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A meta-analysis study on corpus luteum regression in cetaceans

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Abstract
A meta-analysis study of essential exploration can offer experiences into the present status of information, which has various views. To date, there exist several opinions regarding the corpora persistence in cetaceans. This study explores the viewpoints and reports on corpora persistence and compares the data over the mammalian groups. The corpora persistence in cetaceans remains unexplored from an evolutionary perspective. Hence this research, suggests the upcoming evolutionary studies on genes signifying the functional gene expression of morphological and physiological variations in corpus luteum (CL)/albicans (CA) of diverse species.

Keywords: Meta-analysis, corpora persistence, cetaceans, corpus luteum

Introduction
Cetaceans are unique aquatic mammals having several distinct reproductive characters, with bicornuate uterus, vaginal folds, and reabsorption of endometrial blood rather than expulsion (https://baleinesendirect.org/en/discover/life-of-whales/physiology/reproductive-system) [5]. Major portion of data about reproduction was gathered from the dead samples through histological assessment of gonads obtained from fisheries or stranded on shorelines (Todd *et al.,* 1994) [15]. Most of the past investigations depended on the physiological and histological assessments in cetaceans, few were on the endocrinology mechanisms in captive cetaceans (Etsuko Katsumata, 2010) [3]. Nevertheless, it is hard to inspect and recognize the systemic reproductive physiological systems in a vast pelagic habitat.
During the estrus cycle the matured ova releases by the rupture of the follicles and later the follicle changes into CL. The principal function of CL is to secrete progesterone and assist in pregnancy. But after pregnancy period or ovulation, CL diminishes into CA comprised of fibrous scar tissue, which is retained in the ovary for a considerable period of time and later disappears. Whereas in Cetacean order, these scars remain permanent representing the ovulation record of an animal (Tarpley and Hillmann, 1999) [14]. Besides the ovulation records, corpora counts were used to estimate the age of bowhead whales (George *et al.,* 2004; Lubetkin *et al.,* 2008) [4, 9]. CA estimates the reproductive status and age of cetaceans which, has become a valuable means to appraise the lifetime regenerative history (Takahashi *et al.,* 2006) [13]. Besides the scars of corpora persistence, the ovulation pattern (induced/spontaneous), the estrus cycle, and the epitheliochorial type of placental attachment remain uncertain and need more research (Vaughn *et al.,* 2000) [16]. This perspective made us investigate the luteolysis system of cetaceans through a meta-analysis.

Materials and Methods
We searched online databases and websites to locate potentially eligible articles addressing the issue of corpus luteum persistence in cetaceans. We included all the articles that provided information on luteolysis studies in mammals. We extracted the data in CSV file format from the NCBI website. We summarised by identifying the keywords such as luteolysis in mammals, cetacean female reproduction, cetacean corpus luteum, functional luteal regression, structural luteal regression in mammals. Further, we classified based on different families and areas where recommendations were missing or scarce.
We included published articles if they provided at least one key term relating to the luteolysis studies.

The mathematical process involved the consolidating results of studies on an overall estimate, sorted year wise on searchers in association with regression of CL in mammals (Lau *et al.,* 1997) [8].

We identified the articles by searching electronic databases (NCBI) and specific websites associated with cetaceans' reproduction. We summarised the data using a descriptive approach and derived a qualitative thematic analysis (Mueller *et al.,* 2018) [10].

We converted the extracted information into graphs and tables. Reproductive characters associated with mammals were classified and depicted on a phylogenetic tree. Based on Timetree, we constructed a phylogenetic tree that can build the divergence time of a group of species and visualized it through the Evolview software.

Results and Discussion

The mechanism regulating the CL function has been subjected to scientific interest over decades (Kowalewski, 2014) [7]. During the estrus cycle the matured ova releases by the rupture of the follicles and later the follicle changes into CL. The principal function of CL is to secrete progesterone and assist in pregnancy. This process is termed as luteolysis. Luteolysis is classified into two forms; functional and morphological luteolysis. Functional luteolysis is the underlying deterioration of progesterone discharge whereas; morphological luteolysis is the structural changes or shrinkage of corpus luteum to corpus albicans (ovarian scar) (John *et al.,* 1999) [6].

We aimed to search for publications related to luteolysis in cetaceans, but there was no data. Existed data were about the histology examinations and endocrinology results. Evolutionary analysis explaining the gene functions were found missing. Hence we did a meta-analysis to collect the various existing data with the concerned topic. Functional regression studies were numerous than structural luteolysis in mammals.

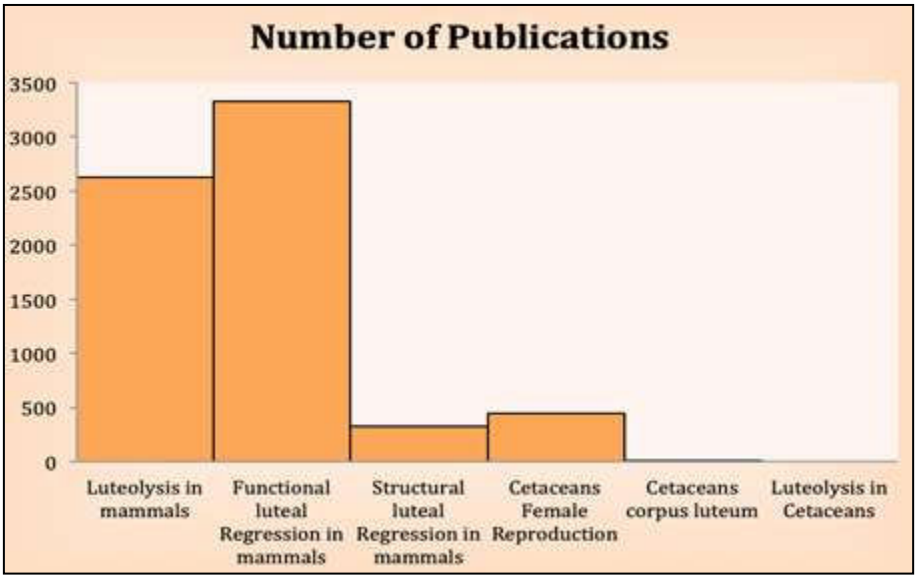

Fig 1: Number of publications associated with the search terms from NCBI website

We used all keywords to find the articles on the cetacean female reproductive system and related terms associated with corpus luteum regression. Cetacean female reproduction had 449 publications, corpus 12 publications on corpus luteum and, none concerning gene expressions and regression in cetaceans (Fig-1). We accumulated the database on the Luteolysis from the NCBI site. There existed a sum of 2631 publications on Luteolysis. We searched the keyword in the abstracts and full texts of each article, books, reviews, systematic reviews, meta-analysis, and clinical trials.

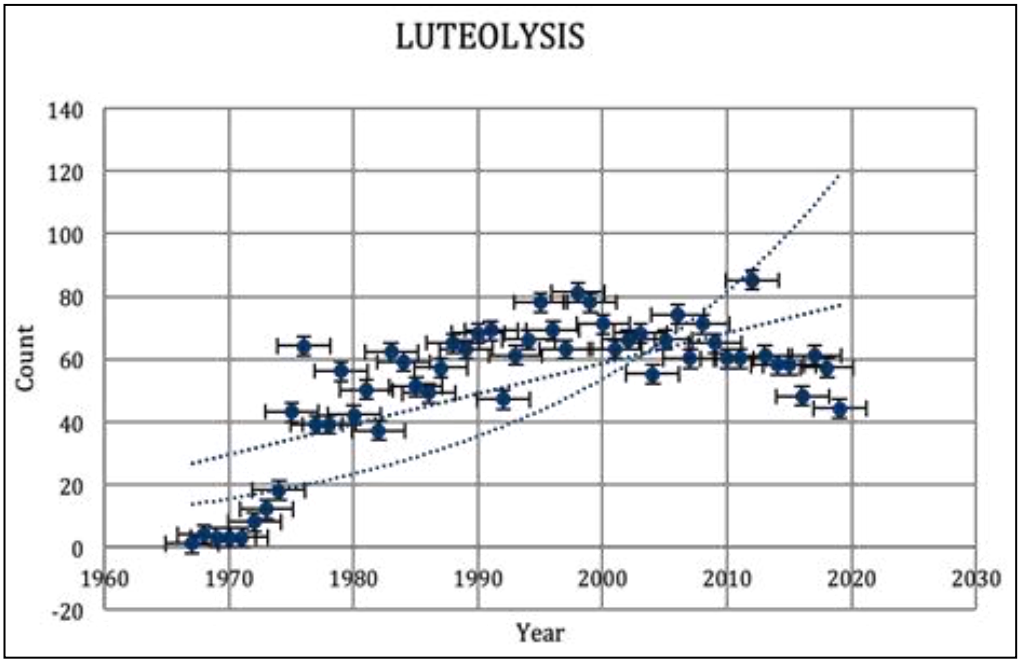

Fig 2: Year-wise publication database on luteolysis

Though the earliest researches were from the 1960s, most of the publications were only in the 20th century, the highest during 2010 – 2020 (Fig-2).

Functional luteal regression had 3326 publications. Functional luteal regression denotes the decline of progesterone hormone and the initiation of corpus luteum regression. The database of the published reports on the corpus luteum and its regression in various mammalian species typically centers on the functional feature with the initiation signals from PGF2α. Numerous studies explained the functional corpus luteum regression and hormonal assays of progesterone, oxytocin, and prolactin levels in mammals. Studies about functional luteal regression were more during the years of 2000-2010 (Fig-3).

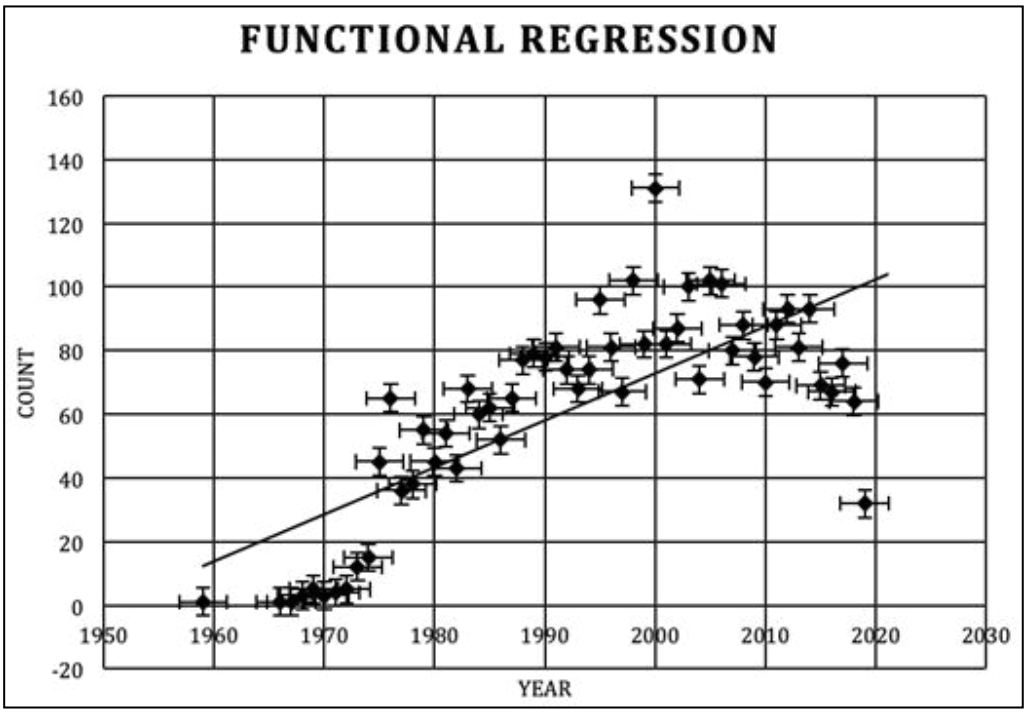

Fig 3: Year-wise publications on functional regression

Structural luteal regression had 323 publications (Fig-4). Structural/morphological regression studies on CL had less interest among the researchers. Few investigators examined the structural regression involving the apoptosis molecular mechanism and recent studies explained the migration of luteal cells to the lymphatic vessels causing rapid regression in CL (Abe *et al.,* 2014) [1].

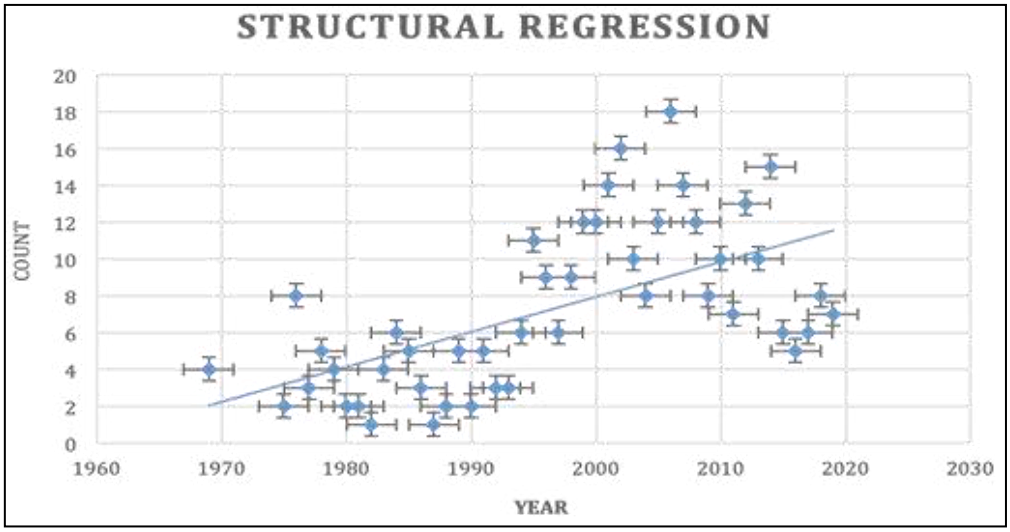

Fig 4: Year-wise publications on Structural regression

Structural regression studies in cetaceans were about the histological findings of the corpus luteum persistence and few enzyme studies. The corpora persistence in cetaceans had various views of observations from the researchers. Many reported life long persistence, while few reported long life persistence after which it had a decline. However, this topic lacks a gene-based evolutionary analysis to date. Most of the studies were only in recent decades (2000-2020).

A reproductive character associated with the female system includes the estrous cycle, type of ovulation, number of offspring/delivery, type of placenta, and gestational periods. We considered the estrous pattern, ovulation type, and the duration of corpus luteum persistence in mammals to construct a phylogenetic tree (Fig-5).

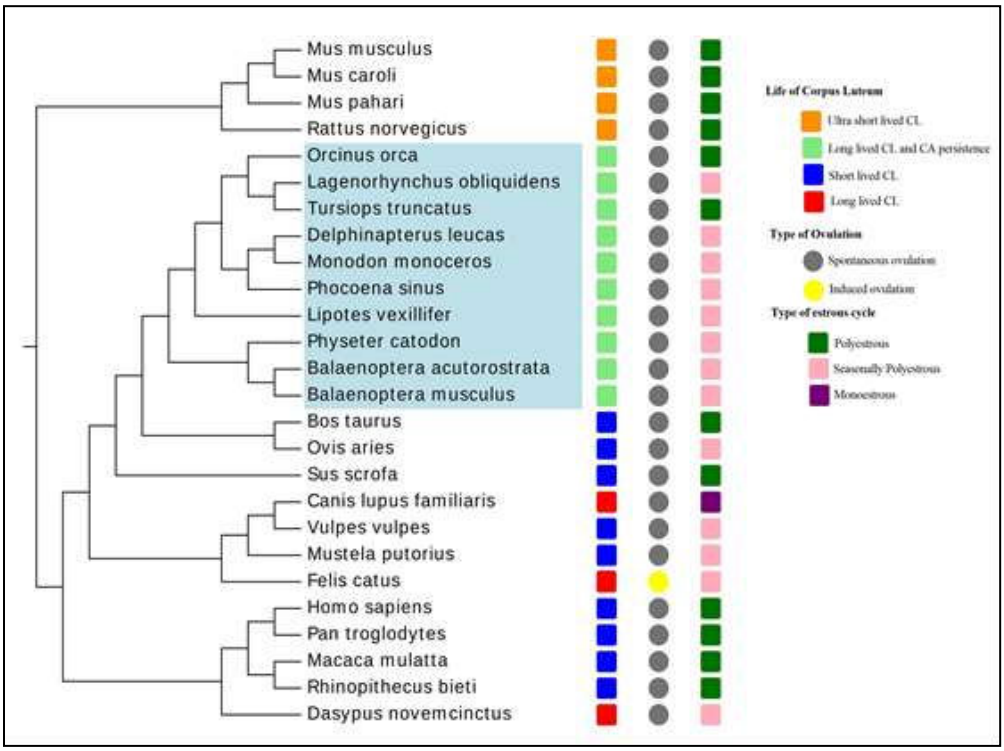

Fig 5: Reproductive characters in mammals with emphasis on Cetaceans

The estrous cycles comprise Seasonal (monoestrous and polyestrous seasonal breeders) and polyestrous (year-round breeders). Cetaceans have distinguishing features of seasonal reproduction, polygamy (Schaeff, 2007) [12], and a moderately extended estrous cycle (Boness, 2009) [2]. Generally, mammals are polyestrous, while cetaceans have both polyestrous and seasonal polyestrous cycles. The majority of the cetacean families seem to be seasonally polyestrous, including the humpback whales (Robeck *et al.,* 2018) [11], while few dolphin species appear to be polyestrous. Though marine mammals have similar reproductive features, the ovulation pattern varies among marine mammals.

Adaptive evolution studies can explain complex mechanisms involving the endocrine activities and structural changes in species where the sample data goes insufficient or not available. Detection of positive selection pressure analysis through genes from the apoptosis and the organo steroidogenesis pathway can explain the long persistence of scars in cetaceans. To determine the dependent/independent

phylogenetic relationship, we can test the ovulation type, estrous pattern, the gestational span, fetus formation (altrical/precocial), and offspring per labour. We can compare the data based on the closely related species and relate the similarity or deviations in numerous species. This meta-analysis study evidences the absence of data regarding the luteolytic mechanisms in cetaceans.

Conclusion

The uncertain assumptions about the persistence of corpora in cetaceans remain unaddressed to date. Cross-examination of the published database on luteolysis and luteal regression in mammals revealed the highest number of studies in cattle whereas luteolysis still remains unaddressed in cetaceans. Hence, we hypothesize that phylogenetic studies can address the scientific problem of these persistent ovarian scars in cetacean families with positive selection pressure analysis to drive meaningful conclusions and our subsequent researches will focus on the above-mentioned strategies. This meta-analysis study intended to inspect the circumstances and logical networks to examine these corpora persistence and to distinguish where data was deficient so as to give knowledge on the potential for the inclusion of phylogenetic mechanisms.

Conflict of Interest

The authors declare that they have no competing interests.

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