REPRODUCTION
EDITORIAL

Hypoxia and reproductive health

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The 2019 Nobel Prize in Physiology or Medicine was awarded to William G Kaelin Jr, Sir Peter J Ratcliffe and Gregg L Semenza for their discovery of how cells can sense and adapt to changing oxygen availability. Their pioneering work revealed the mechanism for one of life's most essential adaptive processes. It resulted in the award of this prestigious prize but, more importantly, their research paved the way for promising new strategies to fight a plethora of diseases, including anaemia, cancer and reproductive disorders.

Oxygen makes up approximately one-fifth of the world's atmosphere and is essential for animal life. These Nobel Laureates discovered how cells adapt to hypoxic conditions to maintain homeostasis. Semenza discovered a protein complex that binds to a specific DNA segment in an oxygen-dependent manner. He called this complex the hypoxia-inducible factor (HIF). Kaelin and Ratcliffe's work demonstrated how oxygen regulated this transcription factor. They revealed that von Hippel–Lindau (VHL) can physically interact with the alpha subunit of HIF and is required for its degradation at normal oxygen levels. Furthermore, they demonstrated that hydroxylation of HIF1A by the prolyl hydroxylase enzymes occurs when oxygen levels are normal, allowing VHL to recognise and bind to this subunit and trigger its degradation. In hypoxic conditions, these prolyl hydroxylase enzymes are not active and HIF1A protein is stabilised, which then dimerizes with the beta subunit and binds to the hypoxic response elements of target genes to increase their transcription. Thus, when oxygen levels are abundant cells will make HIF1A but it is efficiently degraded. This means when hypoxia occurs, cells can rapidly increase HIF1A levels by stopping its breakdown. In the words of Semenza himself, 'it is a really beautiful system'.

Similar to oxygen, reproduction is a fundamental requirement for the survival of animals. The concept that oxygen, and limited oxygen availability, may play an important role in female reproductive processes is not a new phenomenon. Research into the impact of varying oxygen levels in fertilisation, implantation, placentation and fetal development dates back decades. However, untangling the mechanisms of HIF in cells responding to changing oxygen levels has given new life to this research. All too often, this great work is siloed within different reproductive sub-speciality meetings and journals. The aim of this special review issue is to bring together some of the latest work on oxygen and hypoxia from across the reproductive spectrum (Video 1). The diversity in reproductive research, from gynaecological conditions to advanced fetal development, allows us to increase our understanding of how reproduction is influenced by oxygen levels and how reproduction can advance our knowledge of oxygen sensing.

Video 1

Dr Jacqueline Maybin provides a video introduction to this special edition on 'Hypoxia and reproductive health'. This video (http://movie-usa.glencoesoftware.com/video/10.1530/REP-20-0614/video-1) is available from the online version of the article at https://doi.org/10.1530/REP-20-0614.

This series contains seven diverse and impactful reviews of hypoxia and its potential role in reproductive function. We start the series with a review of the presence and role of hypoxia in the non-pregnant endometrium by Martínez-Aguilar *et al.* (2021). This addresses the controversial question of whether hypoxia actually occurs during the menstrual cycle and, if so, its role in the essential endometrial functions of implantation and menstruation.

This is followed by an excellent review of current knowledge of hypoxia in one of the most common gynaecological disorders, endometriosis. Li *et al.* (2021) discuss how hypoxia could be involved in endometriotic deposit formation following retrograde menstruation by affecting cell adhesion, migration, survival and prevention of immune clearance. They also discuss the

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exciting possibility of targeting the hypoxic pathway as a novel treatment strategy for those suffering from endometriosis.

The contribution of hypoxia to ovarian function is reviewed by Lim *et al.* (2021). This informative review details the contribution of hypoxia to follicle development, ovulation and oocyte maturation, highlighting the clinical relevance for *in vitro* ovarian maturation for those undergoing cancer therapy or who have experienced ovarian hyperstimulation. This review discusses a novel role for haemoglobin and 2,3-BPG in the preovulatory follicle, which may represent a clever physiological adaptation to maintain cellular oxygen requirements in a hypoxic environment.

Houghton (2021) then provides a highly informative overview of hypoxia and pre-implantation embryos. She details how embryos cultured under hypoxic conditions may result in the often elusive increased live-birth rate compared with normoxic culture. Furthermore, hypoxic culture may also result in more good quality embryos for cryopreservation following transfer. In addition, this review details how human embryonic stem cell research may facilitate the delineation of hypoxic pathways in the pre-implantation embryo to improve clinical care.

Moving to the pregnant uterus, Burton *et al.* (2021) provide an insightful overview of oxygen levels in the human placenta. This review highlights that the physiological reduction in oxygen levels observed in the human placenta during pregnancy does not result in metabolic compromise. More important may be the fluctuations in these oxygen levels, affecting trophoblast differentiation and invasion. At later gestations, placental oxidative stress may be particularly important in complicated pregnancies.

The penultimate review in this series is from Wray *et al.* (2021), detailing how hypoxia can have both physiological and pathological roles in the myometrium during labour. This review discusses how short, sharp, repeated hypoxic episodes can increase contraction strength and facilitate delivery, known as hypoxia-induced force increase. Conversely, prolonged hypoxia may cause dysfunctional, slow labour. The review describes evidence for a novel bicarbonate treatment prior to augmentation of labour to decrease the requirement for caesarean section. This much-needed intervention may reduce maternal morbidity and make future pregnancies safer.

Concluding the series, Moore (2021) provides a stimulating review of the literature surrounding reproduction at high altitude as a model of chronic hypoxia. She discusses the increased incidence of pregnancy loss and fetal growth restriction in newcomer residents vs multigenerational high-altitude dwellers before reviewing the current understanding of the mechanisms behind these differences. Furthermore, the longer-term impact of living at high altitude is discussed with a focus on both short and long-term morbidity and mortality.

Although by no means an exhaustive review of the work in this area, this series highlights some of the excellent research being undertaken in this rapidly evolving field. My hope is that these articles, read either as a series or in isolation, will provide inspiration and stimulate ideas for future research into the role of hypoxia in reproduction. The study of two such fundamental processes – oxygen sensing and reproduction – is an exciting combination. Perhaps current or future researchers in the field of reproduction will be motivated by this series and, like Kaelin, Ratcliffe and Semenza, change the scientific paradigm with great benefit for humankind.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this editorial.

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