

Ethics, minimal harm and non-therapeutic research in newborns

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In this issue, Cumberpatch et al provide a fascinating and important insight into a unique study of blood glucose in healthy newborns.[1] The GLOW study was designed to help understand what happens to glucose and related metabolites in newborn infants after birth. This is important, because there are a large number of newborns who have their blood sugar measured after birth. Clinicians need to know what a normal sugar level is, yet there is a lack of high quality relevant evidence to guide that determination. This has contributed to striking differences in the recommendations from different bodies about what glucose level to aim for. There is a danger that some newborn infants are being overtreated (with risks of separation from parents, interference with breast feeding, unnecessary medicalisation) or undertreated (with risks of hypoglycaemic brain injury).

One of the reasons for the lack of evidence is the problem that healthy newborn infants do not routinely have blood tests (apart from newborn screening at a couple of days of age). To work out what happens to blood sugar in normal newborns, you would have to perform clinically unnecessary blood sampling on multiple occasions over the first hours and days. Would any research ethics committee allow such a study to be performed? Would any parents of healthy newborn infants agree to their babies being in the study?

Ethical guidelines tend to be fairly restrictive of non-therapeutic research in children and newborn infants. It is all very well for competent adults to volunteer to take part in research, but there is a much more cautious approach to studies for those who cannot consent. Without any prospect that the individual child would benefit from the research, guidelines typically prohibit research that would pose significant risks. Sometimes such guidelines only allow “minimal risk”, others accept that “minor” or “low” risks might be acceptable [2] (though there then remains a serious challenge in establishing what counts as sufficiently low or minor or minimal).

The GLOW study involved taking four 0.1ml heel-prick blood samples in the first twenty-four hours, then up to three more samples per day over the following four days to a maximum of 16 samples. Infants also had a subcutaneous needle placed on the day of birth for continuous interstitial glucose monitoring. Would 16 heel-prick blood tests count as a significant (more than minor or low) risk for a newborn? One response would be to argue that heel prick blood sampling doesn't involve *any* risks for babies, since it isn't likely to cause any lasting harm. Some of the emerging literature on the developmental consequences of painful procedures in newborns might cast a doubt on that claim. There is some preclinical and clinical evidence of altered sensitivity to pain and brain development following repeated exposure to painful procedures, particularly in very preterm infants.[3] However, if there is a long-term risk to newborn term infants from repeated heel prick tests, it does appear to be small in magnitude. What might generate more concern is the short-term burden and discomfort for infants. Is it at a sufficiently low level that parents could reasonably enrol their baby in the research, to benefit future infants? Or is it so high that the study should not proceed, even if parents would participate? The GLOW authors write that “we, and the ethics committee who approved the study, considered that the potential benefits to the wider population outweighed the minimal risk to the baby”. Are they right? While it can't definitively answer the ethical question, the parent feedback in this issue supports the view that heel prick blood tests represent only a minimal burden/risk to newborns. First, it is encouraging that the researchers were able to recruit 70 families over a relatively short period (20 months) to participate in the GLOW study. Second, only 13% of the parents who took part in the study reported that they disliked the frequent blood tests

for their baby. Third (and strikingly), 100% said that they would recommend the study to family or friends, and 96% indicated that they would participate again. Obviously, there is some potential for selection bias: parents who were concerned about unnecessary painful procedures for their infant would have been unlikely to take part. Nevertheless, it is very reassuring (and a credit to the research team) that those who participated in GLOW reflected so positively on their experience.

In terms of the ethics, one argument in favour of the GLOW study would draw on the fact that there are a large number of term newborn infants who have repeated heel prick testing in the first days of life (for clinical reasons). Occasionally families have concerns about those tests, and wish them not to take place. In that setting, health professionals would usually be quick to reassure that the burden for the baby was minimal and the long-term risks non-existent. If such reassurance is justified, it would appear to be required, as a matter of consistency, to make a similar assessment of the burdens and risks of non-clinically-required blood tests.

Apart from its important implications for our understanding of glucose control, the GLOW study may have significant ramifications for research in newborns. If the GLOW study was ethical to perform, that suggests that research studies in newborns could include non-clinically required blood sampling where the information obtained is important and cannot be sought any other way. That could facilitate research into normal levels of electrolytes, inflammatory markers or hormones that are clinically important and fluctuate or change after birth. One potential beneficiary may be the study of pain itself in newborns. There have been very significant recent advances in our understanding of the neuroscience of pain in newborns; however, there is much still to learn. Studies have managed to identify a pattern of neural activity that is associated with pain perception from heel prick testing.[4] There have also been attempts to use these signatures to assess the effectiveness of different pharmacological and non-pharmacological strategies for reducing procedural pain (eg gentle stroking).[5] To date, however, those studies have been limited to clinically required sampling or to mild non-skin-breaking experimental noxious stimuli. A future crossover study, might, for example use fMRI, EEG or other measures to compare directly the effect of different procedures on the neural signatures of pain for newborns who have heel prick tests performed. The report from Cumberpatch and colleagues suggests that such a study might be acceptable to a research ethics committees, might be able to recruit families, and might subsequently be perceived positively by families.

One final point: the GLOW study was possible because a group of 70 parents were prepared to involve their babies in ground-breaking non-therapeutic research. They recognised the value of this research and the benefit to future families. The neonatal community has reason to be profoundly grateful to them.

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2. The Nuffield Council on Bioethics. Children and clinical research: ethical issues. Nuffield Council on Bioethics, 2015. Available at <http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf> accessed

3. Duerden EG, Grunau RE, Guo T, et al. Early Procedural Pain Is Associated with Regionally-Specific Alterations in Thalamic Development in Preterm Neonates. *J Neurosci* 2018;**38**:878-86 doi:10.1523/jneurosci.0867-17.2017.
4. Goksan S, Hartley C, Emery F, et al. fMRI reveals neural activity overlap between adult and infant pain. *eLife* 2015;**4**:e06356 doi:10.7554/eLife.06356.
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