Anaesthesia in pregnant dogs and cats

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> Abstract

Anaesthesia during pregnancy in companion animals is necessary in cases of programmed or emergency Caesarean section or in cases when surgical intervention is required. During pregnancy, there are physiological changes in pregnant animals that should be taken into consideration during anaesthesia. These changes mainly affect the cardiovascular and respiratory system and influence to a lesser extent other systems, such as the digestive tract. In case of a Caesarean section, the preanaesthetic agents are usually either avoided or opioids are selected, although recent data support the use of alpha2-adrenergic agonists. Preparation for surgery occurs prior to the induction of anaesthesia, while oxygen is already being inhaled. The standard intravenous anaesthetics can be used for the induction of anaesthesia. In dogs, propofol is superior to thiopental, whereas etomidate is a very good choice in severely debilitated patients. For cats, the use of an α2-adrenergic agonist with ketamine is an adequate choice in order to ensure anaesthetic maintenance. The latter can be achieved in dogs with inhaled anaesthetic agents such as isoflurane, or with injectable anaesthetics like propofol. Epidural anaesthesia is a viable option in some cases. Postsurgical analgesia is based on opioids and/or nonsteroidal anti-inflammatory drugs and it is necessary so that the mother can take care of the neonates. In cases where the pregnant animal undergoes anaesthesia for a non-obstetric surgical procedure, the risk of embryotoxicity must be prevented, e.g. by avoiding benzodiazepines during the first stages of pregnancy, and accurately assessing anaesthetic depth.

> Introduction

Anaesthesia of the pregnant animal must provide sufficient sedation, while ensuring the health of the dam and viability of the litter.

The pregnant animal usually undergoes anaesthesia for a Caesarean section which is either programmed or an emergency due to dystocia. Dystocia is expected in 5% of deliveries in dogs and in 3-8% of deliveries in cats.[3] Furthermore, a pregnant animal may undergo anaesthesia when its life is at risk, e.g. after a motor vehicle accident. In such cases, anaesthesia should be safe for the mother and the foetuses and not contribute to the initiation of premature labour, which may occur due to trauma, surgical manipulation of tissues and the effect of general anaesthetics.[3,5] In cases of termination of unwanted pregnancy, the primary focus of anaesthetic care is the dam.

It is worthy of note that there are no active substances that can be used with absolute proven safety in all patients, nor any anaesthetic protocol that can "release" the veterinarian from his/her concern about all possible scenarios. Therefore, the clinician is required to evaluate each case separately and select the anaesthetic protocol based on the animal's condition. In order to make the correct decisions, the clinician should originally be aware of the physiological changes in the dam's body during pregnancy and labour, which will be mentioned in this paper, as well as the basic pharmacology of

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Λέξεις κλειδιά

- Anaesthesia
- Cat
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anaesthetic medications.[2]

The aim of the present article is to inform the clinician about the general anaesthetic options that are safe for pregnant companion animals, according to the latest published literature.

> Physiology of pregnant companion animals

During pregnancy, the dam's metabolic needs increase, triggering a series of changes in various organ systems.[1] Most of the relevant data originate from humans and sheep.[1,16] Nevertheless, presuming that the same study results apply also in companion animals is considered acceptable, because hormonal changes during pregnancy are similar between humans and animals.[16] Progesterone serum levels increase during the first stages of pregnancy, remain increased until the midterm and then begin to decrease reaching baseline values (< 2 ng/ml in serum) 24 hours prior to the beginning of labour. Further significant hormonal changes occur in the final weeks of pregnancy, such as an increase in serum levels of prolactine, relaxine and oestrogen. Moreover, as the day of delivery approaches, there is an increase in cortisol, prostaglandins and oxytocin, which may lead to the initiation of parturition. Other changes from an anaesthesiological perspective, which are expected in the second half of pregnancy are attributed to mechanical causes due to pressure exerted on the abdomen by the gravid uterus.[2] It has not been determined if the exerted pressure is more severe in companion animals than it is in humans or other animal species and whether the weight of the fetal and uteroplacental tissues contribute to this. It is worthy of note that the mean weight of neonate kittens and puppies on the day of delivery is equal to 13.2% and 16.1% of the mother's body weight, respectively, whereas the corresponding percentage for people and sheep are 5.7% and 11.4% respectively.[1]

The most important physiological changes during pregnancy mainly affect the cardiovascular and respiratory system of the dam and can directly influence the course of anaesthesia. However, changes occur in other body systems as well, such as the digestive and the urinary tract. Understanding these changes is a prerequisite in order to plan a safe anaesthetic protocol for both dam and fetuses.[16]

Cardiovascular system

Pregnancy affects the cardiovascular system through various pathophysiological mechanisms.[16] During pregnancy the circulating blood volume gradually increases by about 40%.[1] More specifically, it is plasma volume that increases the most and not so much the total red blood cell numbers, resulting in a reduction in haematocrit and blood haemoglobin concentration (this reduction is proportional to the size of the litter).[1,2,4,33] Therefore, the presence of normal haematocrit values in advanced pregnancy can be suggestive of haemoconcentration or a small litter. Also, according to the increase in circulating blood volume, the cardiac output also increases by 30-50%, and there is a simultaneous increase in cardiac frequency.[1] Nevertheless, mean arterial pressure (MAP) is preserved in the normal range.[1,2] The increased intra-abdominal pressure due to the enlarged uterus during advanced stages of pregnancy, combined with dorsal recumbency, can decrease venous return due to compression of the caudal vena cava. Due to compression of the aorta there is a decrease in cardiac output, bradycardia, hypotension and consequent decrease in uterine and renal perfusion. However, in companion animals it seems that this phenomenon does not have the same clinical impact as it does in humans.[1,2] In fact, Abitbol (1978)[7] caused an artificial temporary compression of the caudal vena cava by ligating both the latter and the renal arteries in pregnant and non-pregnant dogs, and noticed a reduction in arterial pressure in pregnant dogs but none of the severe clinical consequences that develop in humans, such as bradycardia and hypovolemic shock. Therefore, even though the dorsal recumbency position is not forbidden, it is preferred for pregnant animals not to remain in this position for an extended time period prior to initiation of surgery.[6] Finally, during pregnancy the cardiac load is increased, leading to relapse in patients with cardiological disorders that were previously under control or subclinical patients, and sometimes leading to temporary congestive heart failure.[1,2] A similar feline case has been reported, in which clinical signs of congestive heart failure developed in a cat in the final stages of pregnancy. The cat underwent treatment for pulmonary oedema and then ovariohysterectomy was performed. Signs of congestive heart failure receded after the procedure. Four months later, treatment for heart failure was discontinued because the cat was healthy and remained asymptomatic for nine years without treatment.[30] A case of congestive heart failure has also been described in a dog six months post labour, which ended in sudden death. Post mortem examination and histopathology of cardiac tissue concurred with peripartum or postpartum cardiomyopathy in people.[29]

Respiratory tract

The volume of inhaled air per minute increases during pregnancy, including the respiratory frequency and lung volume, resulting in a gradual decrease of partial pressure of carbon dioxide in arterial blood ($PaCO_2$), around 28-32 mmHg, in contrast to normal animals in which it ranges between 35-45 mmHg.[4,16] The resulting chronic respiratory alkalosis does not affect circulating blood pH because there is time for adequate renal regulation by reducing the

reabsorption of bicarbonates (HCO_3^-). Furthermore, during pregnancy oxygen consumption increased by 20%.[1] Also, due to the enlarged uterus, the abdomen is distended, the intraabdominal organs are driven dorsally and frontally, the diaphragm is compressed and intraabdominal pressure increases. This leads to a reduction of the lung functional residual capacity (FRC), which can predispose to pulmonary atelectasis, resulting in hypoventilation of the dam.[1,2,6] Based on the aforementioned, in pregnant animals hypoxemia and hypercapnia occur faster than in non-pregnant ones. For this reason, it is recommended that prior to induction of anaesthesia, pure oxygen or oxygen mixed with environmental air should be provided for at least three minutes. The induction of anaesthesia with inhaled anaesthetics occurs faster in pregnant animals due to the increased respiratory volume, decreased lung FRC and possibly due to increased progesterone levels which act as a natural sedative. Moreover, during surgery, support with positive ventilation is necessary in some cases.[1,2,4,6] Finally, in pregnant animals a reduced concentration of inhaled anaesthetic agents is sufficient. In particular, the minimal alveolar concentration of isoflurane or sevoflurane in pregnant animals is reduced by 40%. This pathophysiologic mechanism has not been fully elucidated but it seems to be caused by high levels of progesterone-endorphins in the CNS.[1,6,16]

Other body systems

The increased intra-abdominal pressure, the relaxation of the cardiac sphincter and the reduction in gastrointestinal motility lead to an increased risk of gastroesophageal reflux and possibly vomiting, a phenomenon which has also been described by Anagnostou et al. (2010).[8] Therefore, pregnant animals which undergo general anaesthesia should always be intubated swiftly and the cuff of the endotracheal tube should be filled adequately, so that the risk of aspiration of refluxing gastric contents can be avoided.[1,6,16] It was once suggested by Paddleford (1992)[23] to administer metoclopramide and cimetidine in order to prevent gastroesophageal reflux and aspiration pneumonia, but this treatment was effective only in much higher doses than standard metoclopramide dosage regimen. However this was not proven in the canine species during pregnancy.[34] Nowadays, more antiemetic agents are available such as maropitant, ondansetron, and cisapride, although a research-proven preventative result has not been substantiated in the pregnant dam.[1,36]

Liver function is not extensively affected by pregnancy.[2] It is worthy of note that the levels of plasma proteins are reduced. Most inhaled anaesthetic agents are extensively ionised and bind strongly with plasma proteins. Reduction of such protein levels leads to a prolonged effect of anaesthetic agents due to an increased amount of unbound active component.[1,16]

Renal function is also slightly affected. Creatinine and blood urea nitrogen levels are slightly decreased. Normal range levels in pregnant animals can be caused by kidney disorders, or physiological compensation of the dam's body.[1]

> Anaesthesia in the pregnant for caesarean section

The anaesthetic protocol that is used in companion animals undergoing Caesarean section should achieve swift induction of anaesthesia, preserve uterine perfusion and provide the veterinarian with an option of reversing the anaesthetic effect in the mother as well as the neonates, after delivery. Furthermore, the recovery of the dam should occur in a brief time period after obtaining the neonates so that the dam can provide care to the litter.[31] However, in emergency cases it is considered safer to select an anaesthetic protocol the clinician is familiar with, even if it is not considered an ideal solution in cases of Caesarean section.[24]

Preparation of the pregnant, such as clipping, scrubbing and sterilising the surgical site on the abdomen as well as placement on the surgical table should ideally be performed prior to anaesthetic induction, in order to reduce the total duration of anaesthesia.[16] Also, the animal must be pre-oxygenated, as previously mentioned, and hypovolemia, electrolyte disorders and mostly hypocalcaemia and hypoglycaemia should be corrected.[4,16]

All the anaesthetic agents, minus muscle relaxants, cross the placenta to an extensive degree, enter the foetal systemic circulation and have an impact depending on the administered dose and the duration of action of each agent.[1,16] Sedation of the parturient animal should ideally be avoided, or if applied, depending on the case, mild opioids should be used, such as butorphanol or short-acting opioids, like fentanyl. The use of naloxone when available (0.02 mg/kg sublingually, intramuscularly or through the umbilical cord), on the neonates can counteract the effect of opioids.[3,16] Acepromazine, which is classified as a phenothiazine, is usually avoided due to its prolonged duration of action.[1] On the other hand, it is true that phenothiazines have not been implicated for higher dam or neonate mortality. Therefore, they can be used on occasion, such as in the study of Luna et al. (2004)[18], in which chlorpromazine was administered 0,5 mg/kg iv 15 minutes prior to induction of anaesthesia in bitches that underwent Caesarean section. Nevertheless, due to the negative effect on the cardiovascular system (resulting in hypotension caused by their effect on a1-adrenergic receptors), their prolonged duration of action and the fact that they are metabolised in the liver (the neonate liver is slower in metabolising compared to the dam), they should be avoided.[3,24] Furthermore,

benzodiazepines should also be avoided because they have been implicated for lethargy, depression, hypothermia and neonatal apnea directly post-delivery. Naturally, in cases when benzodiazepines are administered and prolonged lethargy is noted in the neonates or the dam, their effect can be countered by flumazenil, although the latter seems to have no effect on cats.[1,3] Moreover, some of the α2-adrenergic agonists should be avoided because they lead to suppression of cardiovascular and respiratory function in the dam and neonates.[1] Also xylazine has been implicated for higher rates of neonate puppy mortality.[21] There are no relevant studies in companion animals regarding the use of dexmedetomidine prior to Caesarean section.[1] In cases that it is used, its effect can be reversed through atipamezole in neonates that are lethargic after delivery. Recently a retrospective study has been conducted in pregnant dogs that underwent Caesarean section, and medetomidine (7 μg/kg im) was part of the preanaesthetic plan. The results were particularly encouraging regarding dam and neonate survival, a fact that reassures and assists the clinician to a certain extent, when the latter is accustomed to using α2-adrenergic agonists.[35]

Induction of anaesthesia can occur with any of the standard intravenous anaesthetic agents. Traditionally propofol (6-8 mg/kg iv without sedation or 2-5 mg/kg iv if sedation has been administered) is preferred to thiopental due to higher puppy survival rates.[14,28] Moreover, propofol is superior to thiopental and the combination of midazolam/ketamine, because the percentage of neonate puppy lethargy is lower, as proven by Luna et.al. (2004).[18] Also, in a different study by Moon-Massat et al. (2002)[22] the activity level of puppies immediately post Caesarean section was evaluated and was found reduced in cases where ketamine and/or thiopental were injected for anaesthetic induction compared to puppies in which propofol had been used. It is noteworthy that viability of the foetuses does not only rely on the anaesthetic protocol, but also on the duration of delivery and the physical condition of the foetuses and the dam, however there is no mention in the published reports of any of the latter.[3] Obtaining the neonates should occur 15-20 minutes after induction with propofol, so that the anaesthetic agents have been metabolised and redistributed and the neonatal respiratory system can function as naturally as possible. There are no published clinical studies about etomidate in companion animals.[16] Etomidate (1-2 mg/kg iv) is considered a viable option for patients with pre-existing cardiomyopathies or patients in critical condition.[27] The combination of ketamine (4-6 mg/kg) – midazolam (0.1-0.3 mg/kg) in dogs causes suppression of the respiratory system in neonates because of both the ketamine and midazolam. Therefore the neonates may not breathe on their own and may need respiratory support.[28]

Regarding the injectable anaesthetic steroid alfaxalone (not yet released in Greece), Doebeli et al. (2013)[11] compared the survival rates of puppies 5, 15 and 60 minutes post Caesarean section, using the Apgar score (which has been developed to assess the effect of anaesthesia in neonates) after injecting the dams with alfaxalone (1-2 mg/kg iv) or propofol (2-6 mg/kg iv). They observed that neonatal survival rates were higher after delivery in the group that received alfaxalone, but the survival rates three months later were essentially the same. The survival rates of puppies 24 hours after delivery were the same in the study by Metcalfe et al. (2014),[20] where the effect of alfaxalone was compared to propofol in bitches that underwent Caesarean section.

At this point it should be stressed that the selection of agents is based on the clinical condition of the dam and whether it is already debilitated by an already existing major body system failure or at a high risk of the latter, such as the cardiovascular or the central nervous system in cases of cranial trauma.[16] Also, the intravenous anaesthetics should be injected slowly in patients in critical condition, so as to prevent any sudden or major decrease in mean arterial pressure (MAP) and uterine perfusion. Injecting a small dose of fentanyl prior to their administration or a simultaneous injection of lidocaine (0.25-1.0 mg/kg iv) with a low dose of propofol (1-2mg/kg) or thiopental (2-5 mg/kg), may facilitate intubation, so that a high dose of the previous injectable anaesthetic agents is no longer necessary.[3]

The induction of anaesthesia through inhalation, either by mask or in an anaesthetic chamber, may increase stress resulting in the release of catecholamines, which results in vasoconstriction and foetal hypoxia and finally in acidosis in the parturient animal. Furthermore, because its duration is longer than intravenous induction and as there is a constant risk of regurgitation and aspiration, it is best avoided in pregnant bitches.[28] However, as mentioned in the retrospective study of Moon et al. (2000),[21] in 34% of the animals that were included in the study, isoflurane was used during induction, as well as maintenance of anaesthesia, with excellent neonate survival rates. Isoflurane, sevoflurane and desflurane are the preferred inhaled anaesthetics because induction and recovery are faster compared to other inhaled anaesthetic agents.[1]

The maintenance of general anaesthesia can occur either with inhaled or injectable agents.[2,16] The former is considered safer for the foetuses because, according to a study involving the administration of propofol in pregnant sheep, the plasma protein levels of the foetuses are reduced compared to the dam. Therefore the concentration of the active form of the drug is higher than in the dam, and the concentration of propofol in fetal blood was maintained for prolonged periods of time until it was metabolised.[9] Moreover, in a study that focused on anaesthetic maintenance during Caesarean

section in dogs, the use of alfaxalone was compared to isoflurane. It was also noted that in the group which received alfaxalone, the duration of recovery was prolonged and the neonates presented with more pronounced lethargy compared to the group that received isoflurane.[10] The levels of inhaled anaesthetic agents should be reduced by 30-60% compared to what is commonly used in non-pregnant animals for the aforementioned reasons (please consult the Physiology section). Regarding cats, it is preferable to use inhaled anaesthesia after intubation.[2] From the inhaled anaesthetic agents that are available, isoflurane is superior to alothane and methoxyflurane because it has been correlated with higher neonatal survival rates.[21]

Not many studies are available as regards the administration of anaesthesia in pregnant cats. In one of these studies Elovsson et al., (1996)[13] mention that the use of xylazine-ketamine or medetomidine-ketamine are marginally superior to propofol-isoflurane, because newborn kittens are more active when the former were selected. In the study of Robbins and Mullen (1994)[26] in which 26 cats underwent Caesarean section due to dystocia, and induction of anaesthesia was achieved by isoflurane, neonate survival rates reached barely 41%. Due to the insufficient scientific data regarding anaesthesia in cats that undergo Caesarean section and their differences with dogs, selecting an anaesthetic protocol is currently based on anaesthetic drug availability, and the ability of the clinician to use them correctly having comprehended the physiological and pharmacological changes that occur during pregnancy is of particular importance.[3]

The use of epidural anaesthesia appears to be very effective for neonate survival, because local anaesthetics do not cross into the systemic circulation of the fetus.[13,14,18,28,31] Nevertheless, it is not an ideal solution in all cases because it is time-consuming and the clinician needs to be acquainted with the procedure.[16] The most crucial disadvantage of epidural anaesthesia, however, is that in an attempt to prevent the animal regaining consciousness during the surgical procedure, stronger sedation or light generalised anaesthesia is required, negating, as a result, both the advantage of avoiding cardiovascular suppression by the general anaesthetics, and the advantage of epidural injection in neonate survival. Furthermore, oxygen supply can be accomplished by mask or the flow-by method but artificial ventilation is excluded because the animal is not intubated.[28] For the aforementioned reasons, epidural anaesthesia is not usually applied in cases of Caesarean section in companion animals.[28] An undesirable side effect is restlessness-nervousness displayed by the mother during recovery due to reduced sensation and motility in the hind limbs (depending on the drugs that were used, for a duration of half an hour up to two hours) after epidural anaesthesia, because it has a negative effect on the dam's interaction with the neonates. If epidural anaesthesia is desired nonetheless, a mixture of local anaesthetics, such as lidocaine and bupivacaine 1:1 is used, in which an opioid can be added for more effective analgesia.[1] Pascoe and Moon (2001)[24] prefer the use of lidocaine only, due to the shorter duration of action (about 60 minutes) so that the mother can be ready to take care of the litter immediately after the surgery. To the same effect, Traas (2008)[31]suggested that only opioids should be used when the cardiac frequency of the litter can be measured and is normal (200 b.p./min), because it provides adequate postsurgical analgesia and the hind limbs maintain their motility. In any case, the total volume of the drug that is injected is reduced by 25-35% due to the fact that the epidural space is reduced during pregnancy because of venous dilation in the particular anatomic region. The injected volume of the solution should not exceed 6 ml.[28]

Local anaesthesia is particularly useful during preoperative preparation of the dam in or around the surgical site. Local anaesthesia reduces the dose of intravenous and inhaled general anaesthetic agents and provides surgical and postsurgical analgesia.[24,31] The option of splash-block is also available, meaning the instillation of local anaesthetic in the surgical resection site, after suturing the muscular wall and prior to skin closure. This specific technique of local anaesthesia offers excellent post-surgical analgesia and facilitates dam acceptance of the neonates for the first suckling episode.[6]

Postsurgical analgesia is of particular importance because, as it has been proven, postsurgical pain reduces milk production.[31] If opioids have not been administered prior to surgery, then pethidine, methadone, buprenorphine or butorphanol can be given post neonate delivery and before the end of the procedure, to provide an excellent analgesic effect.[6,19] Both opioids and non-steroidal anti-inflammatory drugs (NSAID) cross the blood-mammary barrier and can be traced in the milk. The use of NSAIDs is an adequate option for managing postoperative pain, because it provides the mother with analgesia without affecting the level of consciousness.[19] Even though the preoperative administration of NSAIDs provides a better postoperative analgesic effect,[12] their use prior to obtaining the neonates is avoided because they have been implicated for higher neonate mortality rates.[21] Cyclooxygenase-2 inhibitors (COX-2 inhibitors), such as karprofen and meloxicam, are recommended (based on obstetrician experience, without confirmation from published studies) to be offered only once in lactating animals, because they are excreted by the kidneys of the neonates, which do not attain full function until the age of 6-8 weeks and thus more frequent use can lead to severe kidney disorders. In the same manner, meaning a single use, paracetamol can also be

prescribed in lactating bitches, but never in cats.[19] Recently cimicoxib (an NSAID that has not been released in Greece) was prescribed on day 0 and day 28 post labour, after obtaining the litter in six lactating bitches and it was noted that the exposure of the newborns to the drug was insignificant and the risk of undesirable side effects was minimal.[37] Finally, tramadol can be used safely, though there have been no clinical research studies in pregnant animals.[3]

The selection of a proper anaesthetic protocol is only one of the factors that are involved in neonate survival. The clinician should take into consideration factors including the time lapse from the initiation of labour, the degree of placental detachment and accordingly, the degree of hypoxia or anoxia, which each foetus has suffered prior to the administration of anaesthesia, the time lapse until the definitive management - resolution of dystocia, as well as the overuse or misuse of ecbolic drugs, that lead to unproductive uterine contractions.

> Anaesthesia in pregnant animals for non - obstetric procedures

In pregnant animals that undergo anaesthesia for non-obstetric procedures, the anaesthetic protocol should be adapted to the needs of the dam and the survival of the litter should be ensured, meaning that adequate perfusion and oxygenation should be accomplished and teratogenesis should be avoided.[16] The pregnant animal should initially be relieved from stress, which can lead to resorption, abortion or premature labour depending on the stage of pregnancy. Hypoxia, hypotension and anaemia should be managed if they are already present, and if not they should be prevented. In such patients, blood transfusion is administered in haematocrit values higher than a non-pregnant animal e.g. HCT 25%.[24] Regarding the preanaesthetic treatment, mild short-acting opioids can be selected, such as butorphanol, which offers adequate analgesia, moderate sedation and has minimal effect on the respiratory function of the pregnant animal.[1,31] The a2-adrenergic agonists should be avoided because it has been proven that they are connected to increased uterine contractility which can lead to miscarriage, usually in the initial or the final stages of pregnancy.[2] From the latter, xylazine seems to result in more severe uterine contractility and higher risk of abortion than newer type a2-adrenergic agonists.[2] Jedruch et al. (1989)[15] observed in canine cases in the final stages of pregnancy that a single dose of 60 μg/kg medetomidine causes a greater increase in electrical activity in the uterine wall than a 20 μg/kg dose, however no abortions were noted. Acepromazine is not considered a good choice, because other than vasodilation, hypotension and hypothermia that this drug leads to in the pregnant animal, the duration of its effect is also prolonged.[6] Epidural or other types of topical anaesthesia are desirable, because they decrease the requirements for anaesthetic medications, stress, and postsurgical pain.[24]

Induction of anaesthesia can be achieved by intravenous injection of propofol or etomidate.[16,31] The latter is an ideal choice for patients in critical condition as previously mentioned. Moreover, ketamine is also considered to be an acceptable choice for induction of anaesthesia in ill or debilitated pregnant animals, because it preserves cardiovascular function in the desirable levels.[3] For maintenance of anaesthesia the standard inhaled anaesthetics are recommended. Postsurgical analgesia is mostly based on the administration of opioids[19], even though their long - term use in pregnant animals has not been previously studied. Regarding NSAIDs, they should be avoided during pregnancy because studies in people have shown that they are implicated in cleft palate malformations and renal dysfunction in the newborn.[19]

The risk of embryotoxicity and/or teratogenesis is higher in the beginning of pregnancy (6-45 days), prior to and during organogenesis and especially in the first twenty days of pregnancy, even before the blastocyst implantation.[25] However, when the life of the pregnant animal is at risk, depending on the owner or the clinician's preference and, due to necessity and irrespective of the risk, the possibility of teratogenesis or miscarriage can be disregarded. In the last stages of pregnancy there is no such risk.[24] Most anaesthetics and analgesics can cause teratogenesis at high doses, but the doses used in the clinical setting are considered to be safe. Only nitrous oxide seems to have teratogenic properties in companion animals after repeated administration on multiple days.[3,17] Also, it would be preferable to avoid benzodiazepines, because, according to studies in people, they have been implicated in causing cleft palate malformation in neonates. In companion animals there are no such reports.[3]

> Anaesthesia in pregnant animals that undergo ovariohysterectomy

In cases of ovariohysterectomy, survival of the litter is not a priority. The anaesthetic protocol does not have to adapt to the limitations that were previously mentioned in order to preserve the survival of the neonates.[24] After the removal of the uterus from the abdominal cavity, foetal death will occur swiftly, without the sensation of mortal stress, if the uterus remains unopened and the respiratory center of the foetuses is not activated due to contact with the environmental air. If the resection of the uterus

is necessary, then it should be performed one hour following uterine removal from the abdominal cavity. Foetal movements observed in advanced stages of pregnancy are believed to be involuntary and they occur spontaneously or by stimulation of the amniotic sac, e.g. due to manipulation.[32]

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