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Citation for published version (APA):

Bullens, L., Hout, van der, M. B., Runnard Heimel, van, P. J., & Oei, S. G. (2014). A simulation model to study maternal hyperoxygenation during labor. *Acta Obstetrica et Gynecologica Scandinavica*, 93(12), 1268-1275. <https://doi.org/10.1111/aogs.12486>

DOI:

[10.1111/aogs.12486](https://doi.org/10.1111/aogs.12486)

Document status and date:

Published: 01/01/2014

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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AOGS MAIN RESEARCH ARTICLE

A simulation model to study maternal hyperoxygenation during labor

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Key words

Fetal heart rate, obstetric labor, computer simulation, model, maternal hyperoxygenation, intrauterine resuscitation, fetal distress, translational medical research

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Bullens LM, van der Hout-van der Jagt MB, Van Runnard Heimeel PJ, Oei G. A simulation model to study maternal hyperoxygenation during labor. *Acta Obstet Gynecol Scand* 2014; 93: 1268–1275.

Received: 27 January 2014

Accepted: 13 August 2014

DOI: 10.1111/aogs.12486

Abstract

Objective. To investigate the effect of maternal hyperoxygenation on fetal oxygenation and fetal heart rate decelerations during labor, using a simulation model. **Design.** Use of a mathematical model that simulates feto–maternal hemodynamics and oxygenation, designed in Matlab R2012a. **Setting.** Clinical and engineering departments in the Netherlands. **Methods.** We simulated variable and late fetal heart rate decelerations, caused by uterine contractions with a different contraction interval. We continuously recorded oxygen pressure in different feto–placental compartments and fetal heart rate, during maternal normoxia and during hyperoxygenation with 100% oxygen. **Main outcome measures.** Changes in oxygen pressure in the intervillous space, umbilical vein and arteries, fetal cerebral and microcirculation as well as fetal heart rate deceleration depth and duration. **Results.** Maternal hyperoxygenation leads to an increase in fetal oxygenation: in the presence of variable decelerations, oxygen pressure in the intervillous space increased 9–10 mmHg and in the cerebral circulation 1–2 mmHg, depending on the contraction interval. In addition, fetal heart rate deceleration depth decreased from 45 to 20 beats per minute. In the presence of late decelerations, oxygen pressure in the intervillous space increased 7–10 mmHg and in the cerebral circulation 1–2 mmHg, depending on the contraction interval. The fetus benefited more from maternal hyperoxygenation when contraction intervals were longer. **Conclusions.** According to the simulation model, maternal hyperoxygenation leads to an increase in fetal oxygenation, especially in the presence of variable decelerations. In addition, in the presence of variable decelerations, maternal hyperoxygenation leads to amelioration of the fetal heart rate pattern.

Abbreviations: BOLD MRI, blood oxygen level-dependent magnetic resonance imaging; FHR, fetal heart rate; PO_2 , partial oxygen pressure.

Introduction

Labor contractions, causing alterations in intrauterine pressure, can affect uterine and umbilical blood flow (1–5). Fluctuations in blood flow towards the fetus may negatively influence fetal oxygenation and fetal heart rate (FHR) through several complex pathways (2–5). Hence, abnormal FHR patterns, for example FHR decelerations

Key Message

A simulation model is used to gain insight into fetal condition during labor. The effect of maternal hyperoxygenation on fetal heart rate and oxygenation is simulated; our model shows that maternal hyperoxygenation may be beneficial to the fetus.

induced by labor contractions, may be a sign of fetal hypoxia (6–8). Prolonged fetal hypoxia may lead to hypoxic–ischemic encephalopathy and fetal death (9). Therefore, when fetal distress is suspected, attempts to improve fetal oxygenation should be made before immediate delivery is indicated.

Former studies described several techniques to improve fetal condition, although little evidence is available to prove the beneficial effect of these techniques on neonatal outcome (10–12). Maternal hyperoxygenation is often used to increase oxygen transport towards the fetus. In the last decades, several studies on the effect of maternal hyperoxygenation on fetal condition have been performed, mainly in the non-compromised fetus. Clinical trials performed so far provide contradictory results (13–22). A recent Cochrane review (20) concludes that “there is not enough evidence to support the use of prophylactic oxygen therapy for women in labor, nor to evaluate its effectiveness for fetal distress”, because of the lack of a randomized controlled trial to investigate the effect of maternal hyperoxygenation on fetal condition.

Therefore, a randomized controlled trial would help us to investigate the effect of maternal hyperoxygenation. It makes more sense to design a randomized controlled trial once it has been clarified how maternal hyperoxygenation affects fetal oxygenation and FHR. Simulation models provide the possibility to investigate complex clinical situations, such as feto–maternal oxygenation.

Recently, our group developed a mathematical computerized simulation model to provide insight into the complex pathways affecting feto–maternal oxygenation and FHR (23–25). The model is based on physiological parameters that influence oxygenation and FHR. These include maternal cardiac output, maternal oxygenation, uterine pressure and flow, oxygen diffusion capacity in the placenta, fetal cerebral blood flow, fetal oxygen consumption, and baroreceptor and chemoreceptor responses. This study aimed first to demonstrate how we used this simulation model to study feto–maternal oxygenation and FHR patterns during labor. Second, we demonstrate how we used the model to study the effect of maternal hyperoxygenation during decelerative FHR patterns.

Material and methods

A mathematical feto–maternal oxygenation model was developed by our group and implemented in MATLAB R2012a (MathWorks Inc., Natick, MA, USA) (23–25). The model is based on physiological principles and consists of several modules (Figure 1).

First, the cardiovascular system of mother and fetus are modeled. The model includes cardiac function, blood

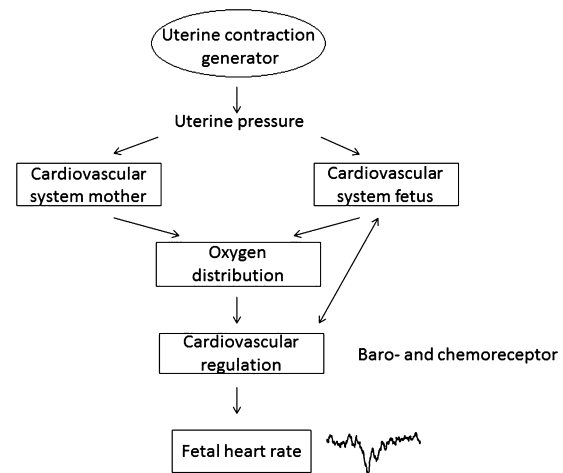


Figure 1. Diagram of the feto–maternal simulation model. Uterine contractions cause changes in uterine pressure which may alter blood pressure and flow in the fetal or maternal circulation. Oxygen pressures as well as blood pressure in the fetus may evoke changes in cardiovascular parameters, including fetal heart rate.

flow, volume and pressure at different locations in the feto–maternal circulation. In the maternal circulation, the uterine compartment is explicitly modeled and the other organs are lumped into the systemic compartment. In the fetal circulation, the systemic and umbilical compartments, as well as the cerebral compartment are explicitly modeled.

Second, an oxygen distribution model is used to calculate oxygen concentrations in all compartments in the feto–maternal circulation. Oxygen transport from the mother to the fetus is dependent on maternal oxygenation, oxygen diffusion capacity in the placenta, fetal oxygen consumption, and feto–placental blood flows and volumes. Maternal arteries supply oxygenated blood into the intervillous space of the placenta. Diffusion of oxygen from the maternal to the fetal part of the placenta is dependent on the oxygen pressure difference between the intervillous space and chorionic villi and on the diffusion capacity of the placental membrane. Oxygen-rich blood from the villous capillaries mixes with venous blood before entering the fetal heart and the arterial circulation. Arterial blood flows to the cerebral and systemic circulation where oxygen is consumed by metabolic uptake, after which it returns to the venous system. In addition, arterial blood enters the umbilical circulation and placenta, where new oxygen uptake takes place.

Third, cardiovascular regulation is provided by the fetal baroreceptors and chemoreceptors, which monitor fetal blood pressure and oxygen pressure, respectively. Stimulation of these receptors leads to changes in parasympathetic and sympathetic activity, which can then induce

changes in cardiovascular parameters, including FHR. In addition, cerebral autoregulation may increase cerebral flow during hypoxia.

Finally, uterine contractions are simulated by a contraction generator. Characteristics of the contractions can be set by the user to investigate the effect of contraction strength, duration and interval. Intrauterine pressure changes may lead to alterations in fetal and maternal vascular resistances through the compression of blood vessels, so affecting blood oxygenation, (local) blood pressure and flow.

In the model, we applied uniform uterine contractions, causing variable or late decelerations. For a complete description of inducing variable and late decelerations, we refer to previous publications (24,25).

We first simulated variable decelerations via contraction-induced umbilical cord compression (contraction duration 60 s, peak strength 70 mmHg) with a varying contraction interval (90, 60 or 45 s). For each simulation, the first uterine contraction was applied during maternal normoxia level [partial oxygen pressure (P_{O_2}) of 98 mmHg] (16). After the first contraction, we simulated 100% oxygen administration to the mother via a non-rebreathing mask by a gradual increase to a maternal P_{O_2} steady state of 475 mmHg, as reported by Vasicka et al. (16). We repeated this exact procedure during the simulation of late decelerations via contraction-induced uterine flow reduction for a placenta with 50% reduction in oxygen diffusion capacity.

The primary outcome measure is the difference in fetoplacental P_{O_2} before and after maternal hyperoxygenation in the presence of variable or late decelerations. We compared P_{O_2} the intervillous space, fetal arteries, umbili-

cal vein and arteries and the fetal cerebral and microcirculation. Second, we compared the difference in duration and depth of FHR decelerations during maternal normoxia and hyperoxia, as a reaction to contractions with a different interval.

As no human or animal subjects were involved in this study, no ethics approval is required according to the Declaration of Helsinki.

Statistical analysis

The simulation model represents one mother and one fetus, with fixed output values per simulation, hence no statistical analysis can be performed.

Results

Figure 2 demonstrates P_{O_2} in different fetoplacental compartments during variable decelerations caused by uterine contractions with an interval of 90, 60 or 45 s. During hyperoxygenation, P_{O_2} in all fetoplacental compartments increases. Maternal hyperoxygenation has a greater effect on fetal P_{O_2} when intervals are longer. When the contraction interval is 90 s, P_{O_2} increases most in the intervillous space (from 43 to 54 mmHg). The increase is less pronounced in the cerebral circulation, where P_{O_2} increases from 15 to 17 mmHg. When the contraction interval is only 45 s, the increase in P_{O_2} is less explicit in both the intervillous space and cerebral circulation (from 43 to 52 mmHg and from 14 to 15 mmHg, respectively).

Figures 3a–c demonstrate the effect of maternal hyperoxygenation during variable decelerations on P_{O_2} in fetal

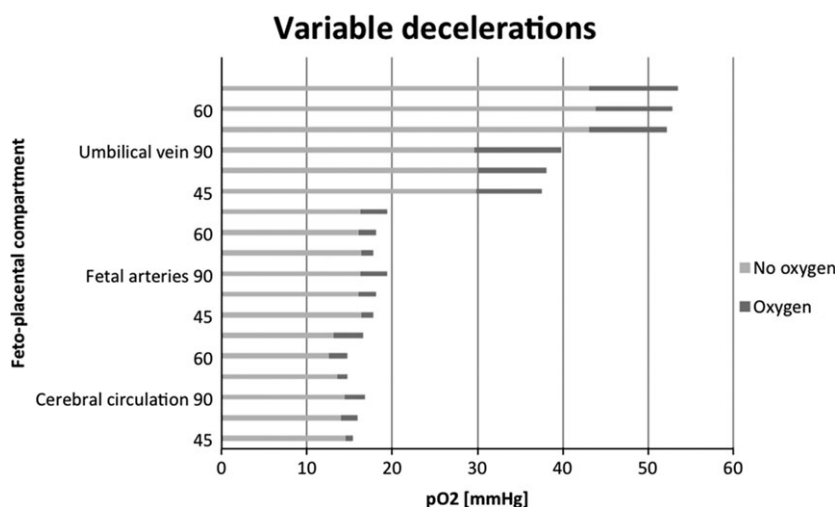


Figure 2. P_{O_2} in different fetoplacental compartments, during variable decelerations caused by uterine contractions with a different interval (45–60–90 s). P_{O_2} with and without 100% oxygen administration is presented.

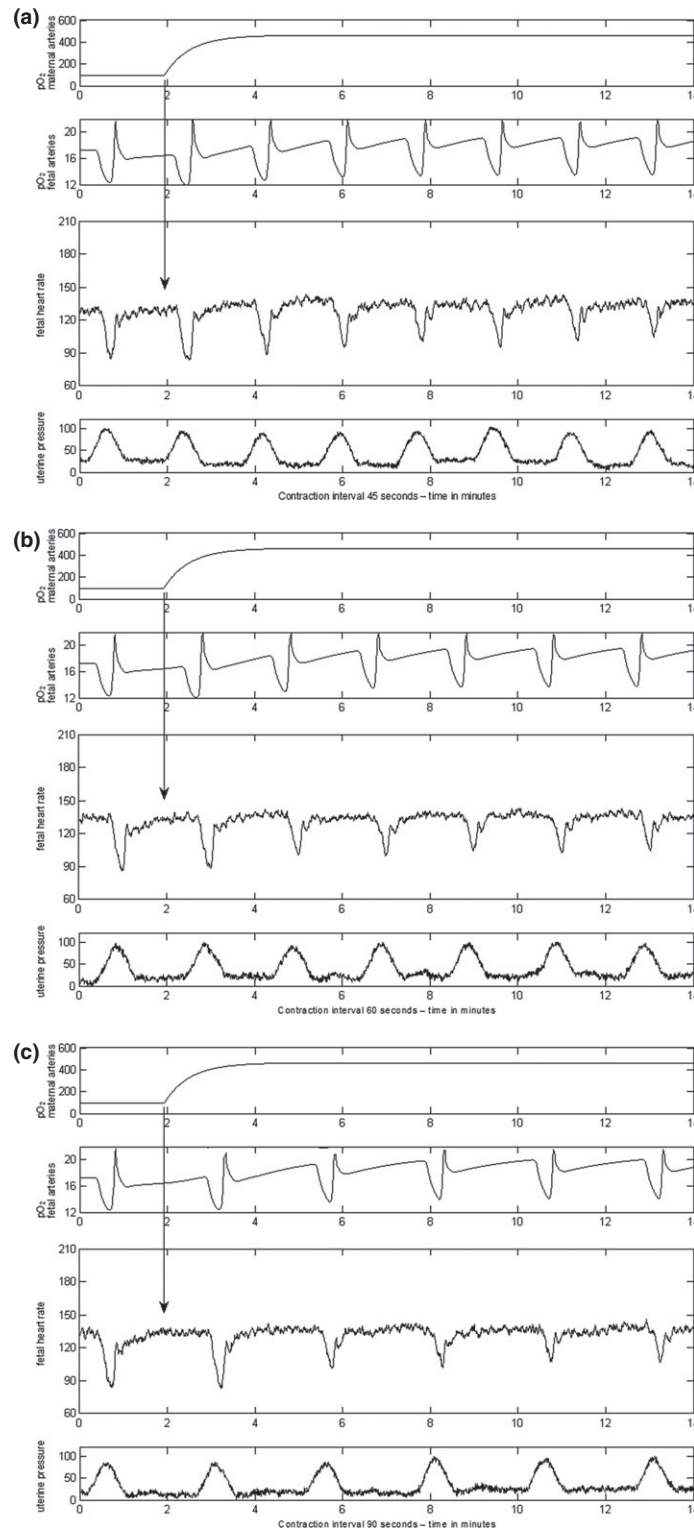


Figure 3. (a–c) Variable decelerations are simulated as a response to uterine contractions with a different interval (45, 60 or 90 s, P_{uterus}). After the first contraction, 100% oxygen is administered to the mother, indicated by the arrow in the figures. The increase in maternal oxygenation is indicated by $P_{O_{2,m}}$. Fetal P_{O_2} ($P_{O_{2f}}$) and fetal heart rate (FHR) are presented before and after 100% oxygen administration. Time in minutes.

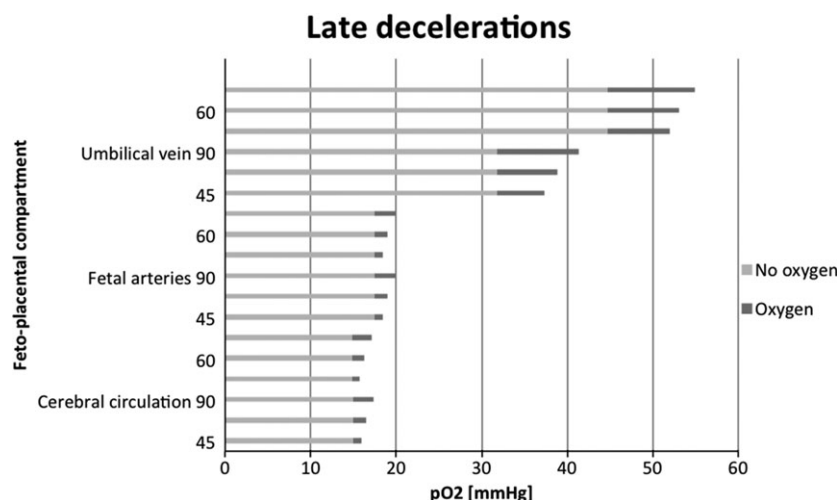


Figure 4. P_{O_2} in different fetoplacental compartments, during late decelerations caused by uterine contractions with a different interval (45, 60, and 90 s). P_{O_2} with and without 100% oxygen administration is presented.

arteries and FHR. At the end of each uterine contraction, fetal P_{O_2} quickly increases due to a temporary increase in oxygenated blood flow toward the fetus as cord compression is discontinued. Maternal hyperoxygenation leads to a quicker recovery of FHR to baseline level compared with maternal normoxia, except when the contraction interval is very short (45 s). For all intervals the drop in FHR is less severe during maternal hyperoxygenation: deceleration depth decreases from 45 to 20 beats per minute.

Figure 4 demonstrates P_{O_2} in different fetoplacental compartments during late decelerations in relation to uterine contractions occurring with an interval of 90, 60 or 45 s. During hyperoxygenation, as in the presence of variable decelerations, P_{O_2} in all fetoplacental compartments increases. Maternal hyperoxygenation has a greater effect on fetal P_{O_2} when intervals are longer. When the contraction interval is 90 s, P_{O_2} particularly increases in the intervillous space (45–55 mmHg). The increase is less pronounced in the cerebral circulation and microcirculation, where P_{O_2} increases from 15 to 17 mmHg. When the contraction interval is only 45 s, in the intervillous space, cerebral circulation and microcirculation, the profit is less explicit (from 45 to 52 mmHg in the intervillous space and from 15 to 16 mmHg in both the cerebral and microcirculation).

Figures 5a–c demonstrate the effect of maternal hyperoxygenation during late decelerations on fetal oxygenation and FHR. There is no difference in time to recovery to baseline level and no substantial decrease in deceleration depth during maternal hyperoxia compared with maternal normoxia.

Discussion

The model simulates a decrease in fetal oxygenation and FHR decelerations as a result of uterine contractions. Simulation of maternal hyperoxygenation with 100% oxygen shows an increase in P_{O_2} in all fetal and placental compartments, with the largest increase in the intervillous space and the smallest increase in the cerebral circulation. The fetus benefits more from oxygen administration to the mother when contraction intervals are longer. This observation is noticed in the presence of both variable and late decelerations, and can be explained by the physiological situation where oxygen transfer towards the placenta and the fetus continues for a longer period of time, leading to an increase in final P_{O_2} . Amelioration of the FHR pattern only occurs in the presence of variable decelerations.

The beneficial effect of maternal hyperoxygenation on fetal oxygenation and FHR is less pronounced during late decelerations. Late decelerations are often a sign of impaired placental function and severe fetal distress. Due to an impaired oxygen diffusion capacity of the placental membrane, the effect of maternal hyperoxygenation is less distinct than in variable decelerations where placental function is normal. It is possible that the level of increase of fetal P_{O_2} during late deceleration does not reach the threshold to considerably improve FHR.

A small number of clinical trials investigating the effect of maternal hyperoxygenation on fetal oxygenation and FHR have been published. However, only a few of these studies are performed in the compromised fetus. In

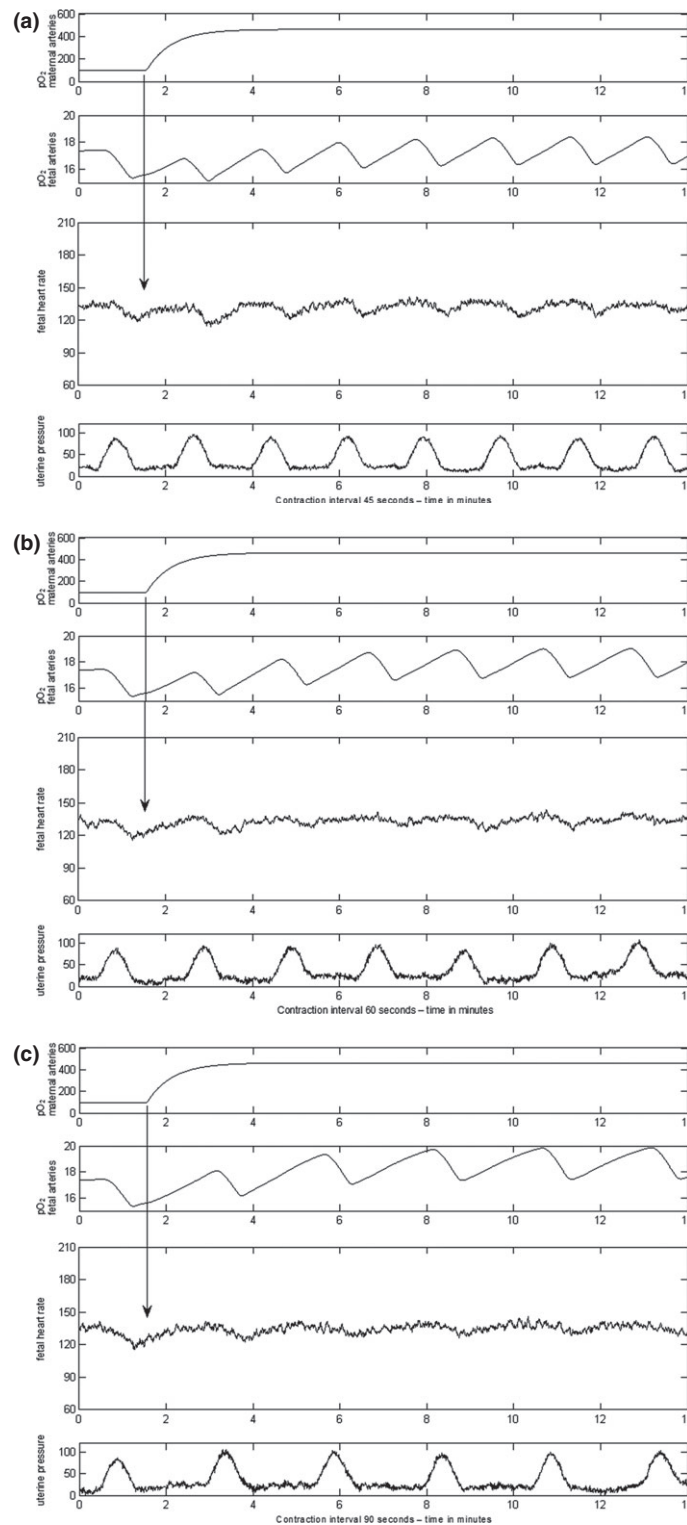


Figure 5. (a–c) Late decelerations are simulated as a response to uterine contractions with a different interval (45, 60 or 90 s, P_{uterus}). After the first contraction, 100% oxygen is administered to the mother, indicated by the arrow in the figures. The increase in maternal oxygenation is indicated by $P_{O_{2,m}}$. Fetal P_{O_2} ($P_{O_{2f}}$) and fetal heart rate (FHR) are presented before and after 100% oxygen administration. Time in minutes.

accordance with our findings, Althabe et al. (13) demonstrated that 100% oxygen administration to the mother of a fetus with a nonreassuring FHR pattern has a beneficial effect: both FHR pattern and P_{O_2} in the peripheral circulation (fetal buttock) improve after 1 minute of oxygen administration. In addition, Haydon et al. (17) showed an increase in fetal oxygen saturation using 40 and 100% maternal inspired oxygen in the case of nonreassuring FHR patterns in 24 pregnant women. The increase in P_{O_2} did not result in consistent changes in FHR patterns, but the authors recommended to further investigate these changes using a study with a larger study group. Hidaka et al. (14) investigated the recovery from type II dips by oxygen inhalation. Type II dips are nowadays described as late decelerations (2). During the first stage of labor, maternal hyperoxygenation successfully recovered FHR in 30% of the cases, even though the fraction of inspired oxygen supplied remains unclear.

Sørensen et al. (26) performed blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) in pregnant sheep under hypoxic, normoxic and hyperoxic conditions. An increase in BOLD MRI signal was assigned to an increase in fetal tissue P_{O_2} (liver, spleen and kidney). This study does not focus on the effect of fetal P_{O_2} on FHR. During maternal hyperoxygenation the BOLD MRI signal in fetal organs increases, suggesting an increase in tissue P_{O_2} . Interestingly, the increase in BOLD MRI signal in the fetal brain did not change under normoxic, hypoxic or hyperoxic conditions. This finding is ascribed to the brain-sparing mechanism of the fetus.

Based on our study results, as produced by the simulation model, it could be useful to apply maternal hyperoxygenation during labor in the presence of variable decelerations. In case of late decelerations, a positive effect on fetal oxygenation is demonstrated, but not as much as in variable decelerations. However, no effect on FHR decelerations is shown. It is possible that the level of increase in fetal P_{O_2} does not reach the threshold to considerably improve FHR. The effect of maternal hyperoxygenation in the presence of late FHR deceleration should be further investigated.

Careful considerations should be made with the translation of model results to clinical practice, since a simulation model is by definition a simplified representation of the complex fetomaternal physiology. Nevertheless, modeling results may be indicative for clinical fetal outcome and may give direction to hypothesis testing in clinical practice.

Our model can provide estimation of physiological parameters that cannot yet be measured in clinical practice, such as fetal oxygenation or blood pressure, thereby enhancing insight into the physiological processes. This means that the model could be helpful in the formulation

of hypotheses and subsequently in the design of clinical studies to evaluate the effect of resuscitation techniques.

Both patients and clinicians may benefit from the use of simulation models. The effect of clinical interventions during labor can be safely tested in a model, before women are exposed to therapeutic interventions. For example, the effect of administration of oxygen, fluids or medication can be investigated without risks for the mother or fetus.

When the simulation model indicates an adverse effect on fetal condition, this finding could be taken into account in the design of a clinical experiment, thereby improving women's safety. Moreover, simulations can be run over and over again, without exposing women to invasive procedures. Ultimately, the model has potential to be used as a clinical support tool in future, following a thorough sensitivity analysis. In its current status the model can be used for educational purposes such as simulation training.

From the study described above, we conclude that this simulation model indicates a beneficial effect of maternal hyperoxygenation on fetal oxygenation and FHR pattern in the presence of variable and – to a lesser extent – late FHR decelerations. We now plan a clinical trial comparing model data with clinical outcome.

Funding

There has been no financial support for this work.

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