

Implementing Effective Investigations for Cause of Stillbirth

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Stillbirth is one of the most common adverse pregnancy outcomes in low and middle-income countries (LMICs), with rates in the range of 40 to 50 per thousand births in some regions [1]. International goals aim for no country to have a rate of >10 per thousand births by 2035 [Hug L, et al. *Lancet*. 2021;398(10302):772-85]. To achieve this, a better understanding of stillbirth causes often requiring additional investigations is critical. For several reasons, including low prioritization, inadequate resources, and hesitancy by families and providers, investigations on stillbirth causes in LMICs have been limited to date.

Bedwell et al used a grounded theory approach to explore the views of women, partners, families, health workers and community leaders in Malawi, Tanzania, and Zambia regarding investigations to determine the cause(s) of stillbirth [Bedwell et al, *BJOG* (in press)]. While most would like more information regarding the stillbirth, the authors noted cultural and religious obstacles to performing the investigations, including preferences for quick burial, reluctance to disfigure the deceased fetus, concerns about blame, as well as costs.

One test to inform cause of stillbirths is minimally invasive tissue sampling (MITS), using needle biopsies to obtain internal organ tissue for histological evaluation and microbial analyses. For a study on causes of stillbirth in Pakistan and India, we explored the acceptability of MITS among parents, relatives, religious leaders, and government officials [Feroz A, et al. *Reprod Health*.2019;16(1):53]. The perceived benefits included knowing the cause of death, and both personal and societal benefits in preventing subsequent stillbirths. Concerns regarded rapid burial and reluctance to disfigure the stillborn. In Pakistan, with some caveats, religious leaders approved, and, when MITS was undertaken, in both Pakistan and India, approximately 50% of the parents consented for the MITS procedure.

Because obstacles to testing in general and to MITS specifically relate to time, cost, and disfigurement, we have considered which examinations feasible in LMICs provide the most information at minimal cost. Page et al., in a similar exercise in a US study, noted that the most useful test was placental histology (65%) followed by full autopsy (42%) [Page JM, *Obstet Gynecol* 2017;129(4):699-706.]. No other tests were useful for >12% of cases. Similar studies have rarely been performed in LMICs. The prevalence of the causes relates to the frequency of tests' usefulness. In high-income countries where birth asphyxia and infection have been reduced, congenital and genetic anomalies have assumed a larger proportion of stillbirths, and testing for those conditions using karyotyping and other genetic tests become proportionately more important.

However, in many LMICs, birth asphyxia remains the major cause of stillbirth and genetic issues play a smaller proportional role.

To develop the most effective methodology to determine cause of stillbirth, the prevalent conditions, and the tests' usefulness to diagnose those conditions should be considered together. Importantly, the community and other stakeholder's perceived benefits and obstacles to various tests as described in the Bedwell, et al must be considered to ultimately be successful in implementing the necessary investigations.

For LMICs, given that asphyxia and infection appear to be major causes of stillbirth, tests to diagnose these conditions will likely be important to implement, including the obstetric history and histological placental evaluation for diagnosing asphyxia and infection. Of potential information gained from MITS, histology of the fetal lung, and bacteriological assessment of the fetal blood and brain/CSF may be the most useful. Thus, by considering the prevalence of the causes of stillbirth, the usefulness of tests to diagnose the prevalent conditions, and importantly addressing the community's sense of benefit and obstacles, an effective approach to stillbirth cause of death investigation can be developed.

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