



Research Article

The lifespan of corpora lutea in nonpregnant females is positively correlated with gestation length

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Abstract

In mammals, a temporary endocrine gland called the corpus luteum forms on the ovary shortly after ovulation and is required for the initiation and maintenance of early pregnancy. However, the corpus luteum persists even when fertilization or pregnancy does not occur, and species-specific variation in the length of this persistence remains enigmatic. Here we perform a comparative evolutionary study across 72 species and show that corpus luteum lifespan in nonpregnant females is positively correlated with gestation length. We argue that the most likely explanation for this correlation is physiological inertia. The corpus luteum begins secreting progesterone prior to implantation, and when pregnancy does not occur it takes time for females to degrade it and prepare the next reproductive cycle. Our study suggests that this physiological inertia is stronger in species with long gestation times.

Key words: corpus luteum, gestation, luteal phase, pregnancy.

Female mammals exhibit extensive maternal investment through gestation, lactation, and nursing of their offspring (Clark and Poole 1967; Gemmell 1981; Gilbert 1984; Van Raaij et al. 1989; Creel et al. 1991; Urison and Buffenstein 1995; Prentice and Goldberg 2000; Gobello 2021). The corpus luteum, a temporary endocrine gland that develops from a ruptured ovarian follicle following ovulation, secretes progesterone and plays a critical role in the initiation and maintenance of early pregnancy in many mammalian species (Moor 1968; Sharman 1970; Tyndale-Biscoe et al. 1974; Gadsby and Landis Keyes 1984; Harder et al. 1985; Hinds 1990; Wiltbank 1994; Bachelot and Binart 2005; McAllan 2011; Amelkina et al. 2015). A functional corpus luteum shifts multiple physiological characteristics in pregnant females, including brain and blood chemistry, bone remodeling, mammary development, uterine development, and immune function (Csapo and Wiest 1969; Graham and Clarke 1997; Karlsson et al. 2001; Neville et al. 2001; Sheehan and Numan 2002; Conneely et al. 2003, 2008; Verstegen-Onclin and Verstegen 2008; Fu and Levine 2009; Brunton and Russell 2010; Mesiano et al. 2011; Shah et al. 2018; Wu et al. 2018).

Even when a reproductive cycle has not culminated in a pregnancy, the corpus luteum remains functional for varying lengths of time across species. In some cases, a functional corpus luteum can cause nonpregnant females to exhibit physiological changes similar to pregnancy (Casida and Warwick 1945; Weitlauf and Greenwald 1967; Csapo and Wiest 1969; Csapo et al. 1972; Shorey and Hughes 1973; Csapo and Pulkkinen 1978; Harder et al. 1985; Baird 1992). Indeed, in many species, a functional corpus luteum prevents a female from entering the next ovulatory cycle (Tyndale-Biscoe et al.

1974; Tyndale-Biscoe and Renfree 1987). What factors might explain variation in the persistence of functional corpora lutea in nonpregnant females?

It is possible that the same molecular mechanisms that maintain a functional corpus luteum in pregnancy may lead to their persistence even when pregnancy has not occurred. This hypothesis of physiological inertia predicts a positive correlation between gestation length and corpora lutea lifespan in nonpregnant females. In addition, monestrous species and seasonally breeding species are predicted to evolve mechanisms that reduce corpora lutea lifespans in nonpregnant females, because they must return to a new reproductive cycle or run the risk of missing their opportunity to reproduce. Here we compile data from 72 species from 12 orders and implement a variety of evolutionary methods to test these hypotheses.

Materials and methods.

Corpora lutea lifespan.

We searched the literature for reports of functional corpora lutea in nonpregnant females across any species (without focusing on any region of the phylogeny). We considered a corpus luteum to be functional if histological data showed robust vascularization, or indirectly from the well-characterized spike in progesterone that corpora lutea produce in the early stages of implantation and pregnancy. We only included studies where females could not have been pregnant—that is, the study had to explicitly state that females were either housed separately from males or were housed with sterile (e.g., vasectomized) males. Otherwise, functional corpora

lutea in “nonpregnant” females could have arisen if females were pregnant but aborted prior to birth. Our primary data came from searches in Google Scholar (<https://www.scholar.google.com>) and Web of Science (<https://webofscience.com/>), with the phrases: *progesterone*, *atresia*, *corpus luteum*, *corpora lutea*, *period*, *corpus albicans*, *corpora albicantia*, *corpora albanica*, *menstruation*, *pseudopregnancy*, *non-pregnant*, *ruptured follicle*, *accessory corpus luteum*, and *corpus luteum regression*.

There are 2 main types of ovulation in mammals—spontaneous and induced. *Spontaneous ovulators* do not require any male cues or signals and will ovulate even in isolation from males, although male cues such as musk, urine, touch, and sounds can still influence corpus luteum lifespan (Bruce 1960; Bruce and Parrott 1960; DeMatteo et al. 2006; Roberts et al. 2012). For spontaneous ovulators, we recorded corpora lutea lifespan from any studies where females were not pregnant, including studies where females were isolated from males.

In contrast, *induced ovulators* require male cues to induce ovulation (Johnston et al. 2000; Brown 2011; Dixson 2021). In some cases, copulation or semen is required to induce ovulation (Chen et al. 1985; Johnston et al. 2004; Kauffman and Rissman 2006; Ballantyne 2015; Schjenken and Robertson 2020). One species (Djungarian Hamster, *Phodopus sungorus*) requires male cues at 2 different stages: one to ovulate, and a second exposure to induce the activation of corpora lutea (Wynne-Edwards et al. 1987; Erb et al. 1993; Edwards et al. 1994; McMillan and Wynne-Edwards 1999). For induced ovulators, we recorded corpora lutea lifespans from any studies where females were exposed to males but could not have been pregnant, e.g., studies where females were housed separately but exposed to male cues like scent, or studies where females were housed with vasectomized males.

Females of some species can undergo both spontaneous and induced ovulation (Hill and O'Donoghue 1913; Foresman and Daniel 1983; Hinds 1989; Clamon Schulz et al. 2003; Steinman et al. 2012). For these species, we only used data in the absence of males for evolutionary analyses.

We also scored corpora lutea lifespans from truly pregnant females, although data were scarcer than for nonpregnant females ($n = 21$ species; Supplementary Data SD1). Progesterone production shifts from the corpus luteum to the placenta at some point during pregnancy, so we could not use progesterone levels to indicate a functional corpus luteum. Instead, we relied on robust histological analyses or ultrasound studies as a proxy for corpus luteum lifespan in pregnant females (Supplementary Data SD1).

Our exhaustive literature search yielded data from 72 species that fell into 6 monophyletic groups: metatherians (23 species from 4 orders); Order Carnivora (20 species); Order Rodentia + Order Lagomorpha (7 species); Order Artiodactyla + Order Perissodactyla (10 species); Order Primates (9 species); and Order Cingulata + Order Pilosa (3 species).

Gestation length and body size.

We searched the literature for gestation length data from the same species for which we gathered corpora luteum lifespan data. Because many physiological features of an organism correlate with body size, we also included body mass of adult females (nonpregnant) as a covariate in the evolutionary models. Most body mass data were derived from Silva (1995), supplemented with additional literature searches (Supplementary Data SD1).

Phylogenetic generalized least squares.

To test for a correlation between corpus luteum lifespan and gestation length, we employed generalized least squares implemented

in the GLS function from the R package “nlme” (Pinheiro et al. 2022). To account for phylogenetic dependence, we included an expected correlation matrix derived from the mammalian phylogeny of Upham et al. (2019), trimmed to only include the species in our data set (Supplementary Data SD2). We derived the correlation matrix with the `CORPAGEL` function in the R package “ape” (Paradis 2012). Using R (R Core Team 2020), the model we tested was `GLS(corpus_luteum_lifespan ~ gestation_length + body_mass, correlation=corPagel, method="REML")`, where “REML” indicates that the model was fit by maximizing the restricted log-likelihood, as advised by Paradis (2012). All metrics were natural-log-transformed prior to regression.

Estrus frequency and breeding seasonality.

We hypothesized that monestrus species and seasonally breeding species would show relatively short corpora lutea lifespans in nonpregnant females. Therefore, we repeated the phylogenetic generalized least squares (PGLS) analyses above after subsetting out species for which we could collect estrus frequency and breeding seasonality.

Results

We scored corpora lutea lifespans in nonpregnant females, body weight of adult females, and gestation length from 72 species representing 12 orders. To our knowledge, this represents the most complete data set to date of species with data on all 3 traits (Supplementary Data SD1). For a subset of 21 species, we found data on corpora lutea lifespans in pregnant females, as well as their frequency of ovulation and breeding seasonality (Supplementary Data SD1).

Corpora lutea lifespan in nonpregnant females was positively correlated with gestation length.

Corpus luteum lifespan in nonpregnant females was significantly positively correlated with gestation length ($F_{1,69} = 22.53$, $P = 0.0001$), but not body mass ($F_{1,69} = 0.14$, $P = 0.70$), with the full linear equation: $\text{corpus_luteum_lifespan} = 0.78 \times \text{gestation_length} - 0.02 \times \text{body_mass} - 0.16$. The lambda estimated from this full model was close to 1 (Lambda = 0.99), indicating that phylogenetic structure accounted for much of the relationships among variables.

Metatherians and Order Carnivora showed relatively long corpus luteum lifespan compared to the other 4 groups (Figs. 1 and 2). Species with the largest gestational investment ($\ln(\text{gestation}) > 4.7$) fell into 2 clusters: the 6 eutherian species that exhibit embryonic diapause showed relatively long-lived corpora lutea while almost all others showed relatively short-lived corpora lutea (Figs. 1 and 2). Embryonic diapause is a life history strategy in some mammalian species wherein embryos remain suspended at the blastocyst stage—sometimes for several months—before implanting in the uterus, all while the corpus luteum continues to produce progesterone (Hoffmann et al. 1978; Foresman and Daniel 1983; Sempéré et al. 1992; Sato et al. 2001; Clamon Schulz et al. 2003; Okano et al. 2006; Sattler and Polasek 2017; Larsen Tempel and Atkinson 2020). The 6 eutherian species included in our analysis that exhibit embryonic diapause are *Ursus arctos* (Brown Bear), *U. americanus* (American Black Bear), *U. thibetanus* (Asian Black Bear), *Capreolus capreolus* (Siberian Roe Deer), *Eumetopias jubatus* (Steller Sea Lion), and *Odobenus rosmarus* (Walrus). The 3 bear species that exhibit embryonic diapause have notably longer corpus luteum lifespans than the fourth bear species included in our analysis, which does not exhibit embryonic diapause (Sun Bear, *Helarctos malayanus*; Fig. 2). Similarly, the only species in the Artiodactyla + Perissodactyla

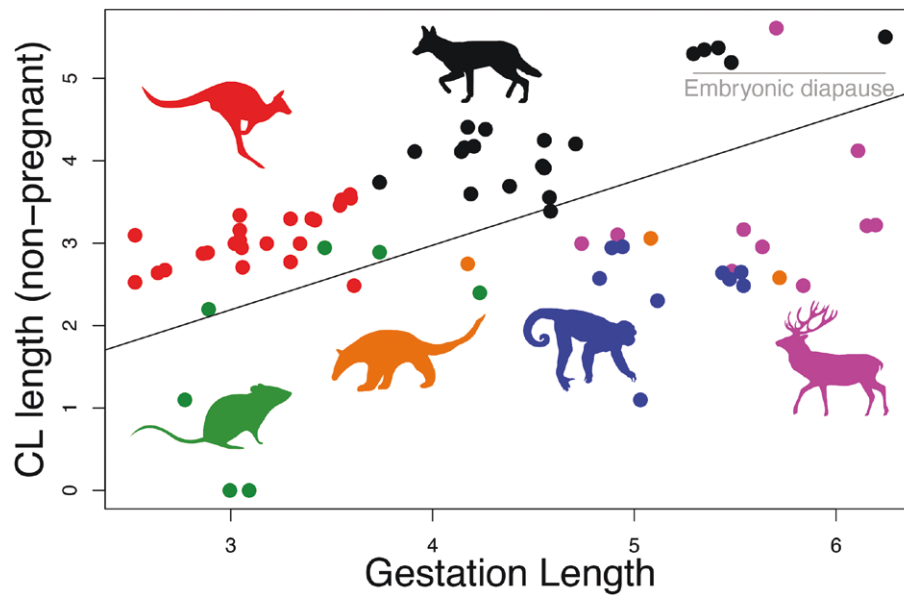


Fig. 1. Corpus luteum lifespan in nonpregnant females was significantly positively correlated with gestation length. Each point on the plot is a species, placed into 1 of 6 groups indicated by color and image: red kangaroo represents 23 species of metatherians; black canid represents 20 species of Order Carnivora; green rodent represents 7 species of Order Rodentia + Order Lagomorpha; magenta deer represents 10 species of Order Artiodactyla + Order Perissodactyla; blue monkey represents 9 species of Order Primates; orange anteater represents 3 species of Order Cingulata + Order Pilosa. For both axes, the units are $\ln(\text{days})$. Species images modified from phylopic.org (exact file names: PhyloPic.156b515d.Sarah-Werning.Callitrichoidea_Cebidae_Cebinae_Platyrrhini.png; PhyloPic.570c7d9e.Alexandra-van-der-Geer.Rattus.Rattus-exulans.png; PhyloPic.6df900f7.Xavier-A-Jenkins.Myrmecophagidae_pan-Myrmecophagidae_Tamandua_Tamandua-mexicana_Vermilingua.png; PhyloPic.96adba97.Margot-Michaud.Canis.Canis-simensis.png; PhyloPic.c306572a.Sarah-Werning.Macropus-Macropus.png; PhyloPic.cc03f5c2.Ferran-Sayol.Cervus-elaphus.png).

group that exhibits embryonic diapause (Roe Deer, *Capreolus capreolus*) shows a notable increase in corpus luteum lifespan compared to its relatives (Fig. 2).

Corpora lutea lifespan in truly pregnant females was positively correlated with gestation length.

Despite exhaustive literature searching, we were only able to score corpus luteum lifespan in truly pregnant females from 21 species (representing 8 orders; Supplementary Data SD1). Employing the same PGLS as described above, corpus luteum lifespan was positively correlated with gestation length ($F_{1,6} = 25.27$, $P = 0.0001$) but not body size ($F_{1,6} = 1.52$, $P = 0.24$) with the full linear equation: $\text{corpus_luteum_lifespan} = 0.82 \times \text{gestation_length} + 0.08 \times \text{body_mass} + 0.67$.

Corpora lutea lifespan was relatively long in monestrous and seasonally breeding species.

From the 72 species in our full data set, we found data on estrus frequency and breeding seasonality for 51 and 47 species, respectively. Monestrous species ($n = 9$) had significantly longer corpora lutea lifespans in nonpregnant females than polyestrous species ($n = 42$), as indicated by significantly higher residuals from the full model above ($t = 2.4$, $df = 49$, $P = 0.02$). Seasonally breeding species ($n = 26$) had significantly longer corpora lutea lifespans in nonpregnant females compared to species that breed year-round ($n = 21$, $t = 2.58$, $df = 45$, $P = 0.01$). Both results are opposite our predictions. In other words, species that seemingly have “more to lose” by maintaining active corpora lutea when not pregnant actually show longer corpora lutea lifespans.

Discussion

The reason for variation in lifespan of the corpora lutea remains relatively unknown in mammals, reflecting the continued need

for basic research on female pregnancy (Hayssen and Orr 2017; Hayssen 2020). During pregnancy, female mammals experience changes to their anatomy, physiology, neurobiology, hormone levels, immune system, vulnerability to predation, and even lifespan (Supplementary Data SD3). Many of these shifts depend on a functional corpus luteum. In every species studied here, we found evidence that functional corpora lutea persist in nonpregnant females.

The hormonal signaling associated with maintaining a pregnancy begins prior to actual conception of offspring, during the estrus cycle. A functional corpus luteum begins secreting progesterone prior to implantation and is critical for early pregnancy. Thus, when a reproductive cycle does not yield successful pregnancy, the corpus luteum may simply represent physiological inertia toward a state of pregnancy. In other words, even when pregnancy fails it takes some time to reverse course and degrade the corpus luteum prior to entering the next reproductive cycle. Our study implies that this physiological inertia is stronger among species with long gestations.

The species studied here vary tremendously in the molecular mechanisms by which they maintain or degrade corpora lutea. Hormones related to corpora lutea are generally classified into 3 categories: (i) luteotropic hormones that sustain corpus luteum development or maintenance; (ii) luteolytic hormones that lead to the degradation of the corpus luteum; and (iii) antiluteolytic hormones that prevent the degradation of the corpus luteum. All 3 of these hormonal classes have been found in eutherian species, while only a single luteolytic hormone has been described from metatherian species (Supplementary Data SD3).

Inbaraj et al. (2021) showed that 9 eutherian species (horses, cattle, humans, camels, rats, sheep, deer, cats, and dogs) showed species-specific combinations of hormones involved in luteal regression. Similarly, Chavan et al. (2016) showed that primates, horses, and rodents each had distinct hormonal mechanisms of luteotropic signaling.

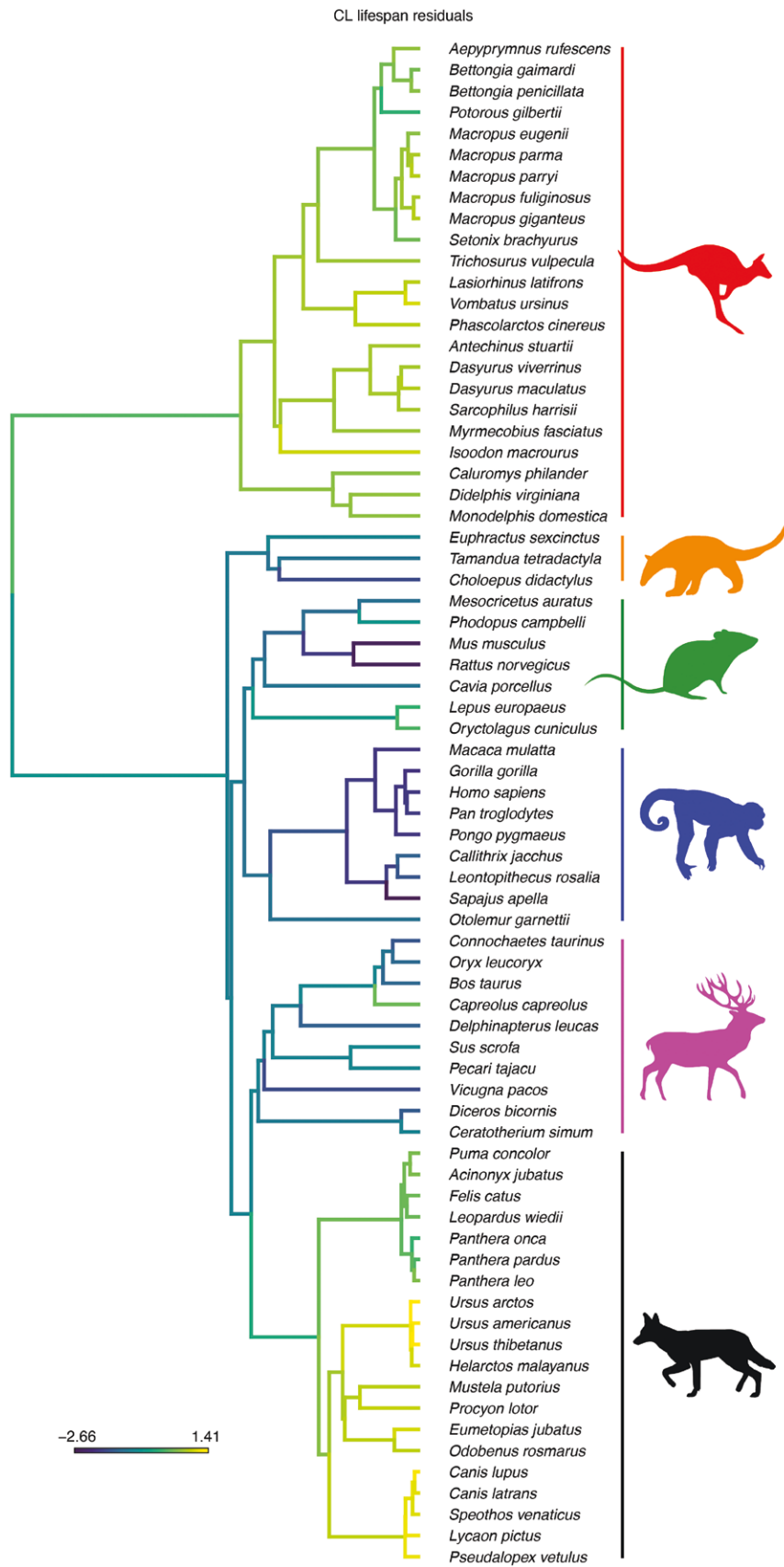


Fig. 2. The phylogenetic distribution of corpus luteum lifespan in nonpregnant females. Taxon colors and images as in Fig. 1. Branches colored according to the residuals of corpus luteum lifespan regressed onto gestation length + body mass. For context, most recent common ancestor of the species shown is roughly 157 million years ago. Image credits as in Fig. 1.

In contrast, only 1 luteolytic hormone (Prostaglandin 2 α) has been shown to influence corpora lutea lifespans in metatherians (Renfree and Young 1979; Tyndale-Biscoe and Renfree 1987; Hinds 1990). Furthermore, it has been argued that the corpus luteum plays a relatively minor role in maintaining pregnancy in marsupials, where gestational investment is much shorter than in eutherians (Shorey and Hughes 1973; Tyndale-Biscoe et al. 1974; Tyndale-Biscoe and Renfree 1987; McAllan 2011). Despite major differences in molecular regulation of and reliance on corpora lutea, the positive correlation between corpora lutea lifespans in nonpregnant females and gestation length extends across mammals, including marsupials (Figs. 1 and 2).

Without more comparative biology on the molecular pathways involved in corpora lutea, the positive correlation between their lifespan in nonpregnant females and gestation length will remain enigmatic. But the correlation implies the same pathways involved in maintaining a pregnancy also extend corpora lutea lifespans in females even when there is no pregnancy to support. This constraint may be especially strong in species with embryonic diapause because they must maintain an active corpus luteum for much longer than species that do not manifest embryonic diapause (Hoffmann et al. 1978; Foresman and Daniel 1983; Tsubota et al. 1987; Sato et al. 2001; Okano et al. 2006; Frederick et al. 2010). Our study offers an explanation for the persistence of functional corpora lutea in nonpregnant females, suggesting that it is constrained by the physiological preparation for a real pregnancy.

Supplementary data

Supplementary data are available at *Journal of Mammalogy* online.

Supplementary Data SD1. Spreadsheet containing all data analyzed, including literature sources.

Supplementary Data SD2. The phylogenetic tree used in the full PGLS.

Supplementary Data SD3. Citations to pregnancy-related changes and hormonal changes in females.

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Author contributions

Conceptualization: ML-S and MDD; Data curation: ML-S and CRG; Formal analysis: MDD; Funding acquisition: MDD; Investigation: ML-S; Methodology: ML-S, MDD, and CRG; Project administration: ML-S and MDD; Resources: MDD; Software: MDD; Supervision: MDD; Validation: MDD; Visualization: MDD; Writing—original draft: ML-S; Writing—review & editing: ML-S, MDD, and CRG.

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Conflict of interest

None declared.

Data availability

Found in [Supplementary Data SD1](#).

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