Elective caesarean in bitch

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Abstract

Elective caesarean in the bitch is a common procedure that is performed for a number of reasons, including but not limited to: fetopelvic disproportion (notably in brachycephalic breeds), poor whelping history, previous caesarean, inherent uterine disease, high-risk pregnancy, highly valuable puppies/bitches, frozen semen pregnancies, or owner convenience. To determine the best time for the caesarean, it is important to accurately identify expected whelping date, most commonly done by accurate ovulation timing, gestational ultrasound staging and progesterone assay of the bitch near term. To improve puppy viability, preterm corticosteroid administration stimulates surfactant production in fetal lung. One of the largest problems with elective caesarean, aside from fetal viability, is mismothering by the bitch. The risk of mismothering may be reduced by the use of prostaglandins to induce luteolysis and intranasal oxytocin administration to the bitch. Ovariohysterectomy at the time of caesarean section is not recommended.

Keywords: Elective, caesarean, bitch, oxytocin, intranasal

Introduction.

Elective caesarean in the bitch is a common procedure that is performed for a number of reasons, including but not limited to: foetopelvic disproportion (notably in brachycephalic breeds), poor whelping history, previous caesarean, inherent uterine disease, high risk pregnancy, highly valuable puppies/bitches, frozen semen pregnancies, or owner convenience. Determination of the correct time to perform an elective caesarean is a balance of identifying the correct time without removing the puppies too soon or too late, minimising distress on the bitch and ensuring optimal mothering and milk production after surgery. In order to determine the best time for the caesarean, it is important to accurately identify the expected whelping date and using as many tools as available to determine the best time to perform the procedure to maximise probability of a good outcome. Pregnancy length in the bitch is defined as 65 days from the LH surge, 63 days from ovulation and 57 days from the onset of cytological diestrus. In order to determine pregnancy duration, it is important to understand and stage the estrous cycle.

Timing of the estrous cycle of the bitch

Bitches spontaneously ovulate a primary oocyte arrested in prophase I of the second stage of meiosis.[1,2] The luteinizing hormone (LH) surge occurs ~ 2 days before ovulation,[3,4] stimulating the granulosa cells of the follicles to luteinize and produce progesterone, which may aid in resumption of meiosis.[1] After ovulation, the corpus luteum forms from luteinized thecal and granulosa cells. The corpus luteum secretes progesterone, with progesterone being solely responsible for pregnancy maintenance in the bitch. Six days after ovulation, the bitch enters diestrus.[5]

Laboratory tests for staging the estrous cycle

LH assay

LH concentrations are undetectable until the point of the LH surge. Daily serum analysis of LH is required due to the short, varied, length of the LH surge in the bitch (24 - 60 hours). There is a rising phase of up to 12 - 24 hours and then a decline over 12 - 36 hours.[6] The only readily available LH tests are qualitative LH tests, which give a positive result for concentrations > 1 ng/ml. Even with daily LH testing, it is possible to not detect the LH surge, since LH concentrations vary (4 - 14 ng/ml[6,7]) at the peak of the LH surge, and there is often a slow rise and fall. LH assays on their own are not recommended, since the LH surge occurs 3 - 8 days before oocyte fertilisation,[7] coupled with the possibility of anovulatory cycles.

Progesterone assay

Progesterone concentrations rise from the LH surge and they can be used as an indirect indicator of ovulation. Progesterone continues to rise through estrus and early diestrus, with the cervix closing under the influence of increasing progesterone. Progesterone is most commonly measured today by chemoluminescence, with serum being recommended rather than plasma.[8] Collection of blood for progesterone is best done on a fasted sample. Refrigeration of samples within the first 2 hours after collection will reduce the measured progesterone concentration.[8]

The LH surge occurs at ~ 6 nmol/l (2 ng/ml) and ovulation at 15 - 25 nmol/l (4 - 8 ng/ml), with ovulation being deemed complete with values > 30 nmol/l (10 ng/ml).[9] In the authors' opinion, there is no 'magical' value of progesterone at which fertility is maximal; changes in values are more important to help identify ovulation. Consistency of progesterone analysis is important, as different analytical machines will give different results.

Vaginal cytology

The cytology of the vagina changes as a result of changing estrogen concentrations. Rising estrogen concentrations from developing ovarian follicles result in hyperplasia of the vagina, represented by increasing cornification of vaginal cytology samples. As the vagina undergoes hypertrophy, the surface cells suffer effects of reduced oxygenation which presents as increasing enlargement of the cytoplasm, nuclear pyknosis and cornification of surface cells.[10] Percentage of anuclear cells increases to 50% of cornified cells by the start of estrus. Six days after ovulation, diestrus ensues, characterised by an influx of neutrophils and parabasal cells reducing the percentage of cornified vaginal epithelial cells.[5] Vaginal cytology alone is a poor indicator for the ideal time to breed;[5] however, in conjunction with progesterone assays and vaginoscopy, it aids in determination of the phase of the cycle (proestrus, estrus, diestrus or anestrus) and appropriateness of insemination.[11,12]

Vaginoscopy

Vaginoscopy is performed using a 25 cm long, 11 mm diameter Welch Allyn sigmoidoscope. Under the influence of rising progesterone and increasing estrogen after the LH surge, the deep edematous folds of proestrus begin to flatten out and reduce. As estrogen concentrations continue to reduce and progesterone continues to rise through estrus, hypertrophy and hyperplasia of the vagina reduces, resulting in a cobblestone appearance of the vagina (crenulation) indicating ovulation is complete and the bitch is in the fertile period. By the start of diestrus, the vagina returns to a flat state with no significant folds in the mucosa.[13]

To determine the LH surge, ovulation time and/or the 1st day of cytological diestrus, a combination of progesterone assay, LH assay, vaginal cytology and vaginoscopy are used.[11]

Ultrasound determination of fetal age

Careful ultrasound examination of the pregnant bitch can aid in ascertaining an approximate due date, and also help to correlate due date with estrous cycle staging. The inner chorionic cavity provides good determination of pregnancy stage up to 37 days of pregnancy,[14-17] whereas measurement of biparietal diameter is most accurate during the last 3 weeks of pregnancy.[15,17,18] The presence of good renal development and fetal peristalsis help to indicate fetuses are mature enough to be removed from the uterus. Ultrasound of the fetal heart rates in the near-term fetus will also help to determine the urgency of a caesarean procedure. Heart rates > 180 bpm indicate stable fetuses, whereas heart rates < 180 bpm indicate fetal distress[19] and the need to proceed quickly to a caesarean section.

Progesterone assay to assess luteal presence

In the whelping bitch, fetal distress will result in a release of oetal ACTH, a rise in fetal cortisol concentrations and in turn a decrease in maternal progesterone due to luteolytic effects of cortisol. Maternal progesterone concentrations will decrease to < 2 ng/ml (6 nmol/l) 24 - 36 hours before whelping; therefore, daily analysis of progesterone to detect a decrease to below this level is often used to indicate the time for an elective caesarean.[20]

Medications indicated in an elective caesarean

In many cases of elective caesarean, fetuses are removed before normal endocrine changes associated with whelping occur. Often to avoid fetal distress, puppies are removed before luteolysis. This process may have detrimental effects on the puppies and mother, as a result of no progesterone drop to stimulate a rise in prolactin for mothering and milk production, and no fetal cortisol release resulting in no stimulation of fetal lung surfactant. To help avoid these issues, corticosteroid administration, prostaglandin $F_{2\alpha}$ and intranasal oxytocin may be used.

Corticosteroid therapy

Short-acting cortisol is given 2 - 12 hours before the scheduled elective caesarean. Short-acting cortisol solutions are too short acting to induce luteolysis and labour. From day 57 of pregnancy, the fetal lung is capable of life outside of the uterus, although pulmonary surfactant is likely limited at this point.[21] Betamethasone stimulates production in fetal lung surfactant[22] and additionally in dogs, is believed to improve fetal survivability after surgery.[23] Therefore, it is recommended to be used in elective caesareans wherein luteolysis has not occurred.

Prostaglandin $F_{2\alpha}$

A low dose of prostaglandin $F_{2\alpha}$ at the end of the elective caesarean procedure (5 - 10 μg/kg) is used to aid luteolysis, reduce progesterone concentrations and thereby increase prolactin concentrations to promote milk production and mothering.

Intranasal oxytocin

Issues of poor maternal bonding in the bitch are commonplace in small animal theriogenology practices. Whilst any new mother can have issues accepting their newborn puppies, the problem presents itself most commonly in nulliparous bitches, more so those that have undergone caesarean section and more so those that have undergone elective caesarean section (observed, unpublished data by author). Whilst prolactin concentrations rise in late diestrus, there is a marked rise subsequent to the progesterone decline from luteolysis induced by a rise in ACTH from fetuses. Thus, there is a delayed rise in prolactin in bitches undergoing elective caesarean due to the procedure being undertaken before luteolysis has begun. Some breeds appear to have more of a problem accepting puppies and not uncommonly will savage their puppies, notably American Pit Bull Terriers, American Staffordshire Terriers, Rottweilers, and German Shepherds (observed, unpublished data). Dealing with a bitch that is not accepting her puppies and trying to harm them is a difficult situation for both the veterinarian and the breeder; suggested treatments are limited and often lead to frustration, poor compliance and detrimental neonatal care.

Traditional therapies

Traditionally breeders would be recommended to sedate affected bitches, use muzzles and physical restraint whilst an assistant would place the puppies on the mammary glands to try and feed. The most commonly used sedatives are diazepam (0.5 mg/kg bid or tid PO) or acetylpromazine (1 - 3 mg/kg bid PO). Diazepam, a benzodiazepine, whilst being a good anxiolytic agent, is poorly sedative, coupled with potential *ante grade* amnesia (inability to create memories after an amnesia effect) which may mean that when used to treat maternal aggression, the bitch may in fact not learn to accept the puppies as she is less likely to remember the feeding event clearly. Acetylpromazine (ACP), a phenothiazine derivative, when used orally has a good sedative effect, and through stimulation of prolactin will improve milk production (like metoclopramide). ACP can have profound side effects including seizures (by reducing the seizure threshold), profound hypotension and should be used in caution in breeds known to carry the mutated Multidrug Resistant 1 (MDR1) gene mdr1-1Δ (notably Australian Shepherds, Border Collies, Collies, White Swiss Shepherds, German Shepherds, Old English Sheepdogs, and Sighthounds). Animals homozygous for the mdr1-1Δ gene have increased susceptibility to many drugs, including ivermectin, moxidectin, milbemycin oxime, digoxin, opioids, ACP, vincristine and other chemotherapeutics. Whilst ACP can result in profound sedation, its use to combat mismothering must be questioned. Any medication given to a nursing mother will pass on to the puppies and additionally there is little positive encouragement of the bitch to accept the puppies, rather merely hoping she will eventually accept them.

Muzzling and physical restraint of the bitch is questionable as a long-term therapy to aid in mothering is difficult. Not only does it require multiple assistants to feed the puppies every 2 - 6 hours, it is likely very stressful for the bitch. The increased anxiety and cortisol concentrations associated with this would be expected to have detrimental effects on both milk let down and milk production. Whilst in some cases it may be necessary in the short term, this is not a long-term therapy.

Many breeders will often resort to supplementary feeding in cases wherein nursing is difficult or not possible. This itself, whilst adequate, is not ideal for the puppies. There are many supplementary milk's for puppies sold on the market. Most are poorly correlated to bitches milk. Many breeders create their own formulas, or follow those of their forefathers, most of which are in no way correlated to bitch milk. Handfeeding can create problems of overfeeding, underfeeding, diarrhoea or nutritional deficiencies whilst creating more work for the breeder.

Emerging therapies

The causative agents of maternal bonding have been long shown to be oxytocin [24-28] and prolactin. Effects of oxytocin on maternal bonding has been investigated in rats, voles and sheep. Extrapolations have been made to humans, with reports of oxytocin concentrations related to postnatal depression in new mothers.[24,29]

Oxytocin, a neuropeptide consisting of 9 amino acids,[30] is synthesized in the paraventricular and supraoptic nuclei.[28] Oxytocin is transported and stored in the posterior pituitary, or via specific projections from the paraventricular nucleus, transported to other structures in the brain including the amyglada, hypothalamus and hippocampus.[28] Oxytocin is well known for its functions on milk let down and uterine contractions, subsequent to release from the posterior pituitary. Oxytocin receptors are present throughout many tissues of the body, not just the uterus and mammary gland, including but not limited to the heart, liver and brain. Oxytocin receptors are a G coupled protein receptor. Binding of oxytocin to the G coupled protein receptor leads to a G qα coupling, leading to an increase in intracellular calcium concentration which leads to muscle contractions (this is important for uterine tissue and mammary tissue related to milk let down). Furthermore, oxytocin receptors located on neurons will lead to release or inhibition of other hormonal neurotransmitters and modulators, e.g. serotonin, endogenous opioids and corticotrophin-releasing factor.[24]

Oxytocin has a number of believed functions other than uterine contraction and milk let down. These include, but are not limited to, love and pair bonding, sexual behaviour, maternal bonding, increasing trust, pro-social behaviours and reduction in anxiety.[28,31] A syndrome in humans, Williams syndrome is characterised by increased trust, increased chance of approaching strangers, reduced social fear and love of music. The syndrome is characterised by deletion of 28 genes and affected individuals have significantly higher plasma oxytocin concentrations, implicating important behavioural effects of oxytocin.[32] In rats, increased intracerebral concentrations of oxytocin and prolactin subsequent to lactating reduces effectiveness of the HPA and reduces cortisol concentrations when subsequently exposed to a stressful stimuli. This has also been shown in humans indirectly, wherein mothers breastfed their babies then were subsequently exposed to a stressful experience; mothers that breastfed first had lower cortisol concentrations, suggesting in humans, too, that the HPA is desensitised by oxytocin and prolactin.[33]

The release of oxytocin both peripherally and centrally has occurs in response to labour, parturition, lactation and vaginocervical stimulation in sheep[34] via multi-synaptic neural pathways.[35] Other stimuli for central oxytocin release includes emotional stress, social interaction and sexual activity/mating.[33] Increased estrogen and reducing progesterone during late pregnancy not only stimulates an increase in prolactin, but stimulates an increase in oxytocin receptor expression +/- sensitivity of brain sites.[35] Subsequently, with stimulation of central oxytocin release from the paraventricular nucleus and upregulation of central oxytocin receptors, there is a positive effect on recognition of offspring odour, increased attractive perception of offspring odour, mobilisation of active components of maternal behaviour, reduced maternal aggression, decreased anxiety and fear and acquisition of maternal memory.[33]

Results on oxytocin related to maternal behaviour in rats is contradictory. In early reports, intracerebroventricular injection of oxytocin improved maternal responses, whereas in subsequent work, rats with the oxytocin gene removed showed immediate maternal instincts postpartum without supplementation. This suggests in rats the effects of oxytocin may be facilitatory rather than the mainstay of maternal bonding.[27] In estrogen-primed ewes, oxytocin induces full maternal responses in non-pregnant ewes in < 30 seconds following intracerebroventricular infusion of oxytocin.[36] Maternal experience improves responsiveness to oxytocin infusion in multiparous versus nulliparous ewes.[37] Research in voles shows good evidence of oxytocin related to social behaviour and bonding. Prairie voles form long-term exclusive bonding with their male counterparts following mating; this same bonding occurs following intracerebroventricular infusion of oxytocin in the female, but no effect if given to the male without mating. In the male if vasopressin is infused then the bonding will occur, showing some sex differences.[27]

Intranasal infusion of many molecules has been investigated. Insulin, melanocyte stimulating hormone, vasopressin, IGF1, neuropeptides, cytokines (erythropoietin) and carbamazepine have all cross the blood brain barrier following intranasal infusion.[38] Conversely, systemic administration of oxytocin intravenously resulted in < 0.1% of oxytocin crossing the blood brain barrier of sheep.[34] The actual mode of transport, if any, of oxytocin into the brain subsequent to intranasal infusion is the topic of current research. Suggested routes of transport include extra neural/peri neural routes along the trigeminal or olfactory nerve pathways, lymphatic transport, intraneuronal transport or active or passive transport from vasculature.[38] There are also suggestions that intranasal administration stimulates the endogenous oxytocin system, which results in both peripheral and central oxytocin secretion. Transport along the olfactory nerve is unlikely, as transport speeds are faster than the transport speed of the olfactory nerve. Endogenous activation or transport via the trigeminal or subarachnoid routes are most likely. Transport into the plasma is likely via the heavily vascularised nasal mucosa and several facial veins into peripheral circulation. In rats, prior administration of adrenaline intranasally before administration of neuropeptides reduced blood concentrations of neuropeptides without reducing CSF concentrations.[39] indicating it is traversing through vasculature.

In humans, intranasal infusion of oxytocin will result in peak plasma concentrations 15 minutes after administration, with return to baseline by 75 minutes. In the same study, peak CSF concentrations occurred at 75 minutes; however, peak brain concentrations are likely to be earlier, as many samples were first taken at 75 minutes, and additionally CSF samples were collected via lumbar puncture which would delay peak concentrations 5 - 10 minutes (assuming 5 mm/min CSF transport in humans).[38] This is concurred via work in non-human primates, wherein peak CSF concentrations occured by 35 minutes, based on cervical puncture. Furthermore, higher doses have earlier peaks (10 minutes, 80 IU) compared to lower doses (60 minutes, 40 IU),[40] creating questions about dose, effect and concentration gradients.

The use of oxytocin in humans shows promise for diseases associated with persistent fear, repetitive behaviour, reduced trust and avoidance of social interactions, with promise for diseases associated with reduced oxytocin concentrations and altered oxytocin metabolism such as autism and schizophrenia.[28] Mothers diagnosed with postnatal depression, then given intranasal oxytocin and subsequently exposed to an intrusive stranger, had greater protective behaviour of offspring than those given a placebo.[25]

For 6 years, the author has administered 10 IU of oxytocin intranasally either every 2 hours or before each feed (2 - 6 hours) to all nulliparous bitches after elective caesarean until good maternal behaviour is noted by the owner. The solution is compounded by a compounding pharmacist to a dilution rate of 10 IU oxytocin/0.1 ml and administered via a human nasal spray bottle (0.1 ml/spray). The dose is extrapolated from that used in experimental studies of pigs (24 IU oxytocin intranasally).[41] The dose frequency has been extrapolated from work in other species showing the lifespan of intranasally administered oxytocin to be at least 2 hours and maybe up to 7 hours.[25] In total, there have been 127 subjects treated with the aforementioned treatment and it has been subjectively assessed that maternal behaviours of nulliparous mothers developed more hastily compared to those that received no treatment in the past or sedation and restraint therapy. It must be noted that this is not a controlled scientific study, only a clinical assessment and many variables may lead to perception of improvement due to chance. In the 2 years since the use of this therapy, the author has not had any nulliparous bitch after elective caesarean harm a puppy. In 1 case, a Bernese mountain dog bitch undergoing therapy began showing obsessive maternal behaviours (overstimulating and cleaning of pups) which resolved after cessation of therapy. It must be noted that the therapy is off label, experimental and still anecdotal; however, from clinical experience it appears to have good promise. Currently the author and others are having good success with administration of 10 IU in alternating nostrils every 2 hours (Lopate C, personal communication) until the bitch is mothering well, usually within 12 - 24 hours. There is scope for a controlled clinical trial observing maternal behaviours of nulliparous bitches after elective caesarean receiving either oxytocin or a placebo intranasally.

Whilst there is no clinical or scientific study of intranasal oxytocin therapy in bitches, there is a good body of literature that increased CSF concentrations of oxytocin after intranasal administration in multiple species. Additionally, with studies showing reduced anxiety, fear and improved maternal behaviour related to higher CSF levels of oxytocin in multiple species, it is not clear why the same would not concur in the bitch. Whether intranasal application of oxytocin leads to direct transit to the CSF or activation of the endogenous oxytocin is not relevant in a clinical situation, as a cause and effect has been developed. Management of the nulliparous bitch after elective caesarean is a challenging case for the both the veterinarian and the breeder, and subjectively on a clinical level, the use of intranasal oxytocin shows promise for aiding in appropriate therapy to improve welfare of breeding bitches and their puppies.

Ovariohysterectomy at time of caesarean section

Whilst advocated by many, ovariohysterectomy at the time of caesarean section is not recommended by the author. Although not directly studied in bitches, the probability of a poor outcome of the bitch after surgery is increased dramatically by ovariohysterectomy at time of caesarean section (observed, unpublished data by author). During pregnancy, there is an expansion of fluid volume of the bitch, and cardiac adaptions to cope with this, notably increased fractional shortening, increased cardiac output and cardiac hypertrophy, all believed to improve blood flow to the gravid uterus.[42] During the puerperium, there is gradual reduction in uterine size and blood flow[43] along with a gradual return of the maternal cardiac changes to the non-pregnant state.[44] A rapid change in hemodynamics with ovariohysterectomy is likely to have detrimental effects on the maternal heart function which may have difficulty adapting quickly. Additionally, the enlarged uterus after removal of the foetuses contains a large volume of blood and its removal is likely to have detrimental effects on thermoregulation of the bitch.

Conflict of interest

None to declare.

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