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KEYNOTE ADDRESS

The worldwide burden of postpartum haemorrhage: Policy development where inaction is lethal

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Abstract

Most maternal deaths occur to women who are not attended by trained health professionals. Postpartum hemorrhage is the single most common cause of maternal death. The delivery of large haemochorial placenta in our species predisposes to heavy bleeding and can be dealt with only by using effective uterotonics. The 1987 Safe Motherhood Initiative has failed to reduce maternal mortality significantly, and shortages of trained personnel will not be remedied in the foreseeable future. Bold new policies are imperative and need to be derived from an appropriate evidence base. It is suggested that these should include the low-cost shock garments in primary health facilities and making misoprostol easily accessible in both the public and private sector.

The problem

Most developing countries lack an adequate vital registration system [1], which makes accurate estimates for maternal mortality rates and progress monitoring mortality extremely difficult; underestimation is not only possible but very likely. Despite numerous efforts and global initiatives, beginning with the Safe Motherhood Initiative launched in Nairobi in 1987, the number of women dying in childbirth has not substantially decreased over the last decade [2,3] (Table 1). With an unprecedented increase in the number of women of fertile age worldwide, it is quite possible that unless bold new policies are adopted, more women will die from pregnancy, childbirth and abortion in the coming 10 years than in any decade in human history.

Table 1 World total maternal deaths

1968–1971	4 years at 250,000	1,000,000 deaths
1972–1975	4 years at 300,000	1,200,000 deaths
1976–1979	4 years at 350,000	1,400,000 deaths
1980–1983	4 years at 400,000	1,600,000 deaths
1984–1987	4 years at 450,000	1,800,000 deaths
1988–1991	4 years at 500,000	2,000,000 deaths
1992–1995	4 years at 550,000	2,200,000 deaths
1996–1999	4 years at 575,000	2,300,000 deaths
2000–2003	4 years at 575,000	2,300,000 deaths
2004–2007	4 years at 600,000	2,400,000 deaths
TOTAL		18.2 million deaths

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At the beginning of the twentieth century, maternal mortality in most developed countries was comparable to parts of Africa today [4,5]. Data from developed countries demonstrates that where a policy to increase the use of midwives came into place, maternal mortality fell rapidly [6–8]. The compelling relationship between the percentage of women attended by a skilled person during delivery and maternal mortality is well documented [9,10].

Ninety-nine percent of the global burden of maternal mortality occurs in developing countries [11]. The largest number of deaths takes place among those women who have no skilled attendant during delivery. The global initiatives of the past 20 years have emphasized emergency obstetric care (EOC). Underutilization of health facilities exists, even in the poorest countries [12], and efforts to improve the referral of women with delivery complications and to improve access to intravenous fluids and cesarean sections are important and worthy endeavors. Even within hospitals and clinics, more deaths from PPH could be avoided if the active management of the third stage were to be adopted universally, instead of the current disappointingly uneven fashion.

The Gonoshasthaya Kendra Health Project (GK) in Bangladesh shows that a 50 bed rural hospital serving 160,000 people can provide outstandingly cost-effective services dealing with life threatening or disabling conditions at a cost of $10.95 per DALY (disability-adjusted life years). In a sample three months, the largest single number of admissions (136/541) was for obstetric causes [13].

However, GK is the exception proving the rule, because few health systems are willing to permit the degree of non-specialist and paramedical involvement that characterizes the work of GK. In most countries where only limited funds are available and geographic coverage of health care is severely limited, focusing on EOC by itself will not come near to meeting the Millennium Development Goal of reducing maternal deaths by three-quarters between 1990 and 2015.

To make matters worse, the health workforce in Africa is likely to decline in the coming decade, as Europe and North America continue to recruit health professionals from developing countries, probably at an accelerating rate. The American Hospital Association reports 118,000 nursing vacancies in the USA and predicts this number will grow to 800,000 by 2020 [14].

If health professionals and goverments want maternal mortality to be reduced, then they must work together to take the solution to the problem. In general terms, the causes of maternal mortality are relatively constant across history and across nations. and postpartum hemorrhage (PPH) is nearly always the most common single course of maternal death [15]. The crucial question that must be answered is: “Do we presently have sufficient knowledge and appropriate technology to control PPH and to save mothers' lives in the villages and slums where women live on one or two dollars a day and where most maternal deaths take place?”

The challenge of controlling PPH

Before proceeding, it is useful to remind ourselves why PPH is such a lethal complication of parturition. The structure of the mammalian placenta is well known [16,17], and many species, such as pigs, have an epithelial-chorial placenta in which six layers of tissue separate the maternal and fetal blood streams. Other species , such as dogs, have five layered endothelial chorial placentae. Most primates, although not all, have a haemo-chorial placenta, and it is this placental structure that predisposes them to PPH. Conventional teaching is that the human two layered haemo-chorial placenta represents the more advanced condition, because it facilitates the transmission of gases and nutrients from mother to fetus. However, offspring nourished by multi-layered placentae do as well as human babies, and a review of the phylogentic distribution of the structure of various placentae suggests that the evolution of viviparous mammals began with a highly invasive trophoblast and a haemo-chorial struture. This scenario, which was first suggested 40 years ago [18,19], has recently been confirmed by an up-to-date phylogentic analysis [20]. Many species have been fortunate to develop mutations that have moved them towards an epithelial-chorial placenta, which is associated with a much lower risk of postpartum bleeding. This type of parallel evolution has occurred in species as diverse as opossums, dolphins, the aye aye and horses, suggesting that it is advantageous to have a multilayered placenta, escaping from the danger of PPH.

Uterotonics

Darwinian evolution is not about what is nice, safe or aesthetic, but about what works. Some primates have been fortunate to evolve a multi-layered placenta, but human beings remain burdened with a highly invasive trophoblast and at delivery, the human placenta leaves a huge, 20 centimeter diameter wound on the inside of the uterus. The potential of catastrophically heavy bleeding can be avoided only by powerful uterine contractions and complete expulsion of all placental material.

Ergot alcaloid is the oldest known medicinal used to control post partum haemorrhage; the first written records describing its use date back to 1582. The successful pharmacological control of PPH based on scientific data as well as the first steps towards active management of the third stage of labor were taken by Moir and Dudley, who isolated ergometrine in 1932 [21,22]. Since the 1950s, this drug has saved numerous women's lives, but because of severe side effects such as myocardial ischemia and the need to avoid using it in the presence of pre-eclampsia, it has become less popular over time. Oxytocin is now the drug of choice for PPH treatment. It is highly effective and has an excellent safety profile.

In recent years, the prostaglandin analogue misoprostol has received considerable attention in terms of its ability to prevent or arrest post partum bleeding. Misoprostol is a low-cost, off patent tablet with an excellent safety profile and a long shelf life. Worldwide, it has been taken as a long-term ulcer drug by millions of people during the last twenty years in daily dosages comparable to the ones used to control PPH and is also used in combination with mifepristone for medical abortion by more than 100,000 women a year. The most common side effects include shivering, fever and diarrhea, all of which most always resolve without additional interventions. Even after intentional overdose with as many as 42 tablets, when more serious side effects such as hyperthermia, tachycardia, nausea and cramping were reported [23—26], resolution was rapid with standard care except in one case [27]. Misoprostol has not been associated with teratogenic or carcinogenic risks when tested in high doses in experimental animals [28].

Case reports on teratogenicity in children carried to term after unsuccessful abortions exist [29—32], and case-control studies vary in opinion about misoprostol and the teratogenic risk for babies with prenatal exposure to high dosages of misoprostol [33—35]. However, the literature reports no cases of teratogenity occurring in a subsequent new pregnancy after the use of misoprostol for PPH or abortion.

Brazil and other countries have vast experience with misoprostol taken as the sole drug to induce abortion in situations where the majority of women do not have access to safe abortions. Research in the Dominican Republic, where abortion is not available in health facilities and women often resort to unsafe methods, shows that as sales of misoprostol rose in the mid-1990s — when widespread use of misoprostol to induce abortions was reported — the number of serious abortion complications admitted to the hospital fell, most likely due to misoprostol replacing unsafe abortion methods [36].

Self administration by lay people with appropriate information is possible. In the Dominican Republic, where information on correct use was limited, the availability of misoprostol was nevertheless associated with reduced morbidity (and by inference mortality) from unsafe abortion. Interestingly, the danger of inappropriate use of misoprostol has been brought about as much or more by physicians than by lay people. Some doctors try to induce labor by cutting up 200 mcg tablets inaccurately and causing excessive contractions, uterine rupture, and fetal death. Nigeria and Kenya are moving forward with plans to import 25 mcg suppositories for labor induction, and it is to be hoped that this will overcome the risk of ruptured uteri resulting from inappropriate use of misoprostol.

Who can give uterotonics and how do we know?

Ergometrine and oxytocin require administration through an IV drip or by injection. Storage over long periods of time without a refrigerator is problematic. In a multi-center, randomized controlled trial (RCT) conducted by the WHO, oxytocin proved modestly more effective than misoprostol [37]. In Egypt, a pre- and post-intervention trial design was used to compare current hospital practices with active management of the third stage of labor (including the use of oxytocin) with 600 micrograms of oral misoprostol. The results showed that women in the misoprostol group were less likely to bleed 500ml or more compared with those in the current practices group [38]. On the whole, an RCT is most likely to be conducted in a sophisticated tertiary hospital, whereas comparisons based on using one drug for three months and then another for three more, as was done in Egypt, can be conducted in facilities closer to the reality of stressed developing country health care settings where refrigerators break, not every women has a drip in place and busy midwives can't always find time to stop and give an injection.

Where maternal mortality is high, as it is in Yemen [39], planning a community based RCT is often unnecessary and can also create insuperable ethical dilemmas. Referral systems for women from rural areas are often insufficient and cannot ensure access to EOC for everybody. A placebo-controlled trial which would require using a placebo as well as the life-saving drug during the trial would imply withholding best available (namely misoprostol) treatment from the placebo-group. Other non-randomized trial designs such as pre/post comparisons of current practices versus a new formula avoid such a dilemma and also produce useful results for policy makers.

RCTs also serve the purpose of reducing bias in clinical studies and are commonly seen as the epidemiological gold standard in determining policies in the West. Where maternal mortality is low and any change in clinical practice, although life-saving, is necessarily small in absolute terms, then RCTs are the only way to go. However, carefully designed non-randomized controlled trials are not only more feasible to implement in settings where health resources are scarce, but can be the most appropriate way to inform policy development. When mortality rates are high, even a single new intervention, such as using misoprostol to treat or prevent PPH, can have a powerful effect that can be demonstrated unambiguously with a simple comparison of treatment and non-treatment regions or time sequences. This was how antibiotics were first introduced, how oral rehydration was adopted and, incidentally, how policies related to the active management of the third stage of labour were initially developed.

A useful framework for determining whether an RCT is appropriate is to compare health expenditures. For example, in Yemen $32.00 is spent per capita per annum on all aspects of health care [40] compared with almost $5,500 in the USA [41]. The use of misoprostol, as an alternative to non-treatment, is likely to have an impact which is so powerful that a bias-minimizing RCT — even if it were ethically acceptable at the community level — might not be needed to set appropriate life-saving policies. An RCT is an appropriate gold standard when the cost of a mistake is high; simpler comparisons are appropriate when the cost of inaction are even higher.

Reaching the most vulnerable women

Of the past several decades many attempts were made to train traditional birth attendants (TBAs) in the hope of reducing maternal mortality. By and large the strategy failed, and there is a current disillusionment with training TBAs [42—44]. However, if we step back and look at the problem, very little of what we could teach a TBA prior to the introduction of misoprostol was likely to make any significant impact on maternal mortality. Of course it is a good idea for a TBA to wash her hands and to cut the cord with a clean razor blade in order to decrease the risk of tetanus in the baby or puerperal fever in the mother, but these basic health interventions are not likely to have a significant impact on MMR. There were also attempts to teach TBAs to refer high risk pregnancies, but most cases of postpartum hemorrhage occur unpredictably in women who were thought to be at low risk of death in childbirth. In contrast, misoprostol is a simple intervention that TBAs can handle with very large potential impact on MMR.

The shock garment is a robust, low-cost technology that has been shown to reduce deaths from PPH in health facilities [45]. It can have a remarkable impact reviving a woman in extremis from blood loss and help her survive the critical time during transportation to the nearest health facility. Low-cost shock garments should be manufactured on a large scale and widely distributed to hospitals and health centers. However, their use is one step removed from treatment at the site of the problem in those countries where most births take place at home.

In countries such as Uganda and Kenya, the majority of women receive antenatal care but fewer than half are attended by a skilled attendant at delivery [46]. The primary reason is poverty. Even a 'free' government service can be too expensive when travel, the purchase of medicines and even sutures are taken into account. The poor often complain of being treated in public hospitals or clinics with little or no respect for their traditional beliefs and customs [47]. It is not as widely understood, as it should be, that among the lowest three economic quintiles in sub-Saharan Africa and countries in Asia such as Afghanistan, of those people who receive any health care, 80% are treated by the private informal sector and not by the government facilities [48]. Of the $32 spent on health in Yemen each year, only $3.60 is paid by the Ministry of Health [49]. In the 600,000 villages of India the majority of people go to Rural Medical Practitioners (RMPs), as the formally trained MBBS doctors usually do not work in these villages. It will not be possible to improve health significantly for the rural poor unless we recognize this fact.

The private informal medical sector in resource-scarce settings represents a range of good and bad services. Some practitioners are ignorant or exploitative. Many others are intelligent and committed, and could be delegated a wider range of medical diagnostic and therapeutic tasks than is currently permitted. The example of GK noted above is revealing because for 30 years this organization has trained village women — many of them illiterate — to undertake a range of medical tasks, including abdominal surgery.

Many parturient women in any number of countries do not receive care even from a TBA. It will be possible to help women who are delivered by family members, or who like women in Tibet are expected to deliver at home, only if they can self-administer misoprostol to prevent PPH. Initial research by JHPIEGO in Indonesia shows that self-administration

of misoprostol at delivery is possible and can work very well [50]. Several options exist for the responsible distribution of misoprostol. In Africa, many women attend antenatal clinics but deliver at home, and the clinic could provide the education and misoprostol for use at delivery. Skilled community workers could also counsel women and provide the drug.

Conclusions

The shock garment is a life-saving technology useful for primary care centers in low resource settings. Other technologies, such as uterine tamponade are being explored and could provide additional ways of treating PPH in low resource health facilities [51]. The most immediate opportunity for saving women's lives is to make misoprostol widely available directly to TBAs and other private health providers, such as RMPs, either to treat PPH with 1000 mcg misoprostol rectally when appropriate protocols exist to measure blood loss accurately and diagnose PPH, or to prevent PPH by giving every women 600 mcg orally as soon as the baby is delivered. The Indian government is ahead of most of the world in recognizing the value of paramedical application of this life saving drug, enabling auxiliary nurse-midwives (ANMs) to use it to control PPH at the village level.

The fact that misoprostol may also be used to induce abortion is not directly relevant to a general discussion of the availability of the drug to save lives by controlling PPH. Women have tried almost any available drug or device to induce abortion [52]. No one has attempted to take coat hangers, aspirin or antimalarials [53] off the market. Similarly, we suggest, we cannot refuse to make a drug available that has the potential to save many women from bleeding to death in their village — simply because it may occasionally be used for other purposes.

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