

Debate

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## Luteal regression: a redefinition of the terms

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The corpus luteum is a transient endocrine gland that is specialized for the production of progesterone and that plays a critical role in the establishment and maintenance of pregnancy. The life span of the corpus luteum varies between species and, within a species, can be dramatically altered by events such as mating or pregnancy. Regardless of the duration of its life span, the corpus luteum eventually enters a dynamic regression process during which it loses the capacity to produce progesterone and undergoes structural involution.

The overall process of luteal regression has been referred to by a variety of terms over the last several decades. In Table 1, we show the results of a cursory MEDLINE/PubMed search on luteal regression performed in November of 2002, which reveals that the most frequently utilized term for this process is "luteolysis," followed by "luteal regression," and then, to a lesser extent, by "functional luteolysis" and "structural luteolysis." Other terms, such as "luteal involution," "functional luteal regression," or "structural luteal regression" lag far behind in usage. The necessity of using several keywords to search for information on luteal regression is illustrated by the fact that in our sample MEDLINE/PubMed search, only 47% of the manuscripts retrieved using the keyword "luteal regression" were also retrieved when using the keyword "luteolysis." This inconsistency in terminology can result in serious under-retrieval and under-citation of papers using less popular keywords.

To quote Rossdale and Cox in their communication entitled *Terminology: a mark of scientific progress* [1]: "Scientific terminology must be as exact as is possible within the state of knowledge available." As our knowledge of the

molecular mechanisms participating in the process of luteal regression evolves, some of the commonly used terms cited above have been rendered obsolete, inappropriate, and even incorrect. The foremost of these is "luteolysis," still one of the most common terms used to define the process of luteal regression, most probably because it is listed among Medical Subject Headings (MeSH), and, therefore, used most frequently. MeSH is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles in PubMed. MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts. In MeSH, "luteolysis" is defined as "degradation of corpus luteum" and further described as "...characterized by the involution and cessation of its endocrine function." From a cell biology point of view, "lysis" means "rupture of cell plasma membrane, leading to the release of cytoplasm and the death of the cell" [2]. If interpreted with strict accordance to the Latin, lysis refers to "disintegration," as recently discussed by Davis and Rueda [3]. Over the last decade, it has become clear that the involution of the corpus luteum is associated with a phenomenon of programmed cell death or apoptosis [4]. Because apoptosis is an organized process that does not involve a major inflammatory response, and because the majority of cells are removed prior to rupture, the term "lysis" when applied to luteal regression is largely inaccurate. Therefore, while the term luteolysis remains very popular – 1251 manuscripts were retrieved using the word "luteolysis" and only 403 were retrieved using the terms "luteal regression" in the MEDLINE/PubMed search (see Table 1) – this term no longer accurately reflects the mechanisms involved in luteal regression. In 1999, McCracken *et al.* [5] stated that "the term luteolysis may be something of a misnomer;" but also re-

**Table 1: Results of a cursory MEDLINE/PubMed search performed on November 2002 using the terms as listed.**

Rank	Terms	Total Number of Articles Retrieved	Retrieval Period	Number of Articles Retrieved for Period 2001–2002
1	"luteolysis"	1251	1967–2002	96
2	"luteal regression"	403	1966–2002	35
3	"functional luteolysis"	82	1973–2002	5
4	"structural luteolysis"	72	1969–2002	14
5	"luteal involution"	41	1978–2002	8
6	"functional luteal regression"	10	1984–2002	0
7	"structural luteal regression"	5	1988–2002	1

ferred to the deep entrenchment of this term in the literature. However, the exponential increase in the number of scientific manuscripts published in recent years ensures that a prompt move to replace the older term with a more accurate descriptor will rapidly result in an overturn of the current ranking displayed in Table 1 and that only a minority of papers will continue to be retrieved using the older term.

Despite the fact that a strict definition of "luteolysis" appears to regard only the structural disintegration of the corpus luteum, broader interpretations are rife within the literature. Rothchild [6] defined luteolysis as "stopping the secretion of progesterone by the corpus luteum." Two other recent reviews take a middle road. Hoyer [7] refers to the fall in progesterone secretion as functional regression but considers structural regression, or cell death, the "true" regression. Niswender *et al.* [8], while referring to luteal regression as the structural demise of the corpus luteum, go on to describe the loss of progesterone synthesis and secretion – not a structural event – as part of the regression of the corpus luteum.

As the previous paragraph shows, the adjectives "structural" and "functional" cannot be overlooked when addressing terminology in the field of luteal regression. These words have had a consistent presence in literature concerning the regression of the corpus luteum since Malven and Sawyer [9] described the process of luteal regression in the rat as having two components: "1) an initial termination of luteal secretory function and 2) a subsequent morphological regression of the nonfunctioning corpora lutea." A few years later Malven *et al.* [10] used the term "structural luteolysis" to describe the morphological regression of persistent, nonfunctional corpora lutea in the hypophysectomized rat. The definition of "nonfunctional" provided in this manuscript expanded upon the 1966 description of the first component of luteal regression in

the rat by explaining that the corpora lutea "did not secrete enough progesterone to induce deciduoma formation following endometrial traumatization." Thus, the corpora lutea were "nonfunctional" in terms of progesterone production and the potential for establishment of pregnancy.

Since the appearance of these early papers, the terms functional and structural regression of the corpus luteum (or the more popular phrasing "functional and structural luteolysis") have gained relative acceptance and usage. The cursory MEDLINE/PubMed search shown in Table 1 turned up 82 references containing the phrase "functional luteolysis," of which 5 were 2001 and 2002 publications, and 72 references containing the phrase "structural luteolysis," of which 14 were 2001 and 2002 publications. The prevalence of the term "structural luteolysis" over "functional luteolysis" in recently published articles may be due in part to a greater disparity in the perceived meaning of the latter term. This stems largely from studies in rats, in which it was revealed that corpora lutea which no longer secreted significant quantities of progesterone retained many functions, including active steroidogenesis [11–13].

It is our contention that these two frequently described components of the process of luteal regression (i.e. cessation of progesterone secretion and disappearance of the structure) merit equal attention. However, the timing and inter-relationship of these two types of regressive changes appears to vary by species. As new information on the molecular steps triggered during luteal regression is obtained, these mechanisms will need to be defined as they relate to these facets of the overall regressive process. Davis and Rueda [3] advised that the terms functional and structural used in the context of luteal regression should be adequately defined by the authors in the context of the particular species and reproductive stage being studied, with which we concur. It is not extreme to predict that with the

advancement of knowledge in the process of luteal regression researchers will find increasing difficulties in establishing the limits as to what mechanisms belong to the "functional" facet of luteal regression, and which ones are part of the "structural" facet, as luteal regression is a process of synchronized events. For example, it now appears that progesterone itself is responsible for preventing the onset of apoptosis and structural disintegration [14–17].

## Conclusions

These authors strongly recommend that the term *luteal regression* should be used to refer to the process of regression of the corpus luteum. Luteal regression represents a broad definition of the process of demise of the corpus luteum that is capable of accommodating all new knowledge evolved on the molecular mechanisms activated or inhibited during the process of regression of the corpus luteum regardless of species or reproductive stage. Further, according to the etymology of the word, luteolysis has a very limited meaning that no longer describes properly the complex sequence of synchronized molecular events associated with the demise of the corpus luteum. The modifying terms "functional" and "structural" can be used in conjunction with the term luteal regression to further identify aspects of the overall process but must be adequately defined within the context of the publication.

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