Off-Label Prescribing in Pregnancy – A Case of Risky Business or Business as Usual?

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The licensing of medications for use in pregnancy represents a double edged sword in need of urgent attention. While product licences are important in instilling some sense of confidence that a medication meets stringent tests of efficacy and safety in the management of a specific condition in a specific population, they remain subject to significant limitations and biases. Given the commercial nature of the pharmaceutical industry, many would consider that product licensing is not just solely reflective of a medication passing a regulatory benefit-risk analysis, but also a more stringent internal profit-loss analysis. The benefit-risk analysis is also skewed as a result of associated medico-legal concerns surrounding the potential harms associated with medication use in pregnancy, often without any consideration of the potential harms associated with ineffective management of the underlying disease. It is this unduly influence of commercial interests mixed with medico-legal concerns, and the relative inactivity of regulatory bodies to address these issues that cuts deep into efforts into ensuring equitable access to safe and effective medications during pregnancy. This is especially important in situations where there is extensive evidence to establish the effectiveness and safety of a particular medicine in pregnancy, but when its use lies outside of the approved product licence or label, resulting in subsequent uses of that medicine being "off-label". Such examples of off-label uses include magnesium sulphate prior to preterm birth for neuroprotection of the fetus and antenatal betamethasone for the prevention of neonatal respiratory distress syndrome, both mainstays of current clinical practice. In such cases, the off-label use denotes that neither the pharmaceutical company nor authorities take any legal or ethical responsibility for unexpected events that may occur. This of course creates concerns regarding medico-legal responsibilities of the prescriber, with such concerns having the potential to influence clinical practice decisions regardless of the available evidence. This is demonstrated clearly in a study by Voigt and colleagues included in this issue of the journal.[1] They undertook a nationwide survey of obstetric units across Germany to identify the prevalence of off-label use of misoprostol for induction of labour and reasons for and against its use. Perhaps not unsurprisingly, the most common reasons provided among 34% of the obstetric units who did not use misoprostol for induction of labour involved it being off-label (69%), and uncertainty regarding the

legal situation surrounding its use (27%). Of further interest was that among the non-misoprostol users, 40% indicated that a change in licensing would constitute a circumstance in which they would use misoprostol. This reflects a more general concern regarding the off-label use of medications in pregnancy, with treatment decisions being based on licensing, rather than the level of evidence substantiating its safe and effective use.

Without doubt, the frequency with which medications are used off-label during pregnancy reflects the poor translation of licensing regulations into this area of clinical practice. For example, such off-label use accounted for 83% of all medications prescribed during pregnancy in a large UK maternity hospital.[2] But at this point it is important to highlight the differences between off-label use due to the reluctance from a pharmaceutical company to apply for a license despite there being adequate evidence, and off-label use due to the reluctance to carry out the necessary clinical trials to establish whether a particular medicine is actually effective and safe. These are critically important distinctions to make, as these are what define the differences between appropriate and potentially risky off-label medication use. While significant ethical questions may be raised in relation to the conduct of pharmaceutical companies and their lack of willingness to investigate and license proven effective treatments, ethical questions can also be raised with respect to clinicians prescribing off-label medications during pregnancy, or any medications for that matter, for which use is not supported through high quality trials. Despite off-label use of medication during pregnancy being common, this should not cloud ethical judgements regarding whether there is sufficient evidence to justify off-label use. There is no room for complacency and in situations where evidence is lacking it is the obligation of the medical community to work to rectify this situation. The subsequent generation of high-quality evidence regarding off-label uses serves not only to protect patients from harmful and ineffective treatments, but also to increase their access to proven beneficial treatments.

It is in this light that professional societies play an important role in providing authoritative, robust and reliable guidance on current best practice. Notably, in the article by Voigt and colleagues, 24% of respondents who stated that they did not use misoprostol for induction of labour indicated that they would use it if there were a clear statement of support from the German Society of Obstetrics and

Gynaecology.[1] Somewhat fittingly, also included in this issue of the journal is a review from Marret and colleagues, regarding the off-label use of misoprostol in obstetrics and gynaecology, based on guidelines issued by the French college of obstetrics and gynaecology (CNGOF).[3] Importantly, such guidelines not only define current best practice for clinicians, but they also define the limits of the existing evidence, creating boundaries for clinical practice and highlighting areas for further research.

While many would argue that pharmaceutical regulation is a good thing, it must be noted that it exists to regulate the pharmaceutical industry, not the medical profession. On one hand licensing regulation serves to protect patients from receiving potentially ineffective or harmful medications, but it has the propensity to promote potentially ineffective and harmful practices as a result of its own well noted limitations. Ultimately, medication licensing does not provide proof of the relative effectiveness and safety of a certain medication in comparison to alternative treatments, and many medications of proven efficacy remain unlicensed. It is also clear that there are many medications for which level of use is not commensurate with level of evidence. The off-label use of medications during pregnancy has been a normal part of clinical practice for many years, and it appears unlikely that this will change anytime soon, but we must not let this create complacency. In the meantime, there remains an urgent need for robust approaches to professional oversight and policy efforts to improve the evaluation of benefits and harms of all medications used during pregnancy, particularly those used off-label. With these in place, it becomes possible to fine tune off-label prescribing to achieve optimal health outcomes.

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