Animal 17 (2023) 100903

Contents lists available at ScienceDirect

Animal
The international journal of animal biosciences

Editorial: Recent scientific advances in reproduction and fertility in ruminants: an overview of the 11th International Ruminant Reproduction Symposium, Galway, Ireland, 2023

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ARTICLE INFO

Article history:
Received 19 June 2023
Accepted 29 June 2023

This supplement to *Animal* contains the papers associated with the keynote lectures delivered at the 11th International Ruminant Reproduction Symposium (**IRRS**) held in Galway, Ireland, from May 28th to June 1st 2023. The IRRS is recognised as one of the most prestigious global conferences on reproduction in ruminant animals. Held every four years, leading scientists from around the world present cutting-edge talks on reproductive biology and technology in a variety of ruminant (and pseudo-ruminant) species, including cattle, sheep, goats, buffaloes, and camelids. Sessions are designed to bridge the gap between basic and applied science and to cover the entire reproductive axis from testicular and sperm function to follicle development and ovulation, oocyte maturation and fertilisation, corpus luteum development and maternal recognition of pregnancy, early embryo development, implantation, placentation and gestation, foetal development, puberty and life-course development, as well as state-of-the-art assisted reproductive technologies applied to reproduction in ruminants.

Reproductive efficiency is the main driver of profitability in most ruminant production systems. Ruminant females are born with a finite population of ovarian follicles and oocytes (the ovarian reserve) and germ cell proliferation in the developing foetal gonad predominantly occurs during early gestation. Mossa and Evans (2023) discuss the relationship between the ovarian reserve and fertility and the impact of management of the dam from preconception to early gestation, and of genetic selection, on offspring performance. The role of follicle-stimulating hormone (**FSH**) in antral follicle development and fertility is reviewed by Morton et al. (2023). Understanding the effects of FSH in ovarian follicle growth is critical for the development of more refined and effective fertility treatments to ensure the production of high-quality oocytes for optimal fertility. Improved knowledge of the reproductive physiology of beef and dairy cattle has facilitated the development of very efficient reproductive management programmes in heifers and cows. Such programmes have contributed to increased profitability of cattle operations and a broader use of assisted reproductive technologies (**ARTs**). Sartori et al. (2023) review ovulation synchrony programmes that control follicular development, comprising synchronised emergence of a new follicular wave, selection and growth of the dominant follicle, and synchronised ovulation of a high-quality oocyte.

On the male side, the fertility of bulls is a major contributor to overall herd reproductive performance. Bollwein and Malamaa (2023) summarise current research on functional and molecular traits that have been explored as potential indicators of sperm quality and fertility in bulls, with a special focus on the sperm nucleus, plasma membrane and acrosome. Sperm cells require interaction with secretions from the male reproductive tract to develop full functionality. In addition, there is growing evidence that these secretions induce changes in the maternal environment

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https://doi.org/10.1016/j.animal.2023.100903

that can affect embryo development. Fernandez-Fuertes (2023) reviews our understanding regarding how seminal plasma shapes fertility in ruminants. While frozen-thawed semen forms the basis of AI programmes in cattle in most countries, the success of cryopreservation in small and wild ruminants is still suboptimal. Cryopreserved sperm can be used to improve the diversity of wildlife populations and to bank genetic resources for the future. Santiago-Moreno et al. (2023) review the current state-of-the-art in sperm cryopreservation in wild small ruminants and highlight the need to establish the molecular mechanisms that mediate the sperm response to cryopreservation and to identify new biomarkers of cryoresistance in different wild ruminant species.

The sixteenth-century anatomist, William Harvey, coined the phrase '*ex ovo omnia*' ('everything from the egg') highlighting the central role of the oocyte in fertility. Costa et al. (2023) review molecular aspects of oogenesis and the impact of follicular fluid constituents on oocyte quality. In addition, they discuss the application of biotechnologies targeting preantral and antral follicles and highlight strategies which positively impact oocyte quality in vivo and improve fertility.

The environment in the preovulatory follicle switches from oestradiol-dominance to progesterone-dominance with approaching ovulation. It is now well accepted that progesterone during the growth of the preovulatory follicle is important for subsequent oocyte developmental competence. Lodde et al. (2023) summarise current knowledge on putative mechanisms through which progesterone receptor membrane component-1 controls the acquisition of developmental competence during oocyte maturation, fertilisation, and preimplantation embryonic development.

In ruminants, after the blastocyst hatches from the zona pellucida, the conceptus elongates before attachment. This is a maternally driven process, which to-date has not been recapitulated *in vitro* and does not occur *in vivo* in the absence of uterine gland secretions. Optimal communication between the developing conceptus and the maternal reproductive tract is essential for the development of a high-quality embryo and functional embryo-maternal signalling for pregnancy recognition, attachment and implantation. Tinning et al. (2023) review current knowledge on conceptus-maternal interactions and identify gaps in our understanding that could be filled with newer *in vitro* approaches, including the use of microfluidics, organ-on-a-chip devices, and bioinformatic approaches. Despite some progress, the underlying regulatory mechanisms controlling conceptus elongation are still only partially understood. Rüegg and Ulbrich (2023) describe the phenomenon of embryonic diapause in the European roe deer (*Capreolus capreolus*), in which the pace of embryo development before elongation is drastically reduced compared with other ruminant species. The roe deer thus represents an ideal model to study the synchronised endometrial support of blastocyst development, and the switch required for initiation of elongation, in slow-motion and could reveal as yet unidentified key molecular factors in embryo-maternal communication.

Rabaglino (2023) reviews studies involving the use of high-throughput techniques to study the transcriptome of the bovine embryo from the blastocyst to the elongating conceptus stage and highlights differences in the transcriptome between blastocysts and elongated conceptuses with divergent abilities to sustain a pregnancy. Transcriptomic data integration highlights the involvement of pathways related to energy metabolism in embryonic competence, which may be altered because of the procedures involved with *in vitro* production.

The corpus luteum (**CL**) is critical for the establishment and maintenance of pregnancy in all mammals. The fate of the CL in ruminants, however, is dependent on the presence of a functional uterus or signals from a developing embryo to modify uterine function to ensure its own survival. Pate and Hughes (2023) provide an overview of some of the mechanisms responsible for the maintenance or regression of the CL and proposes the involvement of specific molecules for future research. Although the role of interferon-tau (**IFNT**) in maintenance of the CL during early pregnancy in ruminants has been established, the mechanisms involved in CL maintenance after the IFNT period have not been determined but they act in a local manner (ipsilateral to pregnancy), and appear to remain functional from day 25 until just before parturition. As pointed out by Wiltbank et al. (2023), the most likely mechanisms mediating the maintenance of the CL of pregnancy after the IFNT period are increased uterine blood flow or decreased prostaglandin transporter expression in the utero-ovarian vasculature, preventing luteolytic doses of prostaglandin F2alpha from reaching the CL.

Recently, the use of colour-Doppler ultrasound imaging has been incorporated into the use of reproductive protocols for both fixed-time AI and resynchronisation of ovulation in cattle through the evaluation of CL function to identify non-pregnant females at 20–24 days after breeding. Pugliesi et al. (2023) provide an overview of the technical and physiological concepts underlying the use of Doppler ultrasonography for the assessment of CL blood perfusion and highlight the applications for reproductive management.

Pregnancy loss has a major impact on reproductive efficiency. Increased knowledge of the cellular and molecular mechanisms governing conceptus differentiation and placentation is critical to understanding and reducing pregnancy loss, thereby increasing farm profitability (Davenport et al. 2023). Pursley et al. (2023) describe a novel model to determine the timing of conceptus attachment utilising daily determination of maternal blood concentrations of pregnancy-specific protein B, a conceptus-derived protein. The key outcome thus far is that timing of conceptus attachment is highly predictive of subsequent pregnancy success or failure.

Apart from embryo loss, another unintended consequence of *in vitro* embryo production, at least in the early days of the technology, was the occurrence of abnormal offspring. Large offspring syndrome (**LOS**) is an epigenetic disorder occurring naturally in cattle, but the incidence is significantly increased among offspring produced from assisted reproductive technologies. The syndrome has important consequences for both animals and producers, due to the increased risk of dystocia and low survival rates of offspring. Improvements in *in vitro* embryo production may help to avoid the introduction of epimutations to gametes and embryos and reduce the incidence of LOS; nonetheless, the development of diagnostic tools for early identification during pregnancy remains crucial (Nava-Trujillo and Rivera 2023).

While the majority of pregnancy loss occurs during the early pregnancy embryonic period, the timing of bovine foetal mortality (>42 days of gestation) is more sporadic. Mee et al. (2023) review bovine foetal mortality and synthesise current knowledge on the associated risk factors, causes and immune responses. The authors highlight the need to re-prioritise research and investigative focus away from 'pathogen hunting' and towards a better understanding of the epidemiology, genetics, nutritional, environmental and management factors underlying non-infectious bovine abortion and perinatal mortality.

Postpartum uterine infection and inflammation have deleterious and long-lasting effects on oocytes, embryo development, and the endometrium, even if the disease is apparently resolved. LeBlanc (2023) reviews recent data and concepts on postpartum reproductive diseases (metritis, purulent vaginal discharge, and endometritis) in dairy cows and the ways in which these diseases affect reproductive performance.

Heat stress directly impacts nearly all facets of animal agriculture, and concern over its far-reaching ramifications has increased alongside the growing threats of global warming. A comprehensive understanding of the physiological responses to heat stress, including elevated body temperature, altered metabolism and circulating lipopolysaccharide, can be used as a basis for improving fertility, and thus, the overall productivity of dairy cattle experiencing heat stress (Rhoads, 2023).

On a global scale, the use of ARTs in small ruminants such as sheep and goats is much less than in cattle. Amongst other reasons, this is due to the limitations in the use of non-invasive methods for AI, embryo transfer and embryo recovery in these species. Surgical methods render these techniques impractical at field level. Souza-Fabjana et al. (2023) review currently available options and requirements for effectively using non-surgical AI and embryo recovery techniques in sheep and goats. This knowledge will significantly increase the use of ARTs in small ruminants.

The adoption of AI and genomic selection in cattle provide dense genotypes and repeated semen quality measurements for thousands of bulls. Pausch and Mapel (2023) highlight how these data enable powerful genome-wide association studies to identify candidate causal variants that contribute to inherited variation in male reproductive performance and how integrating dense genotypes, semen quality measurements, and pregnancy outcomes after insemination can reveal mechanistic insights into the causes of male reproductive variability.

One of the unintended consequences of increasing cow numbers in a post-EU milk quota era has been an increase in the number of male dairy calves of low economic value. Butler et al. (2023) describe the use of ARTs to address this issue by reducing the number of male dairy calves through the use of sex-sorted semen and the use of *in vitro*-produced embryos from (1) elite dairy dams to generate the next generation of dairy AI sires, and (2) elite beef dams to generate beef sires suitable for crossing with dairy cows (using AI) that are not required to generate replacements. This strategy could have a transformative effect on the sustainability of milk and beef production.

The availability of high-quality semen from young genetically elite bulls is essential to support continued genetic gain and the sustainability of cattle production. Byrne et al. (2023) review evidence that accelerated sexual development in bulls can be achieved through enhancing nutrition in early life. They explore the physiological and molecular response to diet in key organs that orchestrate the ontogeny of sexual development in the bull calf. Subsequently, Duittoz and Kenny (2023) review the main physiological changes occurring during the prepubertal period and discuss the role of early determinants and late environmental determinants of puberty onset. Greater understanding of the regulation of postnatal sexual development will facilitate the timely availability of high-quality semen from genetically elite young animals, thus supporting more economically and environmentally sustainable beef and dairy production systems. On the female side, Garza et al. (2023) present an overview of the neuroendocrine mechanisms regulating timing of puberty in heifers, review the effects of nutrition and energy metabolism during prenatal and postnatal development on pubertal attainment, and discuss management strategies that can be implemented to advance growth and puberty attainment in heifers.

A range of ARTs are now well established and available in the toolbox of every producer including AI, multiple ovulation embryo transfer, in vitro embryo production, sex-sorted semen and tools to precisely control the timing of ovulation for timed AI/ET protocols. A new suite of ARTs are now on the horizon, which will no doubt have a major impact on animal breeding in future. Strange and Alberio (2023) review how progress in our understanding of the developmental mechanisms of sperm and eggs has enabled researchers to completely recapitulate these processes in the laboratory resulting in the birth of viable offspring in the mouse. These exciting findings suggest that it may be possible to develop similar methods for the generation of *in vitro* gametes in other species, which offers great opportunities for enhancing genetic selection in livestock, developing human fertility treatments and for the rescue of endangered species. Goszczynski et al. (2023) review advances in pluripotent stem cell establishment and germline differentiation in livestock species, which could have significant implications for the development of advanced breeding and genetic approaches and for ARTs. The progress made in recent years in the derivation and culture of pluripotent stem cells from farm animals raises the possibility of creating livestock chimeras. Chimeras-producing gametes exclusively derived from elite donor stem cells could pass superior genetics on to the next generation, thereby reducing the genetic lag that typically exists between the elite and the commercial tiers of the livestock sector (Ledesma et al., 2023).

Many of the tools developed for livestock species have application in other, less mainstream, ruminants and for the preservation of endangered species. Acevedo and Barfield (2023) review the reproductive physiology of bison and provide an overview of the application of ARTs to the conservation of *Bison bison* (American bison) and *Bison bonasus* (European bison or wisent). Ratto et al. (2023) provide an update on the current understanding of the effects of β-Nerve Growth Factor, the factor in seminal fluid of llamas and alpacas responsible for ovulation induction, in the control of reproductive function in camelids and ruminants, while Baruselli et al. (2023) review the development, adoption, and impact of assisted reproduction in domestic buffaloes.

Finally, with the number of *in vitro*-produced embryos transferred globally increasing each year and now surpassing the number of *in vivo* derived embryos, Hansen (2023) highlights current challenges and unrealised opportunities in the widespread use of the *in vitro*-produced embryo in cattle production.

Ethics approval

Not applicable.

Data and model availability statement

Not applicable.

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PL wrote the first draft of this Editorial. All authors read and approved the final version.

Declaration of interest

None.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use any artificial intelligence-assisted technologies in the writing process.

Acknowledgements

This conference was organised in collaboration with the British Society of Animal Science (BSAS). Sincere thanks are due to the staff at BSAS, particularly Maggie Mitchell, for their enthusiasm and help in organisation at all levels and to the staff at *Animal* for their patience and care in the production of this unique and comprehensive publication.

Financial support statement

Financial support is crucial to the running of any conference. We are very grateful to our many sponsors for their generous support. We realise that such companies and organisations are likely bombarded with similar requests for sponsorship and we appreciate them taking the decision to come to our meeting in Galway, Ireland. We gratefully acknowledge the support of Ceva Animal Health, Calier, IMV Technologies, DSM Nutrition, Society for the Study of Reproduction, Fáilte Ireland, Stroebech Media, IVF Bioscience, EggTech, Minitube, Watanabe Applied Technology, Dyneval, Embryocloud, Genus, Vytelle and the Society for Reproduction and Fertility.

Transparency Declaration

This article is part of a supplement entitled *Keynote lectures from the 11th International Ruminant Reproduction Symposium* supported by the British Society of Animal Science.

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