SELECTED SCIENTIFIC ABSTRACTS

2011–19

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ABOUT PRE-EMPT

Who we are

The PRE-EMPT (PREgnancy Evidence, Monitoring, Partnerships and Treatment) initiative is a consortium of leading global maternal health research and impact initiatives aimed at developing, testing and introducing new knowledge that will reduce the unacceptable maternal, perinatal, family, societal, and global impacts of pre-eclampsia, and the other pregnancy complications.

Our consortium is led by Drs Peter von Dadelszen and Laura A. Magee, who are both currently based in Kings College London, UK.

We are a global consortium of researchers, innovators, advocates and policy influencers who work in diverse areas ranging from clinical medicine, data science, social science, epidemiology, bio banking, medical anthropology, health policy with the agenda of improving maternal health.

What we do

Co-ordinated centrally out of Vancouver, Canada, we work closely with the global health community and local maternal health providers in under-resourced communities.

Research is our focus but we are also passionate about translating new knowledge into real-world settings.

We strive to make a positive impact on the health of pregnant women and their babies globally, particularly among women living in low-resourced communities.

History

PRE-EMPT, formerly the 'PRE-eclampsia & Eclampsia Monitoring, Prevention & Treatment' project was a grant awarded to Prof Peter von Dadelszen, University of British Columbia the Bill & Melinda Gates Foundation. From Nov 2010 – Jun 2019, the PRE-EMPT initiative consists of five inter-related objectives to be conducted over a seven-year period (Nov 2010 – June 2019).

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ABOUT THIS BOOKLET

Knowledge is power, and we believe in the impact of evidence-based policies to improve maternal health. As such, our core missions is to develop, test and promote evidence to improve maternal, fetal and neonatal outcomes, particularly for those who live in the most marginalised communities.

While our current focus spans the breadth of pregnancy complications, we have developed and tested evidence to address hypertensive disorders of pregnancy such as pre-eclampsia which remains one of the top five causes of maternal and perinatal mortality worldwide. Our best estimate is that pre-eclampsia claims the lives of more than 70,000 women per year and more than 500,000 of their fetuses and newborns; this is equivalent to the loss of 1600 lives per day.

In this booklet, we showcase some brief abstracts aimed at preventing, risk assessment, and management of pregnancy complications, and given that maternal (and perinatal) deaths and sequelae result primarily from delays in triage, transport and treatment, we showcase our evidence on testing community-based care.

Even though we have published over 186 publications to date, in this booklet, we have selected a few abstracts accepted in conferences, which are either published or in-press in academic journals.

You can read our publications in full on our website:

PRE-EMPT.BCCHR.CA

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FEATURED ABSTRACTS

Even though we have published over 186 publications to date, in this booklet, we have selected a few abstracts accepted in conferences, which are either published or in-press in academic journals. You can read our publications in full on our website:

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PRE-EMPT studies examine prevention of adverse maternal, foetal and neonatal outcomes. There is a considerable literature devoted to the prevention of pre-eclampsia in order to avoid the associated maternal and perinatal complications. Although the strength of evidence around various interventions to prevent pre-eclampsia varies, at a population level, there is an inverse relationship between dietary calcium intake and both blood pressure among non-pregnant individuals and the incidence of pre-eclampsia.

OBJECTIVE 1: PREVENTION OF PRE-ECLAMPSIA

Pre-Pregnancy and Early Pregnancy Calcium Supplementation Among Women at High Risk of Pre-Eclampsia: A Multicentre, Double-Blind, Randomised, Placebo-Controlled Trial

Prof G Justus Hofmeyr J, Betrán P, Singata-Madliki M, Cormick G, Munjanja, Fawcus S et al., CAP Study Group

Background

Reducing deaths from hypertensive disorders of pregnancy is a global priority. Low dietary calcium might account for the high prevalence of pre-eclampsia and eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy is known to reduce the serious consequences of pre-eclampsia; however, the effect of calcium supplementation during placentation is not known. We aimed to test the hypothesis that calcium supplementation before and in early pregnancy (up to 20 weeks' gestation) prevents the development of pre-eclampsia

Methods

We did a multi-country, parallel arm, double blind, randomised, placebo-controlled trial in South Africa, Zimbabwe, and Argentina. Participants with previous pre-eclampsia and eclampsia received 500 mg calcium or placebo daily from enrolment pre-pregnancy until 20 weeks' gestation. Participants were parous women whose most recent pregnancy had been complicated by pre-eclampsia or eclampsia and who were intending to become pregnant. All participants received unblinded calcium 1·5 g daily after 20 weeks' gestation. The allocation sequence (1:1 ratio) used computer-generated random numbers in balanced blocks of variable size. The primary outcome was pre-eclampsia, defined as gestational hypertension and proteinuria. The trial is registered with the Pan-African Clinical Trials Registry, number PACTR201105000267371. The trial closed on October 31, 2017.

Findings

Between July 12, 2011, and Sept 8, 2016, we randomly allocated 1355 women to receive calcium or placebo; 331 of 678 participants in the calcium group versus 320 of 677 in the placebo group became pregnant, and 298 of 678 versus 283 of 677 had pregnancies beyond 20 weeks' gestation. Pre-eclampsia occurred in 69 (23%) of 296 participants in the calcium group versus 82 (29%) of 283 participants in the placebo group with pregnancies beyond 20 weeks' gestation (risk ratio [RR] 0·80, 95% CI 0·61–1·06; p=0·121). For participants with compliance of more than 80% from the last visit before pregnancy to 20 weeks' gestation, the pre-eclampsia risk was 30 (21%) of 144 versus 47 (32%) of 149 (RR 0·66, CI 0·44–0·98; p=0·037). There were no serious adverse effects of calcium reported.

Interpretation

Calcium supplementation that commenced before pregnancy until 20 weeks' gestation, compared with placebo, did not show a significant reduction in recurrent pre-eclampsia. As the trial was powered to detect a large effect size, we cannot rule out a small to moderate effect of this intervention.

We have created accessible, electronic and mobile health-based systems that can assist in the collection of essential quality health data, and innovative technologies that can assist in triaging, and responding to women based on their risk for complications.

Aimed at exploring whether we can predict risk in women based on their pathophysiological profiles, we have developed risk prediction models, most notably the fullPIERS (Pre-eclampsia Integrated Assessment of RisK Score) and miniPIERS (Pre-eclampsia Integrated Assessment of RisK Score) model.

In addition, our geo-spatial analysis utilizes geographical intelligence to construct geographical influences and how these are useful to inform different decision processes.

In the future, we plan to move beyond risk prediction to improve quality of care. Building off our PIERS research program, our miniPIERS model, and our PIERS On the Move (POM) mobile health app, we plan to create a suite of mobile health apps that will integrate our PIERS and miniPIERS into the mobile app delivery platform to not only predict adverse maternal health outcomes, but also to serve as a communication tool between healthcare workers and settings to improve on the quality of care offered to pregnant women.

Prediction of Adverse Maternal Outcomes in Pre-Eclampsia: Development and Validation of the FullPIERS Model

von Dadelszen P, Payne BA, Li J, Ansermino JM, Pipkin FB, Côté AM et al., for the PIERS Study Group

Background

Pre-eclampsia is a leading cause of maternal deaths. These deaths mainly result from eclampsia, uncontrolled hypertension, or systemic inflammation. We developed and validated the fullPIERS model with the aim of identifying the risk of fatal or life-threatening complications in women with pre-eclampsia within 48 hours of hospital admission for the disorder.

Methods

We developed and internally validated the fullPIERS model in a prospective, multicentre study in women who were admitted to tertiary obstetric centres with pre-eclampsia or who developed pre-eclampsia after admission. The outcome of interest was maternal mortality or other serious complications of pre-eclampsia. Routinely reported and informative variables were included in a stepwise backward elimination regression model to predict the adverse maternal outcome. We assessed performance using the area under the curve (AUC) of the receiver operating characteristic (ROC). Standard bootstrapping techniques were used to assess potential overfitting.

Findings

261 of 2023 women with pre-eclampsia had adverse outcomes at any time after hospital admission (106 [5%] within 48 h of admission). Predictors of adverse maternal outcome included gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations. The fullPIERS model predicted adverse maternal outcomes within 48 h of study eligibility (AUC ROC 0·88, 95% CI 0·84–0·92). There was no significant overfitting. fullPIERS performed well (AUC ROC >0·7) up to 7 days after eligibility.

Interpretation

The fullPIERS model identifies women at increased risk of adverse outcomes up to 7 days before complications arise and can thereby modify direct patient care (eg, timing of delivery, place of care), improve the design of clinical trials, and inform biomedical investigations related to pre-eclampsia.

MiniPIERS (Pre-Eclampsia Integrated Estimate of Risk): Development of a Clinical Prediction Model for Use in Low- and Middle-Income Countries (LMIC)

Payne B, Hutcheon JA, Qu Z, Haniff F, Bhutta Z, Biryabarema C, Duan T, Hall DR, Grobman WA, Groen H, Magee LA, Merialdi M, Mirembe F, Nakimuli A, Qureshi R, Sass N, Sikandar R, Steyn W, Widmer M, Zhou V, von Dadelszen P, PIERS Study Group

Introduction

Pre-eclampsia remains the second leading cause of maternal death globally, with most of these deaths occurring in LMICs. The burden of disease could be reduced with improved clinical management through the development of simple, low-cost tools that allow care providers to accurately predict adverse events within a timeframe that can inform and guide care.

Objectives

To develop and validate a clinical outcome prediction model for use in women with a hypertensive disorder of pregnancy (HDP) using only symptoms and clinical signs, to predict outcomes within 48 h of assessment.

Methods

This study used a prospective cohort design to collect data on women with an HDP at 7 International study sites. Women were included in the cohort if they had hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) with or without proteinuria (dipstick >1+ or >0.3 g/24 h) or suspected HELLP syndrome. Candidate predictor variables were selected that were a priori known to be measurable, reliable, and available in LMIC settings. The model was. developed using logistic regression analysis of all selected predictor variables against the dependent variable of death or severe maternal morbidity. Performance of the final model was assessed based on discrimination ability, stratification capacity and calibration.

Results

From July 1, 2008 to January 31, 2012, 1540 women were recruited to the cohort. 295 (19.2%) developed one or more components of the adverse maternal outcome at any time and 174 (11.3%) within 48 h of admission. The miniPIERS model includes the predictor variables: maternal weight on admission; the symptoms of chest pain/dyspnoea, headache, visual disturbances, epigastric pain/RUQ pain, nausea/vomiting; systolic BP; and dipstick proteinuria. The model performs accurately with an area under the receiver operating characteristic curve (AUC ROC) of 0.78 (95% CI 0.75, 0.80) (Fig. 1). Calibration and stratification capacity are good. When a predicted probability of 30% is used as a threshold for a positive test the positive likelihood ratio of the test is 7.18 (95% CI 5.32, 9.69) showing the model can be used as a rule in test for adverse maternal outcome.

Conclusion

The miniPIERS model accurately discriminates between women with a HDP who will and will not go on to develop an adverse event within 48 h of assessment. Next steps include final model refinement and internal and externalvalidation of the model.

The Incidence of Pregnancy Hypertension in India, Pakistan, Mozambique, and Nigeria: A Prospective Population-Level Analysis

Magee LA, Sharma S, Nathan H, Adetoro O, Bellad M, Goudar S et al.

Background

Most pregnancy hypertension estimates in less-developed countries are from cross-sectional hospital surveys and are considered overestimates. We estimated population-based rates by standardised methods in 27 intervention clusters of the Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials.

Methods and Findings

CLIP-eligible pregnant women identified in their homes or local primary health centres (2013–2017). Included here are women who had delivered by trial end and received a visit from a community health worker trained to provide supplementary hypertension-oriented care, including standardised blood pressure (BP) measurement. Hypertension (BP ≥ 140/ 90 mm Hg) was defined as chronic (first detected at < 0.05 considered significant). In 28,420 pregnancies studied, women were usually young (median age 23–28 years), parous (53.7%–77.3%), with singletons (≥ 97.5%), and enrolled at a median gestational age of 10.4 (India) to 25.9 weeks (Mozambique). Basic education varied (22.8% in Pakistan to 57.9% in India). Pregnancy hypertension incidence was lower in Pakistan (9.3%) than India (10.3%), Mozambique (10.9%), or Nigeria (10.2%) (p = 0.001). Most hypertension was diastolic only (46.4% in India, 72.7% in Pakistan, 61.3% in Mozambique, and 63.3% in Nigeria). At first presentation with elevated BP, gestational hypertension was most common diagnosis (particularly in Mozambique [8.4%] versus India [6.9%], Pakistan [6.5%], and Nigeria [7.1%]; p < 0.001), followed by pre-eclampsia (India [3.8%], Nigeria [3.0%], Pakistan [2.4%], and Mozambique [2.3%]; p < 0.001) and chronic hypertension (especially in Mozambique [2.5%] and Nigeria [2.8%], compared with India [1.2%] and Pakistan [1.5%]; p < 0.001). Inclusion of additional diagnoses of hypertension and related complications, from household surveys or facility record review (unavailable in Nigeria), revealed higher hypertension incidence: 14.0% in India, 11.6% in Pakistan, and 16.8% in Mozambique; eclampsia was rare (<0.5%).

Conclusions

Pregnancy hypertension is common in less-developed settings. Most women in this study presented with gestational hypertension amenable to surveillance and timed delivery to improve outcomes.

Evaluation of The PIERS on the Move Mobile Health Tool for Pre-Eclampsia Triage: The Users' Perspective

Payne B, Kinshella MLW, Sohail Bawani, Sheikh S, Hoodbhoy Z, Charanthimath U, Katageri G, Dunsmuir D, Vidler M, Magee LA, Bellad M, Mallapur A, Qureshi R, Ansermino JM, von Dadelszen P, CLIP Working Group (Canada)

Background

The PIERS on the Move (POM) mobile health (mHealth) application was implemented as part of a complex community health system intervention in the CLIP (Community Level Interventions for Pre-eclampsia; NCT01911494) Trials. In this context, community health workers (CHWs) were trained to use the app and to take on new clinical skills, such as measuring blood pressure and assessing symptoms.

Objective

To evaluate the perceived impact on pre-eclampsia knowledge, self-efficacy and CHW role from use of the POM app. Method: This study used mixed methods including closed and open-ended survey questions and focus group discussions (FGDs) based on the SALT (Stimulate, Appreciate, Learn, Transfer) approach. All health care workers who participated in the CLIP Trials in Pakistan and India were eligible to participate. A random sample, stratified by age and years of experience, was drawn to target participants for qualitative evaluation after completion of recruitment for the Trials. Survey results were summarized, and qualitative data analyzed using grounded theory.

Results

In India, 24 CHWs completed the survey and were interviewed. In Pakistan, 219 CHWs completed the survey and 18 participated in 3 follow-up FGDs. CHWs in both countries reported a high level of pre-eclampsia knowledge and self-efficacy. Qualitative data analyzed from the interviews in India and FGDs in Pakistan indicate a high level of job satisfaction with themes emerging related to positive ability to manage pregnancy complications; happiness with supporting healthy pregnancy and birth and satisfaction with new knowledge and responsibilities. Challenges reported included initial difficulties learning to use a smart phone and technical issues with the device itself (battery life and screen size).

Conclusions

This study supports the ability and desire of community health workers to use mobile health tools such as the PIERS on the Move app to support their performance of clinical tasks related to pre-eclampsia care.

Implementation of the PIERS on the Move Mobile Health App in the Community-Level Interventions for Pre-Eclampsia Trials

Payne B, Dunsmuir D, Qureshi R, Sevene E, Munguambe K, Goudar S, Bellad M, Mallapur A, Magee LA, Sharma S, Vidler M, Bhutta Z, Ansermino JM, von Dadelszen P, CLIP Working Group (Canada)

Background

The PIERS on the Move (POM) app was implemented as part of a complex health system intervention in the CLIP (Community Level Interventions for Pre-eclampsia; NCT01911494) Trials in India, Pakistan and Mozambique. POM guides community health workers through an antenatal/postnatal assessment and provides recommendations for referral to a nearby facility with immediate treatment with $MgSO_4$ and methyldopa when hypertension is detected, based on disease severity.

Objective

To evaluate the implementation of the POM app based on population coverage, compliance and recommendation acceptance.

Methods

As per the protocol, coverage was measured as the proportion of women receiving one or more POM home visit out of all pregnancies registered in the intervention area and compliance was measured as the proportion of women receiving the minimum standard of monthly POM home visits. Acceptance of recommendation and was summarized and rates of outcome for women in intervention areas with and without a recommendation presented.

Results

In total 21,416/36,077 eligible women received 151,893 POM visits (76.2% antepartum, 23.8% postpartum) during the CLIP Trials. Coverage was 90.0% in India, 56.6% in Pakistan and 61.2% in Mozambique. Compliance rates were 55.4% in India; 63.4% in Pakistan; and 77.0% in Mozambique. Rate of triage recommendation was 5.6% (1194/21,416) of the covered population in total. The primary reason for referral was non-severe hypertension. Women's acceptance of recommendations was 77.0% overall. In intervention clusters, the rate of adverse maternal outcomes in women who received recommendations compared to those who did not was higher in India (11.7% vs 4.3%) and Mozambique (11.3% vs. 7.7%) but similar in Pakistan (5.0% vs. 5.0%).

Conclusion

During the CLIP Trials there was good coverage and compliance and a high rate of community acceptance of triage recommendations after implementation of the POM

Risk Prediction Modelling for Obstetric Women in Intensive Care—The Collaborative Integrated Pregnancy High-Dependency Estimate of Risk (CIPHER) Global Study

Ryan H, Payne B, Walley K, Aarvold A, Hutcheon J, Lisonkova S, Lee T, Sharma S, Yong P, Cundiff G, Ansermino M, Seaward G, Lapinsky S, Bhutta Z, Qureshi R, Vasquez D, Ganzevoort JW, de Pont ACJM, Kallen M, Zhou V, Duan T, Geary M, Bowen M, Lambe E, Doyle A, McAuliffe F, O'Herlihy C, Hartigan L, Togal T, Demirkiran O, Lataifeh I, Tadros R, Wallac E, Crozier T, Barrett N, Goffman D, Chazotte C, Cecatti G, Magee LA, von Dadelszen P

Objectives

Currently there are no existing critical care outcome prediction models that accurately predict mortality in pregnant and postpartum women. Existing Intensive Care Unit (ICU) models overestimate pregnancy mortality risk, partly due to unique physiology. To help identify severely ill obstetric women at greatest risk of mortality or life-threatening morbidity, a novel outcome prediction model is required:

- Designed specifically for ICU-admitted obstetric patients
- Optimized for any cause of maternal morbidity/mortality
- Applicable to low and high-income settings.

Our objectives were to:

1. Identify variables which predict adverse outcome in critically ill pregnant and postpartum women
2. Develop an obstetric risk prediction model.

Method

Fourteen sites in a global collaborative study comprising 11 countries worldwide were enrolled. Comprehensive retrospective data were collected from participating tertiary centres for 797 pregnant or recently pregnant women (within 6 weeks of delivery) admitted to ICU for more than 24 hours from 2000–2010. Candidate predictor variables included demographics, symptoms, vital signs and laboratory measures. A risk prediction model, CIPHER, was developed to predict risk of death or severe morbidity (prolonged duration of organ support >7 days), in women admitted to ICU using step-wise multivariable logistic regression analysis. Risk of mortality was also calculated using the previously-published APACHE 2 score.

Results

Initial analysis on completed datasets of 507 cases from 12 sites showed a combined outcome rate of 19.5% (99/507); 9.9% (50/507) mortality and 15% (76/507) prolonged organ support. Following multivariable analysis, six variables were retained as significant predictors of adverse outcome. These included Glasgow Coma Scale and laboratory measurements of coagulation, liver and renal function with high area under the Receiver Operating Characteristic (ROC) curve of 0.89 (95% CI 0.85–0.93) for combined outcome. The CIPHER model had increased discrimination for mortality (AUC ROC 0.88, 95% CI 0.83–0.92) compared with APACHE 2 (AUC ROC 0.82, 95% CI 0.76–0.87) in this cohort.

Conclusions

The area under the ROC curve of the CIPHER model suggests excellent discrimination and future clinical utility. Developed specifically for obstetric patients, CIPHER contains fewer variables and has higher discrimination than APACHE 2, a commonly used general ICU prediction model. CIPHER is a promising first step in the development of a tool for predicting adverse maternal outcome in ICU-admitted pregnant and postpartum women. Ultimately, we hope to apply CIPHER in worldwide settings to reduce the burden of pregnancy-related morbidity and mortality

The Spatial Epidemiology of Maternal Deaths in the Gaza and Maputo Provinces in Mozambique

Makanga PT, Schuurman N, Sacoor C, Firoz T, Lee T, Vilanculo F, Munguambe K, BoeneH, Ukah UV, Vidler M, von Dadelszen P, Sevene E

Objectives

The social and physical environments of a woman have an effect on her maternal health. The social determinants of health framework has been proposed as the paradigm through which this assertion is explored. However, operationalizing this framework in a manner that links these determinants to actual maternal health outcomes has been a challenge. This study aimed to explore the associations between maternal deaths and social and environmental risk factors in 36 localities in Gaza and Maputo Provinces in southern Mozambique.

Method

Socio-economic variables were collected using a census of all households with women of reproductive age (aged 12–49). Women suspected to have died in pregnancy or postpartum were identified during the process. Geographic Information Systems was used to calculate environmental variables including driving times to health facilities and major roads, and the seasonal impact of floods on transport. Delphi consensus was conducted to prioritize all variables. Least Squares Regression was used to identify the statistically significant associations between the chosen variables and maternal mortality ratio for each locality. Geographically Weighted Regression was used to explore spatial non-stationarity of these associations.

Results

14621 pregnancies were reported as having occurred in the 12 months preceding the census and there were 83 deaths suspected to have occurred in pregnancy or postpartum, pending a verbal autopsy. Five socio-economic and environmental factors, aggregated for each locality, showed a statistically significant association with maternal deaths.

These factors are:

1. Absent head of household
2. Unavailability of private transport
3. Marital status
4. Driving time to the nearest major road
5. Driving time to the nearest primary health centre

Geographically weighted regression showed the spatial variation of the effect of each of these characteristics on maternal mortality.

Conclusions

The socio-cultural and physical environment influence the likelihood of maternal-related death. The framework used in this study is a contribution to operationalizing the measurement of social determinants of health and the effect they have on maternal outcomes. Showing the changing effect of environmental factors on maternal outcomes across space has potential to better target interventions, an approach that is especially crucial for low-resource settings.

Best practices suggest that women with severe hypertension, defined as blood pressure of ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic in pregnancy (or postpartum), should be treated with antihypertensive therapy. The World Health Organization (WHO) 'Prevention and Treatment of Pre-eclampsia and Eclampsia' report strongly recommend use of antihypertensive therapy for treatment of severe hypertension during pregnancy, because treatment of severe hypertension in pregnancy or postpartum decreases maternal risk, particular that of stroke. This has been demonstrated in the 'Confidential Enquiries into Maternal Deaths in the UK (2009-12) and through a similar process in South Africa. Antihypertensive therapy for non-severe pregnancy hypertension decreases the risk of severe hypertension and the associated risks.

PRE-EMPT studies have established evidence base for:

Which oral antihypertensive can be administered to safely decrease blood pressure and prevent adverse maternal, foetal and neonatal outcomes (the Gynuity Oral Antihypertensive Trial).

What is the effect on pregnancy complications of 'less tight control' (target diastolic blood pressure, 100 mm Hg) vs 'tight control' (target diastolic blood pressure, 85 mm Hg). pregnancy hypertension (the Control of Hypertension in Pregnancy [CHIPS] Trial).

Oral Antihypertensive Treatment of Severe Hypertension in Pregnancy—A Randomized Trial of 3 Regimens

Easterling T, Mundle S, Bracken H, Magee LA, von Dadelszen P, Winikoff B

Introduction

Management of severe hypertension in pregnancy requires prompt treatment—most commonly with intravenous medications. This strategy presents significant barriers to care, particularly in low resource environments.

Objective

To compare the effectiveness of three oral antihypertensive regimens in pregnant women with severe hypertension.

Methods

In an open-labeled trial in two hospitals in Nagpur, India, (NCT01912677), pregnant women ≥ 28 weeks' gestation with sBP ≥ 160 mmHg or dBP ≥ 110 mmHg were randomized to:

1. nifedipine 10 mg orally repeated hourly up to 2 additional doses for sBP >155 mmHg or dBP >105 mmHg,
2. labetalol 200 mg orally repeated hourly for 2 additional doses as above, or
3. methyldopa 1000 mg as a single dose.

The primary outcome was achieving a sBP 120–150 mmHg and dBP 70-100mHg at 6 h without an adverse outcome or fetal compromise.

Results

894 women were randomized: nifedipine (n = 298), 83.2% achieved primary outcome, (0.7% required additional drugs); labetalol (n = 295), 77.3% achieved primary outcome, (3.1% required additional drugs); methyldopa (n = 301), 76.4% achieved primary outcome, (18.3% required additional drugs), (NvsMD p = 0.04) X2; (LvsMD p = 0.08), X2; (NvsL p = 0.07) X2. Without use of additional drugs, nifedipine and labetalol were superior to methyldopa, (P<0.001) X2. Nifedipine was associated with maternal tachycardia, (p<0.001) X2; persistence of headache, (p = 0.005) X2; and a greater likelihood of neonatal admission to the NICU, (NvsMD p = 0.01) X2; (LvsMD p = 0.6), X2; (NvsL p = 0.06) X2. $MgSO_4$ use was limited, 11.7%. The eclampsia rate was 0.1%. There were no maternal deaths or ICU admissions. 96% of infants were born alive; 95% of live-born were alive at discharge.

Discussion

Each regimen achieved some success. As a single agent, nifedipine and labetalol were superior to methyldopa. A structured approach of measuring BP and intervention with oral medications in a high risk environment achieved low rates of maternal and neonatal complications despite some differences in BP control across groups. This was achieved with a low rate of $MgSO_4$ utilization.

The Control of Hypertension in Pregnancy Study (CHIPS) Randomized Controlled Trial

Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Grulsin A, Helewa M, Hutton E, Lee SK, Logan AG, Ganzevoort W, Welch W, Thornton JG, Moutquin J, CHIPS Study Group

Objectives

Normalizing blood pressure in pregnancy may reduce maternal complications but increase adverse perinatal effects. CHIPS aimed to determine whether a higher (vs. lower) blood pressure target improves perinatal outcome, without compromising maternal safety in non-severe pregnancy hypertension.

Methods

In an open pragmatic international multicenter trial, women at 14+0-33+6 weeks gestation with non-proteinuric pre-existing or gestational hypertension, office diastolic BP (dBP) 90–105 mmHg (or 85–105 mmHg if on antihypertensives) and a live fetus were randomized to 'less tight' (target dBP 100 mmHg) or 'tight' control (target dBP 85 mmHg). The composite primary outcome was pregnancy loss or high level neonatal care for >48 h in the first 28 d of life, and the secondary, serious maternal complications before 6 weeks postpartum. Outcomes were compared between groups using logistic regression adjusted for key prognostic factors.

Results

Of 1030 women randomized, 987 (94 sites) were included in the analysis. 74.6% had pre-existing hypertension. Women in 'less tight' (n = 497) compared with 'tight' (n = 490) control had similar rates of adverse perinatal (31.4% vs. 30.7%; aOR 1.02 [0.77, 1.35]) and maternal outcomes (3.7% vs. 2.0%; aOR 1.74 [0.79, 3.84]), despite higher mean dBP by 4.6 mmHg (95% confidence interval 3.7, 5.4). Severe hypertension (≥160/110 mmHg) developed more frequently in 'less tight' (vs. 'tight') control (40.6% vs. 27.5%; aOR 1.80 [1.36, 2.38]).

Conclusions

'Less tight' (vs. 'tight') control did not improve perinatal outcome but did result in more severe hypertension. Our results do not support 'less tight' control of non-severe pregnancy hypertension.

The Control of Hypertension in Pregnancy Study (CHIPS) Randomized Controlled Trial—Is the Type of Antihypertensive Important?

Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer S, Gafni A, Grulsin A, Helewa M, Hutton E, Lee SK, Logan AG, Ganzevoort W, Welch W, Thornton JG, Moutquin J, CHIPS Study Group

Objectives

The CHIPS Trial (ISRCTN 71416914, http://preempt.cfri.ca/CHIPS) randomized women with non-severe pregnancy hypertension to a diastolic blood pressure (dBP) target of 100 mmHg ['less tight' (LT) control] vs. 85 mmHg ['tight' (T) control]. LT was associated with no perinatal benefit, but more severe maternal hypertension. Labetalol was the recommended post-randomization antihypertensive. We aimed to:

1. Determine whether the difference in outcomes between LT vs. T control depended on antihypertensive used;
2. Compare pregnancy outcomes, taking into account allocated group, between women taking methyldopa and those taking labetalol, the two most commonly used antihypertensives in CHIPS.

Methods

Logistic regression was used for comparisons outlined in objectives 1 and 2. Both analyses adjusted for the influence of baseline factors, including use of any antihypertensive therapy at randomization.

Results

Of 987 women in CHIPS, labetalol (but not methyldopa) was taken by 433/837 women on antihypertensive therapy [186 (LT) vs. 247 (T)] and methyldopa (but not labetalol) by 223/837 [98 (LT) vs. 125 (T)]. Following adjustment:

1. ORs for outcomes in LT vs. T control were similar between antihypertensive groups, but
2. methyldopa use was associated with a reduction in some outcomes (Table).

Additional sensitivity analyses had a trivial impact on results.

Conclusions

In this secondary analysis of CHIPS data, outcomes for LT vs. T control were not dependent on use of methyldopa or labetalol. The non-randomized comparisons between methyldopa and labetalol are subject to residual confounding, but there is no evidence that women treated with methyldopa (vs. labetalol) had inferior outcomes.

Community Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trials (cRCTs) were conducted from Feb 2014 – Feb 2017 in Karnataka, India (cRCT, 12 clusters), Sindh, Pakistan (cRCT, 20 clusters), Maputo and Gaza provinces, Mozambique (cRCTs, 12 clusters) and in Nigeria as an implementation study (5 clusters).

The aim of the CLIP Trials (NCT01911494), was to reduce the burden of deaths and illness in mothers and babies through community-level education, case identification, monitoring, and treatment of pregnancy hypertension.

The intervention

The CLIP Trials package included community engagement, regular monitoring of pregnancies by community health care providers, community level treatment with magnesium sulphate and oral methyldopa and recommendation for referral to higher level health facilities for identified high risk women.

Implications of the Results

- These results offer critical window into understanding the effectiveness of community-based interventions for addressing maternal and perinatal outcomes in three different geographies at varying stages of development in sub Saharan Africa and South Asia.
- The CLIP results offer community-ascertained and physician-reviewed population level rates of maternal and neonatal morbidities.
- Using data from blood pressure measured in women's homes, we have been able to ascertain community rates pregnancy hypertension.

The Community-Level Interventions for Pre-Eclampsia (CLIP) Trials in Mozambique, Pakistan and India: An Individual Participant Data Meta-Analysis

von Dadelszen P, Bhutta ZA, Sharma S, Bone J, Singer J, Wong H, Bellad M, Goudar S, Lee T, Li J, Mallapur A, Munguambe K, Payne B, Qureshi R, Sacoor C, Sevene E, Vidler M, Magee LA, CLIP Trials Working Group

Background

In less-developed countries, adverse maternal and perinatal events associated with pre-eclampsia may be reduced by community-based, mobile health (mHealth)-supported task sharing of early detection, interventions and transport to facility for women with pregnancy hypertension

Methods

In an a priori-designed individual participant data meta-analysis (PROSPERO CRD42018102564) of the Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trials (in Mozambique, Pakistan, and India; NCT01911494; 2014-2017), de-identified data were pooled, and multi-level modelling was undertaken. Included were consenting unselected pregnant women. The intervention comprised community engagement, mHealth-supported, community health worker-led early detection, initial treatment and referral of hypertensive women to facility. The primary outcome was a composite of maternal or perinatal mortality or morbidity. Sensitivity analyses included evaluation of temporal trends.

Findings

The primary outcome occurred in 7871/32,990 (24·4%) vs. 6516/29,698 (21·9%) pregnancies in 22 intervention and 22 control clusters, respectively (adjusted odds ratio [aOR] 1·17 (95% confidence interval 0·90-1·51); p=0·24). A temporal reduction in the primary outcome (by at least 12% odds per quarter) and its maternal (by at least 21% odds per quarter) and perinatal components (by at least 4% odds per quarter) was observed in both arms; the reduction was more rapid in intervention (vs. control) clusters for the primary outcome (p<0·001) and perinatal outcomes (p=0·002).

Interpretation

The CLIP intervention did not reduce a composite of adverse maternal and perinatal outcomes. However, these outcomes were reduced over time, by a large degree, in both trial arms, suggesting that the trial created learning health systems. This large effect may have masked a differential benefit of the CLIP intervention noted in the temporal analyses that was limited to the more vulnerable health systems of Pakistan and Mozambique and not Karnataka, India. The CLIP intervention could be considered for integration into primarily facility-focussed vulnerable health system strengthening, including less-developed regions in India.

OUTCOMES	Comparison of Methydopa vs Labetolol			
	OR	95% CI		p
Primary Perinatal Outcome	0.64	0.41	1.00	0.049
Delivery <37 Weeks	0.55	0.35	0.85	0.008
Birth Weight <10th Centile	0.55	0.32	0.93	0.025
Secondary Outcome: Serious Maternal Complications	0.81	0.28	2.36	0.701
Severe Hypertention	0.51	0.32	0.84	0.008
Pre-eclampsia	0.55	0.36	0.85	0.007

Community-Level Interventions for Pre-Eclampsia (CLIP) in India: A Cluster Randomised Controlled Trial

Bellad M, Goudar S, Mallapur A, Sharma S, Bone J, Charantimath U, Katageri G, Ramadurg U, Ansermino M, Dunsmuir D, Honnungar N, Karadiguddi C, Kavi A, Kodkany B, Lee T, Li J, Nathan H, Payne B, Revankar A, Shennan A, Singer J, Tu D, Vidler M, Wong H, Bhutta Z, Magee LA, von Dadelszen P, CLIP India Working Group

Background

Pregnancy hypertension is associated with 7·1% of maternal deaths in India. Task-sharing care to community health care providers (Accredited Social Health Activists [ASHAs] and Auxiliary Nurse Midwives [ANMs]) may reduce adverse pregnancy outcomes related to delays in triage, transport, and treatment. The objective of the Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trial (NCT01911494) was to reduce by 20% a composite of maternal, fetal, and new-born mortality and major morbidity.

Methods

The CLIP India trial recruited pregnant women in 12 clusters in Belagavi and Bagalkote, Karnataka. The CLIP intervention (6 clusters) consisted of community engagement, ASHA- and ANM-provided mobile health-guided clinical assessment, initial treatment, and referral to facility. Data were collected using the population-based Maternal Newborn Health Registry. Treatment effect was estimated by multi-level logistic regression modelling, adjusted for baseline variables of prognostic significance. Analyses included evaluation of temporal effects (specified a priori) and adjustment for baseline event rates (post-hoc).

Findings

All 14,783 recruited pregnancies (7,839 interventions, 6,944 controls) were followed-up. The primary outcome did not differ between intervention and control arms overall (adjusted odds ratio, aOR 0·92 [95% confidence interval (CI) 0·74, 1·15]; p=0·47; intraclass correlation coefficient 0·013), or after adjustment for outcome rate in the first six months of the trial (aOR 0·97 [95% CI 0·71, 1·31], p=0·83). In both arms, a temporal reduction in the aOR was observed (quarterly aOR 0·98, 95% CI [0·96-1·00], p=0·03), without difference between trial arms (-0·01 [-0·05, 0·04], p=0·81).

Interpretation

Community-level interventions for pre-eclampsia did not improve maternal, fetal, or newborn mortality or major morbidity. However, in both trial arms, there was a significant temporal reduction in adverse outcomes that may have been related to data monitoring-based continuous quality improvement.

Community-Level Interventions for Pre-Eclampsia (CLIP) in Pakistan: A Cluster Randomised Controlled Trial

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Background

In Pakistan, pregnancy related hypertension is an important contributor to maternal, fetal, and neonatal mortality. Its early detection and initial management may be possible by Lady Health Workers (LHWs) but evidence as to its feasibility and benefit is lacking.

Objective

To reduce by 20% a composite of maternal, fetal and newborn mortality and major morbidity through LHW facilitated community engagement and package of interventions to diagnose and stabilize cases of pre-eclampsia.

Methods

The Pakistan Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trial (NCT01911494) recruited pregnant women in 20 union councils (clusters) in districts Matiari and Hyderabad of rural Sindh. Public sector LHWs in intervention clusters (N=10), were provided cell phones and engaged the community, recruited pregnant women and undertook mobile health-guided clinical assessment for pre-eclampsia, initial treatment and referral to facilities as required. Surveillance data were collected by independent quarterly household surveys to assess pregnancy and birth outcomes. The primary outcome was a composite of maternal, fetal, and newborn mortality and major morbidity. Treatment effect was estimated by multi-level logistic regression modelling, adjusted for baseline variables of prognostic significance. Analyses included adjustment for baseline event rates (post-hoc) and evaluation of temporal effects (specified a priori).

Findings

We recruited 39,444 women in intervention (N=20,264) and control clusters (N=19,180) with minimal loss to follow-up (3·7% vs. 4·5%, respectively). The primary outcome did not differ between intervention (26·6%) and control (21·9%) clusters (adjusted odds ratio, aOR, 1·20 [95% confidence interval (CI) 0·84, 1·72]; p=0·31). Adjusting for baseline event rates (8.2% higher in intervention (vs. control) clusters), resulted in a significant intervention-related decrease in the primary outcome (aOR 0·71 [0·53, 0·95); p=0·02). The aOR of the primary outcome fell in each three-month epoch in both intervention (aOR 0·79 [0·76-0·82]; p <0·001) and control (aOR 0·83 [0·79-0·86]; p<0·001) clusters; the rate of fall was more rapid in intervention clusters (p=0·12).

Interpretation

The CLIP Pakistan trial was associated with temporal improvement in a composite of maternal and perinatal mortality/morbidity that was greater in intervention clusters, suggesting benefits of both quarterly household surveillance (common to both trial arms), and the intervention itself. The intervention was well accepted by the community and implemented by the LHW program. Beneficial effects may have been obscured by baseline differences between trial arms, or constraints imposed on implementation of the intervention by limited existing healthcare personnel and infrastructure.

Community-Level Interventions for Pre-Eclampsia (CLIP) in Mozambique: A Cluster Randomised Controlled Trial

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Background

Pregnancy hypertension is the third leading cause of maternal mortality in Mozambique, and an important contributor to fetal and neonatal mortality. Early detection and initial management of pregnancy hypertension by community health workers (CHWs) could improve associated maternal and perinatal outcomes.

Objectives

To reduce by 20% a composite of maternal, fetal, and newborn mortality and major morbidity.

Methods

The Mozambique Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised controlled trial (NCT01911494) recruited pregnant women in 12 administrative posts (clusters) in Maputo and Gaza Provinces. The CLIP intervention (6 clusters) consisted of community engagement, CHW-led mobile health-guided clinical assessment and initial treatment (i.e., magnesium sulphate for pre-eclampsia and oral methyldopa for severe hypertension), and referral to facility, as appropriate. Data were collected in all clusters by six-monthly household surveillance. Treatment effect was estimated by multilevel logistic regression adjusted for baseline cluster- and individual-level factors of prognostic significance. Analyses included evaluation of temporal effects (specified a priori) and adjustment for baseline event rates (post-hoc).

Results

Of 15,013 women recruited, there were 15,120 pregnancies included in both intervention (N=7930) and control (N=7190) clusters, with little loss to follow-up (i.e., 2·0% vs. 2·8%, respectively). The primary outcome did not differ between intervention (1246, 15·7%) and control (1172, 16·3%) clusters (aOR 1·31, 95% confidence interval [CI] [0·70, 2·48]; p=0·40), even after adjustment for the baseline rate that was higher in intervention (vs. control) clusters (aOR 0·93, 95% CI [0·59, 1·46]; p=0·75). In both trial arms, there was a temporal decrease in the aOR of the primary outcome (p<0·001) without a difference between groups (p=0·12).

Interpretation

The CLIP intervention was not associated with an improvement in the primary outcome. However, there were temporal decreases in both intervention and control clusters, particularly for maternal morbidity, that raise the possibility that household surveillance was itself an intervention.

While the global health community realises the potential for mobile health (mHealth) interventions to improve maternal, fetal and neonatal outcomes in low-income and middle-income countries, the evidence is variable based on the vast number of strategies that fall under the aegis of mobile health.

We believe that mobile health can be used as a platform to enhance care in the community and at the facility. We have developed and tested an evidence-based and low-cost tool to improve diagnosis and management of pre-eclampsia (PIERS on the move (POM)), and a non-invasive device to measure blood oxygen saturation (Sensor Project).

Evaluating the Implementation of the PIERS on the Move Mobile Health App in the CLIP India Cluster Randomised Controlled Trial

Payne B, Bone J, Bellad MB, Sharma S, Goudar S, Mallapur A, Vidler M, Magee LA, von Dadelszen P, CLIP Working Group

Objective

The objective of this secondary analysis to examine the implementation and impact of the Piers On the Move (POM) mobile application intervention, and describe the relationship of varying doses of POM to pregnancy outcomes.

Design

Implementation of the POM mobile application was assessed by:

1. Describing intervention reach and compliance;
2. Estimating the impact of increasing exposure to POM (dose-response) on the trial composite primary outcome of maternal, perinatal or neonatal death or morbidity.

Methods

The PIERS on the Move (POM) mobile application was implemented in six intervention-arm clusters in India from February 2014 – October 2016, as part of the intervention for Community Level Interventions for Pre-eclampsia (CLIP) India Trial (NCT01911494). Pregnant women of age 15–49 in the communities were identified, enrolled, and eligible to receive POM-guided visits for antenatal or postnatal care. Of these women, those who had complete follow-up were included in the analysis. Demographic and outcome data were collected from the Maternal and Newborn Health Registry, and clinical data from the POM-guided home visits. Women were grouped according to the number of POM visits in intervention arm (low-dose =<4; high dose=>4 visits to compare baseline characteristics, patterns of care seeking and outcomes. Effect of dose on the incidence of CLIP primary outcome was estimated with a propensity score weighting to account for the effect of known confounders.

Results

In total, 14,738 pregnancies were enrolled in the CLIP India Trial (6944 control, 7839 intervention). Of these, 6034 pregnancies from the intervention arm had been followed up and were included in the analysis. 55,754 visits were completed in this cohort during the trial, reaching 91.6% eligible women in the intervention clusters. Women who received a high dose of POM visits were enrolled earlier in gestation than the low visit group. Women who received a high dose (≥4 visits) had a 3% lower risk then the low visit (<4 visit) group, 95% confidence interval (-9.25%, 2.61%).

Conclusion

Overall, the CLIP India trail did not show significant difference between arms on the composite outcome. The implementation of the POM may have mediated impact. Women who received high-dose of the mHealth intervention appear to be at a decreased risk for the primary outcome in the trial, although given the large confidence interval, we cannot attribute the risk difference with certainty to the high dose of POM visits. We cannot rule out the effect of unmeasured confounders on this relationship. Further investigation into task sharing using the PIERS on the Move application is warranted.

Evaluating the Implementation of the PIERS on the Move Mobile Health App in the CLIP Pakistan Cluster Randomised Controlled Trial

Payne B, Sheikh S, Hoodbhoy Z, Bone J, Sharma S, Vidler M, Bhutta Z, Magee LA, Qureshi R, von Dadelszen P, CLIP Working Group

Objective

The Community Level Interventions for Pre-eclampsia (CLIP) Trial in Pakistan took place from February 2014–2017, and tested the efficacy of triage and treatment of hypertension in pregnancy by Lady Health Workers (LHWs) using the PIERS on the Move (POM) mobile health application. The aim of this planned secondary analysis was to evaluate how the POM app was implemented within the trial.

Design

The objective was assessed by:

1. Describing intervention reach and compliance
2. Estimating the impact of increasing exposure to the POM (dose-response) on the trial composite primary outcome of maternal, perinatal or neonatal death or morbidity.

Methods

Demographic and outcome data used in this analysis were derived from quarterly household surveys and clinical data from home visits by LHWs using the POM app. All women recruited to the CLIP trial who had complete follow-up at the end of the trial were included. Women were grouped by number of POM visits in intervention clusters (low-dose = <4; high dose = ≥4 visits) to compare demographics, care seeking and outcomes. Effect of dose on the incidence of CLIP primary outcome was estimated through a multi-level logistic regression model with and without a propensity score weighting to account for the effect of known confounders.

Results

In total 39,444 pregnancies were enrolled in the CLIP Pakistan Trial (19,180 control; 20,264 intervention). 17,862 pregnancies in the intervention arm were included in this analysis. The LHWs completed 54,413 POM visits during the trial, reaching 10,350/17,862 (57.9%) eligible women in the intervention clusters. Women who received a high-dose (≥4 visits) were more educated, earlier in gestation at recruitment and more likely to seek formal antenatal care than those with less visits or in the control clusters (0 visits, by definition). Women with high-POM dose had a -4.0% absolute risk difference in the primary outcome (95% CI -2.5%, -5.6%) compared to those with a low-POM dose in the intervention clusters.

Conclusions

Overall, the CLIP trial did not show significant impact on the primary composite maternal and perinatal death or morbidity endpoint. Moderate coverage and compliance of the mHealth component of the intervention may have hampered impact. Women who received a high-dose of the mHealth intervention appear to be at a decreased risk for the primary outcome in the trial. We cannot rule out the effect of unmeasured confounders. Further investigation into task sharing using the PIERS on the Move application is warranted.

Evaluating the implementation of the PIERS on the Move Mobile Health App in the CLIP Mozambique Cluster Randomised Controlled Trial

Sevene E, Payne B, Bone J, Lee T, Sharma S, Munguambe K, Sacoor C, Vidler M, Magee LA, von Dadelszen P, CLIP Working Group

Objective

The objective of this secondary analysis to examine the implementation and impact of the Piers On the Move (POM) mobile application intervention, and describe the relationship of varying doses of POM to pregnancy outcomes.

Design

Implementation of POM was assessed by:

1. Describing intervention reach and compliance;
2. Estimating the impact of increasing exposure to POM (dose-response) on the trial composite primary outcome of maternal, perinatal or neonatal death or morbidity.

Methods

The PIERS on the Move (POM) mobile application was implemented in six intervention-arm clusters in Mozambique, as part of the Community Level Interventions for Pre-eclampsia (CLIP) Trial (NCT01911494). Pregnant women of age 12–49 in the communities were identified, enrolled, and eligible to receive POM-guided visits for antenatal or postnatal care. Demographic and outcome data were collected from the six-monthly cross-sectional household survey, and clinical data from the POM-guided home visits. Women were grouped according to the number of POM visits in intervention arm (low-dose <4; high dose ≥ 4 visits to compare baseline characteristics, patterns of care seeking and outcomes. Effect of dose on the incidence of CLIP primary outcome was estimated with a propensity score weighting to account for the effect of known confounders.

Results

7930 pregnancies were identified in the 6 intervention clusters, of which 6826 pregnancies had been followed up. 25,771 visits were completed in this cohort during the trial, reaching 59.9% eligible women in the intervention cluster. Women who received a high dose (≥4) POM visits were enrolled earlier in gestation than the low visit group. Women who received a high dose (≥4 visits) have an approximately 1.0% lower risk then the low visit (<4 visit) group, 95% confidence interval (-2.9%, 1.1%).

Conclusion

Significant efforts were made to provide POM-guided visits to 60% of identified pregnancies in the communities, though challenges of access persist. We explored factors that differ between the dose levels, and patterns were observed in gestational age at enrollment, and timeframe within the trial. Women who enrolled earlier in pregnancy likely had more opportunities to receive POM-guided visits, and women who enrolled in later phases of the trial may have benefited from logistical improvements. Women who received a high-dose of the mHealth intervention appear to be at a decreased risk for the primary outcome in the trial, although the risk difference is not significant. Further investigation into task sharing using the PIERS on the Move application is warranted.

Health Care Worker Evaluation of Implementing the PIERS on the Move mHealth Application with Lady Health Workers in Rural Pakistan

Kinshella MW, Sheikh S, Bawani S, Hoodbhoy Z, La M, Sharma S, Vidler M, von Dadelszen P, Qureshi R, Payne B, CLIP Working Group

Objective

PIERS on the Move (POM) is a mobile health application developed to support community health workers identification and management of women at risk of adverse outcomes from pre-eclampsia. The objective of this study was to evaluate the impact of using POM in Pakistan on Lady Health Workers' (LHWs) knowledge and self-efficacy related to caring for women with pre-eclampsia, and their perception of usefulness of the tool.

Design

An evaluation was designed for health care workers involved in the Community Level Intervention for Pre-eclampsia (CLIP) cluster randomized trial from 2014–2016 in Sindh province, Pakistan (NCT01911494). A semi-structured focus group guide was developed based on the Technology Acceptance Model (TAM), which theorizes that an individual's behavioural intention to use a system is determined by perceived usefulness and perceived ease of use. Focus group discussions engaged participant reflection using the SALT (Stimulate, Appreciate, Learn, Transfer) approach.

Method

Three key informant interviews were conducted with two Lady Health Supervisors and one Senior Medical Officer. Sixty-two LHWs were included in three focus group discussions. Discussions and interviews were conducted in the local Sindhi language and translated in verbatim first to Urdu then to English. Preliminary qualitative analysis was undertaken by the Pakistan and Canadian teams to create a coding framework for full qualitative analysis, which was completed using Nvivo12.

Results

LHWs found the POM app easy to use and useful for their work. They reported that is was a helpful repository for maternal health information and guide for counselling and management of pre-eclampsia. LHWs reported increased knowledge and confidence in their work. Availability of clinical homecare, including during postpartum, was felt to have positively impacted pregnant and postpartum women. Potential community level impacts included strengthening relationships between health care providers and communities and between LHWs and the health system. LHWs shared reports of earlier care-seeking and increased awareness of maternal health issues by community members. However, some LHWs also reported socio-economic and cultural barriers to implementation and well as program challenges around registration policies and misunderstanding of devices.

Conclusions

LHWs carry a large burden of responsibility for community health in rural Pakistan and appreciated the investment in their skills and capacity during the CLIP trial with the POM app. Investing in communications technology for community health workers may strengthen cohesiveness of the health system overall through improved referrals and follow up.

Community Health Worker Evaluation on the Implementation of the PIERS on the Move mHealth Application in Rural Mozambique

Boene H, Kinshella MW, Vala A, La M, Sharma S, Vidler M, Magee LA, von Dadelszen P, Sevene E, Munguambe K, Payne B, CLIP Working Group

Objective

mHealth is increasingly regarded as having the potential to support health service delivery by health workers in low-resource settings. Consequently, it is important to understand the impact of the PIERS on the Move (POM) mobile health application to inform implementation at scale. The objective of this study was to evaluate the impact of using POM in Mozambique on community health care workers' (CHWs) knowledge and self-efficacy related to caring for women with pre-eclampsia, and their perception of usefulness of the tool.

Design

An evaluation was designed for health care workers involved in the Mozambique Community Level Intervention for Pre-eclampsia (CLIP) cluster randomized trial from 2014–2016 in Maputo and Gaza provinces (NCT01911494). A structured survey was designed using themes from the Technology Acceptance Model, which describes the likelihood of adopting the technology based on perceived usefulness and perceived ease of use. The survey included 10 open-ended question eliciting experiences using the mHealth app.

Method

All CHWs (n=116) involved in the Trial were surveyed. Qualitative analysis was undertaken on the open-ended responses from the 43 CHWs from intervention clusters Who used POM; CHWs from control clusters did not use POM and were not asked the open-ended questions. Surveys were conducted in Portuguese and translated in verbatim to English for analysis. Preliminary analysis of open-ended responses was conducted to develop a coding framework for full qualitative analysis, which was completed using Nvivo12.

Results

Many community health workers found the POM app easy to use, useful in guiding their activities and contained important information for the communities. Community health workers reported increases in knowledge about pre-eclampsia and other pregnancy complications and increases in confidence, comfort and capacity to advise women on health conditions and deliver services. A number of community health workers shared that they felt more like a true health professional and cited that the training and POM app improved their relationships with pregnant women, community members and nurses. Program challenges include participants missing visits, distance and lack of transport to visit participants, stock out of some supplies and lack of reliable electricity. Systemic challenges included far distance to the health facility, lack of transport and nurse not present at the health facility.

Conclusions

Many of the community health workers reported that POM improved knowledge, self-efficacy, was empowering and strengthened relationships with the communities they serve. However, findings highlight the need to consider program and systematic challenges to implementation.

With learnings from the CLIP Feasibility studies, an important intervention in CLIP was to mobilise communities to address barriers to care. Our community engagement strategy morphed and adapted to meet each community's needs; in Mozambique for instance, village leaders got together to develop funds for emergency obstetric transport, and in Pakistan, men's groups were organized to increase awareness of pregnancy hypertension.

Community Engagement in the CLIP India Trial

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Objectives

The purpose of this study is to describe the process of community engagement in six clusters in the CLIP Trial in Belagavi and Bagalkote, Karnataka. In the CLIP India Trial (NCT01911494; 2014–2016), community engagement activities took place at different levels within the health system and were facilitated by community health workers-Accredited Social Health Activists (ASHAs) and ANMs (Auxiliary Nurse Midwives). A community engagement strategy was developed to increase awareness of pregnancy complications and improve care seeking and birth preparedness.

Method

At the village level, pregnant women, women of reproductive age and their family members were asked to attend meetings arranged by ASHAs every month. Large primary health centre (PHC) meetings, arranged by the medical officer, were held twice with support from central research team, and included community leaders from all the villages of the PHC and women of reproductive age and their families. At the sub-centre level, community and health system leaders were engaged by the ANMs. Medical officers, ANMs and CLIP central team delivered information.

Results

1,379 sessions were conducted with 39,619 participants (average 29/session). 215 [192,266] sessions were conducted per cluster. Pregnant women, women of reproductive age were present in all sessions, and mothers-in-law were active participants, engaged in 82.7% sessions. The following topics were discussed at all sessions: warning symptoms and signs of pregnancy complications, permission for women to seek care; identification of skilled birth attendant and of facility for delivery; transport and treatment funds, feedback mechanisms about adverse outcomes and the CLIP intervention.

Conclusions

Health workers in Karnataka State can function as key mobilisers for increasing awareness by targeting stakeholders in the community. High penetration of health promotion activities can be achieved by integrating it within the health system.

Community Engagement in The Community-Level Interventions for Pre-Eclampsia (CLIP) Mozambique Trial

Amosse F, Sevene E, Sharma S, Kinshella MW, Vidler M, Boene H, Payne B, Bhutta Z, Magee LA, von Dadelszen P, Munguambe K, CLIP Working Group

Objectives

Community engagement was undertaken to create awareness and action around pre-eclampsia and eclampsia in the Community Level Interventions for Pre-eclampsia (CLIP) Trials (NCT01911494). The purpose of this study is to describe the process of these community engagement activities in the CLIP Trial in Maputo and Gaza Provinces.

Method

In the CLIP Mozambique Trial (2014–2016), women of reproductive age and family members were convened by nurses and community health workers for health talks at local primary health centers and in community meetings. Community stakeholders were engaged by study staff. Community meetings were held bi-weekly in the study regions, led by community liaison officers. Data on attendance and topics covered were recorded in paper logs, which was subsequently entered into a local RedCap database and share with the co-ordinating centre.

Results

A total of 4,284 sessions were held with 10,328 participants over the trial period. 804 [459,902] sessions were conducted per region with an average of 5 participants at each session. Women of reproductive age were present in 3,943 sessions. Mothers-in-law participated in 309 sessions, while husbands/partners participated in 388 sessions. Key stakeholders were reached in 85 sessions. The key messages delivered included pregnancy warning signs, especially the hypertensive disorders; permissions to seek care; identification of skilled birth attendant and delivery facility; and transport and treatment funds.

Conclusions

The study demonstrates a robust process for community engagement in rural Mozambique. These activities highlight that raising awareness and action around maternal health and the hypertensive disorders of pregnancy can be facilitated at the community-level in rural and resource constrained settings.

Data Management Workflow in the Community-Level Interventions for Pre-Eclampsia (CLIP) Trials

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Objectives

The Community Level Interventions for pre-eclampsia (CLIP) Trial comprises three large independently powered cluster randomised trials in India, Pakistan and Mozambique (NCT01911494) coordinated by the central team at the University of British Columbia (UBC). Cross-sectional household-level surveillance was conducted to collect data quarterly (Pakistan), six-monthly (Mozambique) and prospectively (India). The objective of this study was data management workflow.

Method

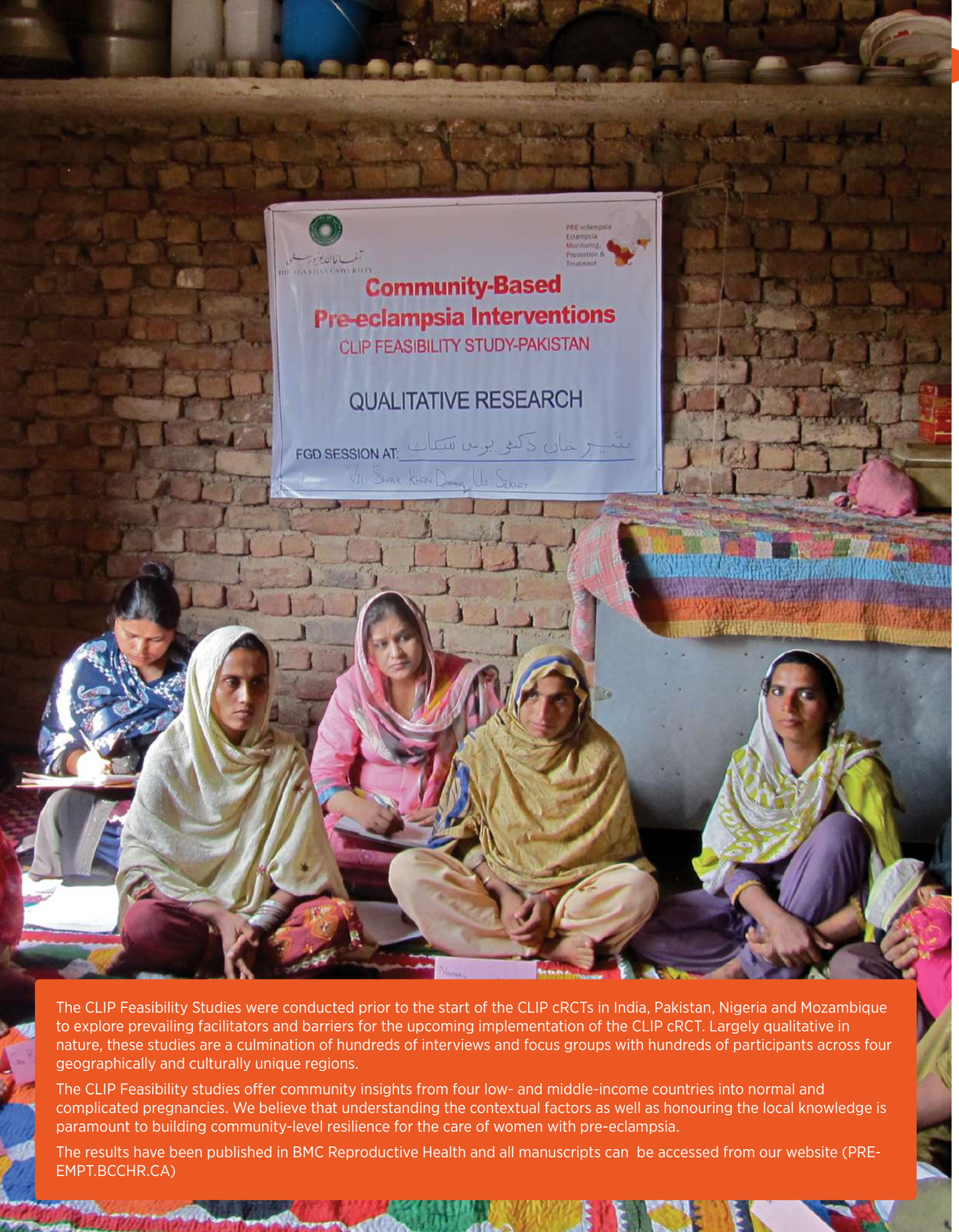
Data collection was done electronically in Pakistan (except in pilot phase) and Mozambique, via Android mobile apps created using LambdaNative in Pakistan, and Open Data Kit (ODK) with OpenHDS in Mozambique. Data collection in India on paper was followed by data entry into the Maternal and Newborn Health (MNH) Registry. Synchronization algorithms were built to transmit data to local REDCap servers. 14,777 pregnancies were collected in India, 39,444 in Pakistan, and 15,224 in Mozambique, and monitored centrally using custom built. NET and R programs driven by Windows Powershell and Tasks Scheduling.

Results

The CLIP data management workflow was mapped to provide a guide for this component of a complex trial. The workflow includes the resources and inputs (system platforms, developers, data managers, analysts), processes and event outputs (developing databases, training, data query, data integration, etc.), and expected outcomes including efficient data monitoring and data quality assurance. It helped create software tools for data management among community health workers, local teams, and central coordinating centre.

Conclusions

Three parallel data management processes were conducted in the three countries, designed to suit local infrastructure and needs. In a complex and large-scale trial such as the CLIP Trial, customization, automation, and quality monitoring are key components of data management. The functional workflow presented was effective and efficient for communication and local team training during the trial.



The CLIP Feasibility Studies were conducted prior to the start of the CLIP cRCTs in India, Pakistan, Nigeria and Mozambique to explore prevailing facilitators and barriers for the upcoming implementation of the CLIP cRCT. Largely qualitative in nature, these studies are a culmination of hundreds of interviews and focus groups with hundreds of participants across four geographically and culturally unique regions.

The CLIP Feasibility studies offer community insights from four low- and middle-income countries into normal and complicated pregnancies. We believe that understanding the contextual factors as well as honouring the local knowledge is paramount to building community-level resilience for the care of women with pre-eclampsia.

The results have been published in BMC Reproductive Health and all manuscripts can be accessed from our website (PRE-EMPT.BCCHR.CA)

Community Perceptions of Pre-Eclampsia in Karnataka State, India: A Qualitative Study

Vidler M, Charanthimath U, Katageri G, Ramadurg U, Karadiguddi C, Sawchuck D, Qureshi R, Dharamsi S, von Dadelszen P, Dermang R, Goudar S, Mallapur A, Bellad M

Objectives

The aim of this work is to describe understandings of pre-eclampsia among community members in two representative districts of Karnataka State, India. This includes use of local terminology, knowledge of causes, danger signs, outcomes, as well as practices related to prevention and treatment in the home.

Background

Despite global efforts, the rates of maternal mortality remain unacceptably high in less developed countries. To reduce the number of morbidities and mortalities it is critical to understand any given community's perceptions of pregnancy and its complications.

Methods

The study was conducted in Karnataka State, India in 2013. The study was designed to examine perceptions of pre-eclampsia using 14 focus group discussions with community stakeholder groups: community leaders (N = 27), male decision-makers (N = 19), female decision makers (N = 41), and women of reproductive age (N = 132).

Results

Although local terminology exists to describe convulsions and hypertension they are not specific to pregnancy. The community's perceived causes of eclampsia included: anemia, lack of medical adherence, not receiving tetanus toxoid injections and exposure to fire or water in pregnancy. Stress and tension along with a poor diet were felt to be responsible for the onset of pre-eclampsia. While the danger signs of eclampsia were not well known, there was a sense that sweating, tiredness, giddiness, swelling, and irritability are signs of pre-eclampsia. Folk remedies are still used for the treatment of seizures, such as providing the smell of onion, placing keys or iron in the hands, and squeezing the fingers and toes.

Conclusions

Improvements in maternal and perinatal health require strategies that involve the community and reflect their knowledge, attitudes and practices. Advocacy and educational initiatives should target knowledge gaps and incorporate cultural understandings of disease. This study achieved its aim of describing the knowledge, attitudes, and practices related to pre-eclampsia and eclampsia among communities in Karnataka State.

Community Perceptions of Pre-Eclampsia in Sindh, Pakistan: A Qualitative Study

Khowaja AR, Qureshi RN, Sheikh S, Zaidi S, Salam R, Sawchuck D, Vidler M, von Dadelszen P, Bhutta ZA

Objectives

This study aimed to explore community perceptions, and traditional management practices surrounding pre-eclampsia and eclampsia in Pakistan.

Background

They hypertensive disorders of pregnancy are the second leading cause of maternal mortality globally, of which >99% occur in less developed countries.

Methods

A qualitative study was conducted in Matiari and Hyderabad Sindh, Pakistan from February to July 2012. Altogether 26 focus group discussions were held with women of reproductive age and female decision makers (N = 173) and male decision makers (N = 65). The data was transcribed verbatim in Sindhi and Urdu, the data were then analyzed for emerging themes and sub-themes using QSR NVivo-version10.

Results

High blood pressure in pregnancy was mainly recognized as severe headache, and there was no local name to describe either this condition or the seizures of eclampsia. The majority of participants were aware that a woman can develop hypertension in pregnancy; however, progression of illness from pre-eclampsia to eclampsia was poorly understood. It was widely believed that mental stress and worries in pregnancy cause pre-eclampsia. Hypertension in pregnancy was considered to be dangerous as it could result in death of mother and baby; whereas, very few believed further complications could occur after birth. Seizures during pregnancy were thought to be caused by weakness, anemia, and stress. Many perceived seizures to be a health emergency for both mother and fetus. Self-medication for pre-eclampsia symptoms was common; in addition, some used alternative treatments for pre-eclampsia and eclampsia.

Conclusions

Community-based participatory health education strategies are recommended to address myths and misperceptions about the hypertensive disorders of pregnancy. These educational initiatives should include information on the presentation, progression, and treatment of pre-eclampsia and eclampsia.

Community Perceptions of Pre-Eclampsia and Eclampsia in Selected Communities of Southern Mozambique

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Objectives

The objective of this study was to describe the community understanding of pre-eclampsia and eclampsia, as a crucial step to improve maternal and perinatal health in southern Mozambique.

Method

This qualitative study was conducted in Maputo and Gaza Provinces of southern Mozambique. Twenty focus groups were convened with pregnant women, partners and husbands, matrons, traditional birth attendants, mothers and mothers-in-law. In addition, ten interviews were conducted with traditional healers, matrons, and a traditional birth attendant. All discussions were audio-recorded, translated from local language (Changana) to Portuguese and transcribed verbatim prior to analysis with NVivo 10. A thematic analysis approach was taken.

Results

The conditions of “pre-eclampsia” and “eclampsia” were not known in these communities in southern Mozambique; however, they were familiar with hypertension and seizures in pregnancy. Terms linked with the biomedical concept of pre-eclampsia were “high blood pressure”, “fainting disease” and “illness of the heart”, whereas “illness of the moon”, “snake illness”, “falling disease”, “childhood illness”, “frightening illness” and “epilepsy” were used for eclampsia. The causes of hypertension in pregnancy were thought to include mistreatment by in-laws, marital problems, and excessive worrying. Seizures in pregnancy were believed to be caused by a snake inside the woman’s body.

Conclusions

Local beliefs in southern Mozambique, regarding the causes, presentation, outcomes and treatment of hypertension and seizures in pregnancy are not aligned with the biomedical perspective. The community is mostly unaware of the link between hypertension and seizures during pregnancy. The numerous widespread myths and misconceptions demonstrate a need for increased community education in southern Mozambique regarding pregnancy and associated complications.

Community Perceptions of Pre-Eclampsia in Ogun State, Nigeria: A Qualitative Study

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Objectives

The objective of this study was to describe community perceptions of pre-eclampsia and eclampsia in Ogun State.

Background

Pre-eclampsia is a common complication of pregnancy and is responsible for high rates of morbidity and mortality, especially in less developed countries. While most studies related to pre-eclampsia and eclampsia has adopted a bio-medical model, this paper adopts a perspective, which recognizes the role of the socio-cultural environment.

Methods

The study was conducted in four Local Government Areas in Ogun State, Nigeria in 2012. Data were obtained through 24 focus group discussions with pregnant women (N = 94), mothers with children less than 5 years old (N = 95), male decision makers (N = 47), community leaders (N = 56), and traditional birth attendants (N = 36). In addition, nine in-depth interviews were conducted with the head of the local traditional birth attendants (N = 4), a local traditional birth attendant (N = 1), and community leaders (N = 4).

Results

We determined that there are no names for pre-eclampsia in the local language, Yoruba, although "hypertension" and "convulsion" as disease entities have local names that are independent of pregnancy status. The cause of pre-eclampsia was perceived to be due to depressive thoughts, and the cause of eclampsia was perceived to result from exposure to cold with a few implicating spiritual forces. While, there seemed to be no local treatment for pre-eclampsia apart from preventive practices, local treatments for eclampsia included the use of herbs, concoctions, incisions, and black soap.

Conclusions

This study shows that knowledge of pre-eclampsia and its progression to eclampsia is limited. It also reveals a gap in knowledge of the etiology and treatment of the condition. A holistic approach is recommended for sensitization at the community level, acquisition of educational skills by health workers, and the adoption of a community perspective as a sustainable approach to reduce the complications of pregnancy.

The Feasibility of Task-Shifting the Identification, Emergency Treatment, and Referral for Women with Pre-Eclampsia by Community Health Workers in India

Charanthimath U, Vidler M, Katageri G, Ramadurg U, Karadiguddi C, Sawchuck D, Qureshi R, von Dadelszen P, Dermang R, Magee LA, Goudar S, Mallapur A, Bellad MB, Community Level Interventions for Pre-eclampsia (CLIP) India Feasibility Working Group

Objectives

The objective of this study was to review the barriers and facilitators to task-shifting to community health workers the identification, emergency treatment and referral for women with pre-eclampsia to in India.

Method

The study was conducted in two districts of Karnataka State in South India. Fourteen focus group discussions were held in 2012–2013: six with women of reproductive age, two with male-decision makers, three with female decision-makers, and three with community leaders. In addition, one-to-one interviews were held with medical officers (N=2), private health care providers (N=2), senior health administrators (N=2), district health officers (N=2), and obstetricians (N=4). All data collection was facilitated by local researchers familiar with the setting and language. Data were subsequently transcribed and translated for thematic analysis using NVivo 10.

Results

There is strong community support for task-shifting of clinical assessments in pregnancy, such as blood pressure measurement. However, there was concern regarding community health workers' clinical knowledge, training and competence in applying interventions. Treatment of pre-eclampsia with oral antihypertensive and $MgSO_4$ in emergency cases by community health workers was generally supported; however, some practitioners and administrators had hesitations. The most prominent barriers to community health worker task-shifting in cases of pre-eclampsia, according to obstetric specialists and administrators was, the perception of insufficient training, unavailability of high-quality equipment (i.e. blood pressure devices) and their inability to appropriately diagnose and intervene.

Conclusions

Task-shifting to community health workers was largely supported by the community stakeholders and health care providers in South India. This strategy may be beneficial for early diagnosis and treatment of pre-eclampsia. This study identified facilitators and barriers to such task-shifting, overcoming these barriers are essential to effectively reduce maternal mortality and morbidity. Mobile health-based support may be important in this regard.

Potential for Task-Shifting to Lady Health Workers for Identification and Emergency Management of Pre-Eclampsia and Eclampsia at Community-Level in Pakistan

Salam RA, Khowaja AR, Qureshi RN, Sheikh S, Zaidi S, Sawchuck D, Vidler M, von Dadelszen P, Bhutta Z, CLIP Working Group

Objectives

Annually around 40 million mothers give birth at home without a skilled provider. Most of the maternal, perinatal and neonatal mortalities occur at the community level due to a lack quality care. This study aimed to explore the feasibility for task-shifting to Lady Health Workers for community level management of pre-eclampsia and eclampsia in Pakistan.

Method

A qualitative exploratory study was undertaken February–July 2012 in two districts, Hyderabad and Matiari, in the southern Province of Sindh, Pakistan. Altogether thirty-three focus group discussions were conducted, seven with Lady Health Workers, ten with Lady Health Supervisors, nine with women medical officers and seven with traditional birth attendants. The data were audio recorded, then transcribed verbatim in Sindhi for thematic analysis using NVivo 10. The Lady Health Worker curriculum and training materials were also reviewed and a self-administered questionnaire was completed by 457 Lady Health Workers for further information regarding their obstetric skills and training.

Results

Findings suggested that Lady Health Workers were responsible for registering pregnant women and conducting episodic home visits; however, they did not carry blood pressure devices or antihypertensive agents. In cases of suspected or confirmed hypertension they referred to the nearest public facility. Ninety-four percent of Lady Health Workers reported that families accept their health advice or referrals. Around 44% of the Lady Health Workers mentioned receiving training to identify pregnancy complications while 56% mentioned receiving training to refer or manage pregnancy complication. These findings suggest a need for periodic training regarding patient triage and the management of pre-eclampsia and eclampsia.

Conclusions

There is potential for task-shifting to Lady Health Workers for the identification and management of pre-eclampsia in Pakistan; however, the implementation needs to be combined with appropriate training, equipment availability and supervision.

Task-Shifting the Identification, Emergency Management and Referral of Women with Pre-Eclampsia in Mozambique, and Facility Capacity to Respond

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Objectives

Maternal mortality is an important public health problem in low-income countries. Delays in reaching health facilities and insufficient health care professionals calls for innovative communitylevel interventions. The study aimed to describe the possibility of task-shifting regarding initial screening and the initiation of obstetric emergency care for pre-eclampsia and eclampsia to community health care providers in Mozambique and to document facility readiness to respond to this task-shift.

Method

The study took place in Maputo and Gaza Provinces of southern Mozambique using qualitative and quantitative methods. The qualitative data were collected through focus group discussions and in-depth interviews with various community groups, health care providers, and policy makers. All discussions were audio-recorded and transcribed verbatim prior to thematic analysis using NVivo 10. Quantitative data were collected through self-administered questionnaires completed by community health workers and health facility assessment surveys, analysed using STATA version 13. Data collection was complemented by reviewing existing documents regarding maternal health and community health workers policies, guidelines, reports and manuals.

Results

Community health workers in Mozambique were skilled in identifying the danger signs of pregnancy; however, they were not able to manage emergencies, or effectively refer to the facility. Nurses at primary health centres were trained to manage eclampsia before referral. The necessary equipment for obstetric emergency care was not available in all primary level facilities: $MgSO_4$ was available in 83% primary level facilities, and 96% had an ambulance for referrals. Although community health workers and patients supported taskshifting, other healthcare providers highlighted the need to first address current barriers: lack of equipment, shortage of supervisors, and irregular drug availability.

Conclusions

This study showed that task-shifting screening and pre-referral management of pre-eclampsia and eclampsia is possible and acceptable by the community, but an effort should be in place to remove barriers at the health system level that could affect the appropriate management of the emergency cases.

We believe that solutions to the most complex problems affecting women's and children's health cannot be achieved in silos. The interconnectedness of what affects maternal, and perinatal and child health in low resourced settings calls on bold intersectoral and innovative approaches.

The goals of CoLab are three-fold. The overarching goal is to improve the health of women and their infants by facilitating research addressing adverse pregnancy outcomes. This would be accomplished by 1) facilitating access to data and biological samples for investigators worldwide, 2) by using the intellectual, data, and biological resources of the CoLab to perform large studies that could not be accomplished by any single centre, and 3) working to establish data and biological sample resources in developing countries.

An Online Data Collection System for Pre-Eclampsia Research to Enable Data Harmonization and Merging Across Studies, with Generation of Very Large, Statistically Powerful Datasets: The CoLab Database Project

Myatt L, Redman CW

Objectives

Pre-eclampsia is a complex syndrome with variable phenotypes that suggest differing underlying pathogenic pathways. Definition of phenotypes and pathways demands very large datasets achieved by combining data from multiple studies. This ideally requires that the data are harmonized before collection and prior to merging. To this end, we have presented a strategy of standardized data and biosample collection. To facilitate its adoption CoLab proposes that a standard database is created to be used online by interested investigators.

Methods

The database will collect minimal and optimal datasets as previously outlined, the latter being an extension of the former. It is designed for online data acquisition and storage but will be available as a standalone system. It will allow for site-specific add-ons to address local priorities and could also serve as the template for study of other adverse pregnancy outcomes and for clinical studies.

Results

The online database will be available free of charge to low- and middle-income countries with a minimal monthly maintenance charge, applicable to high income countries.

Conclusions

Acquisition of data in a standardized format across the globe will allow data to be pooled, achieving sufficient statistical power to discriminate sub-types of pre-eclampsia. These data could then be utilized to analyze underlying pathophysiology and to define phenotype outcomes and specific therapies.

Extending the Scope of Individual Patient Data Met Analyses: Merging Algorithms for Biomarker Measurements from Heterogeneous Laboratory Platforms. The CoLab Pre-Eclampsia Angiogenic

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Objectives

Circulating placental growth factor (PlGF) is a potential biomarker for pre-eclampsia. Prior studies show its limited precision in predicting or diagnosing pre-eclampsia, underscoring a common problem in biomarker data analyses in general—that large studies are needed to overcome clinical heterogeneity and to provide sufficient statistical power. Attaining such sample sizes often requires aggregation of cohorts. Different studies may use disparate platforms for laboratory analyses, complicating data merging. Here, we assessed whether PlGF concentrations could be merged across studies using inter-platform standardization.

Methods

Of 16516 pregnancies from 23 cohorts, 12,804 had at least one PlGF concentration (gestational age >20 weeks), analyzed using one of four platforms: R&D Systems, Alere-Triage, Roche-Elecsys or Abbott-Architect. Two merging algorithms, using Z-Score or Multiple of Median (MOM) transformations, were applied. A single Best Reference Curve (BRC), based on merged non-case PlGF concentrations, was constructed. Case-identification performance of the BRC for PlGF was compared to platform-specific curves.

Results

PlGF concentrations from different analytical platforms were merged (Z-scores marginally better than MOMs) and, overall, BRC case-identification rates out-performed platform-specific curves.

Conclusions

Laboratory measurements from different platforms can be standardised and merged to give reference curves from aggregated PlGF datasets. This method allows for analysis of PlGF as a diagnostic marker for pre-eclampsia and is generalisable to other medical questions, thereby extending the scope of individual studies to answer a variety of important medical questions.

SELECTED ABSTRACTS BY YEAR

2018

Association Between Maternal Age and Adverse Outcomes in Pre-Eclampsia

Ukah UV, Payne B, Hutcheon J, Magee LA, von Dadelszen P

Introduction

Studies have reported that women at more advanced maternal age are associated with a higher risk of developing pre-eclampsia and other pregnancy-related complications. However, fewer studies have explored the association of maternal age of women diagnosed with pre-eclampsia, with demographic characteristics, management and outcomes.

Objective

To examine pregnancy characteristics associated with maternal age for women admitted with pre-eclampsia and to compare the odds of increasing adverse maternal and perinatal outcomes with increasing age.

Methods

In total, 2427 women admitted with pre-eclampsia from 2003 to 2016 from tertiary hospitals in Canada, United Kingdom, Finland and USA were used for this study. Pregnancy characteristics were compared between women of 6 age groups: (i) <21 years old, (ii) 21–24 (iii) 25–29 (iv) 30–34 (v)35–39 and (vi) 40 years old and above. Odds ratios for developing adverse maternal and perinatal outcomes were calculated for increasing maternal age.

Results

Most women admitted with pre-eclampsia were between 30 and 34 years old. The gestational age at disease onset and blood pressure appeared to increase, while the prevalence of smoking decreased, as maternal age increased. Women at the extreme age groups (<21 years or P 40 years) were more likely to be multiparous. Similarly, the rate of antihypertensive medications uses appeared to be higher for the extreme age groups than for women between 29 and 39 years old. Women aged P 40 years were more likely to have multiple pregnancy than all other groups. There were no significant differences in the odds of experiencing an adverse maternal or perinatal outcome between different maternal age groups.

Discussion

Increasing maternal age was not associated with increased risk of adverse maternal or perinatal health outcomes for women admitted with pre-eclampsia. However, this study supports findings that maternal age is more strongly associated with late onset than early onset pre-eclampsia.

Comparison of Management of Women Admitted with Preterm Pre-Eclampsia Between Alerepetra and Non-Alerepetra Groups in the FullPIERS External Validation Data

Ukah UV, Payne B, Hutcheon J, Magee LA, von Dadelszen P

Introduction

There is uncertainty regarding expectant management of pre-eclampsia especially on administration of antenatal corticosteroids and prolongation of pregnancy. Management often varies depending on location and associated guidelines, even among high-income countries.

Objective/Hypothesis

To compare management of women admitted with pre-eclampsia in the PETRA site (USA) versus non-PETRA sites (Canada, UK and Finland) according to a risk prediction probability fullPIERS) for women admitted with pre-eclampsia.

Methods

We used data derived from the external validation dataset of the fullPIERS risk prediction model for pre-eclampsia. The fullPIERS probability of experiencing an adverse maternal outcome for each woman was calculated and women were grouped into <10%, 10–29% and 30% probabilities. Women admitted with preterm pre-eclampsia were then grouped according to data collection sites (PETRA vs Non PETRA) and their management and outcomes were compared.

Results

Majority of the women (82%) were classified into the low-risk group had term pre-eclampsia and 5.5% into the high risk group. Women in NonPETRA data appeared to be older, smoke more and admitted at a later gestational age than PETRA data across all PIERS probability ranges. There was lower administration of corticosteroid and antihypertensive for women but higher administration of $MgSO_4$ for women in PETRA data compared to NonPETRA sites. The women in the PETRA data were also more likely to have a shorter admission to delivery for women except in the highest PIERS risk range. There was no clear pattern in difference between the two groups for the occurrence of adverse maternal and perinatal outcomes except for smaller babies in the PETRA group.

Discussion

These findings show variation in pre-eclampsia management between the USA and other high-income countries (Canada, UK and Finland). However, it is unclear if and how these managements affect pregnancy outcomes for women admitted with pre-eclampsia suggesting the need for further studies.

Confidential Review of Maternal Deaths in the Community-Level Interventions for Pre-Eclampsia (CLIP) Mozambique Trial

Arion K, Aukes AM, Sharma S, Lee T, Li J, Payne B, Vidler M, von Dadelszen P, Magee LA, CLIP UBC Working Group

Introduction

Computer based algorithms, such as the WHO's verbal autopsy tool (InterVA), are often used to attribute cause of death (COD) in low-resource settings despite their variable agreement with physician review. After a large-scale community-level intervention trial for pre-eclampsia in Mozambique, maternal deaths were assessed in order to identify COD and barriers to care.

Objective

To compare COD for women who died in the Community Level Interventions in Pre-eclampsia (CLIP) Mozambique Trial (NCT01911494), 2015–2017, by physician review vs. the InterVA output.

Methods

Two physicians independently reviewed maternal mortality data from the trial (i.e., verbal autopsy [2012 WHO Instrument], baseline data and outcomes, and in the intervention arm, data from a mobile health application that included blood pressure readings), and assigned COD (by International Classification of Disease-Maternal Mortality). Disagreement was resolved by a third reviewer. Assigned COD was compared between physician review and InterVA output (set for high prevalence of malaria and HIV) using Cohen's Kappa.

Results

Of the twenty-one (0.14%) maternal deaths reported, most were postpartum (14/21, 66.7%), and due to indirect causes (12, 57.1%). Malaria during or prior to pregnancy (14/21, 66.7%) and HIV/AIDs (11/21 reported, 52.3%) were found to significantly affect pregnancy. The three most common causes of death were 1) non-obstetric complications, 2) obstetric hemorrhage and 3) pregnancy induced hypertension. Agreement between physicians and InterVA was fair, K = 0.40 [0.10–0.69]). Compared with InterVA, physicians were more likely to assign COD due to non-obstetric complications, specifically infectious diseases (9/21, 42.9%), including malaria and HIV/AIDS.

Discussion

Addressing infectious diseases, such as malaria and HIV/AIDs, obstetric hemorrhage and pregnancy-induced hypertension as most important causes of death is important to reduce maternal mortality in Mozambique. We found a fair level of agreement between COD assigned by InterVA and physician review at an individual case level, particularly for indirect causes of death. doi:10.1016/j.

Geographic Mediation of Dose for PIERS on The Move (POM) in the Community-Level Intervention for Pre-Eclampsia (CLIP) in Mozambique

Makanga P, Dube Y, Sharma S, Bone J, Saccor C, Makacha L, Payne B, Macuacu S, Vidler M, Vala A, Magee LA, Lee T, Sevene E, von Dadelszen P

Introduction

Travel time and distance to health facilities are known barriers for accessing maternal health care, particularly in Mozambique. Community health workers (CHWs) are responsible for extending the reach of antenatal care to isolated communities. Less is known about the geographical barriers faced by CHWs that may hamper their access to these isolated communities.

Objective

This study aimed to evaluate the extent to which related to dose of CHW-led PIERS On the Move (POM) study visit, delivered as an intervention in the Community Level Intervention for Pre-eclampsia trial (NCT01911494) in six clusters in Maputo and Gaza provinces.

Methods

Access to care was measured by calculating the walking time from each community to the nearest PHC using ArcGIS software. Dose of the intervention was measured by the average number of POM visits during pregnancy. A spatial autocorrelation analysis using the Moran I statistic was used to identify regional clusters of communities with both high and low doses of POM visits and how this compared with access to PHCs.

Results

Regional clusters (Moran I $p < 0.001$) of communities with poor access to PHCs had significantly lower doses of POM. The high dose areas had POM visits that were almost sevenfold higher than the POM visits in the low POM dose areas. The low dose areas required more that an additional hour of walking time to PHCs.

Discussion

Inequities in access to pregnancy related care persist, even when the reach of care through community health workers are implemented. Further strategies in addition to assigning community health workers are needed to counter the role of geography in mediating community interventions.

Is Longer Admission to Delivery for Expectant Management in Pre-Eclampsia Associated with Increased Risk of Maternal Outcomes?

Ukah UV, Payne B, Magee LA, Hutcheon J, von Dadelszen P

Introduction

Gestational age (GA) of pre-eclampsia onset is of clinical importance and affects management. Expectant management has been recommended for preterm pre-eclampsia to improve perinatal outcomes. However, prolonged pregnancy could expose the mother to higher risk of adverse outcomes.

Objective/Hypothesis

We sought to compare characteristics of women admitted with pre-eclampsia at different GAs and examine whether longer admission to delivery is associated with higher rates of adverse maternal outcomes.

Methods

Data used for this study were derived from the fullPIERS prediction model external validation cohort, which included 2427 women admitted with pre-eclampsia, diagnosed according to the SOGC. The data were collected from 2003 to 2016 from tertiary hospitals in Canada, United Kingdom, Finland and USA. Demographic characteristics, clinical management practices and rates of adverse outcomes for women admitted with preterm pre-eclampsia ((i) before 32 weeks, (ii) between 32 and 33+6 weeks and (iii) between 34 and 36+6 weeks) and were compared with (iv) term pre-eclampsia (> 37 weeks' gestation). The odds of experiencing adverse maternal outcomes with increasing admission to delivery interval was calculated.

Results

Majority of the women (46.4%) had term pre-eclampsia (Table 1). In general, women with preterm pre-eclampsia appeared to be younger, have multiple pregnancies and more likely to smoke compared with term pre-eclampsia. Women with preterm pre-eclampsia were also more likely to be administered treatment (corticosteroids, Magnesium sulphate and antihypertensive therapy). Longer admission to delivery was associated with a higher rate of adverse outcomes (OR 1.02 (95%CI: 1.00–1.03) although this association was non-significant after adjusting for GA at admission (OR adj: 1.0 (95%CI: 0.98–1.01) as well other demographic factors.

Discussion

Our findings supports reports that women with early onset pre-eclampsia have significantly worse maternal and perinatal outcomes despite receiving more interventions. However, the higher rates of maternal outcomes were not associated with longer admission to delivery interval.

Pregnancy Characteristics, Management and Outcomes According to Different Definitions of Pre-Eclampsia and Other Hypertensive Disorders of Pregnancy

Ukah UV, Magee LA, Payne B, Hutcheon J, von Dadelszen P

Introduction

The classification of hypertensive disorders of pregnancies (HDPs) especially pre-eclampsia (PET) vary according to different guidelines. Pregnancy characteristics, management and outcomes of women admitted with HDPs may differ by these definitions.

Objective

To compare characteristics, management and outcomes associated with different definitions of PET and other HDPs.

Methods

Dataset of 1972 women admitted with pre-eclampsia in a tertiary hospital in Canada from 2011 to 2016 was used for this study. Women were grouped into 8 groups:

1. Chronic hypertension (CH),
2. Gestational hypertension only; PET defined by
3. Hypertension and Hyperuricaemia only
4. Hypertension and accelerated hypertension only
5. Hypertension and proteinuria only
6. Hypertension and proteinuria only
7. PET defined by hypertension, proteinuria, and HELLP syndrome
8. PET defined by hypertension, proteinuria, and either hyperuricaemia or accelerated hypertension.

The demographic characteristics, management and adverse outcomes rates for the different groups of HDPs were compared.

Results

Majority of the women (32.3%) fell under group 8. Women in Group 1 were more likely to be older and multiparous but with the lowest rate of multiple pregnancy. Women in Group 2 were admitted at a later gestational age (GA) with the highest rate of smoking and had the least interventions (administration of antihypertensive, $MgSO_4$ and antenatal corticosteroids, and caesarian delivery); consecutively group 7 had the earliest GA at admission, lowest smoking rate and most administrations with the highest rates of multiple pregnancy and adverse maternal and perinatal outcomes.

Conclusion

The different definitions of HDPs were associated with differences with demographics, management and outcomes. Women in group 2 appeared to have the least adverse maternal and perinatal outcomes while women in group 7 (PET with both proteinuria and HELLP syndrome) had worse outcomes. These differences in outcomes by definitions may aid in directing the management of HDPs.

The Causal Pathway from Pre-Eclampsia to Postpartum Hemorrhage: A Hypothesis

Arion K, von Dadelszen P, Magee LA, miniPIERS Study Group

Introduction

Pre-eclampsia is a risk factor for postpartum hemorrhage (PPH). However, the mediator responsible for the progression of this relationship is unknown.

Objective

To evaluate the proposed mediating effects of placental abruption and thrombocytopenia on the pre-eclampsia and PPH relationship in a hypertensive obstetric population.

Methods

Data were derived from the miniPIERS (Pre-eclampsia Integrated Estimate of Risk) multi-country prospective cohort of 2081 women admitted with any hypertensive disorder of pregnancy in a less-resourced setting. Pre-eclampsia was defined broadly as hypertension with proteinuria or maternal end-organ involvement; PPH as postpartum bleeding requiring blood transfusion or hysterectomy; thrombocytopenia as <50_109/L platelets without blood transfusion; and placental abruption as clinically diagnosed. In a mediation analysis, the association between PPH and pre-eclampsia (compared with a group of women with chronic or gestational hypertension) was estimated using logistic regression, and then adjusted for concurrent diagnoses of thrombocytopenia, placental abruption, or both.

Results

Pre-eclampsia was confirmed in 1238 women (59.5%), of whom 19 (1.5%) had thrombocytopenia (OR 3.00, 95% CI [0.87– 10.32]; p = 0.08) and 57 (4.6%) had placental abruption (OR 2.51 [1.36–4.61]; p = 0.003). PPH occurred in 39 women (3.2%) with pre-eclampsia (ORPPH 2.01 [1.02–3.94]; p = 0.04); PPH risk was attenuated by adjustment for thrombocytopenia (OR 1.87 [0.95, 3.70]; p = 0.07), placental abruption (OR 1.86 [0.94, 3.68]; p = 0.07), or both (OR 1.74 [0.88, 3.45]; p = 0.11).

Discussion

In the miniPIERS cohort, a diagnosis of pre-eclampsia (compared to chronic or gestational hypertension) was associated with PPH. This association was attenuated by adjustment for thrombocytopenia, placental abruption, or both, suggesting that these factors could mediate the relationship between pre-eclampsia and PPH. These findings should be replicated in larger data sets.

The Prevalence of Chronic Hypertension in Pregnant Women: A Systematic Review and Meta-Analysis

Firoz T, Gillon T, Barreix M, Petzold M, Chou M, Magee LA, von Dadelszen P, Say L

Introduction

Within the construct of Sustainable Development Goal (SDG) target 3.1, improving the measurement of maternal health will be key to addressing negative maternal outcomes. As such there has been a shift in focus from maternal mortality to morbidity, and in particular, pre-existing maternal conditions, such as chronic hypertension. This is associated with a number of poor maternal and perinatal outcomes, but the global prevalence of chronic hypertension among pregnant women is currently unknown.

Objective

To determine the global prevalence and regional distribution of chronic hypertension in pregnant women

Methods

We completed a comprehensive search using several electronic data bases as well as a grey literature search using Google. Observational studies from 1990–2015 were included regardless of language. To obtain a pooled estimate of the prevalence of chronic hypertension in pregnancy, a random effects model was used. Potential factors that might affect the prevalence of chronic hypertension were defined a priori (study type, quality, period and country income level) and stratified analyses were conducted in STATA 14.1.

Results

Of 40 relevant studies, 22 were population-based and 30 were from high-income countries; one study was from a low-income country (Togo) and 9 from middle-income countries. The overall prevalence of chronic hypertension was 1.6%, 95% CI 0.12–0.20, without a difference between hospital-based and population-based studies. Chronic hypertension prevalence was lower in middle-income (0.6%, 95% CI 0.004–0.009) than high-income countries (1.7%, 95% CI 0.013–0.022) ($p < 0.001$). Prevalence also increased over time (from 1% to 2%, $p < 0.001$) and was higher in association with lower quality studies.

Discussion

This is the first study to provide a global estimate of the prevalence of chronic hypertension in pregnant women. However, there are several limitations including poor quality studies, predominance of studies from high-income countries and variable definitions of chronic hypertension.

Changes in Management of Pre-Eclampsia Between Two Time Periods at the BC Women's Hospital, Vancouver

Ukah UV, Payne B, Lee T, Vivien Cao, Hutcheon J, Li J, von Dadelszen P

Introduction

The fullPIERS model, which predicts adverse maternal outcomes in women with pre-eclampsia, was developed in 2010 in a cohort of 2023 women in high-resourced settings. The model was internally validated and had a good discrimination with an area under the receiver-operating characteristic curve of 0.88 (95%CI 0.84–0.92). Re-evaluating the model performance in the same setting at a later time (temporal validation) is necessary to ensure its clinical utility. Before temporally validating the model, it is useful to examine any changes in population characteristics and clinical management over time as these will give useful information on the potential performance of the model.

Objectives

To compare changes in risk of pre-eclampsia, adverse maternal and neonatal outcomes and management in one of the development settings (British Columbia (BC) Women's Hospital, Vancouver), between the time period prior to the fullPIERS model development (development data) and after the model development (temporal data).

Methods

Our study population included 1071 women admitted to the BC Women's hospital from 2003 to 2010 included in the model development, and 545 women admitted with pre-eclampsia in the same centre from 2012 to 2014. The demographic characteristics, management of pre-eclampsia and rates of adverse outcomes of the development and temporal data were compared using v2 and Mann Whitney test statistics.

Results

The women in the temporal cohort were more likely to be older, multiparous and had a later onset of pre-eclampsia compared with the development cohort (Table 1). The rate of adverse maternal outcomes within 48 h of admission in the temporal data was 4.2% similar to the development data (4.7%). There were no significant differences in the rates of adverse perinatal outcomes. Regarding the treatment and management of pre-eclampsia, the rate of administration of antihypertensive medication and $MgSO_4$ did not differ between the two groups. However, women in the temporal data were more likely to have a shorter admission-to-delivery interval compared with the development cohort.

Development and Testing of Pictograms for the Symptoms of Pre-Eclampsia in Ogun State, Nigeria Pre-Eclampsia in Low- and Middle-Income Countries

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Introduction

According to the World Health Organization, there were an estimated 45,000 maternal deaths in Nigeria in 2015; where pre-eclampsia was one of the leading causes. Pregnant women, families and the wider communities frequently show inadequate health knowledge of pregnancy complications which may contribute to high rates of mortality and morbidity. Poor knowledge of complex conditions such as pre-eclampsia is of particular concern. There are no universally recognized pictorial aides for the danger signs in pregnancy. To address this gap, pre-eclampsia specific pictograms were developed for use in the Community Level Interventions for Pre-eclampsia (CLIP) project. These were designed to educate pregnant women and relevant community decision-makers regarding these danger symptoms.

Objectives

1. To develop culturally-relevant pictograms of the symptoms of pre-eclampsia.
2. To evaluate the appropriateness and understanding of these pictograms amongst pregnant women of south-western Nigeria.

Methods

Twelve pictograms were designed to represent the danger symptoms of pre-eclampsia: abdominal pain, chest pain, nausea, vomiting, seizure, stroke, unconsciousness, vaginal bleeding, visual disturbances, headache, and finally two images to represent shortness of breath. Symptoms were selected based on those shown to be predictive of adverse maternal outcomes as well the consequences of pre-eclampsia. Pictograms were developed from literature review and consultation with clinical experts, January–June 2012. Evaluation of pictograms was conducted in Ogun State, Nigeria in September 2012. Two focus groups and seventeen interviews were conducted with pregnant women in Nigeria to beta-test the twelve draft images and subsequently updated based on the feedback of the 41 participants.

Results

Pregnant women had difficulty interpreting most pictograms when asked in the absence of additional information: 23 (56%) misinterpreted the image for abdominal pain, 34(83%) and 27(66%) for the two images depicting shortness of breath, 22(54%) for the image of chest pain, 26(63%) for the image of nausea, 26 (63%) for the image of seizures, 18(44%) for the image of stroke, 31 (76%) for the image of unconsciousness, 15(37%) for the image of visual disturbances, 8(20%) for the image of vaginal bleeding. However, all participants correctly identified the symptoms depicted in pictograms for headache and vomiting. Participants provided recommendations that were implemented to improve the pictograms, such as changes in facial expression and the placement of hands.

Conclusion

These findings suggest that women understood only a few of the tested pictograms when shown in the absence of health information. Some pictograms were revised to improve understanding of the complications of pre-eclampsia. In addition, pregnant women should be provided these pictorial aides in conjunction with basic health teaching related to pregnancy and its complications.

Superimposed Pre-Eclampsia is Best Defined Broadly—Analyses from the CHIPS Trial (Control of Hypertension in Pregnancy Study)

Magee LA, von Dadelszen P, CHIPS Study Group

Background

Any definition of superimposed pre-eclampsia should identify women at increased risk of adverse outcomes.

Methods

In the CHIPS trial, women at 14 + 0 - 33 + 6 weeks with non-severe chronic or gestational hypertension and a live fetus were randomised to 'less tight' (target diastolic blood pressure [dBP] 100 mmHg) or 'tight' control (target dBP 85 mmHg). There was no between-group difference in the primary outcome (pregnancy loss or high level neonatal care for >48 h in the first 28 d), secondary outcome (serious maternal complications before 6 weeks postpartum), or pre-eclampsia defined restrictively (by new proteinuria) or broadly (by maternal symptoms, signs, or abnormal laboratory tests). 'Less tight' (vs. 'tight') control was associated with significantly more severe hypertension, platelets <100 x 109/L, and elevated liver enzymes with symptoms. We compared restrictive and broad pre-eclampsia definitions regarding identification of women with adverse outcomes.

Results

For 981/987 women in CHIPS with outcomes, 280 (28.6%) developed pre-eclampsia defined restrictively, and 464 (47.4%) pre-eclampsia defined broadly. The broad (vs. restrictive) definition had higher sensitivity but lower specificity and classification accuracy for all outcomes but severe hypertension (Table 1).

Conclusion

Superimposed pre-eclampsia broadly defined can better identify true cases of risk in hypertensive pregnancy, but the potential harm of increasing false positives requires contextualisation.

Mode of Delivery in CLIP Trials in Rural India, Mozambique and Pakistan: A Descriptive Summary

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Objectives

Caesarean rates are important to consider in the context of maternal and neonatal health because both very low rates under 5% and high rates over 10% are associated with adverse outcomes for mother and baby. Caesarean rates have dramatically risen around the world though unequal usage has been documented, especially in low- and middle-income countries. The objective of this study was to describe the mode of delivery in rural India, Mozambique and Pakistan.

Method

Rates of caesarean section, vaginal home birth, vaginal facility birth and instrumental facility birth in rural India, Mozambique and Pakistan were investigated through a secondary analysis of the data from the Community Level Interventions for Pre-eclampsia (CLIP) Trials (NCT01911494) conducted between 2014 and 2017. Women in the control arm who had delivered (excluding miscarriages) and had a follow up were included; analysis was done using R. A total of 5,337 deliveries from India (6 clusters), 6,161 from Mozambique (6 clusters) and 16,810 from Pakistan (10 clusters), were included.

Results

Among these women, the caesarean section rates were 23.1% (n=1,233) in India, 4.3% (n=262) in Mozambique and 16.1% (n=2,713) in Pakistan. 3.9% (n=208) in India, 8.4% (n=518) in Mozambique and 24.2% (n=4,068) pregnancies in Pakistan reported home-based vaginal births. For facility-based deliveries, the rates of instrumental deliveries were 0.7% (n=39) in India, 20.2% (n=1,247) in Mozambique and 4.6% (n=744) in Pakistan. For facility-based vaginal births, the rates were 72.2% (n=3,857) in India, 67.1% (n=4,134) in Mozambique and 55.1% (n=9,225) in Pakistan.

Conclusions

This study reveals that there can be great disparities in coverage even in rural settings. The rural areas of Pakistan and India in this study have higher than recommended caesarean rates while rates in the rural areas of Mozambique in this study were lower than recommended. Additionally, the findings from Pakistan included both high rates of caesareans as well as high rates of homebirths. This suggests the complexity of delivery modes in rural areas that warrants further exploration of contextual factors and socioeconomic determinants.

A Model for Engagement of Rural Communities in Pakistan Through Education Relating to Pregnancy

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Objectives

To describe a model of engaging with community stakeholders to educate them regarding complications of pregnancy in the context of the CLIP (Community-Level Interventions for Pre-eclampsia) Trials (NCT01911494). Key messages of the community engagement included warning symptoms and signs of pregnancy complications, particularly pre-eclampsia and eclampsia; permission for women to seek care; identification of skilled birth attendant and birthing facility; prior arrangement of transport and treatment funds; CLIP Trial protocol; and addressing barriers that may delay in seeking care.

Method

The CLIP Trial, conducted between February 2014 – December 2016 in Sindh, Pakistan, aimed to reduce hypertensionrelated adverse maternal and perinatal events using task-sharing for appropriate clinical management and referral. Trial-related community engagement (CE) activities were conducted with pregnant women, mothers-in-law and male stakeholders in the intervention clusters. Pregnant women enrolled in the CLIP Trials, and their families were engaged by the lady health workers during home visits while male community members were engaged through village meetings. Data on attendance and topics covered were recorded.

Results

During the Trial period, 17,484 CE sessions were organized across 10 intervention clusters. There were 16,691 CE sessions conducted for pregnant women and their families. There were 793 sessions organized for 2,168 male community stakeholders who included the heads of villages, landlords, social workers and religious and political leaders. Nearly all sessions covered all the key messages of CE outlined. The CE team reported that these sessions helped to increase the awareness regarding pre-eclampsia and other complications of pregnancy.

Conclusions

The findings suggested that engagement of male and female community stakeholders with the proposed strategy is a practical model to impact knowledge to a large number of participants regarding complications of pregnancy and childbirth in low-resource settings. For sustainability, the model should be incorporated within the existing health system through community level health care providers.

Adolescent Pregnancies in the Community-Level Interventions for Pre-Eclampsia (CLIP) Trials

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Objectives

The objective of this paper is to describe adolescent pregnancies enrolled in the Community Level Interventions for Pre-eclampsia (CLIP) Trial in Pakistan, India, and Mozambique.

Method

The study was conducted from 2014–2017 in Sindh Province, Pakistan, Karnataka State, India, and Maputo and Gaza Provinces, Mozambique. Eligible pregnant women were enrolled for participation in the Community Level Interventions for Pre-eclampsia (CLIP) Trials during household surveillance (NCT01911494). Eligible adolescents were defined as pregnant women aged 15–20 years in Pakistan and India and 12–20 years in Mozambique.

Results

In total 4,935 adolescents were enrolled: 1,059 in Pakistan (3% of total), 1,770 in India (12% of total) and 2,106 in Mozambique (15% of total).This mirrors the national rates to some degree: 10% in Pakistan, 22% in India and 42% Mozambique. Adolescents in CLIP were likely to deliver at a CEmOC facility in Pakistan (65%) and India (73%). In contrast, the rate of delivery at CEmOC facility in Mozambique was only 13%. Adolescents were likely to attend ≥4 ANC visits: 46.7% in Pakistan, 75% in India, and 49.7% in Mozambique. These pregnancies had a 5% rate of stillbirth in Pakistan, 3% in India, and 2% in Mozambique. Conclusions: Adolescent pregnancies remain common, particularly in Mozambique where they make up at least 15% of all pregnancies. Further efforts are needed to ensure equitable access to health services, including contraception.

Delivery of Enhanced Antenatal and Postnatal Surveillance in The CLIP India Trial

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Objectives

The objective of this study was to describe the delivery of the CLIP intervention by the community care providers, ASHAs (Accredited Social Health Activists) and ANMs (Auxiliary Nurse Midwives) in the CLIP India Trial (NCT01911494). 102 ASHAs were trained to deliver home-based supplementary antenatal and postnatal surveillance guided by a mhealth application embedded with a clinical risk prediction model, PIERS on the Move (POM). Special permission was obtained from the Government of Karnataka for ASHAs to measure BP.

Method

Clinical training included assessing signs of an emergency condition (unconsciousness, significant vaginal bleeding, stroke or seizure), and symptoms related to HDP, assessing proteinuria, and blood pressure using a semi-automated, validated BP device. 21 ANMs were further trained to administer either a loading dose of 10 g $MgSO_4$ i.m. and/or oral antihypertensives, as recommended. All data was entered electronically at the time of the visit,and transferred to a central REDCap server at UBC. Descriptive summaries were undertaken using R.

Results

7046 pregnancies received a home-based POM visit (median of 7 [3–13] visits per enrolled pregnancy). The ASHAs performed a total of 64,089 home visits and effectively measured BP in 63,698 (99.3%) visits, and proteinuria in 92.2% (6996 booking and hypertensive visits). 74 visits resulted in a recommendation for $MgSO_4$, and 67.6% of the times it was accepted by the patient and delivered by the ANM. No serious adverse events (signs of infection or hematoma at the injection site) were observed after community administration of loading dose of $MgSO_4$ for prevention of eclampsia.

Conclusions

ASHAs and ANMs were able to triage and treat high risk pregnancies effectively and safely within the CLIP Trial. This study provides data that provides evidence that task sharing is be a feasible solution to address health worker density challenges in rural and remote settings.

Understanding the Return to Functional Ability in Postpartum Women in Three Less-Developed Countries

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Objectives

The objective of this study was to gather information on recovery to functional ability during the postpartum period for women in the Community Level Interventions for Pre-eclampsia (CLIP) trials in India, Pakistan and Mozambique. In the CLIP Trials (NCT01911494), functional ability data were collected on enrolled postpartum women between 2014–2017 by cross sectional surveillance of households, undertaken quarterly in Pakistan, six monthly in Mozambique and prospectively in India. The data were gathered by interviewing respondents using a close-ended survey, developed in consultation with the local expertise.

Method

This tool evaluated eight dimensions of the woman's ability to 'take care of baby', 'wash baby's clothes', 'prepare meals', 'clean the house', 'get water', 'work in fields', 'go to market', and 'return to paid employment'. The respondents were asked to select the earliest time at which they could perform these tasks (India and Mozambique), or to select the perceived difficulty with which they could perform each task (Pakistan). The pre-specified time intervals were postpartum: within 3 days, between 4–7 days, between 8–14 days, between 2–4 weeks, between 4–6 weeks, and between 6 weeks – 3 months.

Results

We have developed a cohort of 21,448 total women: 4,886 in India, 2,694 in Mozambique, and 13,868 in Pakistan. All women in India were able to complete 'baby care' and 'walk about home' at 6 weeks postpartum. In Mozambique, women were able to complete 'baby care' and 'washing the baby' s clothes' fastest following delivery, whereas it took the most time for women to 'work in the fields' and 'return to work'. In Pakistan, the proportion of women being able to complete each task 'without difficulty increased over time, and to complete a task 'not at all' decreased over time.

Conclusions

The time it takes for recovery of functional ability in less- developed settings could provide an insight into the processes of care and delivery during pregnancy. This trend may reflect the level of difficulty of these tasks, or the women's priorities during the postpartum period. Cultural contexts are important to understand the data for instance, a majority of the women in India moved to their maternal homes and had support available, and thus did not answer any questions related to chores around the household. A life course approach towards women's health is crucial to achieve the sustainable development goals.

Factors Related to High Caesarean Use in Rural India, Mozambique and Pakistan

Kinshella MW, Bellad M, Sevene E, Qureshi R, Vidler M, Bone J, Li J, Goudar S, Munguambe K, Sacoor C, Sharma S, Payne B, Bhutta Z, Magee LA, von Dadelszen P, CLIP Working Group

Objectives

While discussions of increasing caesarean rates have looked at disparities between urban and rural settings, especially in low- and middle-income countries, this study examines factors associated with a higher likelihood of caesarean section deliveries in rural India, Mozambique and Pakistan.

Method

Factors associated with the higher likelihood of caesarean deliveries less developed settings were investigated through a secondary analysis of data from the CLIP Trials (NCT01911494) 2014–2017. Factors associated with C-section included were maternal age, parity, education level, private/public facilities where available, and female decision-making power. Relationship with an adverse outcome was not examined. Women who had delivered (excluding miscarriages) were included for analysis, which was undertaken using R. A total of 5,337 deliveries from India, 6,161 from Mozambique and 16,810 from Pakistan were included.

Results

In India, 68.9% of women who had a C-section completed primary education (51.6% of facility vaginal births). In Pakistan, 37.6% of women who had a C-section completed primary education (14.8% of facility vaginal births). In Mozambique, 72.5% of women who had a C-section completed primary education but low rates preclude conclusions. Among women who had a C-section in Pakistan, 62.6% delivered in a private facility. Maternal age and parity was not clearly associated with a higher likelihood of caesarean delivery. Female decision-making power was low across all women with modes of delivery for Mozambique and Pakistan.

Conclusions

Among rural women in India, Mozambique and Pakistan, higher levels of education was a factor associated with higher frequencies of caesarean deliveries. Availability of private facilities varied between regions but where available, deliveries in private facilities appear to be associated with higher caesarean rates.

Confidential Review of Maternal Deaths in the CLIP India Trial

Arion K, Katageri G, Sharma S, Goudar S, Bellad M, Mallapur A, Charantimath U, Lee T, Li J, Payne BA, Vidler M, Bhutta ZA, von Dadelszen P, Magee LA, CLIP Working Group

Objectives

To assign cause of death (COD) and assess quality of care of women who died in the CLIP India Trial (NCT01911494), 2014–17.

Method

Confidential review of maternal deaths was undertaken using:

1. baseline data and outcomes;
2. verbal/social autopsy (2012 WHO Instrument);
3. and in the intervention arm, clinical data from a mobile health application that guided clinical assessment including blood pressure measurement.

Two physicians reviewed the data independently, assigned cause of death (COD, ICD-MM) and contributing conditions, and identified improvements in care that might have made a difference to outcome; any disagreement was resolved by consensus. Using Cohen's Kappa, assigned COD was compared between physician review and InterVA output.

Results

16 (0.11%) maternal deaths occurred; most were postpartum (10, 62.5% [38.8–86.2%]) and due to direct causes (11, 69.8% [47.3–92.3%]): haemorrhage (4, 25.0% [3.8–46.2%]) or hypertension (2, 12.5% [0–28.7%]), each of which was a contributing condition in an additional woman. Improvements in health care may have modified outcomes in 7 women (43.8% [19.5–68.1%], 3 hypertensive), related to transport or suboptimal facility care. COD agreement between physicians and InterVA was 0.34 [0.09–0.59], and highest for obstetric haemorrhage. Physicians were more likely than InterVA to assign COD to other obstetric complications.

Conclusions

None of the maternal deaths in CLIP India represented a failure of community-level intervention for pre-eclampsia. Opportunities for improved care were frequent, primarily related to facility-level care; use of antihypertensives as well as procedures for PPH. We confirm the poor agreement between COD assigned by InterVA and physician review at an individual case level, particularly for COD related to direct causes other than haemorrhage, hypertension, or sepsis.

2016

CHIPS-Child: Testing the Developmental Programming Hypothesis in the Offspring of the CHIPS Trial Randomized Trials

Magee LA, Synnes A, von Dadelszen P, Hutfield A, on behalf of CHIPS-Child Working Group

Introduction

CHIPS-Child is a follow-up to the international CHIPS trial that showed that 'less tight' (vs. 'tight') control of maternal blood pressure (BP) was associated with no decrease (or increase) in either the primary perinatal outcome (pregnancy loss or high level neonatal care for >48 h) or measures of fetal growth (in utero).

Objectives

In CHIPS-Child, we tested the developmental programming hypothesis by determining if children born of mothers in 'less tight' (vs. 'tight') BP control arms of CHIPS showed differences in postnatal growth and health.

Methods

Follow-up was extended to 12 ± 2 months corrected postgestational age for anthropometric measurements. For CHIPS subjects who consented to a CHIPS-Child study visit, we collected biological samples from the child (hair samples, buccal swabs) to evaluate hypothalamic–pituitary–adrenal axis (HPA) function (hair cortisol levels) and epigenetic change (DNA methylation analysis of buccal cells). The primary outcomewas 'change in z-score for weight' (95% CI) between birth and 12 ± 2 months, compared between groups using linear regression adjusted for maternal pre-randomisation factors (hypertension type and centre, antihypertensive type, and maternal body mass index, body mass index [BMI]) (two-tailed $p > 0.05$) and any between-group differences at baseline among babies followed-up. Secondary outcomes were genome-wide and targeted DNA methylation status (from buccal swabs, measured using the Illumina infinium HumanMethylation450 array platform) and hair cortisol (as a measure of hypothalamic–pituitary activation).

Result

Of 683 eligible CHIPS babies (59 sites), 500 (73.2%) were followed up in CHIPS-Child [244 (70.1%) in 'less tight' vs. 256 (75.7%) in 'tight' control] and 414 consented to participate [196, (80.3%) vs. 218 (85.2%)]. 272 (76.8%) of babies had anthropometry at 12 ± 2 months. Babies in 'less tight' (vs. 'tight') probably differed with regards to change in z-score for weight (primary outcome) [-0.27 (-0.54, 0.00); $p = 0.05$]; there was no difference in z-scores for length [0.14 (-0.20, 0.49); $p = 0.42$] or head circumference [0.19 (-0.89, 1.26); $p = 0.71$], or waist circumference (cm) [0.99 (- 1.75, 3.72); $p = 0.45$]. Secondary outcomes were measurable only among the babies who were eligible for a study visit (N = 92), consented (N = 45), and supplied biological samples (N = 41). 16 DNA samples (9 vs. 7) passed quality control testing; no difference in DNA methylation was seen based on a false discovery rate >20%. In the 35 adequate hair samples, cortisol levels were significantly lower in 'less tight' (vs. 'tight')[-496 (-892, -100); $p = 0.02$].

Conclusions

The results of CHIPS-Child suggest that 'tight' BP control may be associated with both more rapid postnatal growth (birth to age 12 months) and developmental programming of the HPA axis. These results are limited by small sample size. Longer follow up would be necessary to determine if the findings are associated with important clinical outcomes. (CHIPS-Child Working Group: JP Chanoine, AM Côté, A Devlin, A Gafni, W Ganzevoort, A Gruslin, M Helewa, E Hutton, G Koren, Lee SK, D McArthur, E Rey, WP Robinson, T Roseboom, J Singer, S Wilson, JM Moutquin).

Is BP Level Achieved Related to Maternal and Perinatal Outcomes? A Secondary Analysis of BP Values From the CHIPS (Control of Hypertension in Pregnancy Study) Randomised Controlled Trial Randomized Trials

Magee LA, von Dadelszen P, Ganzevoort W, for the CHIPS Study Group

Background

Blood pressure (BP) level and variability have been associated with adverse cardiovascular outcomes, particularly for younger age groups, and the outcome of stroke. We examined the relationship between pregnancy outcomes and both BP level and variability among participants in the CHIPS Trial (Control of Hypertension In Pregnancy Study, NCT01192412).

Methods

BP level was defined as mean systolic (sBP) and diastolic (dBP) between randomisation and delivery. Our primary definition of BP variability was the SD of the two highest and two lowest post-randomisation office visit BP values (a better estimate of relevant variability because numerous measurement at a stable BP would give an underestimate of the type of variability with which we are concerned), and measured at least a week apart because measures taken close together tend to be both highly correlated and more frequently recorded when BP is unstable or 'spiking'. Relationships were explored between outcomes and each of BP level and variability for the major outcomes in CHIPS: perinatal loss or high level neonatal care for >48 h (primary outcome), birth weight <10th centile, serious maternal complications (secondary outcome), severe maternal hypertension, pre-eclampsia, and delivery at <34 or <37 weeks. Mixed effects regression was used to compare BP level, while logistic regression adjusted for treatment group ('less tight' vs. 'tight'), gestational age at randomisation (categorical), last BP, and centre (as a random effect) was used for BP variability. $P < 0.05$ was considered of statistical and potential clinical significance.

Results

Of the 987 women in CHIPS, 961 had at least one office visit (median 7, IQR 4, 10). For each of 'less tight' (vs. 'tight') control, BP was higher among women who had an adverse outcome (vs. women who did not) for all but serious maternal complications of which there were few [N = 28]: primary outcome [$p < 0.0001$ for systolic BP (sBP) and diastolic BP (dBP) in both groups]; birth weight <10th centile (in 'less tight' control: $p = 0.04$ for sBP and $p < 0.0001$ for dBP; for 'tight' control: $p = 0.27$ for sBP and $p = 0.002$ for dBP); severe hypertension and pre-eclampsia ($p < 0.0001$ for sBP and dBP for both groups for each outcome). Despite adjustment that included last BP, BP variability (particularly for dBP) was associated with adverse outcomes: higher variability was associated with more severe hypertension and pre-eclampsia, but lower BP variability with more primary perinatal outcomes, birth weight <10th centile and delivery at <34 wk or <37 weeks.

Conclusions

Higher BP is a biomarker for adverse outcomes, even when target BP is low as in'tight' control. Although CHIPS showed that BP-lowering with antihypertensive therapy can reduce maternal risk (i.e., less severe hypertension), CHIPS did not show that perinatal risk is lowered (or increased). BP variability has a significant complex relationship with outcomes, possibly related to an adaptive response from the feto-placental unit. Our data suggest that when antihypertensive therapy is not achieving target BP values or BP is not stable, enhanced surveillance may be prudent.

The Ability and Safety of Community-Based Health Workers to Initiate Lifesaving Therapies for Pre-Eclampsia in Ogun State, Nigeria: An Analysis of 294 Community Treatments with $MgSO_4$ and/or Methyldopa

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Introduction

Pre-eclampsia and its associated complications are the leading cause of maternal death in Nigeria. Many of these deaths occur at home or in primary health centres. Nevertheless, management of pre-eclampsia is limited to secondary and tertiary facilities. In Nigeria, community-based health workers serve as a bridge between the community and health facilities; therefore, these providers may be key in reducing the incidence of adverse pregnancy outcomes by way of early detection and treatment.

Objectives

This study aimed to assess the ability of community based health workers to safely administer methyldopa, magnesium sulphate, and complete referral to a higher level facility when indicated. Methods: The Community Level Intervention for Pre-eclampsia (CLIP) study was implemented by community-based health workers in Ogun State, Nigeria. These providers (i.e., Community Health Extension Workers, Health Assistants, midwives and nurses) utilized a mHealth platform to guide antenatal and postnatal visits, pre-eclampsia treatment with oral methyldopa (one dose = 750 mg) and intramuscular magnesium sulphate (one dose = 10 mg) prior to referral, based on evidence-based practice and the miniPIERS (Pre-eclampsia Integrated Estimated of RiSk) model.

Results

Findings of this study indicate that community-based health workers in Nigeria safely administered 137 doses of magnesium sulphate; this resulted in no infections or hematomas. Fifty-one doses of magnesium sulphate were given by community health extension workers, while nurses administered sixty-four: the high rate of administration by nurses can be explained by turf protection as well as their seniority within the health system. In addition, there were 139 doses of methyldopa administered, and a total of 127 urgent referrals completed. No safety concerns were reported.

Conclusion

These findings confirm the ability of community based health workers to safely administer magnesium sulphate for severe pre-eclampsia with appropriate training; this is a big step towards reducing the negative impact of pre-eclampsia in Nigeria. The use of task-sharing, therefore, could drastically reduce the three delays (triage, transport and treatment) associated with high maternal mortality and morbidity in rural communities in low and middle-income countries.

2015

Hypertensive Disorders of Pregnancy: A Systematic Review of International Clinical Practice Guidelines

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Objectives

Clinical practice guidelines (CPGs) are developed to assist health care providers in decision-making. We systematically reviewed existing CPGs on the HDPs (hypertensive disorders of pregnancy) to inform clinical practice.

Methods

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessments, and Database of Abstracts of Reviews of Effects (Ovid interface), Grey Matters, Google Scholar and personal records were searched for CPGs on the HDPs (Jan/03 to Nov/13) in English, French, Dutch or German.

Results

Of 13 CPGs identified, three were multinational and three developed for community/midwifery use. Length varied from 3 to 1188 pages and three guidelines did not formulate recommendations. Eight different grading systems were identified for assessing evidence quality and recommendation strength. No guideline scored ≥ 80% on every domain of the AGREE II tool; two CPGs did so for 5/6 domains.

Consistency was seen for:

1. definitions of hypertension, proteinuria, chronic and gestational hypertension;
2. pre-eclampsia prevention for women at increased risk: calcium when intake is low and low-dose aspirin, but not vitamins C and E or diuretics;
3. antihypertensive treatment of severe hypertension;
4. $MgSO_4$ for eclampsia and severe pre-eclampsia;
5. antenatal corticosteroids at <34 weeks when delivery is probable within 7 days;
6. delivery for women with severe pre-eclampsia pre-viability or pre-eclampsia at term;
7. active management of the third stage of labor with oxytocin.

Notable inconsistencies were in:

1. definitions of pre-eclampsia and severe pre-eclampsia;
2. target BP for non-severe hypertension;
3. timing of delivery for women with pre-eclampsia and severe pre-eclampsia;
4. $MgSO_4$ for non-severe pre-eclampsia;
5. postpartum maternal monitoring.

Conclusions

Existing international HDP CPGs have areas of consistency with which clinicians and researchers can work to develop auditable standards, and areas of inconsistency that should be addressed by future research.

Preliminary External Validation of the FullPIERS Risk Prediction Model for Women with Pre-Eclampsia Using the MiniPIERS Dataset

Ukah UV et al. for the fullPIERS Study Group

Objectives

Hypertension in pregnancy, especially pre-eclampsia, is one of the leading causes of maternal mortality worldwide. The fullPIERS model was developed and internally validated in a cohort of 2023 women with 5% outcome rate admitted in tertiary centres in high-resourced settings, as a tool to improve clinical management and, therefore, maternal outcomes. The fullPIERS model predicted adverse outcomes within 48 h of admission with AUC ROC 0.88 (95%CI 0.84–0.92). Our objective was to externally validate the fullPIERS model in a new setting, to support its application in clinical practice.

Methods

External validation of the fullPIERS model was based on complete data available from 757 of 2081 women in the miniPIERS dataset, collected in low-resourced women was evaluated in the second year of life with the Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III Screening).

Results

The mean age of pregnant women was 25.8 years and the mean gestational age of 23.6 weeks review. The average pulsatility index of the uterine artery was 0.89 and 1.47 for the 95th percentile. Evaluation of children, showed no increased risk associated with delay in pulsatility index of uterine artery greater than or equal to the 95th percentile development (cognitive performance: RR 0.76, 95% CI 0.3–1.96, receptive communication: RR 1.17, 95% CI 0.46–3.01, expressive communication: RR 0.66, 95% CI 0 0.67–1, 36, fine motor: RR 1.26, 95% CI 0.5–3.27, gross motor: RR 1.14 95% CI 0.44–2.94).

Conclusions

The high flow resistance of the uterine artery in the second quarter, without deleting other perinatal factors, cannot be considered as a risk factor for the delay in child development. Additional studies should be performed excluding the perinatal risk factors such as prematurity that may adversely affect psychomotor performance of children.

Table 1. Risk Stratification of Adverse Maternal Outcome within 48 h for the Recalibrated Intercept and Slope

Group #	Prediction Score Range	Number of Women (%)	Confidence Interval	Number of Women with Outcome (%)	True Positive Rate (%)	False Positive Rate (%)
1	0–0.99%	6 (0.8%)	0.32–1.8%	1 (16.7%)[CI 0.88–63.5%]	–	–
2	1–2.4%	24 (3.2%)	2.1–4.8%	1 (4.2%)[CI 0.22–23.1%]	99%	99%
3	2.5–4.9%	115 (15.9%)	12.8–17.9%	3 (2.6%)[CI 0.68–8.0%]	98%	96%
4	5.0–9.9%	253 (33.4%)	30.1–36.9%	16 (6.3%)[CI 3.77–10.26%]	95%	78%
5	10–19%	225 (29.7%)	26.5–33.1%	33 (14.7%)[CI 10.45–20.13%]	81%	42%
6	20–29%	61 (8.1%)	6.3–10.3%	12 (19.7%)[CI 11.0–32.22%]	50%	12%
7	≥30%	73 (9.6%)	7.7–12.0%	43 (58.9%)[CI 46.77–70.09%]	39%	4.6%
Total		**757**		**109 (14.4%) [CI 12.0–17.2%]**		

The Pre-Empt (Pre-Eclampsia and Eclampsia Monitoring, Prevention and Treatment)—Lessons to Date

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Background

Pre-eclampsia remains a leading cause of maternal and perinatal morbidity and mortality. Of the 5–600,000 maternal and perinatal lives lost to pre-eclampsia annually, more than 99% are lost in less-developed countries. The PRE-EMPT initiative is endeavouring to reduce that unacceptable burden of loss.

Methodology

We are using discovery science and clinical research, meta-analysis, randomised controlled trials, health services research and knowledge translation methods, strengthened by advocacy and community engagement, to address the burden of death and damage related to pre-eclampsia, in Africa, South America, South Asia, and Oceania.

Results

To date (5 of 7 years completed), we have determined:

1. impact of low-dose calcium replacement to prevent pre-eclampsia in the existing literature;
2. effect of low-dose calcium replacement of the blood pressure of non-pregnant, calcium-deficient women;
3. ability to provide precise risk estimates to women with pregnancy hypertension, and the role of pulse oximetry in improving precision;
4. socio-cultural contexts of women, their communities and their caregivers as they relate to pregnancy complications;
5. ability of mHealth-supported community care providers to direct hypertensive women to receive hospital-based care;
6. feasibility of oral methyldopa, labetalol and nifedipine use to treat severe pregnancy hypertension;
7. best evidence for pre-eclampsia prevention and treatment;
8. gaps in advocacy tools.

Conclusions

Through a cross-methodological approach, we are beginning to observe improvements in health outcomes for women at risk of, and with, pre-eclampsia. New knowledge is directed towards providing mHealth-supported precision medicine to women wherever they reside. This approach should be generalizable to other pregnancy complications and for newborns.

The Influence of Relationships on Maternal Well-Being in Southern Mozambique

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Objectives

The objectives of this qualitative study, situated within a framework of a larger study on the influence of the social determinants of health on maternal outcomes, were to:

1. Identify the relationships that are important to maternal well being;
2. Understand the nature and impact of these relationships;
3. Determine the programmatic implications based on the findings.

Method

Twelve focus group discussions were conducted with reproductive age women, matrons, male decision-makers, community leaders and community health workers in Gaza and Maputo provinces in Mozambique in 2013. Participants were recruited using sample of convenience and snow balling. Focus groups had an average of 6 participants. To understand the broader social and political contexts, twelve in-depth interviews were conducted with administrative post chiefs of each study locality. Data were coded thematically and analysed using nVIVO software.

Results

Four main relationships were identified as being important for a healthy pregnancy. It was described that pregnant women could avoid intimate partner violence by behaving properly with their husbands. While women relied on neighbours for help with pregnancy complications, they also felt that if good relations were not maintained, neighbours could perform witchcraft which could affect pregnancy outcomes. Matrons in the community played a key role by providing advice and assisting with deliveries. Women voiced that organized groups like xitique were not possible due to economic constraints but that informal networks of female friends were important for support during pregnancy.

Conclusions

The study highlights the role of relationships within a woman's community that affect her wellbeing in pregnancy. Particularly, it draws attention to gender norms and gender violence during pregnancy. The findings also emphasize the critical role of matrons in the care of pregnant women and the importance of support from other females in the community. Based on these findings, programmes are needed to address gender inequality and violence during pregnancy. Programmes focusing on maternal health education should target other women in the community and provide opportunities for building women's support groups.

Policy Review on Management of Pre-Eclampsia and Eclampsia by Community Health Workers in Mozambique

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CLIP Mozambique Feasibility Working Group

Objectives

Maternal mortality ratio (per 100,000 live births) in Mozambique has decreased from 500 in 2007, to 480 in 2013; however, this remains high. Hypertension in pregnancy is the third leading cause of maternal death in this region. The limited capacity of the Ministry of Health, low availability of emergency obstetric care, and insufficient skilled health care personnel, indicate a need for community level innovative interventions. Policies must be in place or adapted to accommodate such innovations. This study aimed to review policies related to the use of community health workers to manage pre-eclampsia or eclampsia in Mozambique.

Method

A variety of documents with information regarding the community health workers programme in Mozambique were reviewed. These documents included formal government and institutional policies and other relevant official documents, such as community involvement strategies, community health worker training programmes, monitoring and evaluation manuals, meeting minutes and reports. Both published and unpublished information was used for this analysis. This document review further involved the identification of the timeline of key events and consultations with stakeholders: staff and colleagues familiar with these events were approached to gain insight into the policy process.

Results

In 1976, Mozambique introduced policies to strengthen and extend primary health care. Subsequently in 1978, the community health worker programme was established for health promotion and prevention. The programme was then scaled back; prior to the resolution to revitalize it in 1995. In 2010, a new programme expanded the use of community health workers to manage common illnesses: malaria, diarrhoeal disease, and acute respiratory infections. Community health workers have provided limited services in pregnancy; simple health promotion, detection of warning signs, and referrals. Their role to date has not included care specific to the hypertensive disorders of pregnancy.

Conclusions

The policies regarding the provision of maternity care by community health workers in Mozambique focuses on health promotion and the detection of pregnancy risk. In order to strengthen community level response and reduce maternal and perinatal mortality, there is a need for task-shifting to community health workers. Recommendations for their utilisation in the provision of basic maternal health services should be broadened to include the detection and pre-referral management of pre-eclampsia and eclampsia.

Treatment Challenges for Obstetricians in Rural Karnataka, India—A Qualitative Study

Mallapur A, Bannale S, Vidler M, Ramadurg U, Katageri G, Charanthimath U, Karadiguddi C, Dharamsi S, Sawchuck D, Qureshi R, Bellad M, Goudar S, von Dadelszen P, Magee LA, Derman R, CLIP Pakistan Feasibility Working Group

Objectives

To identify challenges faced by obstetricians while providing care in Karnataka State, India.

Method

This qualitative study was conducted in Belgaum and Bagalkot Districts of Karnataka State, India in 2012–2013. Data were collected by interview with obstetricians (N=6) from private, district and tertiary teaching facilities. A semi-structured interview guide was used, to allow the participants to express their views in-depth. All interviews were conducted in English. The interviewer collected field notes and audio recordings; audio was reviewed and transcribed verbatim with the incorporation of field notes. Interview data were analysed using NVivo10. Member checks with interview facilitators were employed throughout the analysis process to ensure validity, reliability, and accuracy.

Results

Obstetricians discussed the challenges faced in providing care in rural Karnataka, the most common challenge was the poor health status of women upon arrival to facility. Poor health status at arrival was thought to be due to delays in accessing care; which were reportedly associated with poor availability of 24-hour transport, significant distance to facility, low health-related knowledge, irregular antenatal care attendance, and poverty. Obstetricians were further challenged by unavailability of necessary materials in facility. Some obstetricians expressed a lack of adequate training and experience to safely and confidently manage pregnancy complications, particularly at district level facilities in rural communities.

Conclusions

Obstetricians continue to encounter pervasive challenges in providing high-quality care to women in pregnancy, labour and postpartum. These challenges include delayed arrival to facility, unavailability of materials, and insufficient training. To improve maternal outcomes in rural Karnataka efforts must be made to encourage women to access services in a timely manner, to ensure access to materials for comprehensive emergency obstetric care in all hospitals, and to provide additional targeted trainings for high-risk complications.

Facility Preparedness for Routine and Emergency Obstetric and Newborn Care in Northern Karnataka, India

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Objectives

This study aimed to assess the resources and services available for obstetric and newborn care at facilities in northern Karnataka. Furthermore, the study examined facility management of obstetric emergencies.

Method

This study was conducted in Belgaum and Bagalkot Districts of northern Karnataka, India in 2012–2013. Staffs of six primary health centres (3 in each district) were asked to identify the facilities at which pregnant women in their community regularly accessed obstetric care. A total of 88 facilities were identified. The health care providers at these facilities were then interviewed to gauge the available resources and services. For the purpose of this study, only facilities higher than primary health centres offering inpatient care were considered. Eleven of these facilities were thus excluded. Data from remaining 77 were analysed.

Results

Most facilities assessed were private hospitals (n=56), and the remainder were public (n=21). Thirty-three facilities had adult intensive care units and 48 had neonatal intensive care units. All 77 provided emergency maternal care whereas only 47 provided emergency neonatal care. The availability of specialists was assessed; obstetricians, paediatricians, radiologists and anaesthesiologists; only 19 facilities had all four. Basic laboratory services were available in all facilities and 51 had capacity for haematologic, renal and hepatic parameters. Blood transfusions were available in 67 facilities. Sixty-nine facilities could perform caesarean sections; however, only 29 could do so within 30 minutes of decision.

Conclusions

This study highlights the vast differences in obstetric services provided by the facilities in northern Karnataka. Although the majority of facilities provided reasonably comprehensive obstetric services, many were lacking in the availability of newborn care. Basic investigations were available in all facilities; however, in order to manage complicated cases, a more elaborate setup is needed. Timely provision of caesarean sections is crucial in preventing many maternal and neonatal morbidities and even mortalities. Though caesarean sections were widely performed, the decision to delivery interval was unacceptably high in many facilities.

Utilization of Maternal Health Care Services and Their Determinants in Rural Karnataka State, India

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Method

Twenty three focus groups and twelve interviews were conducted in rural Karnataka State in 2012–2013. Four focus groups were held with Auxiliary Nurse Midwives and staff nurses, four with Accredited Social Health Activists, three with community leaders, two with male decision-makers, three with female decision-makers, six with women of reproductive age, and one with medical officers. One-to-one interviews were held with medical officers (N=2), private health care providers (N=2), health administrators (N=2), district health officers (N=2), and obstetricians (N=4). All discussions were audio recorded, transcribed verbatim, and translated for thematic analysis using NVivo 10.

Results

Most women in the focus groups reported attending routine antenatal care, for an average of three visits during pregnancy, and more frequently if high-risk. Antenatal care was typically delivered at the periphery by non-specialised community-based providers. Women reported that they sought care if they experienced any danger signs in pregnancy. Postpartum care was reportedly rare and was mainly sought for purpose of neonatal services. Factors that influenced women's care-seeking in pregnancy and postpartum included their limited autonomy within the family and society, poor access to transport services, perceived poor quality of health care services and providers, and low socio-economic status.

Conclusions

South Indian communities reported regular use of health care services during pregnancy; however, barriers to access were prominent. Postpartum care continued to be rare. In spite of new government programmes and increased availability of maternity care services, some women still delayed or deferred accessing health services. More efforts should be made to address the reported barriers that persist to maternity care services for women in rural Karnataka.

Health Care Seeking Behaviours in Pregnancy in Rural Sindh, Pakistan: A Qualitative Study

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Objectives

Pakistan has alarmingly high numbers of maternal deaths along with sub-optimal care-seeking behaviour. It is essential to identify the barriers and facilitators women encountered when they sought antenatal care. The aim of this study is to understand health-seeking patterns of pregnant women in rural Sindh, Pakistan.

Method

A qualitative study was undertaken in rural Sindh, Pakistan as part of a large multi-country feasibility study in 2012. Twenty six focus group discussions and in-depth interviews were arranged with mothers (n=174), male decision-makers (n=64), Lady Health Workers (n=64), Lady Health Supervisors (n=10), Women Medical Officers (n=9) and Traditional Birth Attendants (n=7) in Hyderabad and Matiari Districts. A set of a priori themes regarding care seeking during pregnancy and its complications as well as additional themes as they emerged from the data were used for analysis. Qualitative analysis used NVivo 10.

Results

Women stated they usually visited health facilities if they experienced pregnancy complications or danger signs, such as heavy bleeding or headache. Husbands and mothers-in-law were important decision makers regarding health care utilization. Participants expressed that lack of transport, financial constraints and the unavailability chaperones were important barriers to accessing services. Private facilities were often preferred due to the perceived superior quality of care.

Conclusions

Maternal care utilization is influenced by social, economic and cultural factors in rural Pakistani communities. The perceived poor quality of care at public hospitals is a significant barrier to accessing health services for many women. In order to avert maternal deaths, policy makers need to develop processes to overcome these barriers and ensure easily accessible high-quality care for women in rural communities.

Barriers and Facilitators to Health Care Seeking Behaviours in Pregnancy in Rural Communities in Southern Mozambique

Munguambe K, Boene H, Vidler M, Bique C, Sawchuck D, Firoz T, Makanga PT, Qureshi R, Macete E, Menéndez C, von Dadelszen P, Sevene E

Objectives

In countries such as Mozambique, where maternal mortality remains high, the greatest contribution to mortality comes from the poor and vulnerable communities in remote and rural areas with limited access to health care services. This study aimed to describe women's health care seeking practices during pregnancy, as well as barriers to accessing timely appropriate care, in Maputo and Gaza provinces, southern Mozambique.

Method

The study followed an ethnographic design. Qualitative data were collected through in-depth interviews and focus group discussions with women of reproductive age, including pregnant women, household-level decision makers (partners, mothers and mothers-inlaw), traditional healers, primary health care providers (both facility and community-based), and community leaders. Data analysis was performed by thematic analysis using Nvivo 10.

Results

Antenatal care was often sought for the purpose of opening the antenatal record; women without an antenatal card fear mistreatment during labour. Antenatal care was also sought when women experienced discomfort or complications: headache, flu-like symptoms, and body pain. Male partners consider lower abdominal pain as the only symptoms requiring care. In addition, husbands discouraged women from revealing their pregnancy early in gestation. The decision-making process can be complex and time-consuming in the absence of a matron or family member. Traditional healers provided services in the community, but they were highly discouraged particularly when treatment involves bitter medication.

Conclusions

Women do seek antenatal care at health facilities; however there are additional factors that prevent prompt care-seeking for obstetric emergencies and delivery, namely unfamiliarity with warning sings among pregnant women and partners, discouragement from revealing pregnancy early in gestation, and complex and timely decision-making processes in the advent of an emergency. Ensuring that pregnant women are followed up by matrons and community health workers as well as regular antenatal care could enhance the likelihood of prompt referrals due to their decision-making power and authority in these communities.

Health Care Seeking for Pregnancy Complications in Ogun State, Nigeria

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Objectives

This qualitative study aimed to describe the health care seeking behaviour of women in Ogun State, Nigeria.

Method

The study was conducted in four Local Government Areas of Ogun State, in south-western Nigeria. Data were collected through focus group discussions with pregnant women, recently pregnant mothers, male decision-makers, opinion leaders, traditional birth attendants, health workers, and health administrators. A thematic analysis approach was used with NVivo 10.

Results

Findings showed that women utilized more than one type of provider in pregnancy; with a preference for traditional providers. There was a strong sense of trust in traditional providers with long-term residence in the communities. The patriarchal nature of these communities influenced health-seeking behaviour in pregnancy. Economic factors contributed to the delay in access to appropriate services. There was a consistent concern regarding the cost of accessing health services. The challenges of accessing services were well recognised and these were greater when referral was to higher level of care which most times attracted unaffordable costs.

Conclusions

While high cost of care is a deterrent to health seeking behaviour, the cost of death of a woman or a child to the family and community is immeasurable. To reduce deaths from pregnancy complications, all stakeholders including policy makers, opinion leaders, health care consumers and providers are crucial in shaping the health care seeking behaviour. The use of innovative mechanisms for health care financing may be beneficial for women in these communities to reduce the barrier of high cost services.

Community Health Care Worker Knowledge and Management of Pre-Eclampsia in India

Ramadurg U, Vidler M, Charanthimath U, Katageri G, Bellad M, Mallapur A, Goudar S, Bannale S, Karadiguddi C, Sawchuck D, Qureshi R, von Dadelszen P, Derman R, Community Level Interventions for Pre-eclampsia (CLIP) India Feasibility Working Group

Objectives

This study aimed to describe the current state of knowledge regarding pre-eclampsia and eclampsia among community health care workers (Auxiliary Nurse Midwives, Accredited Social Health Activists, staff nurses) in India. Furthermore, this study will describe the treatment approaches by various cadres of community health workers for these conditions.

Method

Data were collected as part of a larger study aimed at assessing the feasibility of community-based treatment for pre-eclampsia using community health care workers. Eight focus group discussions were conducted in 2012–2013 in Karnataka State, India: four with staff nurses and Auxiliary Nurse Midwives and four with Accredited Social Health Activists. In addition, 12 self-administered questionnaires were distributed to Auxiliary Nurse Midwives and staff nurses. The purpose of this survey was to reveal health worker competence and self-efficacy in the identification and management of pre-eclampsia. Qualitative data were audio-recorded, transcribed verbatim and translated for thematic analysis using NVivo 10.

Results

Community health workers described the origin of hypertension and seizures in pregnancy. Psychological explanations of hypertension were most common: stress, tension, and fear. The most common explanation for eclampsia was not receiving a tetanus vaccination. These community health workers demonstrated a good grasp of the potential consequences of hypertension in pregnancy. According to Auxiliary Nurse Midwives and staff nurses, if hypertension was detected they encouraged rest, decreased salt intake, iron supplementation and tetanus vaccination. In addition, some staff nurses administered antihypertensives, $MgSO_4$, or other anticonvulsants. All Auxiliary Nurse Midwives had awareness of $MgSO_4$, but none had administered it themselves.

Conclusions

There is limited knowledge of pre-eclampsia among community health workers in India, some misconceptions are prominent. Pre-eclampsia was most commonly attributed to mental stress and tension. Responses from the self-administered questionnaire demonstrated varied levels of comprehension and confidence in screening and referring cases of pre-eclampsia and eclampsia.

Health Care Provider Knowledge and Regular Management of Pre-Eclampsia in Pakistan

Sheikh S, Qureshi RN, Khowaja AR, Salam R, Vidler M, Sawchuck D, von Dadelszen P, Zaidi S, Bhutta Z, CLIP Working Group

Objectives

The maternal mortality ratio is estimated to be 93–320 per 100,000 live births in Pakistan. Eclampsia is responsible for every tenth maternal death despite the fact that management of this condition is inexpensive and the medications have been available for decades. There are widespread health care shortages in low and middle-income countries combined with limited formal training in high-risk obstetrics. Hence, this study aimed to explore the knowledge of various cadres of health care providers regarding aetiology, diagnosis and treatment of pre-eclampsia and eclampsia in Pakistan.

Method

This qualitative study was conducted in Hyderabad and Matiari Districts in Sindh Province, Pakistan in 2012. Focus group discussions and interviews were conducted with community health care providers, which included Lady Health Workers and their supervisors, traditional birth attendants and facility-based doctors. In total, ten focus groups and twenty-six interviews were held. Data were transcribed verbatim and analyzed in Sindhi. NVivo 10 was used for analysis and to identify emerging themes and sub-themes.

Results

Health care providers had longstanding experience providing care for pregnant women; all but two had been working in the field for at least ten years. According to community health care providers, the origin of pre-eclampsia was due to the stresses of daily life, excessive strenuous labour, and short birth spacing. All health care providers, except traditional birth attendants, correctly identified the signs, symptoms and complications of pre-eclampsia. Community providers referred women suspected of pre-eclampsia and eclampsia to tertiary facilities. Only doctors were aware of $MgSO_4$ as the drug of choice for eclampsia, nevertheless, fears regarding the use of $MgSO_4$ persisted.

Conclusions

This study found several gaps in knowledge regarding aetiology, diagnosis and treatment of pre-eclampsia among the various cadres of health care providers. Findings suggest that limited exposure to women with pre-eclampsia, the lack of refresher training, and no written guidelines for the management of pre-eclampsia are important factors leading to inadequate knowledge. It is suggested that regular health worker training include management of pre-eclampsia and that management protocols are made available at all health facilities.

Community Health Care Worker Knowledge and Management of Pre-Eclampsia in Mozambique

Boene H, Vidler M, Augusto O, Sidat M, Macete E, Menéndez C, Sawchuck D, Qureshi R, von Dadelszen P, Munguambe K, Sevene E, CLIP Feasibility Working Group

Objectives

Two hundred and eighty nine thousand women died in 2013 from pregnancy related causes, the vast majority of these deaths were in Sub-Saharan Africa. Mozambique's maternal mortality ratio is estimated at 480 deaths per 100,000 live births. Women in rural areas, with limited access to health facilities are at greatest risk. To reach these vulnerable women, in 1978 Mozambique introduced a community health worker programme known as Agentes Polivalentes Elementares. This study aimed to describe the current state of knowledge regarding pre-eclampsia and eclampsia by these community health workers in southern Mozambique.

Method

This mixed method study was conducted in Maputo and Gaza Provinces, in southern Mozambique in 2013. Eighty one selfadministrated questionnaires were completed by community health workers. In addition, eight interviews were conducted with district medical officers, community health worker supervisors and gynaecologists and obstetricians, and five focus group discussions were convened with matrons. The data were translated from local language to Portuguese for analysis using NVivo 10.

Results

Ninety three percent of community health workers demonstrated an awareness of various pregnancy-related complications. Forty one percent were able to describe the signs and symptoms of hypertension. In cases of eclampsia, community health workers claimed to immediately refer pregnant women to the health facility. This quick action indicates their limited knowledge and skills to manage complications independently. Over half of the community health workers surveyed believed they could neither measure blood pressure nor proteinuria, and only 57% were confident in providing oral medications (47%) of any kind. Even fewer reported confidence in providing oral antihypertensive (14%) and injections (5%).

Conclusions

These results illustrate the limited knowledge of community health workers and the need to enhance their training to include curative activities including the management of pre-eclampsia. As community health workers are the first point of contact for primary care, particularly in rural areas where other services are difficult to access, these providers must be equipped with the knowledge to identify, stabilize, and refer obstetric emergencies.

2014

Economic Evaluation of Community-Level Interventions for Pre-Eclampsia (CLIP) in South Asian and African Countries: A Study Protocol

Khowaja A, Mitton C, Bryan S, Magee LA, Bhutta Z, von Dadelszen P

Background

Globally, hypertensive disorders of pregnancy, particularly pre-eclampsia and eclampsia, are the leading cause of maternal and neonatal mortality, and impose substantial burdens on the families of pregnant women, their communities, and health care systems. The Community Level Interventions for Pre-eclampsia (CLIP) Trial evaluates a package of care applied at both community and primary health centres to reduce maternal and perinatal disabilities and deaths resulting from the failure to identify and manage pre-eclampsia at the community level. Economic evaluation of health interventions can play a pivotal role in priority setting and inform policy decisions for scale-up. At present, there is a paucity of published literature on the methodology of economic evaluation of large, multi-country, community-based interventions in the area of maternal and perinatal health. This study protocol describes the application of methodology for economic evaluation of the CLIP in South Asia and Africa.

Methods

A mixed-design approach i.e. cost effectiveness analysis (CEA) and qualitative thematic analysis will be used alongside the trial to prospectively evaluate the economic impact of CLIP from a societal perspective. Data on health resource utilisation, costs, and pregnancy outcomes will be collected through structured questionnaires embedded into the pregnancy surveillance, cross-sectional survey and budgetary reviews. Qualitative data will be collected through focus groups (FGs) with pregnant women, household male decision makers, care providers, and district level health decision makers. The incremental cost-effectiveness ratio will be calculated for health care system and societal perspectives, taking into account the country-specific model inputs (costs and outcome) from the CLIP Trial. Emerging themes from FGs will inform the design of the model, and help to interpret findings of the CEA.

Discussion

The World Health Organization (WHO) strongly recommends cost-effective interventions as a key aspect of achieving Millennium Development Goal (MDG)-5 (i.e. 75 % reduction in maternal mortality from 1990 levels by 2015). To date, most cost-effectiveness studies in this field have focused specifically on the diagnostic and clinical management of pre-eclampsia, yet rarely on community-based interventions in low-and-middle-income countries (LMICs). This study protocol will be of interest to public health scientists and health economists undertaking community-based trials in the area of maternal and perinatal health, particularly in LMICs.

2013

Maternal Circulating PlGF Concentrations and Placenta Related Pregnancy Complications: First Results from The CoLab AngF Study

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Introduction

Circulating angiogenic factors are potential markers for pre-eclampsia, but heterogeneous studies have failed to identify precise predictive/diagnostic properties. The Global CoLaboratory is investigating how to merge published data of angiogenic factors for meta-analysis on an individual sample basis.

Objective

To amalgamate pregnancy angiogenic factor studies, investigate diagnostic and predictive properties of these markers in pre-eclampsia and placenta-related pregnancy complications, and to test if measures from disparate platforms can be standardised. This is the first report using PlGF measures to diagnose pre-eclampsia.

Methods

Data were derived from 15 cohorts, within and outside the CoLaboratory network. Women were classified as either case (confirmed diagnosis of pre-eclampsia at sampling) or non-case (no pre-eclampsia at sampling). Individual PlGF measurements from four different analytical platforms were used, along with transformations of the data (e.g. log transformations, transformations to a baseline platform). Transformed measurements were standardised both for specific platforms and globally, stratifying on gestational age. Different statistical techniques were compared.

Results

The database currently contains 1442 cases and 11,512 non-cases, which were used to define an algorithm to merge PlGF measurements from different platforms. Non-case distributions were used to standardise case results. Diagnostic PlGF measurements in relation to pre-eclampsia will be presented and confirm feasibility. Conclusions: Future studies can extend this approach to other angiogenic factors, prediction as well as diagnosis and to other placenta-related disorders.

2012

Magnesium Sulphate for Prevention and Treatment of Eclampsia in Low- and Middle-Income Countries: Systematic Review of Tested Regimens

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Introduction

Magnesium sulphate ($MgSO_4$) is regarded as the most effective prophylactic and therapeutic agent for eclampsia. Although well studied and widely used in high income countries (HICs), $MgSO_4$is underutilized in low and middle income countries (LMICs) due to many factors including lack of adequately trained health care providers, supplies for administration, or the $MgSO_4$ itself, in addition to fear of potential adverse effects.

Objectives

To systematically review the dosing and effectiveness of $MgSO_4$ regimens administered in LMICs to women with pre-eclampsia or eclampsia.

Methods

We searched Medline, EMBASE, IPA, CINAHL, CDSR and CENTRAL databases for English language randomized controlled trials (RCT) and observational studies of $MgSO_4$ regimens administered in LMICs to women with pre-eclampsia or eclampsia. Two authors independently reviewed search results and extracted relevant data from eligible studies. No quality assessment was performed.

Results

Twenty two papers (7 RCT and 15 observational studies) from 12 LMIC met our inclusion criteria, of which 21 were conducted in hospital settings. Two studied $MgSO_4$ for eclampsia prevention,14 for eclampsia treatment and 6 studied $MgSO_4$ for both. In 20 studies, both loading and maintenance $MgSO_4$ dosing was administered, with intravenous (IV) or combined IV and intramuscular (IM) loading doses of 4–15 g and IV or IM maintenance doses up to 2g/h. Five studies used only the IV route of administration, while the remainder coupled IV with IM administration. All studies were effective at preventing the initiation and/or recurrence of eclamptic seizures. One study of 265 women with eclampsia found that $MgSO_4$ loading dose administration in the community (4g IV over 20 min plus 3g IM in each buttock) before referral and administration of maintenance therapy in hospital was more effective in decreasing recurrent eclampsia compared with the standard practice of referral to hospital where the initial dose of $MgSO_4$ was administered [RR of 0.23, 95% CI 0.11, 0.49]. The two studies of 4g IV plus 10g IM loading dose-only regimens did not show a significant reduction in eclamptic seizures compared with identical loading dose plus 5g/4h IM maintenance dose regimens [RR of 1.38, 95% CI of 0.23, 8.45]. However the combined sample size was small (N=180 women).

Conclusion

In LMICs, most studies of $MgSO_4$ for pre-eclampsia or eclampsia were conducted in high level health care facilities and administered $MgSO_4$ by the IV route, at least in part. The one study of community administration of a $MgSO_4$ loading dose showed this approach to be effective. There are limited data to support loading dose-only regimens.

Oral Antihypertensive Therapy for Severe Hypertension in Pregnancy

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Introduction

The hypertensive disorders of pregnancy are among the leading causes of maternal mortality and morbidity. The vast majority occurs in low- and middle-income countries. It is widely accepted that women with severe hypertension are at increased risk of stroke and benefit from blood pressure (BP) reduction. Although traditionally, parenteral antihypertensive agents have been studied for treatment of severe hypertension in pregnancy, oral agents would be ideal for use in the community and in under resourced settings.

Objectives

To review the published evidence for the effectiveness of oral antihypertensive therapy for severe hypertension in pregnancy.

Methods

The following databases were searched (to May/ 11) for randomised controlled trials (RCT) of oral antihypertensive therapy for severe hypertension in pregnancy: MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews. Inclusion criteria were: severe hypertension [an inclusion criterion or average enrollment BP of: systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 110 mmHg), use of oral or sublingual antihypertensive therapy in at least one of the treatment arms, and at least one relevant measure of maternal or perinatal outcome within a week of administration. Data were abstracted independently by two reviewers and discrepancies resolved by consensus. The Cochrane Revman 5.1 software was used for statistical analysis according to standardised methodology.

Results

We identified 14 eligible trials (796 women). Most compared oral/sublingual (SL) nifedipine 5–10 mg (10 trials, 606 women, 8/10 trials specified capsule preparation), with either: intravenous (iv) hydralazine 5–20 mg (6 trials, 282 women), oral nifedipine 10 mg PA tablets (1 trial), oral prazosin 1 mg (1 trial), iv labetalol (1 trial), or iv/ intramuscular (im) chlorpromazine 12.5 (1 trial). Three trials (154 women) compared oral methyldopa (250–500 mg initially) with either oral labetalol (100mg), atenolol (50–200 mg) or kentanserin (80–120 mg) (1 trial each). One trial (36 women) compared SL isosorbide 1.25 mg with IV magnesium sulphate (4 g iv then 1 g/hr). No trials were identified that compared oral labetalol with either parenteral hydralazine or oral nifedipine. Nifedipine compared favourably with parenteral hydralazine with no differences seen in BP control or maternal or perinatal outcomes. Heterogeneity between trial results was seen within the oral/SL nifedipine vs. iv hydralazine subgroup in which one trial evaluated treatment success and side effects over 20 min and found that nifedipine was associated with relatively lower success and fewer side effects. The incidence of maternal hypotension in the nifedipine capsule arms of these trials was low (1/102, 3 trials), but hypotension was common in both arms of a trial of nifedipine 10 mg capsule vs. 10 mg PA tablet trial (i.e., 11/31 vs. 3/33, risk difference 26%, 95% CI7% to 46%).

Conclusion

Given the available RCT data on which to base oral antihypertensive treatment of severe hypertension in pregnancy, the choice of antihypertensive agent may need to be driven by the availability of the drug, setting in which it is to be administered, and by whom. For facility use, the evidence supports oral nifedipine capsules.

Pharmacotherapy for Pre-Eclampsia in Low- and Middle-Income Countries: An Analysis of Essential Medicines Lists (EMLS)

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Introduction

Pre-eclampsia is the second leading cause of maternal mortality in low- and middle-income countries (LMIC). Pharmacological management of pre-eclampsia has five major components including antihypertensive therapy for severe and non-severe hypertension, magnesium sulphate for prevention or treatment of eclampsia, treatment of pre-eclampsia-related end-organ complications, antenatal corticosteroids for acceleration of fetal pulmonary maturity given iatrogenic preterm delivery for maternal and/or fetal indications, and labour induction for such indicated deliveries. Essential medicines are defined by the World Health Organization (WHO) as “drugs that satisfy the health care needs of the majority of the population”. Essential Medicines Lists (EMLs) detail these essential medicines within an individual country and support the argument that the medication should be routinely available.

Objectives

To determine how many drugs required for comprehensive pre-eclampsia management are listed in national EMLs of LMIC.

Methods

We conducted a descriptive analysis of relevant drug prevalence on identified EMLs. We searched for the national EMLs of the 144 LMIC identified by the World Bank. EMLs were collected by broad based internet searches and in collaboration with the WHO. The EMLs were surveyed for therapies for the different aspects of pre-eclampsia management: hypertension (non-severe and severe with oral or parenteral agents), eclampsia, pre-eclampsia complications (e.g., pulmonary oedema, thrombosis), preterm birth, and labour induction.

Results

EMLs were located and reviewed for 58(40.3%) of LMIC. One or more parenteral antihypertensive agents were listed in 51(87.9%) EMLs. The most common agents were: hydralazine (67.2%), verapamil (58.6%), propranolol (39.7%) and sodium nitroprusside (37.9%); parenteral labetalol was listed by only 19.0% of EMLs. The most prevalent oral antihypertensive therapies listed were: nifedipine (96.6%, usually 10 or 20 mg intermediate-acting tablets), methyldopa (94.8%), propranolol (89.7%), and atenolol (87.9%). Captopril, enalapril, hydrochlorothiazide and spironolactone were commonly listed. Magnesium sulphate for prevention and management of eclampsia was present in 86.2% of EMLs (and its antidote, calcium gluconate in 82.8%). To manage complications of pre-eclampsia, oral frusemide was listed in 94.8% of EMLs and parenteral heparin in 91.4%. Most EMLs listed parenteral dexamethasone (91.4%) for acceleration of fetal pulmonary maturity and oxytocin (98.3%) or a prostanoid (usually misoprostol, 39.7%) for labour induction.

Conclusion

EMLs of LMIC provide comprehensive coverage of all aspects of recommended pre-eclampsia pharmacotherapy. These EMLs may be used as advocacy tools to ensure the availability of these therapies within each country.

Timely Prediction of Maternal Complications in Pre-Eclampsia Analysis of the FullPIERS Model

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Introduction

In pre-eclampsia, reliable prediction of a complication up to 48 hours prior to its occurrence would improve clinical management due to administration of steroids, transfer to a perinatal centre and timely delivery. Recently von Dadelszen et al. developed and internally validated the fullPIERS model [1] and have suggested that a predicted probability >0.15 can be used as a rule-in test for adverse maternal events. Because the model predicts adverse maternal outcome within 48 hours after eligibility using parameters within the same timeframe, uncertainty exists whether enough time is left to properly guide treatment [2].

Objectives

To analyze the time course of predicted probability of an adverse outcome, as calculated by the fullPIERS model, in order to determine the maximum time frame that allows reliable prediction.

Methods

All measurements from the fullPIERS database were divided into women who had an adverse outcome as specified in the original fullPIERS article [1] (group A) and women who did not (group B). A calibration time point was determined for both groups, respectively the time of outcome (A) or the time of delivery (B). Only measurement sets taken between 1 and 96 hours prior to the calibration time point were used. Incomplete sets were completed by carrying forward the last observation with a limit of 48 hours. Sets that could not be completed were omitted. Full-PIERS probability scores were calculated for each measurement set. These scores were stratified into 4-hour groups and for each 4-hour group the median probability score was calculated. Results were plotted in a graph (1).

Results

A total of 2.587 women were included in the original study of whom 325 (12.5%) developed combined adverse maternal outcome at any time after inclusion. In total 20.636 measurement sets were recorded at different time points. After exclusion of incomplete measurement sets and data beyond 96 hours, a total of 2.060 women remained with 5.046 complete measurement sets. Group A consisted of 258 (12.5%) women with 1.018 (20%) complete measurement sets and group B counted 1.802 (87.5%) women with 4.028 (80%) complete measurement sets. In the group of women without adverse event there was no upward trend in average fullPIERS predicted probability in the time leading up to delivery with a baseline average predicted probability of <0.05. In the group of women who had an adverse outcome an increase in the average predicted probability above 0.05 was seen at around 60 hours prior to occurrence of the adverse outcome, which gradually increases to approximately 0.15 at 4 hours.

Conclusion

In this post-hoc hypothesis-generating analysis there appears to be an increase in predicted probability of an adverse outcome well in advance of the actual occurrence. Implementation studies should follow to establish statistical cut-off points and clinical implications.

Unexpected Random Urinary Protein: Creatinine Ratio Results— Insights from Clinician-Laboratory Medicine Collaboration

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Introduction

Proteinuria assessment is important in pregnancy, particularly in determining whether or not a woman has pre-eclampsia. The random protein to creatinine ratio (PrCr) has been recommended as a confirmatory test for dipstick proteinuria in pregnancy, defined as random PrCr ≥ 30 mg/mmol. However, it has been our clinical impression that women with normal pregnancy outcomes have fluctuating or persistently elevated PrCr values.

Objectives

As the primary goal of proteinuria testing in pregnancy should be to identify women at increased risk of adverse outcomes, we sought to explore our clinical impression that an elevated PrCr is seen not infrequently in pregnancies with normal outcome.

Methods

In this prospective cohort study, consecutive inpatients or outpatients (attending high-risk maternity clinics) were evaluated at a tertiary care facility. Random midstream urine samples were obtained as part of normal clinical care. Urine protein was measured using a pyrocatechol violet molybdate dye-binding method, and urine creatinine by an enzymatic method, both on an automated analyser (Vitros® 5.1 FS or Vitros® 5600, Ortho-Clinical Diagnostics, Rochester, NY) followed by PrCr calculation. Maternal and perinatal outcomes were abstracted from the hospital case notes.

Results

160 women (81.9% outpatients) were screened at one/more antenatal visits providing a total of 233 samples for analysis. Ninety one (39.1%) samples had a random PrCr ≥30 mg/mmol. This result was more common when urinary creatinine concentration was <3 mM [64 (94.1%)] compared with ≥ 3 mM [27 (16.4%)], even among the 32 (20.0%) women with known normal pregnancy outcome [(13 (92.9%) vs. 0 (0%), respectively] (Panel A). In dilution studies using the same automated analyser, urinary protein (at a concentration of 0.12 g/L) was 'detected' in deionised, double-distilled water. Method-specific re-analysis of data from two other published cohorts from our centre revealed substantially less inflation of PrCr values in dilute 24 h urine samples tested using a pyrogallol red dye-binding based protein assay. When results were categorized according to urinary creatinine <3 mM vs. ≥3 mM, PrCr ≥30 mg/mmol occurred in 12 (66.7%) vs. 99 (55.3%) respectively (p = 0.35) in a 24-h urine completeness cohort and 92 (73.6%) vs. 313 (64.9%) respectively (p = 0.07) in a cohort of women hospitalised for pre-eclampsia (Panel B).

Conclusion

Random urinary PrCr results may be inflated in dilute urines because of overestimation of proteinuria in a common pyrocatechol violet dye-based method. This inflation was reduced but not eliminated when the dye used was pyrogallol red. Analytical methods do matter in the assessment of proteinuria in pregnant women. It may be prudent to consider the potential for falsely positive PrCr ≥30 mg/mmol in dilute urine, and to order PrCr testing on first voided (concentrated) urines whenever possible.

2011

Sildenafil Citrate Therapy for Early-Onset Severe Intrauterine Growth Restriction

Dwinnell S, Magee LA, Lim K, Liston R, Miller S, Payne B, Rurak D,Sherlock R, Skoll MA, Wareing M, Baker P, von Dadelszen P, Gruslin A, Carleton B, Lee B

Objective

Currently there is no effective therapy for severe early onset intrauterine growth restriction (IUGR). Sildenafil citrate vasodilates myometrial arteries isolated from women with IUGR-complicated pregnancies. We tested the hypothesis that Sildenafil citrate therapy will increase the likelihood of improved growth velocity of severely growth-restricted fetuses remote from term.

Study Design

Women were offered Sildenafil (25mg t.i.d. until delivery) through a process of innovative therapy consent if their pregnancy was complicated by severe early-onset IUGR (abdominal circumference < 5th percentile) and either gestational age < 25 +0 weeks' or estimate of fetal weight <600g. Sildenafil was not offered if there was either known aneuploidy/fetal anomaly/syndrome/congenital infection and/or a plan to terminate the pregnancy. Contemporaneous, institutional Sildenafil-naïve controls were selected according to maternal age, gestational age at eligibility, parity, and eligibility to be offered SildenafIL Other than Sildenafil, for those women who received it, all women received increased fetal and maternal surveillance.

Results

Other than one stillbirth within 48h of commencing Sildenafil treatment, Sildenafil-treatment was associated with increased post-eligibility fetal abdominal circumference growth velocity (9/10 (treated) vs. 7/17 (naïve); odds ratio 12.9 [95% CI 1.3, 126]). Using women as their own controls, Sildenafil therapy was associated with a significant increase in fetal growth velocity (Wilcoxon p = 0.004), while remaining Sildenafil-naïve was not (p = 0.251).

Conclusions

Sildenafil exposure in IUGR fetuses appears to have a significantly positive effect on abdominal circumference growth in the immediate time period following initiation of therapy. Sildenafil treatment may offer a new opportunity to improve perinatal outcomes for pregnancies complicated by severe early-onset IUGR. Randomized controlled trial confirmation of these findings is required

Between Center Variation in Perinatal and Maternal Outcomes of Women Presenting with Very Preterm Labor

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Objective

To evaluate between center variation in perinatal and maternal outcomes in women presenting with very preterm labor.

Study Design

This prospective cohort study included women in the Canadian Perinatal Database, admitted Aug 2005–Aug 2009 with preterm labor (PTL), between 22 0/7wks and 28 6/7wks gestation, to one of 14 tertiary perinatal units. The primary outcome was perinatal mortality or serious morbidity, with the major secondary outcome being serious maternal complication (death, chorioamnionitis, blood transfusion, ICU admission or severe maternal morbidity). Between center variation in the outcomes of interest was evaluated, controlling for potential confounders(maternal age, parity, income, multiple pregnancy, smoking, alcohol, illicit drug use, previous PTB < 34wks, gestational age on enrollment, congenital anomalies, severity of PTL, presence and severity of secondary conditions(short cervix without contractions, prolapsing membranes, PPROM, IUGR, gestational hypertension or APH), latency, and interventions including Caesarean delivery, corticosteroid and tocolytic use.

Results

A total of 570 women and 557 infants were included. Gestational age at enrollment was 26.0 +/- 1.9 weeks, with PTB > 28wks occurring in 55.6% of pregnancies. Perinatal mortality or serious morbidity occurred in 52.2% (291/557) of infants (perinatal mortality[150/557,26.9%], serious neonatal morbidity[172/522 live born infants,33.0%]). Serious maternal complication occurred in 25.6% (146/570) of women. Significant between center variation was found for perinatal morbidity and mortality, and serious maternal complication, even after controlling for potential confounders, Caesarean delivery, corticosteroid and tocolytic use.

Conclusions

Women admitted with very preterm labor are at high risk of perinatal morbidity/mortality and serious maternal complication. Significant between center variation in these outcomes was noted. It is important that future studies evaluate obstetric management at different centers, to identify those interventions and practices that are associated with improved perinatal and maternal outcomes.

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