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MATERNAL HEALTH

Moving beyond silos: How do we provide distributed personalized medicine to pregnant women everywhere at scale? Insights from PRE-EMPT

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ABSTRACT

While we believe that pre-eclampsia matters—because it remains a leading cause of maternal and perinatal morbidity and mortality worldwide—we are convinced that the time has come to look beyond single clinical entities (e.g. pre-eclampsia, postpartum hemorrhage, obstetric sepsis) and to look for an integrated approach that will provide evidence-based personalized care to women wherever they encounter the health system. Accurate outcome prediction models are a powerful way to identify individuals at incrementally increased (and decreased) risks associated with a given condition. Integrating models with decision algorithms into mobile health (mHealth) applications could support community and first level facility healthcare providers to identify those women, fetuses, and newborns most at need of facility-based care, and to initiate lifesaving interventions in their communities prior to transportation. In our opinion, this offers the greatest opportunity to provide distributed individualized care at scale, and soon.

1. Background

PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment), a Bill & Melinda Gates Foundation-funded initiative, is designed to develop, test, and introduce new knowledge to reduce the unacceptable maternal, perinatal, family, societal, and global impacts of pre-eclampsia, and the other hypertensive disorders of pregnancy [1,2]. At the time of publication, we will be five of seven years into the initiative.

We believe that pre-eclampsia matters because it remains a leading cause of maternal and perinatal morbidity and mortality worldwide [3,4]. However, in parallel with our current focus on pregnancy hypertension, we are convinced that the time has come to look beyond single clinical entities (e.g. pre-eclampsia, postpartum hemorrhage [PPH], obstetric sepsis) to look for an integrated approach that will provide evidence-based personalized care to women wherever they encounter the health system. In our view, only an integrated approach (across disease entities and between community and facility) will overcome all three delays in triage, transport, and treatment that make individual women vulnerable to maternal mortality [5].

2. Outcome prediction: The key to distributed personalized medicine

In our opinion, major advances in maternal, fetal, and newborn health can be achieved through making outcome prediction models available to women, parents, their families, and all levels of healthcare

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workers. At a time of improvements in general conditions for women, in absolute numbers, the ongoing British Confidential Enquiries into Maternal Deaths provide evidence that the introduction of the National Health Service with free maternity care and, soon thereafter, reproductive choice was associated with a rapid decline in the number of maternal deaths attributed to the hypertensive disorders of pregnancy, primarily pre-eclampsia and eclampsia (Fig. 1). The accelerating pattern of maternity care (four-weekly visits until 28 weeks, fortnightly to 36 weeks, and weekly thereafter) was designed in Edinburgh largely for the identification of pre-eclampsia to afford the opportunity for timely delivery [6]. Since the first triennial report (1952–54), pre-eclampsia- and eclampsia-related deaths have fallen by approximately 90%. Over 90% of that fall was achieved prior to the introduction of either effective antihypertensives for the management of pregnancy hypertension [7] or the use in the UK of magnesium sulfate (MgSO4) for eclampsia prevention and treatment following the Collaborative Eclampsia and Magpie Trials, respectively [8,9]. Similar data exist for Sri Lanka following the introduction of comprehensive maternity care, including vital registration, registration of midwives, prenatal coverage (health center- and home-based), and facility strengthening [10]. Therefore, the process of individualized risk assessment through prenatal care is an effective tool for reducing adverse pregnancy outcomes, especially when included in a package of health service enhancements.

Accurate outcome prediction models are a powerful way to identify individuals at incrementally increased (and decreased) risks associated with a given condition [11]. By stratifying the population into true risk groups, interventions and timely delivery can be targeted to those most in need so that maximum benefit is achieved in a resource-constrained setting. For mothers, fetuses, and newborns, examples of such conditions could be pre-eclampsia, decreased fetal movements, or sepsis, respectively. Approximately half of maternal deaths occur in the home [12], so it is critical to develop a distributed model of diagnosis and risk assessment. To do so, there are two challenges that need to be addressed:

(1) To be able to identify, from within a population with such conditions, the specific individuals who are likely to become critically unwell prior to their clinical decompensation (e.g. development of seizures or sepsis) so that they can receive early interventions (e.g. MgSO4 or antibiotics) and, if they are still in the community, so that they can be transported rapidly for definitive, facility-based care. For use in resource-constrained settings at the community level, such outcome prediction models can include only demographics, symptoms, and signs (augmented by low-cost, noninvasive, robust but accurate sensors to measure blood pressure, temperature, or pulse oximetry) while findings from laboratory tests could also be added as predictors for use at the facility level.

(2) To develop clinical algorithms that respond to levels of risk using predictive modelling techniques that incorporate guidance from the WHO, other organizations that promulgate expert guidelines, and large robust clinical data sets, tailored to the various settings (i.e. community vs primary health center vs inpatient facility in resource-constrained vs well-resourced settings).

Within the scope of our activities, we have developed and validated two outcome prediction models, the PIERS (Pre-eclampsia Integrated Estimate of RiSk) models that identify those pregnant women with pre-eclampsia who are most likely to develop life-threatening complications. Both models have accurate ability to identify women at low risk of developing imminent complications.

The fullPIERS model, which includes demographics, symptoms [13], pulse oximetry [14], and maternal laboratory tests [15,16], identifies clinical relevant risk categories (area under the curve of the receiver — operator characteristic [AUC ROC] 0 · 88 [95% CI, 0 · 84 — 0 · 92]) [17,18]. Currently, fullPIERS is undergoing external validation; a preliminary validation exercise is reassuring [19].

The validated miniPIERS model is solely demographics-, symptom-, and sign-based and can be administered by (1) community healthcare providers (cHCPs) in the home and at primary health centers; and (2) facility-based practitioners as they initially triage women admitted with pregnancy hypertension prior to the availability of laboratory results (or in lieu of laboratory results in some less-developed settings) (AUC ROC 0.77 [95% CI, 0.74 — 0.80]) [20].

The PIERS on the Move (POM) smart phone app integrates miniPIERS and clinical decision algorithms to support cHCPs (e.g. Lady Health Workers in Pakistan) as they provide prenatal care, diagnose pre-eclampsia, and initiate lifesaving therapies in the woman's home prior to urgent transfer to an effective facility [21–23] (Fig. 2). When using the miniPIERS model alone, and if we choose a 25% probability for developing an adverse outcome as a threshold for "high risk," we identify 65% of women who will go on to suffer a severe complication. Through the POM project we have learnt that, by adding pulse oximetry, using the same 25% risk threshold, we improve the prediction rate to 85% of women who will go on to suffer a severe complication [22]. Currently, the POM app is being tested at scale in the Community-Level Interventions for Pre-eclampsia (CLIP) Trials in Nigeria, Mozambique, Pakistan, and India with pulse oximetry limited to

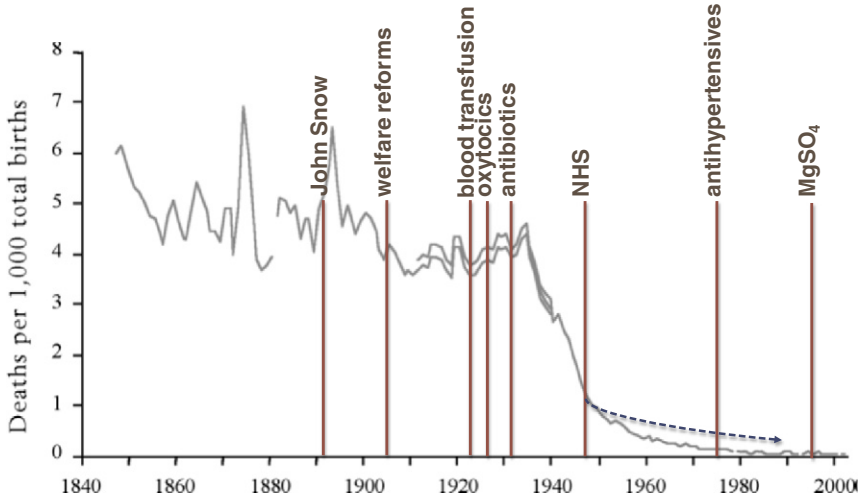

Fig. 1. Modified from Why mothers die 2000–2002. Report on confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH; 2004. The dotted line represents the probable rate of decline without the introduction of the National Health Service (NHS). Vertical lines represent important dates in the evolution of health care in the UK relevant to maternity outcomes.

Fig. 2. PIERS on the Move mHealth application screenshots (Nigerian version of pictograms).

Mozambique and Pakistan (http://pre-empt.cfri.ca/treatment/clip-trial; accessed November 10, 2014). Within the context of the CLIP Trial, hypertensive women identified within their community to be at greatest risk of maternal complications receive 10 g intramuscular MgSO4 and, with severe hypertension, oral 750 mg methyldopa prior to urgent referral to a referral facility (i.e. completed referral within four hours). In CLIP intervention clusters, all women identified as being hypertensive are referred to facilities within 24 hours as none is without risk and many will have disease evolution to more severe disease.

3. Translational biomarkers at point of care

It is clear that the identification of angiogenic imbalance, especially decreased maternal serum placental growth factor (PlGF) concentrations, strengthens the ability to identify women with pre-eclampsia when clinical uncertainty exists [24,25]. From the PELICAN Study, it appears that PlGF has the additional benefit of being able to discriminate between women who are most unwell with pre-eclampsia from those who are least unwell [24]. There is ongoing research to investigate how PlGF might strengthen the PIERS models. However, the largest diagnostic benefit of PlGF appears to be prior to 35 + 0 weeks of pregnancy, whereas the majority of pre-eclampsia (and associated maternal deaths) arises nearer to, or at, term. In addition, to be most useful in less developed settings, a low cost, whole blood point-of-care diagnostic platform, as in HIV management, for example [26], is required. Finally, low maternal serum PlGF is not specific to pre-eclampsia, but is observed in women with small-for-dates fetuses due to placental dysfunction (but not constitutionally small fetuses) [27].

Low PlGF appears to identify a pregnancy complicated by placental dysfunction and/or failure. This last point may be important in terms of the generalizability of PlGF to obstetric populations at scale.

4. Looking beyond hypertension to hypotension: Labor and the puerperium

We are confident that the PIERS model and POM app can guide individualized care and improve outcomes for women with pregnancy hypertension; however, pregnancy hypertension only accounts for approximately 15% of maternal deaths [4].

In temporal order, the other leading causes of direct maternal mortality are prolonged labor, PPH, and puerperal sepsis [4]. To us, a priority is to develop (an) outcome prediction model(s) comparable to the PIERS models so that women vulnerable to labor, postpartum, and puerperal complications can be identified before they clinically decompensate. We anticipate that all such models will include pulse oximetry—the "fifth vital sign" [28].

Women thus identified could have lifesaving therapy initiated in the community or at first level facility (e.g. antibiotics or a heat stable uterotonic), and be referred urgently for evidence-based definitive care at a higher level. Such an approach would have the added benefit of being able to detect deteriorating maternal health due to intercurrent communicable (e.g. HIV, malaria, tuberculosis) and noncommunicable (e.g. acquired valvular heart disease), in addition to direct obstetric causes of maternal death.

To this end, we have developed a modified blood pressure device (Microlife 3AS1-2; Microlife, Widnau, Switzerland) specifically for use in low- and middle-income countries (LMICs), which fulfils WHO requirements for suitability for use in low-resource settings [29]. The device has been validated for use in both non-pregnant and pregnant populations (including both women with pre-eclampsia and low blood pressure), according to the British Hypertension Society protocol [29,30]. It has been evaluated in a feasibility study in Sub-Saharan Africa (Tanzania, Zambia, and Zimbabwe) and shown to be acceptable, feasible, and resulted in increased referrals to higher level institutions for suspected hypertensive disorders by cHCPs.

We have determined the normal range of conventional vital signs as well as shock index, which is the ratio of heart rate to systolic blood pressure. Thereafter, we retrospectively analyzed datasets of women with PPH (one dataset in the UK and another large dataset of women in four African low-resource settings) to evaluate the predictive value of conventional vital signs and shock index. The shock index was shown to be a more consistent predictor of adverse clinical outcomes than conventional vital signs. Currently, we are evaluating our retrospectively determined thresholds for the shock index, relating to increased risk of adverse outcome. Based on these results, we expect that the shock index will be used as a trigger for action to help guide cHCPs and staff at first level facilities.

A traffic light early warning system has been incorporated into the device, to alert users to abnormalities in blood pressure and pulse, using these developed shock index thresholds along with well-recognized thresholds to indicate hypertension in pregnancy. For the shock index (SI), a green light (SI threshold <0.9) would provide reassurance, an amber light (SI ≥ 0.9 and ≤ 1.7) indicates need for intervention, and a red light (SI ≥ 1.7) indicates the need for urgent referral to higher level facilities. These thresholds are being validated prospectively.

5. Stillbirth and newborn health

While the focus of the present paper is maternal health, we believe that the greatest advantage can be obtained through integration of maternal, fetal, and newborn health silos. In brief, stillbirth remains an underrecognized and under-investigated scourge [31]. The daily toll of lost wanted fetuses is unacceptable; however, we consider that it should be possible to combine maternal awareness of fetal well-being (e.g. fetal movements), mHealth-supported fetal heart screening and, quite probably, the point-of-care use of a biomarker such as PlGF to identify individual fetuses at increased risk of stillbirth prior to the occurrence of that devastating complication. Such an outcome prediction model could be integrated into a maternal — fetal — newborn mHealth platform.

In addition, pulse oximetry has been shown to be an effective screening tool for congenital heart disease and early newborn sepsis [32,33]. Integration of pulse oximetry into a community-based newborn outcome prediction model such as the TRIPS score might enable cHCPs and staff at first level facilities to deliver effective newborn screening, risk identification, and initiation of lifesaving therapies in the home prior to transfer [34,35]. In time, this approach could be extended to cover the leading causes of mortality in children under five years old: diarrhea and pneumonia [36].

6. Long-term maternal health: Pregnancy as a risk identifier for noncommunicable diseases

In addition to the peripartum advantages offered to women by such an integrated mHealth platform, there is an opportunity to intervene to the benefit of women's long-term health. While there is increasing recognition of the role of pre-eclampsia as a risk identifier for premature cardiovascular disease [37], as is well recognized for gestational diabetes and type 2 diabetes [38], what is less well recognized is the association of a whole range of "placental complications" of pregnancy with cardiovascular disease [39,40].

Using data from the Scottish health dataset, Smith et al. [39] identified that maternal risk of ischemic heart disease admission or death was associated with delivering a baby in the lowest birth weight quintile (i.e. <20th percentile) for gestational age (adjusted hazard ratio [aHR] 1.9 [95% CI, 1.5 — 2.4]), preterm delivery (<37 + 0 weeks; aHR 1.8 [95% CI, 1.3 — 2.5]), and pre-eclampsia (aHR 2.0 [95% CI, 1.5 — 2.5]). These associations were additive as women with all three characteristics had a seven-fold greater risk of ischemic heart disease admission or death (95% CI, 3.3 — 14.5) than normotensive women delivering appropriately grown babies at term [39]. These data conform to other datasets, linking pregnancy outcomes with noncommunicable diseases [37,40]. This may be very important in the context of less developed countries. In most countries, health provision for mothers is dissociated from pediatric care after birth, although it is usually mothers who bring their children for that care.

Given the ability to use pregnancy to identify women with increased cardiovascular and endocrine risks, there exists an opportunity to use childhood immunization infrastructures to support targeted ongoing surveillance of blood pressure, urine, and glucose for women who have had complicated pregnancies. Such an approach would be facilitated by a maternal — newborn — child mHealth platform that maintains the link between women and their children to coordinate clinical care.

7. Community versus facility focus

Our experience with the PIERS models informs us that it is possible to identify those who would most benefit from focused and timely facility-based care. There is a compelling argument that all pregnant women should receive woman-friendly facility-based intrapartum care, despite many health systems remaining challenged to provide sufficient resources to offer such care to all pregnant and laboring women. At present, there is a pressing need to determine whether or not community-level risk stratification can accurately identify and promote access for those women who require urgent transfer to and management and delivery in a facility under routine conditions. We are more confident that facility-based risk stratification will support personnel to respond to individualized risks and to prioritize the care of those women in greatest need.

Through an integrated mHealth-supported approach, which includes elements such as diagnostic and decision algorithms, prenatal visit booking, and text reminders, we will be able to offer personalized risk assessment to women in their homes or primary health centers. This would provide an evidence-based, portable continuum of care from home to hospital that can be used by all level of healthcare workers. Our view is all levels, across this continuum from home to hospital, need strengthening in parallel, achieving complementarity between the community and facilities and prioritizing facility resources to those women, fetuses, and newborns who will most benefit.

8. Community engagement

Clearly, none of this will be effective without engaging communities to gain buy-in, especially around the uptake of innovations [41–43]. Many societies hold a conservative and limiting view of women's autonomy and value within their family and community. Individuals such as community leaders, faith leaders, traditional and political leaders, volunteers, and traditional birth attendants should be engaged in the process of implementing any mHealth-supported approach that introduces new technologies and task shifting to community members.

9. Integration with existing health system strategies

As with communities, so must those who wish to innovate across the maternal — fetal — newborn continuum engage with, and take into account, existing health system strategies and interventions [42–45]. In our view, to be attractive to those who fund health delivery, whether governments, multilaterals, nongovernmental organizations, or the private sector, strategies for mHealth-supported individualized care must be integrated into existing and evolving health systems, and be comprehensive enough to be attractive to implementers. Attempting to create a parallel platform will be counterproductive in the long term, as it will be unsustainable by design. Engagement with decision makers and thought leaders from the initial design phase of an intervention will improve ownership and the likelihood of implementation at scale. Again, it is our opinion that trials and implementation projects of mHealth-based interventions require health economic analyses that clearly show to those who make often difficult decisions what the return will be on the resources invested. As a benchmark for comparison, in 2001 US dollars, it cost $12 942, $1179, and $263 to avoid one seizure of eclampsia using MgSO4 in high-, middle- and low-income countries, respectively, limiting its use to women with severe pre-eclampsia [46].

10. Summary

As a group of investigators coming from apparently disparate academic foci in obstetrics, maternal medicine, midwifery, newborn medicine, pediatric anesthesia, infectious diseases medicine, and electrical and computer engineering, we are of a joint view that we can accelerate progress toward Millennium Development Goals 4 and 5 through integrated efforts that take us out of our silos. In our opinion, the use of scientifically robust outcome prediction models integrated with decision and intervention algorithms into mHealth applications offer the greatest opportunity to provide distributed individualized care at scale, and, if resources can be found to undertake the remaining work quickly, soon.

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Conflict of interest

J. Mark Ansermino and Guy A. Dumont are cofounders and shareholders of LionsGate Technologies.

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