RESEARCH SUMMARY

CREATING AN ENABLING ENVIRONMENT FOR DIAGNOSIS AND TREATMENT OF HYPERTENSIVE DISORDERS IN PREGNANCY

INDIA

Background

Hypertensive disorders of pregnancy (HDP) are an important cause of severe morbidity and mortality among mothers and babies.[1] In Africa and Asia, nearly 1 in 10 of all maternal deaths are associated with HDP. In Latin America, more than 1 in 4 of maternal deaths are associated with complications of hypertension (HTN). [2]

HDP include:

1. chronic HTN
2. gestational HTN
3. preeclampsia/eclampsia
4. preeclampsia superimposed on chronic HTN

Treatment of severe hypertension in pregnancy reduces serious maternal complications such as cerebral edema and hemorrhage and blood pressure (BP) monitoring is a key component of antenatal and postnatal care.

The World Health Organization (WHO) recommends treatment with antihypertensive medications (hydralazine, labetalol, nifedipine immediate-release capsules, or alpha methyldopa) for acute treatment of severe hypertension in pregnancy. According to WHO, choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy "should be based primarily on the prescribing clinician's experience with that particular drug and its cost and local availability, while ensuring that the medication has no adverse fetal effect." [3]

Barriers to effective treatment of HDP include problems with equipment (missing or dysfunctional blood pressure machines), medicines (stock outs of antihypertensives or inappropriate formulations or dosages), and policy (national guidelines that do not reflect the current evidence base or do not allow for stocking of medicines at facilities providing emergency obstetric care).

RESEARCH SUMMARY

Project Overview:

Gynuity selected three countries (Uganda, Mexico and India) for a focused assessment of the availability of essential supplies for the management and treatment of hypertensive disorders of pregnancy (specifically, antihypertensive medications and blood pressure devices). The landscaping exercise employed a mixed methods approach and collected global, national and sub-national data from three sources: document reviews, in-depth stakeholder interviews, and health facility readiness assessments.

Goals:

- To assess readiness of primary and secondary health facilities to diagnose, monitor and treat women with pre-eclampsia and eclampsia and other HDP.
- To identify gaps in equipment, medicines and policy and procurement practices that may pose barriers to recommended management.

Methods:

Document review:

- National treatment standards and guidelines for the diagnosis and management of HDP
- National and sub-national guidelines and reports for procurement and supply of oral AHT and BP cuffs (Including Essential Medicines Lists, forecasting reports of essential medicines and devices etc.)

In-depth interviews with 12-15 key stakeholders in each country including government health sector officials, members of professional medical societies, and non-governmental organizations and researchers working on maternal health

Cross-sectional mixed methods facility survey in a sub-sample of health care facilities and private pharmacies in two districts in each country

INDIA

In India, Amhi Amchya Arogyasathi (AAA), a Nagpur-based NGO, conducted the facility based survey. The survey was conducted in Gadchiroli and Nagpur districts in Maharashtra state. Nagpur district is a better performing district according to Government of India reproductive health indicators and is home to the Government Medical College, Nagpur. Gadchiroli is a tribal and poor performing district located 170 kilometers away from Nagpur city. We were unable to obtain government approval to conduct the survey in public sector facilities in the two districts. Instead, we conducted the survey in a sample of private maternity homes in the two districts. The final sample included 24 private maternity centers (Nagpur: 15 centers; Gadchiroli: 9 facilities) or approximately 40% of private maternity homes in the districts (n=60). The team also assessed the availability of essential medicines in the two closest pharmacies to these medical facilities (Nagpur: 27 pharmacies; Gadchiroli: 26 pharmacies).

RESEARCH SUMMARY

Indian Context

- About **one fifth** (56,000) **of global maternal deaths occur in India**.
- MMR has declined from 167 to 130
  - (2030 target: 70)
- HDPs (11%) were the second leading cause of maternal death (HMIS, MoHFW, 2014-15)
  - Incidence of preeclampsia: 8-10% of pregnant women
  - Prevalence of HDP: 7.8%
  - Among women who received ANC for most recent birth in past 5 years (NFHS 2015-16), 89% had their BP measured and 88% had urine assessed

Antihypertensive Medications

Essential Medicines List

Table 1. Health Facility Level for Stocking Essential Medicines as per National EML

Medicine	Dosage	Lowest level of care	
		NLEM 2015	IPHS
Labetalol	Injection 5 mg/ml	Primary, Secondary, Tertiary	
Methyldopa	Tablet 250 mg Tablet 500 mg	Primary, Secondary, Tertiary	**Primary,** Secondary, Tertiary
Nifedipine	Tablet 10 mg (for preterm labor)	Secondary, Tertiary	**Primary,** Secondary, Tertiary
Diazepam	Oral liquid 2 mg/5 ml Injection 5 mg/ml Suppository 5 mg	Primary, Secondary, Tertiary	**Primary,** Secondary, Tertiary
Magnesium sulphate	Injection 500 mg/ml	Secondary, Tertiary	**Primary,** Secondary, Tertiary

References: India National Essentials Medicine List (NEML 2015); Indian Public Health Standards (IPHS 2016)

Treatment Protocols

Table 2. Treatment Guidelines for Treatment of Severe Hypertension in Pregnancy

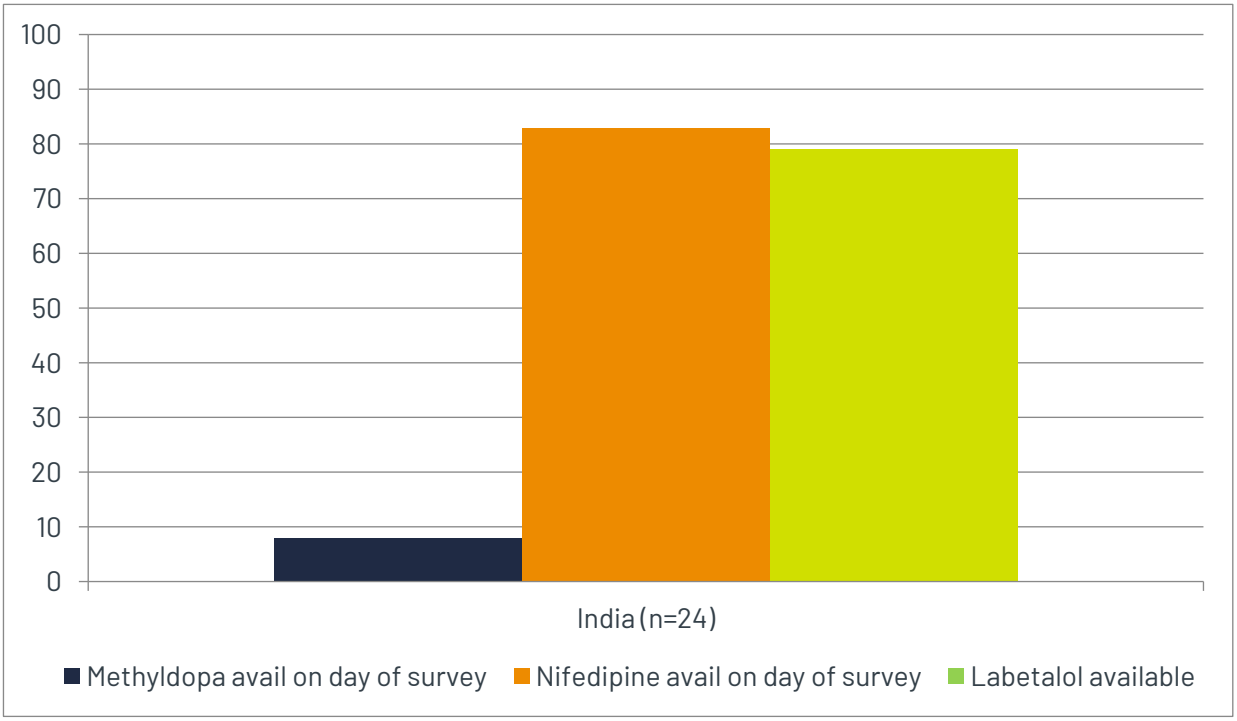
Drug	World Health Organization	NELM 2015
Antihypertensive drug treatment guideline	**ORAL** **Methyldopa** 750mg oral with a repeat dose after 3h until BP goal achieved. Max dose: 3g in 24 h. **Nifedipine** 5-10mg immediate-release capsule oral with a repeat dose after 30 minutes if response is inadequate until BP goal achieved. Max dose in acute treatment setting: 30mg. **Labetalol**: 200mg. Repeat dose after 1h until BP goal achieved. Max dose: 1200mg in 24 h. **IV** **Hydralazine** 5mg IV repeated every five minutes until BP goal achieved. Repeat hourly as needed or give 12.5 mg IM every two hour as needed. Max dose: 20mg in 24 hours. **Labetalol** 10mg IV and, if the response is inadequate after 10 minutes, then 20mg IV. Maximum total dose: 300 mg.	**ORAL** **Methyldopa** 250/500 mg 3-4x per day. Repeat every 3 hours (max 2-3 gm/day) **Nifedipine** 5-10mg. Repeat 30 min (max 30/120mg/day) **Labetalol** 100-200 mg every 12h (max 1200mg) **IV** **Labetalol** 20 mg stat, 40 mg after 20 mins; increase to 80 mg (max 300 mg/day) **Hydralazine** 5 mg IV, slowly, repeat / 5 mins OR 12.5 mg IM/ 2 hrs (max 20mg/day) **IV Nitroglycerine** 50mg in 500ml 5% Dextrose

References: *Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors* – 2nd ed (WHO, 2017). WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0 IGO. *National Essential Medicines List (NEML 2015)*

Given the large pharmaceutical industry in India, there are several nifedipine, labetalol and methyldopa products (tablet and IV) available in the market. Companies must register any drug intended for sale with national (Drug Controller General of India), regional and state-level registries and these authorities are required to maintain a list of registered products. However, none of these agencies maintain an online or publicly accessible database of registered products, so it was impossible to confirm the number of registered methyldopa, nifedipine, labetalol or hydralazine products.

RESEARCH SUMMARY

Figure 1. Availability of antihypertensives in surveyed private maternity homes



Key Findings: Antihypertensive Medicines

- Greater coherence needed between procurement and treatment guidelines
  - GOI guidelines recommend use of hydralazine but hydralazine is not included on the EML
  - Methyldopa is the only oral medication included in the NEML for treatment of severe hypertension in pregnancy
  - EML does not allow for use of nifedipine and MgSO4 at primary level but IPHS does recommend
- National Clinical Guidelines:
  - ANM authorized to provide MgSO4 but not authorized to give antihypertensive in case of PE/Eclampsia although stocked at PHC level

Antihypertensive Medications

Challenges

- The national EML alone may be insufficient to promote treatment of HDP
  - Labelled indications and/or formulation may require further clarification in practice guidelines.
  - Oral medications may not be considered first line treatment for severe hypertension in pregnancy in national guidelines and/or not stocked at health facilities providing either basic or emergency obstetric services.

Recommendations

- Provide clarification and guidance in global and national EMLs and treatment guidelines on use of
  - oral medications
  - different nifedipine formulations (immediate and modified release) and different dosages (e.g. 20mg tablets)
  - dose escalation protocols
  - treatment of mild vs. severe hypertension in pregnancy

Quality Assurance Measures for Blood Pressure Devices

Our landscape assessment found **very little regulation or national policy guidance on procurement of blood pressure devices in all three project countries.**

- In India, BP monitors are not a notified device and thus do not require registration with the national drug authority (Drug Controller General of India). Instead, manufacturers must only obtain a No Objection Certificate (NOC) from the DCGI stating that the product does not require registration and can be imported freely.

Financing for the Replacement or Repair of Existing Blood Pressure Devices

In India, all government health facilities from the sub-center to the tertiary care center are expected to be equipped with a fully functional blood pressure apparatus (usually manual sphygmomanometer) and a stethoscope. In case of disrepair, the health service providers can either requisition those from the central store identified for supply or purchase them locally with the untied funds availability within the facility. *However, one key informant working in the public sector noted that while funds are locally available, the decentralization of the procurement process has sometimes proved challenging and resulted in stock outs in devices.* The respondent noted that medical officers in charge of lower level facilities were either not at their posts and/or often slow to order and/or do not account for the days needed for supplies to reach a facility. As a result, equipment was frequent missing.

RESEARCH SUMMARY

Blood Pressure Devices

Challenges

- Very little regulation or national policy guidance on procurement of blood pressure devices
- Financing mechanisms for replacement or repair of devices or provision of consumable supplies such as batteries unclear

Recommendations

- Improve technical specifications and financing guidance for blood pressure devices
- Collaborate and partner with broader efforts to improve access to blood pressure devices as part of national and international advocacy and quality improvement programs for improving care for general hypertension and non-communicable diseases.

References

[1] World Health Organization. WHO Recommendations: Drug treatment for severe hypertension in pregnancy 2018.

[2] Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet Lond Engl 2006;367:1066–74. doi:10.1016/S0140-6736(06)68397-9.

[3] WHO | Managing complications in pregnancy and childbirth: a guide for midwives and doctors – 2nd ed. WHO n.d. http://www.who.int/maternal_child_adolescent/documents/managing-complications-pregnancy-childbirth/en/ (accessed September 23, 2019).

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