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EDITORIAL

The ethical conundrums of antenatal corticosteroid therapy

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Introduction

We all know the dictum, *primum non nocere* or "first do no harm", often attributed to Hippocrates (460–370 BC) and to one of the earlier versions of his famous oath to desist from doing harm. Although the specific phrase may have been uttered and adopted much later in the 17th century, its importance in more contemporary medicine is commonly invoked when risking more harm than good. This fundamental bioethics principle of nonmaleficence should really guide our daily clinical practice in concert with the other three pillars: beneficence, autonomy, and justice.[1,2]

Prematurity, defined as delivery before 37 weeks of completed gestation,[3] is accompanied by considerable risks for acute respiratory distress syndrome (RDS), chronic bronchopulmonary dysplasia, necrotising enterocolitis, neonatal jaundice, cardiovascular disorders, hearing impairment, retinopathy of prematurity, hypoxic ischaemic encephalopathy, cerebral palsy, seizures, intraventricular haemorrhage and mortality.[4-5] It is estimated that around 13–15 million infants are born prematurely each year.[6-7] Annually, four million neonatal fatalities occur, primarily from the immediate consequences of RDS caused by immature lungs that lack surfactant.[8]

In their landmark study, Liggens and Howie (1972) reported that administering antenatal corticosteroids (ACS) to pregnant women at risk for early delivery, significantly decreased RDS in their premature babies.[9] These findings brought hope to the obstetrics, gynaecology and paediatrics communities, and the utilisation of synthetic corticosteroids to induce lung maturation has been hailed as one of the most significant breakthroughs in perinatal medicine.[10] However, in the past two decades, boundaries in preterm labour and delivery have continued to be pushed to the point where there is currently controversy about babies existing at the threshold of viability, especially those born between 22 and 24 weeks gestation.[11] Children delivered in this periviable period who survive to adulthood are unlikely to function at their full potential. Up to 50% of those who survive, do so with significant impairment, half of whom have a major handicap.[11-12]

Although ACS therapies have become game changers in reducing RDS risk, consideration should be given to their ethical use. The placenta usually protects the foetus from exogenous corticosteroids as well as from maternal cortisol as the enzyme, 11 beta-hydroxysteroid dehydrogenase-2 (11β-HSD-2), transforms these hormones to metabolically less active 11-keto forms. This enzymatic degradation assures a low cortisol intra-uterine environment for most of the pregnancy, which is critical for normal mammalian foetal development.[13] In humans, the foetus starts producing cholesterol from its own adrenal glands from about 28 weeks gestation.[14-15] Cortisol in turn is derived from cholesterol through the steroidogenesis pathway.[16-17]

Exogenous antenatal betamethasone and dexamethasone are ill-fitting substrates for 11β-HSD-2 and easily cross the placenta unchanged, thus allowing almost direct delivery to the foetus before the appropriate gestational time. These are therefore the drugs of choice for inducing lung maturation.[13,18] There is a caveat, though: ACS administration clearly benefits the foetus if delivery takes place prematurely (< 34 weeks gestation), but has the potential to cause harm when, despite threatened prematurity, pregnancy progresses to labour at full term. Adverse systemic effects may become apparent in later life and long-term effects on children, adolescents, and adults exposed to these agents *in utero* are currently the focus of numerous human and animal studies.[4,13,19-28] There is a growing body of evidence showing pervasive complications, especially of the hypothalamus-pituitary-adrenal (HPA) axis, blood pressure and glucose metabolism as these children, adolescents and adults have a lifelong altered adrenal stress response and are at higher risk for developing diabetes mellitus.[11,29] As the greatest burden of preterm births affects sub-Saharan Africa and Asia, this is particularly relevant in under-resourced South Africa.[6,30] The major bioethical principles are highlighted in this context.

Beneficence

Beneficence simply means that it is the responsibility of a medical practitioner to act for the well-being and benefit of the patient.[2] Administering ACS to expectant mothers at risk of premature delivery reduces RDS and thus increases the neonate's chances of survival, thus meeting beneficence criteria. Unfortunately, as many as 50% of foetuses exposed to ACS are ultimately delivered after 35 weeks gestation,[31-32] when precautionary ACS exposure/prophylaxis becomes redundant. In fact, unnecessary ACS does not benefit the unborn child, but instead may be detrimental:

almost all immature organ systems may be adversely affected as corticosteroids promote differentiation but not proliferation. This may often have lifelong consequences. This leads to the principle of first doing no harm.

Nonmaleficence

The principle of nonmaleficence compels physicians to refrain from causing harm or inflicting pain and suffering on their patients.[2] Foetuses delivered prematurely benefit from intra-uterine ACS exposure. Reduced risks for mechanical ventilation and other invasive therapies, significantly alleviate the potential for acute pain and suffering. In this regard, nonmaleficence is achieved. Yet ACS therapy is also associated with greater risks for anxiety, attention deficit disorder, behavioural disorders, autism spectrum disorders and even suicide.[33-34] Negative mental health outcomes in later life due to *in utero* ACS exposure are real causes for concern, begging the question of whether or not healthcare providers inadvertently set in motion a chain of potentially harmful events before the foetus is born. For instance, alterations in HPA axis function cause abnormal, lifelong stress responses,[13] while fertility in male and female offspring may be adversely affected, even transgenerational.[35-38] Are pregnant women at risk for preterm delivery aware of the potential harms of this life-saving intervention?

Autonomy

The concept of autonomy is understood and acknowledged as an ethical principle that grants all individuals an inherent entitlement to make rational decisions and choices, permitting each person to express their capacity for self-determination.[2] It may be argued that the unborn child lacks the ability to make rational decisions and lacks the capacity for self-determination because of an insufficiently developed central nervous system.[39] Therefore, there is no justification in asserting that a foetus possesses a viewpoint of its own interests. Consequently, there can also be no obligation of autonomy towards any foetus.[39] It may also be argued that pregnant women, and sometimes their partners, are in an autonomous position to make well-informed, voluntary and ethical choices regarding the handling of their pregnancy. There is both a legal and an ethical obligation to inform expectant mothers of all the risks and benefits of the proposed treatment.[12,39]

Informed consent

The prerequisites for obtaining informed consent for a medical or surgical procedure, or for research, are that the patient is competent to comprehend and make decisions, receives comprehensive information, understands the information, acts of their own volition, and agrees, without pressure, to the suggested course of action.[2] The expectant mother should be fully aware of the short-term advantages as well as the potential long-term effects of ACS therapy so that she is able to consent to its administration or is able to refuse this course of action.[39] The unborn foetus does not possess the capacity to give informed consent.

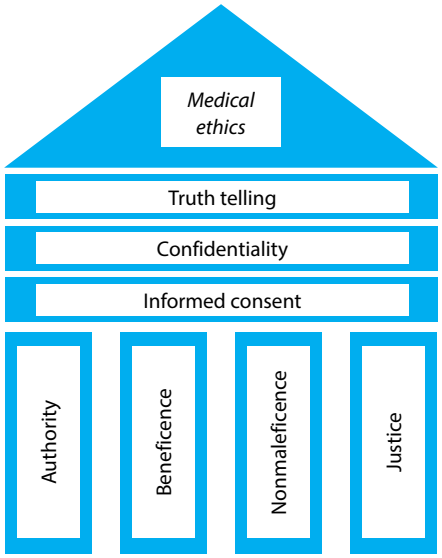

Figure 1: Medical ethics

Prioritising ethical principles

How do we prioritise the different principles/pillars of biomedical ethics, especially when they may be perceived as being in conflict with one another? (Figure 1). First and foremost are the best interests of the patient that are widely regarded as the sum of autonomy, beneficence and nonmaleficence. Secondly, patient autonomy takes preference over beneficence and nonmaleficence. Thirdly, the interests of others may sometimes outweigh respect for patient autonomy, and lastly, when the possibility of harm and benefit are proportionate, nonmaleficence takes preference.[40]

There are other facets to medical ethics, which can provide a more nuanced practice, and these include telling the truth, patient confidentiality, informed consent and justice.

Truth Telling

A self-governing patient possesses the right to be informed about their diagnosis, prognosis, and treatment alternatives, but also retains the choice to decline this information.[2] In the context of ACS therapy, should the mother and/or her treating physician also inform her offspring about possible mental and physical health risks associated with its exposure during its foetal period?

Confidentiality

Both clinical and non-clinal physicians are actually obligated not to disclose any information given by a patient to another party without the patient's prior authorisation.[2] This contrasts a 2 000 year history of medical practitioners sharing their experiences freely in order to advance medicine. Patients' tacit approval for divulging their information in order to benefit others who may have a similar condition, was assumed, although the treating doctor was under a legal and ethical obligation to protect patient confidentiality. Now, however, according to the General Medical Council (GMC) in the United Kingdom, information may be shared between medical researchers only with the patient's clear consent. The additional hurdle that needs to be overcome

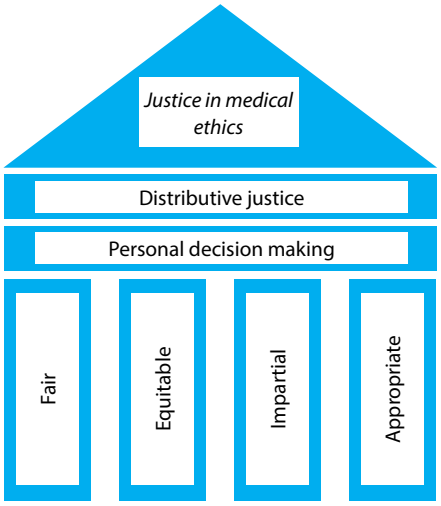

Figure 2: Justice in medical ethics

for epidemiological and retrospective research is designed to protect the patient, yet may possibly not benefit the population at large.[11]

Justice

Justice is the fair, equitable, and appropriate treatment of persons. There are several categories of justice, of which distributive justice, which includes the distribution of healthcare resources, is the most prominent.[2] This means that patients with similar conditions should be treated equally, and that there is equity in resource distribution. An example could be the aggressive management of an extremely premature baby with a poor prognosis and a slim chance of survival, constituting inappropriate use of available resources.[12] It could also be extrapolated to patients from lower income countries, such as much of sub-Saharan Africa, but also to patients from countries with large dispersive healthcare systems, who have the equal right to life-saving medication, technology and new advances. It should not only be the "rich and privileged" or a select few that have access to optimal care.

The foetus as a patient

Advances in foetal diagnosis and care aimed at maximising foetal well-being have gained widespread traction and have fostered the idea of the foetus as a patient.[40] The foetus is regarded as a patient on presentation to the doctor for medical procedures, either for diagnosis or treatment, that are anticipated to yield a more favourable balance of medical benefits (beneficence) over potential risks or harm (nonmaleficence) for both the foetus and the future child.[41] Providing guidance for the benefit of the foetus is ethically defensible.

Healthcare providers have responsibilities towards the expectant mother, grounded in the principles of "doing good" and respecting her autonomy, as well as responsibilities towards the foetus, also based on the principle of "doing good". This suggests that the foetus may not be treated as a distinct patient independent of the pregnant woman.[12]

When regarding the foetus as a patient, offering advice on the well-being of the unborn is ethically justifiable. This guidance enables the pregnant woman to exercise her autonomy and should not be labeled as "paternalism" from the mother's side.[39]

Conclusions

The ethical principles of beneficence, emphasising the promotion of well-being, and nonmaleficence, stressing the avoidance of harm, have long been fundamental in the field of medical ethics. They necessitate physicians to strike an optimal balance between the benefits and potential harms to the patient. Beneficence stands as a key compass in endeavours to preserve the lives of children who cannot survive independently. Conversely, the principle of nonmaleficence is paramount in cases where decisions are made to prolong life amid intense suffering or when administering treatments that carry potential risk for damage.[12] The ethical challenge in this scenario is that it is not possible to talk about quality of life, if there is no life.

As evolving research of ACS therapy reveals that there may be medium- and long-term risks associated with its use, it is deemed ethical to inform expectant mothers of the possible consequences for their children. Medical ethics expects the treating physician to possess the clinical and technical expertise to give appropriate and professional advice to the expectant mother, in the context of considering the best interests of two patients, i.e. mother and child.[2,40]

At present, the best available drugs to enhance foetal lung maturity in those at risk for preterm delivery are dexamethasone and betamethasone. However, it is paramount that updated treatment guidelines are adhered to in order to prevent overexposure to ACS. Future research should focus on developing targeted drugs or seeking different routes of administration of ACS so that only the relevant organ system is targeted, i.e. the immature foetal lung.[32] In the meantime, we should adhere to the overarching principle of "first do no harm."

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