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PREGNANCY TOXAEMIA/KETOSIS IN FEMALE RABBITS

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Abstract: In this study we determined clinical and epidemiological aspects of clinical pregnancy toxaemia/ketosis (CPTK) in female rabbits housed in commercial farms in Portugal and Spain. Information was gathered through 12 611 visits to 1422 doe farms during 1994-2024. The median size of the doe farms visited by the end of the period was 868 does (mean size: 1067 does, ranging from 100 to 6000 does). Diagnoses were based on macroscopic post-mortem examinations by veterinarians. Over the 31-yr study, we conducted 5117 necropsies of does on 607 rabbitries. Within a sub-set of 126 farms, we identified 401 does presenting CPTK lesions. The at-risk female population across the 126 farms totalled 152 218 does. From this data, we estimated the relative incidence of the disease at 0.26% of at-risk females on the day of the visit. The median size of farms with females at risk was 400 does (minimum to maximum: 100-3015 does). In this study, age emerged as a significant risk factor: does in their first-pregnancy or first-lactation were more predisposed to CPTK, mostly between days 27 and 32 of gestation. Additionally, 20.2% of females that died from CPTK experienced abortions between days 23 and 30 of pregnancy. Seasonal variation also appeared to influence disease occurrence, with lower incidence during autumn. CPTK in farmed female rabbits carries a poor prognosis, often going unnoticed due to the large number of kindlings in each batch. From this study we infer that the most efficient control strategies on farms were medical prophylaxis and management-based prevention. These include monitoring indoor climate and providing careful feeding for young does. Clinically, it is useful to check for the presence of hard faeces bound with hair.

Key Words: female rabbit, metabolic diseases, pregnancy toxaemia /ketosis, clinical features, occurrence, prevention.

INTRODUCTION

Pregnancy toxaemia /ketosis (PTK) is a syndrome due to disorders of energy metabolism and other organ systems. It is characteristic of the transition phase from pregnancy to lactation, respectively (Constable *et al.*, 2017). Periparturient females of the domestic rabbit (*Oryctolagus cuniculus*), have disturbances in glucose, fatty acid and mineral metabolism (Minuti *et al.*, 2015). Deficiency states occurring in the transition phase affect health and wellbeing

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(Broom and Fraser, 2015), as well as the reproduction and lifespan of rabbit does (Fortun-Lamothe, 2006). PTK in doe-farm is often subclinical and goes unnoticed. However, in some females it is manifested and causes death, either alone or in synergy with digestive or respiratory disorders, among others. Although cases of clinically manifested PTK (hereafter referred to as CPTK) are isolated, outbreaks of the disease have also been diagnosed. Greene (1937) conducted a detailed clinicopathological study of pregnancy toxaemia in female rabbits. He proposed an aetiopathogenic hypothesis centred on signs of endogenous intoxication. He also reported reproductive disturbances, including reduced fertility and prolificacy, conceptus loss and abortions. CPTK has been classified in various ways over time. Flatt *et al.* (1974) categorized it as metabolic disease, Cheeke (1994) in nutrition-related disorder, Di Girolamo and Selleri (2020) and Rosell *et al.* (2020) as a reproductive disorder, and Varga (2023) as a condition associated to the digestive tract.

The first step in approaching the problem is to understand the feeding behaviour of the female rabbit. According to Lebas (1975), healthy females reduce their feed intake around parturition and often (>60%) do not meet their needs and those of their foetuses (Fekete *et al*., 2005). Therefore, there is a negative energy balance, until the first days of lactation. In cows, unlike the sheep and the female rabbit, the deficit is greater postpartum than at the end of pregnancy (Grummer, 1995). Rabbit does regain their body weight and body condition in the first week postpartum (de la Fuente and Rosell, 2012). Nevertheless, some rabbit does maintain a negative energy balance until peak lactation (Garreau *et al*., 2017). When there is a negative balance, hypoglycaemia stimulates lipolysis and females mobilise free fatty acids from their reserves, via the liver (Parigi-Bini, 1983), with intracellular accumulation of triglycerides in the hepatocytes. The excess causes hepatic lipidosis or fatty liver (Cullen and Stalker, 2016). There is an insulin-resistant state between days 24 and 30 of pregnancy (McLaughlin and Fish, 1994), then followed by an increase of triglyceride hydrolysis. Its metabolism produces ketone bodies; if production exceeds degradation, ketoacidosis occurs (Varga, 2023). Ketonaemia rises slightly but significantly on day 27 of gestation (Jean-Blain *et al*., 1985). Most pregnant rabbits cope with these challenges. Therefore, ketoacidosis and lipidosis are subclinical, but sometimes cause death mainly by hepato-renal failure, with little or no previous clinical signs (Coudert, 1997). In female rabbits housed on farms, lipidosis is diagnosed through necropsy, with the liver being the key organ affected. In a previous study, we reported pathological findings of fatty liver in CPTK as well as in other disorders observed in farmed rabbit does (Ferreras *et al*., 2025).

In the peripartum period there are changes in gut motility, microbiota and intestinal pH (Varga, 2023). According to Harcourt-Brown (2002), the accumulation of hair in the stomach is a consequence of gastrointestinal hypomotility and anorexia, not the other way around; various factors enable hypoperistalsis (e.g., low indigestible fiber diet, stress, and pain). Trichobezoars are nuclear in the aetiopathogenesis of CPTK (Patton *et al*., 1983). Thus, pyloric obstruction even leads to death, which is frequent in Angora rabbits (Risam *et al*., 2005). Another relevant aspect is that there are clinical and subclinical diseases that affect feed intake, because they reduce appetite, as a defence mechanism (Johnson, 2002).

Obesity deserves special attention in metabolic diseases (Constable *et al*., 2017). Overweight female rabbits are most susceptible to CPTK *because they have already accumulated triglycerides in the hepatocytes* (Varga, 2023). Sánchez *et al.* (2012) evaluated the body condition of 18 510 individually examined female rabbits on 103 farms. The body condition score (BCS) was assessed by palpation, using a linear scale from BCS=1 (emaciated) to BCS=9 (obese). They considered obese females as those with BCS>7/9. In this context, there are three critical phases in the life of the doe. The first is the rearing period, from 2-2.5 mo of age until the first parturition at 5.5-6 mo old (Rommers *et al*., 2004). Another important risk factor is a low pregnancy rate (IRRG, 2005). We defined it as less 75% of pregnancies. If a female does not conceive at first service, the risk of CPTK at the first kindling (corresponding to the second artificial insemination [AI]) is higher (Rosell *et al*., 2020). Subsequent failures might result in worsening obesity. To mitigate these risks, keepers should restrict feed intake to 130-150 g/d (Maertens, 2020) or provide a rearing diet with high content of indigestible fibre and low energy: <10.5 MJ DE/kg (Pascual *et al*., 2002).

Several authors have described the proportional mortality of female rabbits due to pregnancy toxaemia /ketosis (Rosell and de la Fuente, 2009; Espinosa *et al*., 2020, among others) or the relative mortality (Rosell and de la Fuente, 2016). Regarding the occurrence of CPTK in rabbit does, Boucher and Nouaille (2013), reported that fatty degeneration of the liver is exacerbated by increased production, similar to what is observed in dairy cows (Leblanc, 2010). On rabbit

farms, lactation and pregnancy often overlap. In short, the current production of the does (quantity and quality of milk, number of foetuses) is high, evolves rapidly and therefore the metabolic effort is exceptional (Lebas, 1975; Xiccato and Trocino, 2020).

The relative occurrence of CPTK outbreaks on farms has been reported as low (Rosell *et al.*, 2009). According to Thrusfield (2005), several predisposing on-farm risk factors contribute to this disease, including a) physiological state, particularly in peripartum period; b) genetic type and specialisation, with paternal lines being heavier than maternal lines and more prone to problems (Sánchez *et al.*, 2012); c) high prolificacy, averaging 10.9 live newborn per kindling, based on 429 French farms in 2021 (Pedro, 2023) and similar figures in Spain (Gullón *et al.*, 2023); d) the degree of adaptation to heat (Marai *et al.*, 2006); e) intercurrent pathological processes, such as digestive or respiratory disorders, mastitis and dystocia (Wu, 2020); f) poor body condition, particularly obesity (Sánchez *et al.*, 2012); g) enteric stasis (Reusch, 2005) and gastric obstruction with hair (Rosenthal, 2015).

Additionally, there are risk factors enabling fatty liver: a) reproductive management practices, particularly overlapping pregnancy and lactation (Fortun-Lamothe, 2006); b) diets deficient in cystine and methionine (Koteish and Diehl, 2001) or low sapid diet, e.g., due to excess ash in feed or mycotoxin contamination (Tsouloufi, 2024); c) heat stress (Cervera and Fernández-Carmona, 2020); d) inadequate feeding management, such as overfeeding and rapid weight gain in rearing young breeders (Martínez-Paredes *et al.*, 2022). In each doe or farm /cohort at risk, these factors might act in combination, producing co-effects.

Control of CPTK is based on information, timeliness of diagnosis and application of corrective measures. Angora rabbits are prone to disease. The best prevention of trichobezoar in this breed is daily feed restriction, plus fasting one day per week; this should be preceded by the administration of straw the previous day (Rougeot and Thébault, 1989). The treatment aims to debride the pyloric hairball, e.g., with paraffin oil, and also to improve peristalsis (Boucher and Thébault, 2000). Medical prophylaxis of CPTK is discussed below.

Based on this review, we may accept that CPTK impacts the health and well-being of rabbits, and their production. Therefore, our aims were to (1) estimate the relative incidence of CPTK through on-farm necropsies of does conducted in Portugal and Spain between 1994 and 2024, (2) investigate the predisposing and enabling risk factors related with the disease, and (3) describe the farm visits made to affected herds and the control measures implemented.

MATERIALS AND METHODS

This retrospective study was conducted from January 1st, 1994 to December 31st, 2024 (a 31-yr period). We included records from 12 611 visits to commercial rabbit doe farms, comprising 210 visits in Portugal and 12 401 in Spain. The visits were carried out as part of routine veterinary practice, health monitoring and surveillance, and consultancy activities on farms. Approval by the Animal Care and Use Committee was not required for this study as it was exempt from the RD 53/2013 and EU Directive 63/2010 and data were obtained from female rabbits bred on commercial farms obliged to comply with European recommendations and legislation on animal welfare, food safety, public health and the environment.

Characteristics of the studied farms

The present observational study includes findings from visits to 1422 doe farms; 1329 located in Spain and 93 in Portugal (from Lisbon to the north). In this study we only included commercial farms with female rabbits, with or without male rabbits. Therefore, we excluded visits to insemination centres, farms with weaned rabbits only or farms rearing young does, i.e., before the first service (4.5-5 mo old). On the farms there was a monthly flow of young females, due to the removal (>10% monthly), including mortality (3%) and culling risk (7%), as reported by Rosell and de la Fuente (2009). The farms visited represented a significant proportion of the farms present. In May 2025, in the official Spanish register (REGA), there were 698 farms keeping ≥20 rabbit does, with an average size of 796 does. Previously, according to the Ministry of Agriculture, Fisheries and Food (MAPA, 2025), there were 5000 rabbit farms in 2003. In 2008 there were 3400 farms and in 2017 <1000. In our visits, we asked producers about their rabbit lines, as well as about the census of does, i.e., ever serviced, by natural mating or AI. The median size of the

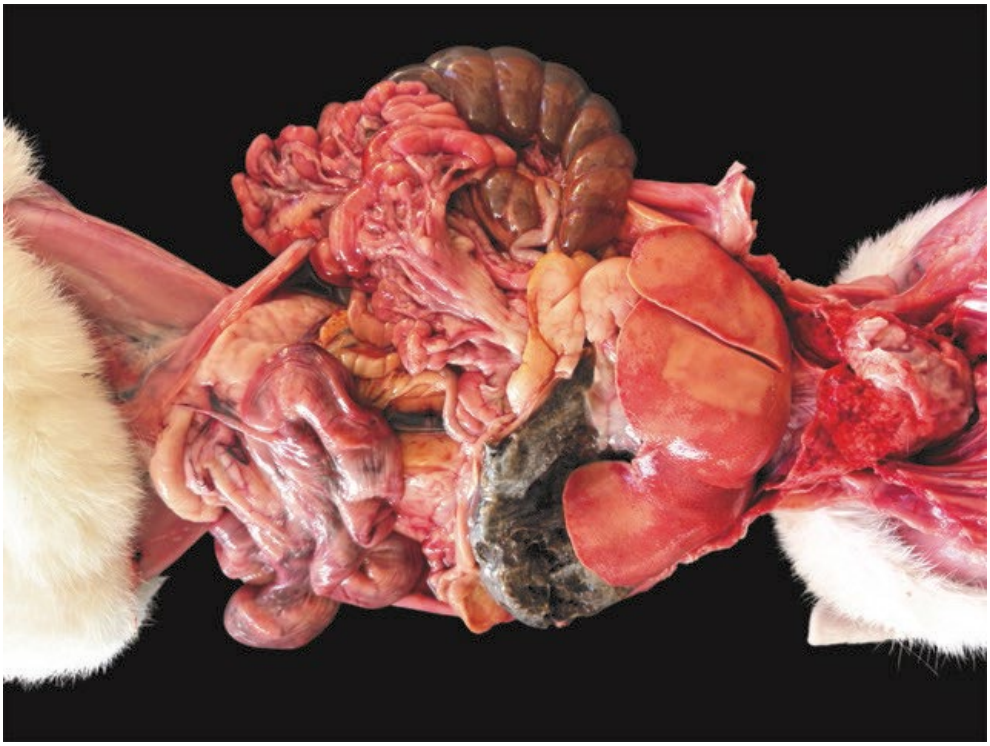

Figure 1: Female rabbit died the day of parturition from pregnancy toxaemia /ketosis. She had abdominal fat, fatty liver, hairball in the stomach, and lung congestion (spontaneous death, no bleeding).

doe-farms visited ranged from 350 females in 1994 to 868 does (average size: 1067 does, ranging from 100 to 6000 females), in 2023. The rabbit genetic types on visited farms were described by de la Fuente and Rosell (2012). Purebreds are rarely used on commercial rabbitries (Bolet *et al.*, 2004).

On-farm management procedures

The main management aspects in rabbit production include housing, husbandry and feeding. We visited rabbitries with a broad array of habitat and environmental characteristics. During the study, we visited individually housed female rabbits and recorded the breeding practices used on each farm, including the reproductive rhythm (e.g., service at 11-18-25-32…up to 56 or 120 d postpartum), and the type of service (does bred by AI or mount). The number of batches per farm was also documented, with a batch defined as a group of does serviced on the same day. The use of a single batch enables an *all-in-all-out* system, allowing for cleaning and disinfection of the housing (Huneau-Salaün *et al.*, 2015). In these cases, full-term pregnant does are moved to a clean barn.

Veterinary visits to the rabbit farms and diagnostic workup

In this study, we collected clinical information on productive and health events during veterinary visits. In classifying them, we only considered the main cause, e.g., *review* (no relevant problems) or *urgency*, e.g., CPTK, among others, as explained in a previous paper (Rosell *et al.*, 2009). The diagnoses were based on available reports of gross post-mortem examinations performed by veterinarians on the farms, eventually by pathologists at various universities. From 1990 onwards, the on-farm necropsy protocols used were those learned of Dr. L. Cuervo from the SIMA in Derio, Vizcaya, Spain (*pers. comm.*) The case definition of a female rabbit affected by CPTK (Figure 1) was based on

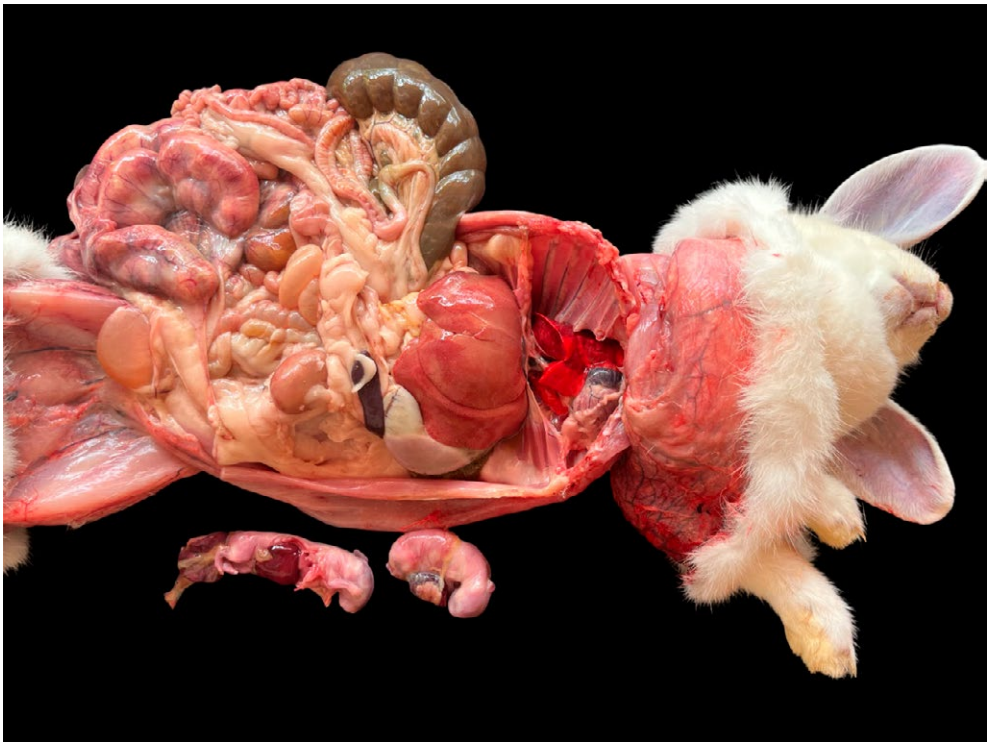

Figure 2: Female rabbit died on day 27 of pregnancy. This doe had fatty liver and renal lipidosis, as well as splenomegaly. The pathology laboratory diagnosed comorbidity of lipidosis and hepatitis. The virology laboratory confirmed rabbit haemorrhagic disease virus (RHDV2) (courtesy of Dr. K. Dalton). We classified the case as RHD.

two criteria: (1) the physiological state (near parturition) and (2) examination of the liver, compatible with steatosis. We classified a fatty liver when there was a yellowish organ, with blunt edges, friable and oily to the touch. This was the main finding to classify a primary CPTK; eventually also with renal lipidosis, trichobezoar, or pancreatic necrosis (Ferreras *et al.*, 2025). Following the criteria of Constable *et al.* (2017), we classified as secondary CPTK cases those in which, in addition to fatty liver, there was comorbidity with enteritis or pneumonia.

Differential diagnosis was required on several occasions, with the most common cases being secondary CPTK. There were cases of fatty liver with severe pneumonia or enterotoxemia, which we did not classify as secondary CPTK but rather as pneumonia or digestive disorders, as described in Ferreras *et al.* (2025). There were predictable cases due to heat stress, especially in open-air farms. Besides, there were cases with uncertain diagnosis. Figure 2 illustrates the case of a female that we found dead on a farm where the first cases of rabbit haemorrhagic disease (RHD) were observed by the producers in weaned rabbits and young breeding does.

We classified *a case as an affected cohort or farm* when, (1) CPTK was the most serious problem. Diagnosis was based on necropsies, records and observation of the females. In the last week of pregnancy, the does are resting and it is not easy to distinguish clinical signs, because they are large batches of females at term (e.g., 500-1000 does). There is an interesting sign, which is the presence of faeces with hair attached (Figure 3). Therefore (2), when we observed several females with hair in the faeces, we considered that, if they were close to parturition, there was a risk of CPTK, in agreement with Patton *et al.* (1983). We assessed this condition on a farm where we had observed it. The farm had 1600 does in a single batch, in a barn with natural ventilation and large windows facing south. They were females managed at an extensive rhythm (>56 d).

Figure 3: Hair-attached faeces in pregnant doe at term. It is a sign of interest in the prevention of metabolic diseases.

In this case study, we evaluated does housed in the same row, where sunlight enabled identification. This subgroup included pregnant nulliparous, primiparous and multiparous does. We observed them from AI, when they were already weaned, until 15 d after parity, when the kits started to come out of the nest.

On-farm prevention and treatment features

In terms of prevention, in this section we first describe different management used in the farms of the study. Particular attention was given to the rearing of young does. Housing and feeding practices varied widely across farms. Figure 4 illustrates housing for young females where manual feed restriction could be implemented.

There are farms where the feeders are large or have feed distribution systems that do not allow feed restriction (Figure 5). Therefore, it is interesting to use specific feed for future breeders, with low energy content as we have indicated before. Another preventive measure employed on farms at risk of CPTK, is the distribution of straw over the housing of each female (Figure 6).

For CPTK medical prevention on farms, propylene glycol has been used in drinking water for years, e.g., 5 to 10 mL/L, even up to 2%, in the days before kindling or AI (Luzi *et al.*, 2001). In the experimental field it was also included in the feed (Nicodemus *et al.*, 2005). In later years, this practice was extended or replaced using other feed supplements in peripartum. As examples, we use the following generic products: (1) a hepatoprotector (and growth stimulant) with magnesium sulphate, propylene glycol and several vitamins, 3 mL/L in water (5-7 d) or, (2) a compound with glucose, methionine, arginine, fructose, 5 mL single-dose subcutaneous (SC) or, (3) another product containing sorbitol, fructose, methionine, among others, 1 mL single-dose SC or, (4) 1 mL SC single-dose of a compound with phenoxy-2-methyl-2-propionic acid as sodium salt. In other concerns related to periparturient does, we used low dose of acetylsalicylic acid, i.e., 15 mg/ L (<5 mg/kg BW), in a few cases due to heat stress; Fisher and Graham (2023) indicate 5-20 mg/kg BW. On the occasion of parturition and gut stasis, Varga (2023) suggests paracetamol 10-30 mg/kg. Indeed, this mitigates pain, consequently hypoperistalsis and lastly, can avoid the risk for hepatic lipidosis. To finish this outlook, during 1992-2002, we visited a farm with 1300 females and intensive rhythm (24 h), where calcium gluconate injection was used at parities. Coudert (1997) advised the use of calcium salts before parturition.

Figure 4: Young does housed individually before first service (18-20 wk) and on restricted feeding.

Figure 5: Young female rabbits group housed until 7 d before parturition. Feeding ad libitum with specific rearing feed.

Figure 6: Pregnant full-term rabbit does with feeder filled with feed. Use of grass hay or straw alleviates hypoperistalsis and the risk of pregnancy toxaemia /ketosis.

Laboratory procedures

During the years of study, we sent samples to analytical laboratories to support the presumptive diagnosis in several necropsies. In addition, some periparturient female rabbits were submitted to the pathology diagnostic service of the Veterinary Faculty of León, as we reported in Ferreras *et al.* (2025).

Data recording

For this 31-yr retrospective study, the outcomes of the visits were organized in two databases. One database was at the farm level, grouped by cohort, including the day of visit, farm, and batch. The other database was at the individual female level. Data were initially recorded on-farm in paper form and later compiled into various spreadsheets. Compiled information included the date, farm, and locality. Moreover, we recorded the number of rabbit does in production (ever served, empty, pregnant, lactating or both states), does at risk (peripartum), and the parity number or physiological state of each necropsied female. Although 90% of the visited farms maintained individual records for each doe, access to this detailed information was not always available.

RESULTS AND DISCUSSION

CPTK occurrence at farm level

The main outcome of this 31-yr observational study concerns female rabbits dead due to CPTK. During this period, we made 12 611 visits to 1422 doe farms. We performed 5117 on-farm necropsies of does found dead or euthanized on 607 rabbitries. In a sub-set of 126 farms, we found 401 does with CPTK lesions. Some instances were primary, i.e., does in peripartum and with fatty liver, eventually with hairballs in the stomach or hair pellets in the intestine, obesity and sometimes fat necrosis plus pancreatic necrosis (Ferreras *et al.*, 2025). In addition, we classified cases of secondary CPTK, due to comorbidity with enteritis or mild pneumonia. Of the total number of necropsies, those due to CPTK were remarkable: 401 females. In contrast, we only made 6 visits for CPTK outbreaks. Underestimates of the number of CPTK cases might have occurred. For example, in emergencies classified as *heat stress*, despite the fact that several females died from CPTK. In addition, we often found more severe disorders, as we show in Table 1.

Table 1 shows the most common diseases in the clinical practice of the first author. The purpose of this overview is to highlight the residual occurrence of CPTK. Over the 31-yr period, only six urgent visits were related to CPTK, with none recorded from 1994 to 1996 (data not shown). In addition, we can infer the following. The rate of emergency visits in each period declined from 52% to 36.5%, while total emergencies for digestive disorders decreased from 49.4 to 27.9%. There were fewer emergency visits for mucoid enteropathy as well as fewer visits for enteritis-diarrhoea. Our experience suggests that this decline resulted from improved control by farm managers and their advisers. However, the number of visits increased, primarily due to RHD, beginning in 2011, with the onset of the RHDV2 pandemic in Spain (Dalton *et al.*, 2012). We made also many visits for myxomatosis, staphylococcosis, or for mastitis. It is possible that our attention or awareness of certain problems influenced the focus of visits. In previous studies, we observed that primiparous lactating females were prone to developing mucoid enteropathy. According to Coudert (1997), some cases attributed to enterotoxaemia were metabolic processes; *however, bacterial complications are common.* In fact, underconsumption, hypoperistalsis and dysbiosis can promote the proliferation of *Clostridium* spp. (Varga, 2023). This is a scope of interest.

Seasonality of clinical pregnancy toxaemia /ketosis

Table 2 describes the basic traits of the 31-yr work, grouped by season. We first included the winter outcomes (from January to March). The number of visits in each season was similar. Total necropsies decreased in autumn: -22.7 % compared to spring. But diagnosed cases of CPTK were: -45.8%. There might be environmental factors enabling the lower occurrence of CPTK in autumn.

Table 1: Description of the reasons[1] for urgent visits made to commercial farms[2] in Portugal and Spain from 1997 to 2024 [number of visits (percentage of urgent visits)].

	Period	
Trait[3]	1997-2007[4]	2008-2024
Total number /No. of visits (No. farms)	4307 (868)	7496 (695)
Urgent number /No. of visits (No. farms)	2237 (660)	2737 (508)
No. visits due to mucoid enteropathy[5]	648 (29 %)	310 (11.3%)
No. visits due to enteritis-diarrhoea	457 (20.4%)	454 (16.6%)
Total No. visits due to digestive troubles	1105 (49.4%)	764 (27.9%)
No. visits due to myxomatosis	237 (10.6%)	442 (16.1%)
No. visits due to reproductive diseases	152 (6.8%)	118 (4.3%)
No. of visits due to respiratory disorders	145 (6.5%)	172 (6.3%)
No. of visits due to staphylococcosis + mastitis	114 (5.1%)	262 (9.6%)
No. of visits due to salmonellosis	55 (2.5%)	114 (4.2%)
No. of visits due to ringworm	45 (2%)	66 (1.8%)
No. of visits due to rabbit haemorrhagic disease	28 (1.3%)	299 (10.9%)
No. visits due to toxicosis	32 (1.4%)	46 (1.7%)
No. visits due to mange	26 (1.2%)	47 (1.7%)
Visits due to clinical pregnancy toxaemia/ ketosis CPTK	1 (0.5%)	5 (0.2%)

[1] There was one reason per visit.

[2] There were farms with rabbits of all ages.

[3] This table contains the main reasons for emergencies, in addition to the visits for clinical pregnancy toxaemia/ketosis (CPTK).

[4] The data for this period were adapted from Rosell *et al.* (2009).

[5] Mucoid enteropathy (ME) similar to epizootic rabbit enteropathy (ERE).

Heat is a contributing factor for CPTK, as it exacerbates the reduction in feed intake observed in pregnant females at term (Cervera and Fernández-Carmona, 2020). We initially expected a higher number of CPTK-related deaths from July to September. However, this was not observed, likely due to improvements in farm environmental management, such as cooling, during the summer months. The total number of necropsies of doe deaths due to this cause was 401 on 126 rabbitries. Then, we made a sub-set of 394 does, for which we knew the day of pregnancy or lactation in 123 farms. In addition, we obtained another sub-set of 279 does with pregnancy number on 83 farms. This allowed us to evaluate other risk factors.

Pregnancy toxaemia /ketosis occurrence in a production cycle

Females died throughout the production cycle. Figure 7 shows the daily relative incidence of mortality in rabbit does. All the causes were included: dystocia, infectious diseases and metabolic diseases.

Table 2: Database including number/No. of visits to 1422 doe farms, with total on-farm necropsies of females and necropsies due to clinical pregnancy toxaemia /ketosis. Data were grouped by season, in Portugal and Spain, from January1994 until December 2024.

Season	No. visits	Total no. necropsies of does	No. necropsies due to CPTK
January to March	3111	1218	118
April to June	3141	1444	118
July to September	3291	1339	101
October to December	3068	1116	64
Total	12611	5117[a]	401[b]
Doe farms	1422	607	126

CPTK: clinical pregnancy toxaemia/ketosis.

[a] Necropsies grouped in 2513 cohorts.

[b] Necropsies grouped in 288 cohorts.

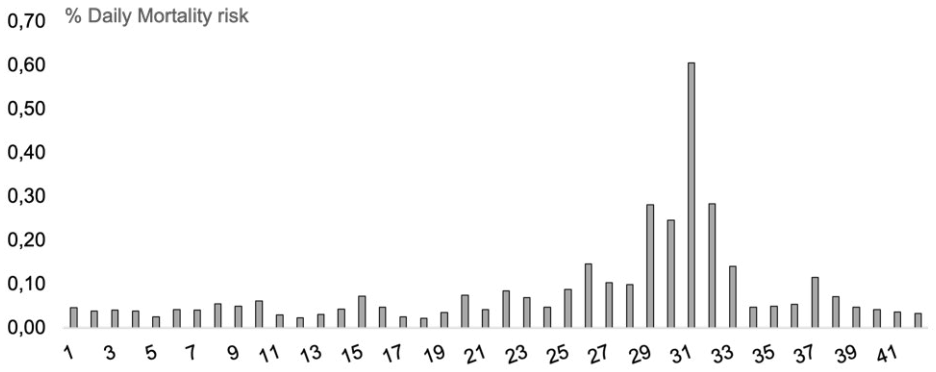

Figure 7: Mean Daily Mortality Risk (%) of 1949 necropsied female rabbits over 2,123,026 does at risk. They were relative to day of kindling (31st). These data are adapted from Rosell and de la Fuente (2016). Day of the 42-cycle. Service (AI) on days 1 and 42. Kindling on the 31st (1-11 and 32-42 d lactating, non pregnant, 12-24 d lactating and pregnant, 25-31 d pregnant.

In single-batch farms with AI at 11 d postpartum, doe mortality was 3.8% during the 42 d (Rosell and de la Fuente, 2016). We found that 70% of farms in Portugal and Spain used the 11-d rhythm (Rosell *et al.*, 2020). Therefore, we analysed 42-d cycles between kindlings; this data differs of median kindling interval per doe: 51.4 d. In addition, median age of removed females was 6 parities (Rosell and de la Fuente, 2009). Mortality was highest in the transition phase from pregnancy to lactation. We found this to be an interesting evaluation target. To this end, we examined data from 401 does with CPTK on 126 farms. The population of rabbit does at risk was 152 218 on these farms on the day of the visit. The median size of the farms with females at risk was 400 does and the mean: 481 does, with ranges from 100 to 3015 females. We estimated that the relative incidence of CPTK in our study was 0.26% of females at risk on the day of the visit. We determined previously the mean monthly mortality risk and binomial confidence interval (95%): 0.16% (0.13-0.19), with 140 dead females due to CPTK from 2433 from the total necropsied (Rosell and de la Fuente, 2016). The present study explains a part of the periparturient rabbit casualties: those due to CPTK (Figure 8).

The highest rate of CPTK deaths was recorded between day 27 and 32 of pregnancy. These are critical days in the transition phase from pregnancy to lactation in the domestic rabbit doe. Literature review and our experience suggest that this phase comprises 4 d before kindling, the day of kindling and approximately 3 d after kindling. This

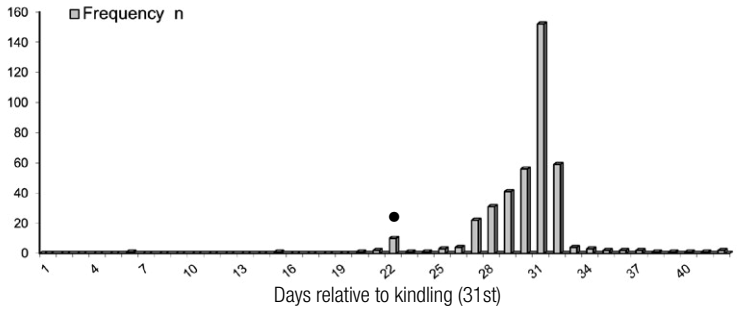

Figure 8: Descriptive daily mortality due to clinical pregnancy toxaemia /ketosis. Relative to day of kindling (31st), with 394 necropsied does on 123 farms from 1994 until 2024. • Heatstroke (40°C): 10 dead females, farm with 1500 does.

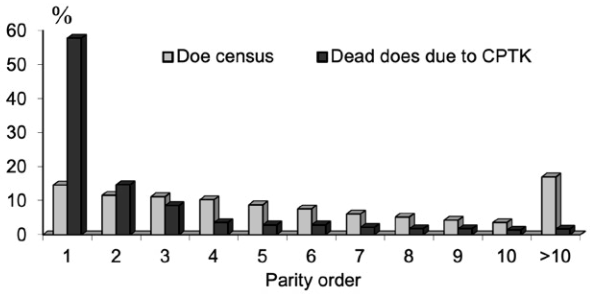

Figure 9: Descriptive age traits of lactating female rabbits (n=50,230) randomly examined on 265 farms in Portugal and Spain, from 2006 to 2020 (grey columns). Black columns: age traits of 279 dead female rabbits on 83 farms due to pregnancy toxaemia/ ketosis, from 1994 until 2024.

is epidemiologically comparable with other domestic females, although the duration is different (Grummer, 1995). The rapidity in physiological evolution or in the appearance of metabolic diseases corresponds with the opinion of Lebas (2021, referred to as 1975): …*the female rabbit is not a delicate animal. It is simply an animal that goes fast*. Moreover, *the swift recovery from challenges* (in peripartum) *is key in the* (metabolic health) *and production of rabbits* (Theilgaard *et al*., 2007). Before and after the transition phase (around days 27-34), we diagnosed few cases with lipidosis: 23 lactating does re-inseminated from 394 (5.8%) and 12 lactating non-served from 394 (3%). Greene (1937) found 43 pregnant, 15 lactating and 14 resting females out of 72 dead rabbits. In our case, 20.2% of the female rabbits that died due to CPTK had aborted. Abortions between day 23 and 30 were the most frequent. The threshold rate of total abortions in farmed female rabbits may be 1% of those inseminated (Rosell *et al*., 2020).

Occurrence of pregnancy toxaemia/ketosis according to age

Figure 9 provides the age descriptions of the does that died from CPTK. Some 57.7% of those affected were in first pregnancy or first kindling. This result was compared to the live does checked on 265 farms. In the age pyramid, 14.6% of the females on the farms were in their first kindling (Rosell *et al*., 2020). In France, during 2021 the rate of first-kindling does was 13.9% on 429 commercial farms, as referred by Pedro (2023).

Age of the doe is a predisposing risk factor for CPTK. The rate of dead primiparous does was higher than in the work of Greene (*op. cit*.); in the 13 mo of his study with 72 necropsies, he found 66 multiparous. There are differences in susceptibility between genetic types or age of does, depending on the allocation of food resources (Pascual *et al*., 2013). The integrated approach of genomics with precision feeding is of interest. Lastly, CPTK in rabbit does is a current problem on farms and its aetiopathogenesis is not known in detail, similarly to cows (Zhang and Ametaj, 2020). However, despite the gaps, there has been progress in understanding the metabolism and factors related to the disease, such as the rearing of young does. But it clearly must be applied.

Control measures: diagnosis, prevention and treatment strategies

Diagnoses were based on full post-mortem macroscopic examination made on-farm by rabbit vet practitioners. In our clinical practice, blood and urine analyses were limited to a few cases of *toxicosis* (78 visits from 1994 to 2024). For this purpose, there are documentary sources, such as the work of McLaughlin and Fish (1994) or more recently that of Ferreira *et al.* (2024). In visits to farms where pregnant does were present at term, clinical (e.g., anorexia, dyspnoea, prostration) and organoleptic (smell of ketone bodies) observation did not provide relevant information. In Figure 10 we show the evolution of the occurrence of females with hard faeces with hair attached, during one cycle. There was no overlap of pregnancy with lactation.

The percentage of females with hair-bearing faeces gradually increased in the 5th d prior to kindling to 70% of affected females. After parturition, the occurrence decreased to 20% of affected females on day 14 of lactation, when we finalised the evaluation. The rabbit does were housed individually, fed *ad libitum* although they consumed

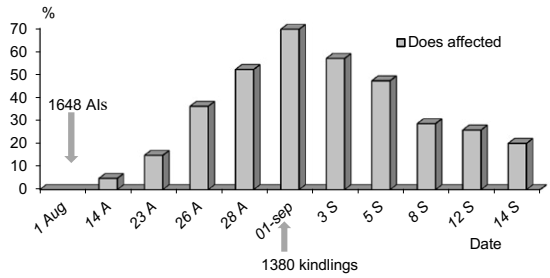

Figure 10: Rabbit does with hair-bound faeces, hanging from the floor of their housing. It was a single-batch farm with 1648 females in extensive rhythm. There was a sub-set of 226 females of various ages in the same row, evaluated during August-September 2023.

little (data not shown). After parturition they received feed, with less indigestible fibre and more energy and protein, as suggested by Xiccato and Trocino (2020). Females pluck out hair for nesting at the end of pregnancy (González-Redondo *et al.*, 2015). Although they don't remove hair 5 d before; in fact, they can't, due to hormonal mechanisms. They can hair-pulling themselves a few hours prior to parturition, as pointed out by Lukefhar (2022). Females mix the hair with the nest material. On commercial farms, barley straw and, in particular, wood shavings are used for nesting. Grass hay is beneficial for pregnant rabbit does (Veenstra *et al.*, 2020), but feeding ryegrass, sainfoin, oat forage, or wheat straw was uncommon on visited commercial farms. Producers open the nests 2-3 d before kindlings. Some primiparous does kindle on 29th and 30th days (mainly in summer), and the majority of does between 31st and 32nd days of pregnancy. Lastly, rabbit does with few, large fetuses kindle later. Females also ingest hair when grooming, or biting a neighbouring doe.

The key to the control of CPTK is based essentially on prevention, as most females fail to respond to treatment, according to Barthold *et al.* (2016). We based prevention on rationing during the rearing of young does. In our clinical practice, we pay special attention to the first stage of this period, from the time the rabbits are sold and the future breeders enter rearing at around 60-75 d old, up to 3.5 mo old. During this phase, the young does are given, first, restricted feed for growing rabbits to reduce the risk of enteropathies. They then switch to low-energy feed (<10.5 MJ DE/kg) or standard feed restricted to 130-150 g/d, depending on the genetic type and season. They are fed this way until 4 d before the first AI, and then they are *ad libitum* for 4 d (fewer *flushing* days that suggested by Szendrő *et al.*, 2012). After AI, does should be restricted again until the first kindling. Restriction reduces the risk of obesity and feed intake improves in the last week of pregnancy (Parigi-Bini, 1983); but this practice is uncommon since it is time-consuming. Body weight control during rearing is recommended. In commercial breed lines, the first schedule service is at 4.5-5 mo old. Thus, median age of the first service was 4.8 mo (Rosell and de la Fuente, 2009). Those that exceed 3.3-3.7 kg body weight are accepted, depending on the season and genetic type. This corresponds to 75-80% over 4.17-4.85 kg mean adult BW of maternal crossbred lines, according to de la Fuente and Rosell (2012). In terms of pregnancy management, another important consideration involves females that fail to conceive at the first AI. The reference failure rate at first AI is 10%. Some producers choose to cull these females because, while waiting for the next service, they gain weight and might develop other problems. When such females are not culled, they are considered at higher risk for CPTK. Other producers allow primiparous does to rest and feed restrict them for one reproductive cycle, up to 4 d before the next AI. Additionally, the practice of group housing young does from 60-75 d old up to 4 mo, and in some cases even up to one week before kindling, is an interesting area for further study.

From a preventive medical outlook, the use of oral or injectable solutions was not widespread. Some producers used liver metabolism protectants in the week before parturition, depending on the time of year, type of rabbits (heavy paternal breeders) or age (e.g., on the 1st and 2nd pregnancies). Extensive use over time and to all does was applied

on a few farms. Nevertheless, we advocate that antepartum application in nulliparous does improve health, the onset of lactation and newborn survival. Lastly, in our clinical practice occasionally we have used sodium bicarbonate to treat ketoacidosis; e.g., days 30th and 31st, 0.5 g-1.0 g/L.

Challenges and prospects of CPTK for rabbit producers

The extraordinary metabolic effort of female rabbits, the rapid changes in their lifespan and the high number of females per kindling batch are relevant drawbacks in the monitoring of peripartum disorders in commercial farms. The first key factor is the animal. The use of robust, resilient strains has clearly contributed to improved longevity (Savietto *et al*., 2013). The qualifier "*metabolic athletes*" used by Leblanc (2010) for cows, in our opinion, also apply to rabbit does. The second factor is housing. It is useful for rabbit producers to have appropriate tools to measure temperature, relative humidity, air speed and air quality (ammonia, carbon dioxide). Our experience suggests that this is very favourable from a technical and economic standpoint. In the field of precision livestock farming (PLF) applied to rabbit farms (Norton and Cambra-López, 2025), in addition to the monitoring equipment and other measures, it is necessary for caregivers to pay attention to the indoor environment in the morning and evening, recording this information. It is also advisable to pay attention to the weather forecast (sudden changes). Moving the pregnant does to a clean, warm and dry parturitions room has few drawbacks (as opposed to a cold and damp kindling room, due to setbacks, of course); with the exception for the initial stress, due to the animal handling and change of neighbouring does. The third factor is reproductive management. In our study, 30% of farms service their females at >11 d, with a limit of 120 (3 batches/yr). The search for a balance between reproductive rhythm, doe body reserves, reproductive efficiency and longevity has been a relevant issue for years as pointed out by Castellini *et al.* (2010) and Szendrő *et al.* (2012). Our data derived from previous studies suggest that rhythms ≥32 d are favourable for the reproduction and health of the doe. But metabolic diseases appear. Therefore, the fourth key area, also related to PLF in doe-farms, is the control of feed and water consumption. Fifth, but not least in this framework to improve, is that farm managers need to be informed, among other qualities and skills.

Challenges and insights for rabbit farm veterinarians and technicians

In our opinion, veterinarians attending rabbit farms should focus on females at higher risk, such as (1) during the rearing period, (2) 4 d before service, (3) on the day of kindling or in post-term pregnancies (i.e., beyond 32 d, particularly in aged, obese, or heat stressed does), and (4) during close monitoring does and kits prior to weaning. Regarding CPTK, risk assessment can be performed at the batch level, but not for each individual female, unlike in dairy cows (Leblanc, 2010). Monitoring and surveillance include assessment of health and body condition. Our experience, based on previous studies, suggests the following prevalence risk thresholds: 15% of lactating females with rhinitis (slight increase in summer), 4% mastitis, 6% sore hocks and none with sarcoptic or psoroptic mange. Body condition /BCS baseline should be between 5/9-6/9 (in days prior to AI) and 4/9-5/9 (in the third week of lactation). This is a useful criterion, although it does not always reflect deficiency states, e.g., at peak lactation (Garreau *et al*., 2017). BCS is multifactorial, although the influence of health is a priority (Sánchez *et al.*, 2012). In addition to feed underconsumption, there are other signs due to the interaction of pain with the behaviour of sick rabbits (Tynes, 2024). Suspicious signs of CPTK include inactivity, prostration, squinting eyes and in severe cases, abortions. But these are signs common to other diseases. From another perspective, to understand the problem, it seems to be interesting to evaluate the metabolome (and metabolic signals) or the microbiome of rabbits with CPTK (Jin *et al*., 2024). One of the aspects that producers find difficult to maintain is the recording of data, in notebooks or on-farm computerised record systems. Technicians should encourage them to record basic data. This information allows us to overcome knowledge gaps and make progress in the prevention of, for example, CPTK.

CONCLUSIONS

Clinical pregnancy toxaemia/ketosis (CPTK) in female rabbits represents a rare but serious condition with significant implications for animal welfare and farm productivity. This study highlights that first pregnancy and first lactation does are at higher risk. It occurs mainly during the transition phase between days 27 and 32 of gestation. CPTK can lead to reproductive losses such as abortions. The disease often goes unnoticed in commercial farms due to the high

number of kindlings per batch, carrying in a poor prognosis. Effective control relies primarily on preventive strategies, including careful rearing of young does, monitoring feed intake, environmental management of housing, and attention to clinical signs such as hard, hair-bound faeces. We advocate that antepartum application of liver metabolism protectants in nulliparous does improve health, the onset of lactation and newborn survival. Although knowledge gaps remain regarding metabolic processes in rabbit does, existing evidence provides practical guidance for reducing CPTK incidence. Continued research into other causes of periparturient mortality will further improve health management and welfare outcomes in breeding female rabbits.

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