defined protocols, Microlife has now altered the algorithm and changed the deflation characteristics of their suitable BP device to improve accuracy to an acceptable standard. To field-test this device, a pilot study in Ethiopia and Tanzania taught healthcare workers in rural community settings to use these machines. They were found to be acceptable and easy to use, long-lasting and have the potential to increase detection rates of hypertension in pregnancy, enabling referral and targeting women for interventions with the potential to save maternal lives (6).</p> <p>Placental growth factor (PIGF) as a biomarker in suspected pre-eclampsia</p> <p>PIGF is a placentally-derived angiogenic factor with concentrations in normal pregnancy peaking at around 30 weeks' gestation. An almost complete absence of this typical gestational rise is seen in women who subsequently develop pre-eclampsia, many weeks before the onset of clinical signs. KCL researchers were among the first to undertake rigorous prospective longitudinal studies of</p>

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pregnant women who subsequently developed pre-eclampsia (7). Due to this work, along with their track record in delivering multicentre studies in pregnant women and in PIGF research (8), the KCL group were approached in 2009 by Alere Inc. (a company at the forefront of PIGF testing) to help develop a commercial PIGF test. KCL undertook the definitive prospective multicentre study of PIGF in cases of suspected pre-eclampsia to accurately identify those at greatest risk of adverse outcomes and thereby substantially improve management. The KCL team (PELICAN group) designed the study, obtained the necessary approvals and recruited 649 women across seven leading maternity centres in the UK/Ireland. The study showed that low PIGF (<5th centile) had very high sensitivity (96%) and negative predictive value (98%) for confirmed pre-eclampsia requiring delivery within 14 days of testing. PIGF concentrations were low or very low in all seven cases of stillbirth, preceding abnormal foetus scan findings (9).

3. References to the research

1. Golará M, Benedict A, Jones C, Randhawa M, Poston L, Shennan AH. Inflationary oscillometry provides accurate measurement of blood pressure in preeclampsia. *Br J Obstet Gynaecol* 2002; 109:1143-147. Doi: 10.1016/S1470-0328(02)01987-0 (16 Scopus citations)
2. Reinders A, Cuckson AC, Jones CR, Poet R, O'Sullivan G, Shennan AH. Validation of the Welch Allyn 'Vital Signs' blood pressure measurement device in pregnancy and preeclampsia. *Br J Obstet Gynaecol* 2003;110:134-38. Doi: 10.1046/j.1471-0528.2003.02038.x (11 Scopus citations)
3. Chung Y, de Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy: Microlife WatchBP home. *Hypertens Pregnancy* 2009;28(3):348-59. Doi: 10.1080/10641950802601286 (3 Scopus citations)
4. Reinders A, Cuckson AC, Lee JT, Shennan AH. An accurate automated blood pressure device for use in pregnancy and pre-eclampsia: the Microlife 3BTO-A. *BJOG* 2005;112(7):915-20. Doi: 10.1111/j.1471-0528.2005.00617.x (39 Scopus citations)
5. de Greeff A, Nathan H, Stafford N, Liu B, Shennan AH. Development of an accurate oscillometric blood pressure device for low resource settings. *Blood Press Monit* 2008;13(6):342-8. Doi: 10.1097/MBP.0b013e32830fd07c (4 Scopus Citations)
6. Baker EC, Hezelgrave N, Magesa SM, Edmonds S, de Greeff A, Shennan A. Introduction of automated BP devices intended for a low resource setting in rural Tanzania. *Trop Doct* 2012;42(2):101-3. Doi: 10.1258/td.2011.110352
7. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;354(9181):810-6. Doi: 10.1016/S0140-6736(99)80010-5 (537 Scopus Citations)
8. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamins in Pre-eclampsia (VIP) Trial Consortium. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet* 2006;367(9517):1145-54. Doi: 10.1016/S0140-6736(06)68433-X (347 Scopus Citations)
9. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, Simpson N, Waugh J, Anumba D, Kenny LC, Redman CW, Shennan AH. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. *Circulation* 2013;128(19):2121-131. Doi: 10.1161/CIRCULATIONAHA.113.003215 (Recent publication)

Grants

- 2006-9. PIs: Shennan AH, Coleman A, Liu B. Longitudinal validation and calibration of devices. GSTT charity, £59,685
- 2010-11 (\$100,000); 2013-16 (\$1,000,000). PI: A Shennan. Community BP monitoring to detect pre-eclampsia in Africa. Grand Challenges Exploration Grants, Gates Foundation
- 2010-13. KCL PELICAN team. Tommy's Charity. Alere Inc, £470,000

4. Details of the impact

KCL-developed blood pressure (BP) monitoring device makes an impact in rural settings

KCL researchers have worked closely with the Taiwanese company Microlife to help them develop a BP device that can be accurately used in pre-eclampsia, especially in the home setting. This company cites Reinders 2005 as the sole source of clinical validation for the Microlife BP 3BTO-A(2) device, saying that it is "currently, the only reliable monitor which can be used for the measurement of BP during pregnancy and pre-eclampsia" (1a). Working with a number of rural antenatal clinics in African countries, KCL researchers and Microlife have transposed the utility of

their BP monitors to this setting. Here, pre-eclampsia is frequently under-detected for a number of reasons including lack of training and competency in using supplied devices; queries to the robustness, safety and accuracy of both mercury containing models and aneroid replacements and reliance of automated BP devices on a power supply or source of batteries that may be inadequate or open to theft. In these circumstances, under-diagnosis of early pre-eclampsia until it presents as hypertensive emergencies or eclampsia is common.

A pilot study in Tanzania (Baker 2012) showed the validity of the Microlife BP device. This work was featured on a news story including Prof Shennan by Voice of America, the largest international broadcast operation in the US (1b). The pilot led to an award of \$1 million from the Gates Foundation Grand Challenges in Global Health initiative. This project is twofold in that it both supplies devices to rural clinics and uses clinic feedback as part of a research project with the University of British Columbia, Canada (PRE-EMPT) (1c). Since May 2013 PRE-EMPT has supplied 1340 devices and training to screen for pre-eclampsia to rural antenatal clinics: 400 in Nigeria, 400 in Mozambique, 360 in Pakistan and 180 in India. Microlife, who have greatly benefitted financially as all the devices were purchased from them, has in return committed to improving the device based on KCL recommendations from findings from these clinics (1d).

KCL research contributes to BP monitoring recommendations in Europe

KCL research determined that BP may be underestimated by automated BP devices in pre-eclampsia. As such, they have developed protocols to assess BP devices in pregnancy that now inform many international guidelines. Most significantly, Reinders 2003 and Golará 2002 are in the 2009 American National 'Standard for Non-invasive sphygmomanometers,' which dictate international standards. Here the methodology includes an adaptation of that laid out in these papers and they are cited when discussing the use of sphygmomanometers in pregnancy and pre-eclampsia (2a). In the European Society of Hypertension 2008 guidelines for home BP monitoring these studies, as well as Reinders 2005, are used in a meta-analysis to produce a table showing the validity of home blood testing in pregnancy. They are also cited as recommended reading with regard to pre-eclampsia (2b). Prof Shennan is an advisor to this society's Working Group on Blood Pressure Monitoring (2c), as well as being on the NICE committee for Guidelines on Hypertension in pregnancy (2d) and the WHO Committee on BP Measurement in Low Resource Settings, whose 'field-test protocol' is used by groups investigating the use of BP devices (e.g. 2e).

It is soon to become EU law that mercury sphygmomanometry be phased out for health and safety reasons and be replaced with oscillometric automated BP monitoring. This is predominantly due to a 2009 report from the Scientific Committee on Emerging and Newly Identified Health Risks, who provide the European Commission with the scientific advice it needs when preparing policy and proposals documents, for which Prof Shennan was an external expert. For the report, the committee needed to determine if BP devices to replace mercury ones were accurate and suitable for use. In consideration of this they drew on a number of KCL references including Chung 2009 when discussing automated oscillometric devices (2f).

Placental growth factor (PIGF) is developed into a commercial product

KCL researchers have also worked to develop another aspect of pre-eclampsia screening in the form of a test for PIGF. Measurement of PIGF can augment clinical assessment and improve risk stratification, enabling healthcare professionals to provide more objective and accurate information to their patients. The advent of a highly sensitive test for pre-eclampsia enables identification of those at greatest risk of adverse outcomes, while those with a normal test result can avoid costly and unnecessary intervention. The test provides an advantage to women who do not wish to have to remain in hospital for monitoring. In a survey carried out by Action on Pre-eclampsia (APEC-UK), 86% said that if a new robust test (e.g. PIGF) were introduced that enabled them to be monitored safely as an outpatient they would prefer this to being in hospital (3a).

Alere Ltd. is a global diagnostics and health management company that provides products and services that allow healthcare decisions to be taken at the point of care. The KCL-led, multi-centre PELICAN study of PIGF testing strategy in women with suspected pre-eclampsia (Chappell 2013) provided validation of PIGF and led to Alere developing the test as a commercial product: Alere

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Triage® PIGF. This definitive study led to the establishment of novel thresholds of PIGF levels on which to base clinical management. A 'normal' level indicates low risk of needing delivery within the next 14 days for pre-eclampsia, so a woman can return to outpatient care; a 'low' level shows an increased risk and requires surveillance to be stepped up; a 'very low' level means a woman is at high risk (median time to delivery for pre-eclampsia of 9 days) and should be admitted for assessment. Alere's product brochure highlights the findings from KCL's study and uses their management algorithm as a 'traffic light' system for risk assessment (3b). To date, Alere have marketed 12,500 PIGF tests for ongoing global use for pre-eclampsia prediction/diagnosis and the study findings are being used by Alere to lobby US Congress and the FDA for faster regulatory approval times for innovations in pregnancy.

Alere also provide an educational website with a globally recognised Editorial Board aimed at healthcare professionals. This highlights the use of PIGF tests and the PELICAN study results (3c). This research was also subject of a widely reported press release by Alere in 2012 (3d). Additionally, an international registry – Management of Pregnancy Complication With PIGF Testing – has been established by Alere to collate outcomes across consultant-led centres. Here, consecutive patients will be managed using KCL's PIGF threshold algorithm with the audit coordinated by an International Steering Group (3e). Throughout their research, the KCL group has been one of the first to routinely incorporate patient and public involvement through Tommy's Charity and APEC-UK at all stages from design and execution to dissemination. For instance, APEC-UK incorporated this new strategy for pre-eclampsia diagnosis and management into a recent educational study day for health care providers (July 4th, 2013) (3f).

5. Sources to corroborate the impact**1) KCL-developed Blood Pressure monitoring device makes an impact in rural settings**

- a. Microlife: <http://www.microlife.com/healthguide/hypertension/validations/pregnancy/>
- b. Voice of America <http://www.voanews.com/content/world-health-days-raises-awareness-of-deadliest-condition/1635019.html>
- c. PRE-EMPT: <http://pre-empt.cfri.ca/> and on last page of newsletter: <http://pre-empt.cfri.ca/Portals/0/PRE-EMPT%20Newsletter%20September%202013.pdf>
- d. Confirmation of shipping details of devices from the University of British Columbia PRE-EMPT Trial manager (available on request)

2) KCL research contributes to BP monitoring recommendations in Europe

- a. ANSI/AAMI/ISO 81060-2:2009. Non-invasive sphygmomanometers - Part 2: Clinical validation of automated measurement type (pdf available on request)
- b. Parati G, et al. European Society of Hypertension guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. *J Hypertens* 2008;26(8):1505-26. Doi: 10.1097/HJH.0b013e328308da66
- c. O'Brien E, et al. European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults. *Blood Press Monit* 2010;15(1):23-3. Doi: 10.1097/MBP.0b013e3283360e98
- d. NICE 2010. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy: <http://www.nice.org.uk/nicemedia/live/13098/50475/50475.pdf>
- e. Parati G. A new solar-powered blood pressure measuring device for low-resource settings. *Hypertension* 2010;56(6):1047-53. Doi: 10.1161/HYPERTENSIONAHA.110.160408
- f. SCENIHR. Mercury Sphygmomanometers in Healthcare and the Feasibility of Alternatives. 2009: http://ec.europa.eu/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_025.pdf

3) Placental growth factor is developed into a commercial product

- a. APEC-UK survey: Letter available from APEC
- b. Alere Triage® PIGF brochure: <http://www.alere.co.uk/pdf/180413025212-Alere%20Triage%20PIGF%20Brochure.pdf>
- c. PIGF.com: <http://plgf.com/scientific-publications/pelican-study.html>
- d. Alere press release. 8.10.2012: <http://uk.reuters.com/article/2012/10/08/idUS35512+08-Oct-2012+PRN20121008>. Picked up by Bioportfolio.com: <http://www.bioportfolio.com/news/article/1192365/Groundbreaking-study-shows-that-a-simple-rapid-PIGF-test-can-accurately-risk.html>
- e. Management of Pregnancy Complication With PIGF Testing: <http://www.plgf.com/>
- f. APEC-UK study day: <http://action-on-pre-eclampsia.org.uk/professional-area/apec-study-days/>