

## Oxygen at Caesarean section: too much of a good thing?

Paracelsus (1493–1541), a scientist of the Middle Ages, exclaimed: “All things are poison and nothing is without poison; only the dose permits something not to be poisonous”.

Might this be true of oxygen during Caesarean section? Should oxygen, like most other drugs that we use in medicine, be administered within a tight therapeutic range, where too much of the drug may result in side-effects, but too little will allow insufficient benefit to be conferred by the drug on the patient? Should oxygen only be administered when indicated; thoughtfully and for a limited duration, with the dose being reviewed at regular intervals?<sup>1</sup>

To this day, supplemental oxygen still remains one of the most widely used drugs in clinical medicine and anaesthesia. Its use is virtually universal, but very little consideration seems to be paid to the potential side-effects of its administration.<sup>2</sup>

This question of “How much is too much?” has raised the eyebrows of doctors, particularly anaesthetists, since the late 1940s. With specific reference to the administration of supplemental oxygen to the otherwise healthy parturient undergoing Caesarean section, this editorial serves to examine the dilemma of routine supplemental oxygen administration, not only from the perspective of reviewing the literature, but also by examining the physiological processes in play. Hopefully, this should shed some light on the long-standing debate as to the risks versus benefits to both mother and baby.

The fetoplacental circulation is remarkably well adapted to accommodate inefficient oxygen transfer, and adequate fetal oxygenation is facilitated predominantly by a few factors unique to this circulation:<sup>3</sup>

- The significant difference in oxygen partial pressures and concentrations within the fetomaternal circulation system.
- The higher affinity of fetal haemoglobin (HbF) for oxygen compared with that in the adult. The P50 value of HbF is reduced by approximately 5 mmHg, compared with that for adult haemoglobin (Hb), i.e. a left-shifted oxygen haemoglobin dissociation curve.
- When the pH decreases, or partial pressure of carbon dioxide increases, the affinity of Hb for O<sub>2</sub> decreases (Bohr effect). This facilitates the offloading of O<sub>2</sub> at placental level, where fetal CO<sub>2</sub> is offloaded and decreases the pH of the maternal blood. The double Bohr effect occurs during placental gas exchange because CO<sub>2</sub> offloading from the fetal blood increases the affinity of Hb for O<sub>2</sub>, while CO<sub>2</sub> transfer to the maternal blood reduces that affinity, thus freeing up more O<sub>2</sub> for transfer to the fetus.
- The concentration of haemoglobin in the fetus is approximately 50% higher than that in the mother.
- Pregnancy causes a right shift of the maternal Hb-O<sub>2</sub> dissociation curve and so increases placental oxygen delivery.

Oxygen itself is not toxic. Rather, it is the reactive oxygen species (ROS) formed as a byproduct of its metabolism that confers potential harm.

ROS are all not all bad though, and when formed in moderation, may confer potentially physiological benefits. These include the regulation of the perinatal circulation, cellular signalling and local homeostasis.<sup>4</sup> Mechanisms are in place, in health, to regulate the production of ROS. However, if these mechanisms are overwhelmed, as might be demonstrated when supplemental oxygen is unnecessarily provided, or when there is reduced antioxidant protective capacity, as seen in the preterm neonate, it is likely that the ROS will become cytotoxic, possibly resulting in complications such as bronchopulmonary dysplasia or retinopathy of prematurity. They react readily with cellular DNA, proteins and lipids, and impair the function of important intracellular molecules, resulting in apoptosis and premature cell death. ROS may also promote an inflammatory response, leading to secondary tissue injury. It is not only the hypoxia that causes fetal damage, but the oxidative stress mediated by the ROS generated on restoration of oxygenation; an ischaemia-reperfusion type injury.<sup>5</sup>

The formation of ROS involves various different pathways, two of which are of specific relevance to the peripartum period. The genesis of the ROS during periods of hyperoxia, as seen with the liberal administration of supplemental oxygen, and ischaemia-reperfusion injury, as seen for example, in fetal distress, are different. However, we tend to associate the presence of these products with adverse fetal condition on the basis of their observation in the latter. The question remains as to whether or not it necessarily follows that the acute hyperoxic formation of ROS implies fetal harm.

This then begs a few questions. If the fetus is so well adapted to a low PO<sub>2</sub> (normal being 25–40 mmHg), is there an advantage to increasing that PO<sub>2</sub> above physiological values? If so, what is the nature of this advantage, and is it clinically significant? When, and under what circumstances, might increasing oxygenation be advantageous? And then, after all those questions have been answered: Is the administration of an increased maternal-inspired oxygen concentration the best way of improving oxygen delivery to the fetus? What concentration and what flow rates of the inspired oxygen are optimal? Might there be an advantage, not just for the fetus, but also for the mother, in receiving additional oxygen? And ultimately, do the benefits so far outweigh the risks that the use of oxygen in this scenario should become routine during all Caesarean deliveries?

While supplemental oxygen is obviously essential in any patient at risk of hypoxia, the maternal benefits in the non-hypoxic patient, such as the proposed reduction of surgical site infection, are doubtful in the obstetric setting. Although it has been suggested in some earlier work, the results of the recent PRavastatin and atorvastatin effects on OXidative stress and Inflammation (PROXI) trial showed that high perioperative inspired oxygen fractions were not associated with less surgical site infection rates.<sup>6</sup> Supplementary oxygen may be useful in “buying time” before desaturation during an obstetric catastrophe requiring rapid conversion to general anaesthesia. This was demonstrated by McClelland et al in 2009, where, using

a simulator, they showed an extremely rapid desaturation in labouring patients during apnoea. An extraordinary 95% of the maximum change in the arterial oxygen partial pressure occurred within just 47 seconds of apnoea, even after pre-oxygenation with 100% oxygen.<sup>7</sup> Despite this though, there remains little evidence that the routine use of supplemental oxygen confers much benefit, and in fact may even harm the fetus.<sup>1,5</sup>

Khaw et al found that while supplemental oxygen improved both maternal and umbilical venous PO<sub>2</sub>, it also resulted in higher levels of the markers of lipid peroxidation, namely 8-isoprostane, malondialdehyde and hydroperoxide. This was accounted for by an excess of oxygen-free radical activity in both the child and mother.<sup>8</sup> He also concluded, in a later study, that supplemental oxygen did not significantly improve fetal oxygenation, even in cases with prolonged uterine incision to delivery time. Overall the “data (did) not support the routine use of supplemental oxygen for that purpose”.<sup>9</sup>

Cogliano et al, in 2002, showed linear increases in fetal oxygenation as maternal fraction of inspired oxygen (FiO<sub>2</sub>) was increased. However, all fetal PO<sub>2</sub> values, including the group breathing room air, were above the threshold physiological 25 mmHg mark. No clinical outcomes were investigated in this study.<sup>10</sup>

Most recently, in a Cochrane review in 2013, Chatmongkolchart et al concluded that the use of supplemental oxygen during Caesarean section under regional anaesthesia resulted in:

- Improved oxygen saturation and arterial partial pressure of oxygen in mothers.
- Increased umbilical venous and arterial oxygen content.
- No significant difference in neonatal clinical outcome, as evidenced by Apgar scoring.
- Higher markers of oxygen-free radical activity in both mothers and newborns.

Overall, it was concluded that there was no convincing evidence that the administration of supplemental oxygen confers either benefit or harm to the mother or child.<sup>11</sup>

The argument against the routine use of supplemental oxygen is somewhat less convincing when it comes to emergency Caesarean section under regional anaesthesia. Supplementary oxygen might confer the most benefit in these cases. However, given the practical and ethical obstacles to studying this population, the literature remains somewhat inconclusive. The vast majority of studies show a benefit of supplemental oxygen when the Caesarean section is for cases with suspected fetal compromise. Again, Khaw et al showed that breathing a very high 60% inspired oxygen via face mask during emergency Caesarean section afforded better fetal oxygenation with no concomitant increase in free radical activity, when compared with room air.<sup>12</sup> Not surprisingly, these findings were predominantly relevant to the group of patients in whom there was suspected fetal compromise. These results resemble those published by Haydon et al in 2006, who studied the effects of supplemental oxygen in labour on fetal oxygenation, using fetal oximetry, one of the only studies that has examined the real-time effect of oxygen on the fetus. A significant improvement

in oxygenation was demonstrated in the fetuses of women who received supplemental oxygen via face mask during their labour, compared with those who breathed room air, and the fetuses who appeared to benefit the most were those with the lowest initial oxygen saturation.<sup>13</sup>

What of Caesarean section carried out under general anaesthesia? As early as 1971, Dr Gertie Marx, a pioneer in obstetric anaesthesia, investigated 75 healthy term pregnant women whom she randomised to receive either low (28–33%), medium (66%) or high (93–97%) inspired oxygen concentration. She found not only higher umbilical venous and arterial oxygen content in the groups with high inspired oxygen concentration, but also more vigorous neonates, as determined by the mean time to sustained respiration, as well as Apgar scores.<sup>14</sup>

However, Dr Marx's work was largely performed in elective cases under less stringent experimental conditions than those expected of today's clinical trials. Her work was neither randomised nor blinded, and while her results were interesting and certainly relevant, obstetric anaesthesia practice has changed somewhat since her time, with general anaesthesia now globally far less common for elective cases. This makes extrapolation of her findings to today's practice difficult.<sup>4</sup> Two issues need to be considered. Firstly, after pre-oxygenation with 100% oxygen, does the exposure to a different FiO<sub>2</sub> in the very brief time between anaesthesia and delivery influence the outcome? Secondly, does the relative increase in the concentration of the inhalational agent given when high FiO<sub>2</sub> (and thus low fractional inspired nitrous oxide) is given, negate the potential benefit of improved oxygen content?<sup>5</sup>

Many years after Marx's work, in 2002, Khaw et al also investigated the effects of differing inspired oxygen concentrations during elective Caesarean section under general anaesthetic,<sup>15</sup> and again examined this question in 2010, this time also testing for markers of lipid peroxidation. Confirming the findings of Piggott et al in 1990,<sup>16</sup> indices of fetal oxygenation correlated with maternal FiO<sub>2</sub> in both trials. It is worth mentioning that none of the studies that exhibited differences in umbilical arterial pH or increased products of peroxidation with increasing FiO<sub>2</sub> went on to show relevant between-group differences in neonatal outcome, either in the short term (Apgar and the Neurologic and Adaptive Capacity scores), or in the longer term (developmental milestones). Interestingly, the 2010 study showed markedly raised free radical activity in all groups receiving general anaesthesia, suggesting that the general anaesthetic itself, irrespective of the oxygen concentration delivered, resulted in an increase in lipid peroxidation.<sup>16</sup>

So where does this leave us? After a complete review of the available evidence, it seems apparent that oxygen, although commonly considered a panacea, a “universal remedy”, is far from innocuous. For any medical intervention to become routine, there must be absolute certainty that either it is beneficial to all patients, or in those patients in whom no benefit is conferred it must lack the potential to do harm.

Can First World guidelines be directly extrapolated to, and followed, in peripheral units in South Africa? Essential Steps in the Management of Obstetric Emergencies (ESMOE) is an obstetric care training programme designed to improve the quality of emergency obstetric care in South African hospitals. Most maternal deaths in South Africa occur in level 1 healthcare facilities. Thus, in the interests of safety, the ESMOE guidelines advocate the provision of 40% inspired oxygen via face mask to parturients who present for emergency Caesarean section, regardless of the presence or absence of fetal compromise.<sup>17</sup>

In keeping with what Shakespeare first suggested when he wrote (perhaps of oxygen): "Fair is foul and foul is fair", the authors' recommendations to specialists in a tertiary institution are as follows: "First and foremost, in keeping with most current intrauterine resuscitation protocols, the promotion and restoration of adequate fetal oxygen delivery should take the form of appropriate maternal positioning, the reduction of uterine activity and appropriate intravenous fluid and vasopressor therapy; all of which help to ensure adequate uterine blood flow".<sup>18,19</sup>

Thereafter...

1. Healthy mothers presenting for elective Caesarean section under spinal anaesthesia should receive room air. Oxygen saturation must be continuously monitored and supplemental oxygen must be available, should the need arise.
2. Healthy mothers presenting for elective Caesarean section carried out under general anaesthesia do not require > 30% inspired oxygen. However, higher inspired concentrations do not cause lipid peroxidation *per se*.
3. Those mothers presenting for emergency Caesarean section under spinal anaesthesia where fetal compromise is not suspected (category 1 CTG tracings), should be anaesthetised breathing room air, but when fetal compromise is suspected (category 2 and 3 tracings), consideration must be given to the provision of supplemental oxygen via 60% face mask at a flow rate of at least 8 l/minute, while employing other strategies concurrently to improve fetal oxygen delivery. The duration of oxygen therapy is equally important, and as with most other drugs, should be limited to as short a time as possible. There are scenarios, such as the delivery of premature neonates, in which limiting the duration of oxygen therapy becomes significantly more important. This does not apply to patients at risk of hypoxia, such as the morbidly obese.
4. All decisions with regard to the use or omission of supplemental oxygen in the setting of Caesarean section delivery, should be made by the clinician using his or her judgement, based on oximetry and clinical evaluation, to determine optimal therapy for both the mother and child. Quite clearly, the administration of supplemental oxygen to a hypoxic or severely hypotensive mother is always indicated for maternal and fetal benefit.

Therefore, although supplemental oxygen sometimes has a role to play during Caesarean section, in most situations, it is more likely that the fetus is telling us: "Give me flow!" rather than "Give me oxygen!"

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