Animal Reproduction Science 130 (2012) 198–212

Contents lists available at SciVerse ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

Health management of ewes during pregnancy☆

G.C. Fthenakis[a,*], G. Arsenos[b,1], C. Brozos[b,1], I.A. Fragkou[a,1], N.D. Giadinis[b,1], I. Giannenas[a,1], V.S. Mavrogianni[a,1], E. Papadopoulos[b,1], I. Valasi[a,1]

[a] Veterinary Faculty, University of Thessaly, Karditsa, Greece
[b] School of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

ARTICLE INFO

Article history:
Available online 25 January 2012

Keywords:
Abortion
Anthelmintic treatments
Clostridial infections
Dry-ewe mastitis
Health management
Nutrition
Pregnancy diagnosis
Pregnancy toxaemia
Sheep
Vaccinations

ABSTRACT

The objectives of health management of ewes during pregnancy are as follows: (i) successful completion of pregnancy at term, (ii) birth of healthy and viable lambs, with optimal birth and potential weaning bodyweight, (iii) optimum milk production during the subsequent lactation and (iv) improved management in relation to drug residues in animal products. Knowledge of the physiological background of pregnancy in ewes: changes, mechanisms and interactions, during pregnancy is important for the overall health management of ewes during pregnancy. Health management of pregnant ewes includes diagnosis of pregnancy and evaluation of the number of foetuses borne, which will support strategies for subsequent management of the flock. Nutritional management of ewes depends upon the stage of lactation and specifically aims to (i) prevention of pregnancy toxaemia and other metabolic diseases during the *peri-partum* period, (ii) formation of colostrum in appropriate quantity and quality, (iii) production of lambs with normal future birth bodyweight and (iv) support of increased milk yield during the subsequent lactation. At the end of lactation, udder management of pregnant ewes includes its clinical examination, culling of ewes considered unsuitable for lactation and, possibly, the intramammary administration of antibiotics; objectives of that procedure are (i) to cure infections which have occurred during the previous lactation and (ii) to prevent development of new mammary infection during the dry period. Management of abortions includes the correct and timely diagnosis of the causative agent of the disorder, as well as the strategic administrations of chemotherapeutic agents, aiming to prevent abortions in flocks with confirmed infection with an abortifacient agent, especially if no appropriate vaccinations had been carried out before the mating season. During the final stage of pregnancy, health management of ewes includes administration of appropriate anthelmintic drugs, aiming to eliminate gastrointestinal helminthes (thus, increasing production output of ewes) and preventing the built-up of parasitic burdens in the environment (thus, reducing infection of lambs during their neonatal period). Vaccinations of pregnant ewes aim to protect these animals, as well as their offspring, especially against diseases which are a frequent cause of neonatal mortality (e.g., clostridial infections). Health management also aims to prevent the main metabolic disorders of pregnant ewes (i.e., pregnancy toxaemia and hypocalcaemia), as well as to monitor flocks for development of these disorders. Health management of pregnant ewes is completed with application of husbandry practices before the start of the lambing season. Finally, in some cases, health management may include induction and synchronisation of lambings, which is a management or therapeutic procedure.

© 2012 Elsevier B.V. All rights reserved.

☆ This paper is part of the special issue entitled: Reproductive Health Management of Sheep and Goats, Guest Edited by G.S. Amiridis and G.C. Fthenakis.

* Corresponding author.
E-mail address: gcf@vet.uth.gr (G.C. Fthenakis).

[1] These authors have all contributed equally to the manuscript and are mentioned in alphabetical order.

0378-4320/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.anireprosci.2012.01.016

1. Introduction

In ewes, pregnancy lasts a little less than five months, i.e. a significant part (~40%) of the annual production cycle. Taking into consideration the reproductive cycle of ewes (Bartlewski et al., 2011), which allows for extended breeding period, it is likely that, in total, there may be pregnant ewes in a flock for up to six months every year. Therefore, health management of ewes during pregnancy covers a large component of the annual health management cycle in sheep flocks.

In general, the objectives of health management of ewes during pregnancy are as follows: (i) successful completion of pregnancy at term, (ii) birth of healthy and viable lambs, with optimal birth and potential weaning bodyweight, (iii) optimum milk production during the subsequent lactation and (iv) improved management in relation to drug residues in animal products.

There are no 'blueprint' approaches in the health management of pregnant ewes. The objective of the present account is to discuss guidelines, which should be modified accordingly and on farm-by-farm basis, in order to address health issues according to locally prevailing production systems and health problems. Actually, there are differences in the health management of pregnant ewes between various production systems, which are related to the production priorities in the various systems, as well as between flocks within the same production system. For example, some differences exist as a result of the season of the year when the mating season occurs, i.e., in consequence, at least partly, of the geographical latitude of the farm's location, which affects the seasons of the year when animals are pregnant. Although the present paper might be considered biased towards management of dairy ewes, the principles of health management of pregnant ewes can be applied regardless of the production system. Thus, based on this paper, one can adapt details for application in other production systems.

In practice, not all the procedures described in this account would be routinely applied in any flock. Some procedures are carried out routinely (e.g., nutritional management; Section 4), others frequently (e.g., vaccinations; Section 8), others selectively (e.g., administration of anthelmintics; Section 7 – intramammary administration of antibiotics; Section 5), whilst others only sporadically or in exceptional circumstances (e.g., induction and synchronisation of lambings; Section 11). In fact, the exact procedure(s) to be applied in any farm should be decided on farm-by-farm basis by the attending veterinarian.

2. The physiology of pregnancy

Knowledge of the physiological background of pregnancy in ewes: changes, mechanisms and interactions, during pregnancy is important for the overall health management of ewes during pregnancy, among that for pregnancy diagnosis and timely prevention of pathological conditions of ewes. Pre-natal life may be divided into three main periods: (i) period of fertilised ovum, which ends with the initial attachment of the embryo, (ii) embryonic period, from 12th to about 34th day, when rapid growth and differentiation occur, with initial formation of major organs and features of external body and (iii) foetal period, characterised by growth and changes in the foetus (Jainudeen and Hafez, 2000a). Growth of the conceptus can be characterised as 'relative growth', more rapid in early stages of pregnancy, and 'absolute growth', maximum during late gestation. Rate of foetal growth depends primarily on feed supply and the ability of the fetus to use the feed, although other factors (e.g., are genetics, environment and foetal hormones) may also be implicated (Jainudeen and Hafez, 2000a).

2.1. Early stages of pregnancy

A cascade of morphological, functional and endocrinologic changes of the reproductive system is initiated with a successful oocyte fertilisation. In order for the embryo to attach to the uterus, the fertilised oocyte has to develop into a morula and then to a blastocyst, hatch from the *zona pellucida*, signal its presence to the dam and participate to the formation of the extra-embryonic membranes. Morula-stage embryos enter the uterus 4–6 days post-mating and, then, form a blastocyst with an inner cell mass and a blastocoele or central cavity surrounded by a monolayer of trophectoderm. After hatching from the zona pellucida, blastocysts develop into a tubular form and, then, elongate, on the 12th day, to filamentous conceptuses that occupy the entire length of the uterine horn (Taverne and Noakes, 2009). The elongated or filamentous conceptus (embryo/foetus and the associated extra-embryonic membranes) is composed mainly of extra-embryonic trophectoderm lined with endoderm. Elongation of the blastocyst is critical for developmentally regulated production of interferon-τ, the pregnancy recognition signal, and for implantation (Spencer et al., 2008).

Establishment of pregnancy in ewes begins at the blastocyst stage and includes pregnancy recognition signaling, conceptus implantation and placentation. Maternal recognition of pregnancy is mediated by interferon-τ, secreted by the elongating conceptus on the 12th–13th day of pregnancy (Taverne and Noakes, 2009). Interferon-τ acts on the endometrium to inhibit development of the luteolytic mechanism by inhibiting transcription of the oestrogen receptor-α gene in the luminal and superficial ductal glandular epithelia, which prevents oestrogen-induction of oxytocin receptors and production of luteolytic prostaglandin F_{2a} pulses (Spencer et al., 2007, 2008). Implantation involves shedding of the zona pellucida, followed by orientation, apposition, attachment and adhesion of the blastocyst to the endometrium. Endometrial invasion does not occur in domestic ruminants, thus definitive implantation is achieved by adhesion of the mononuclear trophoblast cells to the endometrial lumenal epithelium and formation of syncytia by the fusion of trophoblast binucleate cells with the lumenal epithelium (Spencer et al., 2004). Attachment of the developing embryo onto the uterine endometrium creates a transient relationship, which affords an advantage to the developing conceptus by providing nutrients and protection during development.

As the embryo develops, the placenta is formed. This is a metabolic and endocrine organ between the developing conceptus and the uterine endometrium. The placenta is also an important source of signaling molecules capable of manipulating the pregnant ewes' physiology to maintain an environment conducive to a successful pregnancy. A unique feature of the ruminant placenta is the population of foetal chorionic binucleate cells, which, in sheep, first become apparent around the 16th day of pregnancy. This time-point corresponds roughly to the period of trophoblast attachment to the uterine epithelium. These cells have at least two main functions, namely the formation of a hybrid syncytium formed between the pregnant ewe and her foetus, for successful implantation and subsequent cotyledonary growth in the placentome and the synthesis and secretion of steroids (progesterone), prostaglandins (prostaglandin I_2, prostaglandin E_2) and protein hormones (placental lactogens), as well as protein products with no known, at the moment, function (pregnancy-associated glycoproteins) (Bhanu and Green, 2007; Spencer et al., 2008).

2.2. Hormonal profiles in pregnancy

Various hormones participating in pregnancy exhibit fluctuations and interact between them depending on the stage of pregnancy. Apart from their physiological role to ensure successful outcome of pregnancy, from a clinical approach, detection of their concentrations can be used as a method for pregnancy diagnosis (Section 3). Principal hormones involved are progesterone, oestrone sulfate, pregnancy specific protein B, pregnancy-associated glucoproteins, prolactin, placental lactogen, prostaglandins and relaxin (Tamasia, 2007; Taverne and Noakes, 2009). According to recent findings, ghrelin (Harrison et al., 2007; Miller et al., 2010) and leptin (Devaskar et al., 2002; Ehrhardt et al., 2002; Forhead et al., 2002; Yuen et al., 2002; Muhlhausler et al., 2003), hormones related to energy balance in pregnant animals, are also involved in growth and/or function of the foeto-maternal unit. Leptin may also be involved in nutrient partitioning during placental and/or foetal development (Thomas et al., 2001); this could be correlated with the impact of pregnant ewes' undernutrition on plasma leptin concentrations during late pregnancy, which is dependent on foetal numbers (Edwards et al., 2005).

2.3. Principles of pathophysiology of embryonic or foetal death

Pregnancy loss can be the result of one or more of the following events during pregnancy: (i) death of embryo or foetus, (ii) failure of recognition of pregnancy (interferon-τ insufficiency), (iii) inappropriate uterine environment (defects of endometrium or hormonal pattern), (iv) placental deficiency or (v) decreased progesterone concentration. Hence, abnormal termination of pregnancy may occur at various stages: (i) before recognition of pregnancy, which cannot be distinguished from fertilisation failure (early embryonic death), in which case the length of the oestrus cycle would not be affected and the ewe returns to oestrus, as if she had never conceived, (ii) after recognition of pregnancy, but before foetal formation (late embryonic death), in which case the ewe returns to oestrus after a longer than normal period of time or (iii) during the foetal stage (foetal death), leading to mummification or abortion (Section 6) (Jainudeen and Hafez, 2000b). Mortality is more common during the embryonic period. Although fertilisation rates may reach up to 90–95%, risk of embryonic death can be as high as 20–30%. In some cases, particularly in multiple pregnancies, early embryonic deaths may be a process of eliminating unfit genotypes, which would not have survived the entire length of intrauterine life anyway. In contrast, foetal deaths should always be considered as an abnormal process. Cumulatively, microbial abortions account for a significant proportion of embryonic or foetal deaths in ewes (Jainudeen and Hafez, 2000b; Spencer and Bazer, 2004; Diskin and Morris, 2008).

In general, factors related to embryonic deaths in ewes may be as follows: (i) genetics (e.g., chromosomal defects, individual abnormal genes, genetic interactions), (ii) hormones (e.g., reduced progesterone concentration, oestrogen–progesterone imbalance, inadequate interferon-τ concentration), (iii) nutrition (e.g., over- or undernutrition of pregnant ewes), (iv) age of ewes (ewe-lambs, ewes older than six years), (v) endometrium, (vi) number of ovulations (embryo survival rates decline as ovulation numbers increase), (vii) lactation, (viii) infection, (ix) environmental factors (e.g., heat stress) (Martal et al., 1997; Jainudeen and Hafez, 2000b; Spencer and Bazer, 2004; Deligiannis et al., 2005; Hansen, 2007; Bazer et al., 2008; Diskin and Morris, 2008). Improving knowledge regarding biological and immunological interactions between the pregnant ewes and its embryo(s), as well as the identification of corresponding genes, will provide the potential to identify causes of embryonic deaths, thus improving embryo survival in early pregnancy.

2.4. Prinicples of pathophysiology of pregnancy toxaemia

During late pregnancy, increased energy demands of the rapidly developing foetus(es), in combination with hormonal interactions (insulin, prolactin), have an impact on lipid and carbohydrate metabolism of the pregnant animal, putting it at risk to developing pregnancy toxaemia (Andrews, 1997). The disease is the result of negative energy balance, usually secondary to increased energy requirements of the foetuses, and is usually observed in multiparous ewes on limited-energy diets (Andrews, 1997; Brozos et al., 2011). Various nutritional, metabolic, genetic, physiologic, environmental, health and/or management factors can influence development of clinical disease and all these should be addressed during its prevention (Section 9.1).

At late pregnancy, hormonal effects in fat and carbohydrate metabolism predispose to decreased glucose, increased fatty acid and increased ketone body (mainly β-hydroxybutyrate) concentrations (Drackley et al., 1992). Moreover, insulin secretion rate and plasma concentrations decrease, whilst growth hormone concentrations increase; growth hormone is responsible for inhibiting glucose transfer to tissues and mobilisation of body fatty reserves, as

well as reducing fatty acid synthesis and lipolysis (Strang et al., 1998). Growth hormone effect is highly dependent on other hormone (prolactin, placental lactogen, oestrogens, progesterone) effects; for example, interactions between prolactin and growth hormone lead to re-distribution of amino-acids between the liver and various other body tissues. At the end, all above lead to incomplete glucose synthesis and mobilisation, as well as to fatty acid accumulation to liver, which hampers normal function of the organ with end results increased oxidation of fatty acids and increased production of ketone bodies (Andrews, 1997; Henze et al., 1998; Panousis et al., 2001; Sargison, 2007).

2.5. Foetal programming in twin embryos

Formation of twin embryos takes place soon after conception, hence they develop in a different environment than singles throughout their embryonic life, from conception until birth, and thereafter. Twin foetuses develop a between-them competition for nutrients, are enveloped by a smaller placenta than single foetuses and live in a restricted physical space. After birth, twins compete for milk supply and attention from the same dam. Nowadays, there is extensive literature applied to humans and the topic is discussed in another article in this special issue (Fleming et al., this issue), hence few details, specifically pertaining to sheep, will be discussed here.

Twinning results in decreased foetal growth during late pregnancy and it has been concluded that twin foetuses, in late pregnancy, can have features similar to those of single foetuses borne by ewes experiencing undernutrition (Section 4.4) (Rumball et al., 2008). These authors showed that effects of twinning on late-pregnancy ovine foetuses have many similarities to the effects of undernutrition, which causes a documented decrease in future birth bodyweight of foetuses. Nevertheless, differences between the two situations also exist: in twin pregnancies, the pregnant animal's metabolic and endocrine environment, the foetal and placental growth and the function of the foetal glucose–insulin axis differ than those in single pregnancies.

3. Pregnancy diagnosis in ewes

3.1. Principles of pregnancy diagnosis in sheep

Early and accurate pregnancy diagnosis is important, in order to apply proper and successful management of pregnant ewes. Clearly, the result of pregnancy diagnosis could be only one of the following: (i) the ewe is pregnant, (ii) the ewe is not pregnant or (iii) the findings cannot support an accurate diagnosis, hence the ewe needs to be re-examined.

Subsequently to diagnosing pregnancy in a flock/group of ewes, the animals can be grouped and managed according to stage of pregnancy and number of foetuses carried. Moreover, correct pregnancy diagnosis can lead to avoidance of culling pregnant animals, as well as to successful induction of lambing if necessary (Section 11). Moreover, ewes found not-pregnant can be appropriately managed or else culled.

3.2. Methods for pregnancy diagnosis in sheep

Several methods are currently in use for pregnancy diagnosis in sheep. These include management approaches (evaluation of non-return of mated ewes to oestrus), clinical methods (transabdominal or rectal-abdominal palpation, udder examination, palpation of caudal uterine arteries), biochemical tests (measurement of progesterone, oestrone sulphate, ovine pregnancy-associated glycoprotein, pregnancy-specific protein B or early pregnancy factor concentrations), imaging methods (radiography, ultrasonographic examination), vaginal biopsy and laparoscopy (Table 1) (Noakes, 2003; Tamasia, 2007; Taverne and Noakes, 2009). In practice, the methods most frequently employed are the evaluation of non-return of mated ewes to oestrus, the transabdominal palpation, the udder examination and the ultrasonographic examination. Currently, diagnostic kits are also commercially available, which can detect concentrations of various hormones, e.g., progesterone, ovine pregnancy-associated glycoprotein etc., therefore may also be employed for pregnancy diagnosis of ewes. Ultimately, choice of the method for use depends on the operator's skills, the stage of pregnancy and the availability of facilities and equipment. In any case, the method chosen should satisfy as many as possible of the following criteria: sensitivity, specificity, accuracy, speed, safety, low cost (Tamasia, 2007).

3.3. Ultrasonographic examination

The method for early pregnancy diagnosis that meets most of the above criteria is real-time B-mode ultrasonographic examination (Scott and Sargison, 2010; Scott, this issue). This is advantageous, despite the requirement for expensive equipment, because the operator may diagnose viability, growth, size, number, age and sex of foetus(es), as well as placental development (Meinecke-Tillmann and Meinecke, 2007).

There are two different approaches for ultrasonographic examination of pregnant ewes: transcutaneous and transrectal ultrasonography. Choice of the technique depends on the stage of pregnancy, the available ultrasound probe, the working conditions and the experience of the operator.

Ultrasonographic images characteristic of pregnancy are multiple anechoic luminal sections of the uterus, presence of anechoic fluid and/or 'C'- or 'O'-shaped placentomes, as well as presence of embryo(s) or foetus(es) showing heartbeats. Using transrectal examination, embryonic vesicles can be identified 12–20 days after mating, while embryo(s) can be recognised 16–25 days after mating. Placentomes and the amnion can be seen from about the 25th day of pregnancy. Following transabdominal scanning, pregnancies can be diagnosed on 17th–30th day of pregnancy, while transrectal examination is more accurate until the 35th day. Between 35th and 70th day, both methods appear to be equally accurate. Taking into account cases of embryonic deaths occurring early in pregnancy, an accurate diagnosis can be performed after the 40th–50th day of pregnancy (95–99%). The transcutaneous approach is preferable during the second half of pregnancy. Early estimation of the number of foetuses can be done until

Table 1
Methods available for pregnancy diagnosis in ewes.

Method		Recommended pregnancy period for successful application of the method
Measurement of early pregnancy factor concentration in blood		1st day
Measurement of progesterone concentration in blood or milk		15th–19th day
Measurement of ovine pregnancy-associated glycoprotein in blood		18th day
Observation of ewes for oestrus signs		16th–18th day
Laparoscopy		17th–28th day
Measurement of pregnancy-specific protein B concentration in blood		>18th day
Transrectal ultrasonographic examination for pregnancy diagnosis		25th–30th day
Measurement of oestrone sulfate concentration in blood		>28th (best: 40th–50th) day >70th day
Transcutaneous ultrasonographic examination	For pregnancy diagnosis For diagnosis of numbers of foetuses	>35th day 45th–100th day
Rectal-abdominal palpation		49th–109th day
Palpation of the vaginal artery		>60th day
X-ray examination		>65th–70th day
Udder development		>110th day
Abdominal increase		>130th day

the 40th day by using the transrectal technique; the most reliable estimation is possible between 45th and 100th day by using transcutaneous examination, with an accuracy of 90–95% (Kähn, 2004; Meinecke-Tillmann and Meinecke, 2007). Estimation of foetal age, when date of mating is not known, can be performed by monitoring embryonic or foetal parameters (Meinecke-Tillmann and Meinecke, 2007), with the best period for an accurate diagnosis being between 40th and 80th day of pregnancy.

4. Nutritional management of pregnant ewes

4.1. Nutritional management before mating and during the first month of pregnancy

Start of pregnancy is not always clearly defined, especially so in extensive or semi-intensive management systems. Hence, there is some scope for describing, in brief, pre-mating nutritional management of ewes, especially as a similar regime is also applied during the first month of pregnancy.

Before the mating period, ewes can be given additional feed with increased energy content ('flushing'). At the beginning of the mating period, animals should have a body-condition score of '3' to '3½' on the five-point scale. 'Flushing' consists of administration of an additional quantity of concentrate feed mixture of 200–400 g daily, on top of the ration administered to cover maintenance requirements of the animals. In dairy sheep, it may also be necessary to sustain lactation, which is progressively approaching its end. Administration of the increased energy feeding should commence at least 35 days before start of the mating period; that interval is equivalent to the length of two full oestrous cycles of sheep. In animals with appropriate body-condition score, this increased energy feeding aims to producing increased ovulation numbers, leading to increased number of lambs born per ewe. In animals in lower body condition score, there is a benefit to other reproductive parameters (e.g. earlier start of the annual reproductive activity, improved cycling and lambing rate), but no significant improvement in fecundity of ewes (Heasman et al., 1998).

The same increased energy diet should also be provided during the initial stages of the mating season. This has two benefits: (i) animals that had not conceived during the first oestrous cycle of the season, are maintained in a good body condition and (ii) animals that had conceived, have a lower risk of early embryonic death (Parr et al., 1982).

On the other hand, inadequate nutrition, particularly in energy, around the mating season, depresses reproductive performance of extensively (Hill Farming Research Organisation, 1979) or intensively (Orskov, 1982) managed sheep. Inadequate energy allowance at that period leads to reduced cyclic activity, reduced ovulation rates and suboptimal ova survival, as well as increased risk of early embryonic deaths (Gunn, 1967).

4.2. Nutritional management from second to fourth months of pregnancy

During the first 100 days of pregnancy, there is a slow foetal growth (Blanchart and Sauvant, 1974; Economides, 1981). During the second month of pregnancy, when foetal attachment has been established and placental growth has been completed, foetus(es) can acquire up to 15–25% of their future birth bodyweight. During that period, fat deposistion in pregnant animals should be limited, but, conversely, excessive bodyweight loss can put ewes at risk to develop pregnancy toxaemia. Protein requirements of animals can be fully covered if proportion of total protein content in ration at that stage of pregnancy is over 8% per dry matter content of feeds provided (Cannas, 2004). At

that point, body-condition score of animals should be '2' to '2½' on the five point scale.

Nutrients are also required for the growth of the placenta, the uterus, the mammary glands and the body reserves of pregnant animals. The placenta has a key role in ensuring that the foetus(es) would receive optimal supplies of nutrients, but overfeeding during mid-pregnancy can lead to restriction in placental size, hence to suboptimal future birth bodyweight of lamb(s) (McDonald et al., 2011).

The major impact of placental size on foetal weight in sheep has been clearly demonstrated using the technique of carunclectomy, which results in placental and foetal growth retardation (Owens et al., 1995). Maximal proliferative growth of the placenta occurs between 50th and 60th day of pregnancy (Ehrhardt and Bell, 1995) and placental weight normally peaks by mid-pregnancy (Shneider, 1996). A number of studies has shown that restricted nutrition of ewes in early- to mid-pregnancy can inhibit optimal placental growth (McGrab et al., 1992; Kelly et al., 1992; Clarke et al., 1998). Few studies have determined whether nutritionally mediated alterations in placental growth can extend to term or what the impact is on conformation of the newborn. However, where such measurements have been carried out, results obtained at term have been confounded by a compensatory increase in ewes' nutrition compared with controls over the second half of pregnancy (McGrab et al., 1991). Clarke et al. (1998) have demonstrated that feeding of ewes bearing a single foetus at close to half their energy requirements between 30th and 80th day of pregnancy significantly reduced the mean weight of individual placentomes and total weight of the foetal component of the placenta. Moreover, the effects of pregnant ewes' nutrient restriction were not confined to the placenta, but, also, had a significant influence on their plasma thyroid hormone concentrations, despite no change in plasma concentrations of glucose and free fatty acids (Clarke et al., 1998).

4.3. Management of ewes during the last month of pregnancy

During the final stage of pregnancy, the ovine foetus(es) can develop rapidly, to acquire up to 75–80% of their future birth bodyweight. Hence, energy requirements of pregnant ewes increase progressively, as end of pregnancy is approaching. In the final month of pregnancy, protein requirements of pregnant animals also increase, due to foetal requirements and the need to prepare colostrum in the mammary glands. Hence, it is important that pregnant ewes are given protein-rich, easily digestible forages; proportion of total protein content of ration can be increased up to 10% (per dry matter content). Ideally, body-condition score of ewes should be '2½' to '3½' one month before lambing and '2' to '2½' at lambing (Cannas et al., 2004).

Stress increases during late pregnancy, especially for ewes bearing multiple foetuses (Economides and Louca, 1981). Foetal energy requirements in the final stage of pregnancy have been calculated as 1.5 MJ ME per kg foetus per day (Hill Farming Research Organisation, 1979). This means that a 50 kg ewe carrying twins would have an energy requirement of about 2.5–3 times that of a non-pregnant ewe. However, it is not proposed to cover in full these high requirements, as provision of 25% less energy than above requirements would reduce future birth bodyweight of lambs by only 10%, which is acceptable on biological and economic considerations (Hill Farming Research Organisation, 1979). However, administration of low levels of energy during late pregnancy would lead to pregnancy toxaemia (Morand-Fehr and Sauvant, 1978; Economides and Louca, 1981). On the other hand, high energy of feeding throughout pregnancy can also lead to the same disorder (Orskov, 1982), as well as to dystocia due to excessive foetomaternal disproportion.

Feed provided should be of excellent quality, as quantity that may be consumed by pregnant ewes is limited. Progressively, roughage quantity should be decreased, whilst that of concentrates should be increased. At that stage, animals also have a gradually reduced feed intake, hence provision of a high energy diet is important (Cappio-Bornilo et al., 2004; Rassu et al., 2004).

Nutritional management during that period aims specifically to (i) prevention of pregnancy toxaemia and other metabolic diseases during the *peri-partum* period (e.g., hypocalcaemia, hypomagnesaemia), (ii) formation of colostrum in appropriate quantity and quality, (iii) production of lambs with normal future birth bodyweight and (iv) support of increased milk yield during the subsequent lactation.

During early- to mid-pregnancy, grazing animals do not have additional requirements to cover. Frequently, these may be covered only through the consumption of a small quantity of concentrates coupled to their grazing intake. Consequently, their body-condition score is usually satisfactory, if grazing possibilities are available. However, in winter months, when herbage availability in pastures is decreased, additional feed should be provided to the animals (McDonald et al., 2011).

In intensive production systems, feeding is formulated based on nutrient requirements of animals and nutritive value of feeds provided, in order to meet daily requirements of the animals. Under these conditions, feed intake of sheep can be measured easily and appropriate feeding can be carried out; for example, ewes may be fed according to the number of foetuses that they carry or according to their body-condition score or age. Bocquier et al. (1995) have considered that allocation of ewes into groups would be the best way for correct nutritional management of pregnant ewes in intensive systems.

In dairy ewes, it has been documented that milk yield of animals could be improved by feeding increased energy quantity during the final stage of pregnancy. This leads to building-up body reserves, which subsequently, during lactation, would be expressed as increased milk production (Morand-Fehr and Sauvant, 1980; Skjevdal, 1982). To note, that under such conditions protein supplementation would also be required.

Recently, Tedeschi et al. (2010) have proposed a mechanistic model that predicts nutrient requirements and biological values of feeds for sheep (Cornell Net Carbohydrate and Protein System®, CNCPS-S; Cornell University, Ithaca, USA). The model suggests that pregnancy

requirements are best met when the metabolisable energy for pregnancy requirements are estimated by using the recommendation and models published by the Agriculture Research Council (1980), as these were adopted by the Agriculture and Food Research Council (1993) and modified by the Commonwealth Scientific and Industrial Research Organisation (1990, 2007). Similarly, the metabolisable protein for pregnancy requirements can be calculated by using the recommendations of the Commonwealth Scientific and Industrial Research Organisation (1990, 2007), which were also derived from the Agriculture Research Council (1980) recommendations.

According to the model by Tedeschi et al. (2010), the metabolisable energy for pregnant ewes, from the 63rd day of pregnancy to lambing can be calculated by means of the following equation:

$$\mathrm{ME_p} = \frac{9.2438 \times \mathrm{LBW} \times e^{(-11.465 \times e^{(-0.00643 \times t)} - 0.00643 \times t)}}{k_\mathrm{p}}$$

where $\mathrm{ME_p}$: metabolisable energy for pregnancy (Mcal per day), LBW: expected future birth bodyweight of lambs(s) (kg), t: day of pregnancy and $k_\mathrm{p} = 0.13$. The metabolisable protein for pregnancy in sheep can be calculated in the following equation:

$$\mathrm{MP_p} = \frac{1428.06 \times \mathrm{LBW} \times e^{(-11.22 \times e^{(-0.00601 \times t)} - 0.00601 \times t)}}{0.7}$$

where $\mathrm{MP_p}$: metabolisable protein for pregnancy (g per day), LBW: expected future birth bodyweight of lambs(s) (kg) and t: day of pregnancy.

4.4. Nutrition of pregnant ewes and foetal programming

Undernutrition of pregnant ewes can trigger mechanisms, which can affect disease risk in newborn lambs. Nowadays, there is extensive literature applied to humans (Fleming et al., 2004) and the topic is also being discussed in another article in this special issue (Fleming et al., this issue), hence few details, specifically pertaining to sheep, will be discussed here.

Undernutrition of ewes, from 60 days before to 30 days after mating, changes foetal growth trajectory (Oliver et al., 2005) response to undernutrition (Harding et al., 1997), insulin response to glucose supplementation (Oliver et al., 2001) and ACTH response to decreased negative feedback (Bloomfield et al., 2004), with some of these effects possibly persisting in newborn animals as well (Todd et al., 2009). Undernutrition, from 45 days before to 7 days after mating, leads to changes in relationships between pregnant ewes' weight change and placental weight (McLaughlin et al., 2005), whilst undernutrition from mating to 30 days after it alters pituitary, adrenal (Gardner et al., 2006) and cardiovascular function of newborn lambs (Gardner et al., 2004).

Inadequate nutrition during pregnancy leads to intrauterine growth restriction, which, in sheep, may be prevented by intravenous or intragastric nutrient supplementation of the foetus(es) (Charlton and Johengen, 1985, 1987), but cannot be reversed once established (Eremia et al., 2007). Moreover, undernutrition of pregnant ewes leads to restriction of foetal growth, as a result of decreased foetal insulin-like growth factor 1 concentrations (Oliver et al., 1996). It has thus been postulated that foetal growth during late pregnancy relies on the 'glucose/insulin/insulin-like growth factor 1' axis, although a paraplacental route, via the amniotic fluid, has also been considered. According to the latter model, foetuses swallow amniotic fluid (Harding et al., 1984), using nutrients and growth factors ingested (Pitkin and Reynolds, 1975; Phillips et al., 1991; Bloomfield et al., 2002a). In fact, oesophageal ligation in sheep foetuses has been shown to lead to intrauterine growth restriction (Kimble et al., 1999), whilst direct intragastric nutrient supplementation prevents the condition, even in the presence of nutrient restriction of the pregnant ewes (Charlton and Johengen, 1985), as does supplementation of amniotic fluid with insulin-like growth factor 1 (Bloomfield et al., 2002b).

5. Udder health management

The principal component of mammary physiology during pregnancy involves the process of involution at the end of lactation preceding pregnancy. The aims of effective udder health management at that period are (i) to cure infections which have occurred during the previous lactation and (ii) to prevent development of new mammary infections during the dry period. In lactating dairy ewes, staphylococci (coagulase-negative staphylococci and *Staphylococcus aureus*) account for the largest proportion of aetiological agents of subclinical mastitis, leading to reduced milk production (Fthenakis and Jones, 1990a; Saratsis et al., 1999). Staphylococci and *Arcanobacterium pyogenes* are the most frequent causative agents of mastitis in ewes during the dry-period (Saratsis et al., 1998; Spanu et al., 2011).

It is now well documented that incidence risk of mammary infections increases during the first two weeks of the dry-period (Barkema et al., 1998; Saratsis et al., 1998). This increased infection risk has been associated with compromised mammary defences during that period; neutrophil dysfunction, depression of lymphocyte function and decreased cytokine production have been suggested as possible reasons for the increased infection risk of dry mammary glands. Subclinical infection which has occurred during the previous lactation, may also lead to recrudescence of clinical disease at the end of lactation and the start of the dry-period, as a result of the reduced mammary defences of the animal (Fthenakis and Jones, 1990b).

The first step to effective udder health management of pregnant ewes is the thorough clinical examination of the mammary glands at the end of lactation; this will help to identify ewes, which should be culled. The udder of all ewes in the flock should be examined by palpation, whilst the animals are run through a race (Saratsis et al., 1998). If mammary abnormalities are suspected, animals can be individually examined; mammary secretion samples may also be collected for microbiological examination (Fthenakis, 1994; Saratsis et al., 1998; Mavrogianni et al., 2005). Diffuse hardness, abscesses and nodules in the mammary glands are the most common clinical findings during that examination (Saratsis et al., 1998).

The following categories of ewes should be considered for culling based on the results of this examination: (i) animals chronically affected, (ii) animals which had showed relapsing mastitis during the previous lactation, (iii) animals with one mammary gland permanently damaged and (iv) animals which had not fully responded to mastitis treatment during the preceding lactation. The benefits of culling such animals include: (i) decrease of veterinary expenses for mastitis control in the flock, (ii) elimination of sources of potential infection for other animals in the flock and (iii) decrease of bulk somatic cell counts in the subsequent lactation (Mavrogianni et al., 2011). Moreover, lambs (especially from multiple births) from ewes with extensive mammary lesions do not thrive as well as those from healthy dams and may require additional feeding (Fthenakis and Jones, 1990a), which adds to labour expenses in the flock.

Subsequently, intramammary administration of antimicrobial agents should be carried out to animals, which will be maintained into the subsequent lactation. Administration of intramammary antimicrobial agents at the end of lactation is effective in reducing *post-partum* mammary infection risk in dairy ewes, and, in some cases, leads to decreased bulk somatic cell counts in the flock (Hueston et al., 1989; Chaffer et al., 2003; Gonzalo et al., 2004; Scwimmer et al., 2008; Spanu et al., 2011). The procedure may be just as beneficial in ewes in mutton-type production systems (Hendy et al., 1981). The principle of antibiotic administration at the end of lactation relies on administration of an intramammary preparation once, to both mammary glands of all ewes in the flock, after thorough disinfection of the teats. Good hygiene conditions during application, as well as definite and complete cessation of lactation after administration are essential for success of the procedure. Strategic administration of injectable antibiotics in ewes, at the end of lactation, has also been found to be beneficial in reducing incidence of *post-partum* mastitis (Croft et al., 2000). Although a variety of products is licenced for administration in ewes, ideally, the product for administration should be selected on the results of susceptibility testing of bacteria (Constable and Morin, 2003; Mavrogianni et al., 2011) isolated from the mammary secretion samples of ewes individually examined, as detailed above.

Finally, there seems to be lack of evidence regarding the effects of method of cessation of lactation (i.e., abrupt cessation of lactation practiced in mutton-type sheep production systems versus progressive cessation of lactation frequently taking place in dairy production systems, which aims to increase total milk production of the animals) in subsequent mammary infection and development of mastitis. However, the results of recent work do not support a hypothesis that the procedure followed for udder drying-off could affect the risk of infection of the mammary glands during the dry period and the immediately *post-partum* period (Petridis et al., 2011).

6. Management of abortions

In sheep, abortion refers to the expulsion of a foetus before the 135th day of pregnancy, after which a newborn lamb is usually able to survive. Abortion is a significant problem in pregnant ewes and a major source of financial losses. An incidence risk of abortion cases <5% during a season is considered acceptable, whilst a risk <2% is excellent; a repeated, year after year, abortion rate between 2% and 5% suggests the presence of endemic diseases in the flock (Menzies, 2007a).

The great majority of abortion cases is of microbial aetiology; various non-infectious agents (e.g., stressors, pharmaceutical agents, nutritional factors) have also been identified to cause abortion in ewes, but are not highly prevalent (Edmondson et al., 2002). Generally, the most common causes of abortion in sheep are the following: *Brucella melitensis*, *Campylobacter fetus* subsp. *fetus*, *Chlamydophila abortus*, *Coxiella burnetti*, *Toxoplasma gondi* and *Border Disease Virus*; of lesser importance can be various other bacteria (e.g., *Salmonella* spp., *Mycoplasma* spp., *Leptospira* spp.) and viruses. Hence, early control of cases of abortion can prevent a subsequent abortion 'storm'. In such cases, one faces two problems: (i) to establish an accurate diagnosis of the causative agent and (ii) to control the disease. Causative diagnosis cannot be achieved in all cases and, frequently, several cases remain undiagnosed (Linklater, 1979; Kirkbride, 1993). As a general rule, it is recommended that the first 10 cases of abortions occurring in a lambing season should be investigated in detail, whilst, thereafter, only 10% of cases should be investigated (Mavrogianni and Brozos, 2008).

Diagnosis of abortion cases should start with a detailed history, as closely pertaining to the abortion problem, since it is not rare for a stillbirth case to be perceived and reported as abortion. Certain points can offer valuable information and facilitate diagnosis; for example, the incidence of abortion may be higher in certain age groups or in different stages of pregnancy. Other important factors for a successful causative diagnosis include the number of foetuses borne per ewe, possible introduction of replacement animals in the farm, details of vaccinations and nutrition, exposure to toxic plants or drugs and abnormal findings in the animal(s) that had aborted, before, during or after abortion (Menzies, 2011).

Ewes that had aborted, must be isolated and abortion material should be destroyed by burning. Healthy animals must be examined first, whilst securing no contact with animals that had aborted. Farmers of infected flocks should be advised to wear protective clothing that is changed before entering the area of healthy pregnant ewes. If animals that had aborted, need to be milked or mated during the subsequent breeding season, they should remain isolated for at least three weeks. If it is decided to cull them, they should be sent directly to the slaughterhouse, thus avoiding any contact with healthy animals.

Confirmation of the cause of abortion in a flock can be achieved only after appropriate laboratory examinations. These depend on correct selection of samples, which should reach the laboratory in a state allowing examination. It is advisable to accompany the samples with a brief case history. Generally, the following material are useful and will support a diagnosis of the causative agent of the problem: (i) at least two cotyledons with intercotyledonary placenta from a ewe that had aborted, (ii) fresh foetuses

from ewes that had aborted, (iii) whole blood or serum samples from ewes that had aborted and/or (iv) vaginal discharge samples from ewes that had aborted. Material for microbiological examination should be freshly collected and individually packed in sterile containers. Material for histopathologic examination can be fixed in 10% formalin solution. In all cases, deep freezing should be avoided.

In general, abortive disease can be well-controlled by means of vaccination, which is best taking place before start of the breeding season. The possibility of vaccinating pregnant ewes, in front of an abortion 'storm' is discussed in another article in this special issue (Menzies, this issue), hence there is no need for elaboration here.

In flocks with a confirmed abortive disease problem, where vaccination had not been carried out, there may be a need for a strategic administration of chemotherapeutic agents. For example, in flocks with prevailing *C. abortus* problem, starting after the 80th day of pregnancy administration of long-acting oxytetracycline at a dose rate of 20 mg per kg bodyweight and repeated every three weeks, will significantly decrease the abortion risk, although there is some disagreement whether multiple treatments are justified (Menzies, 2011). Although oxytetracycline is effective in the control of an outbreak caused by *C. burnetii*, the literature regarding value of strategic administration of the drug in infected, non-vaccinated flocks is conflicting (Sahin et al., 2008; Angelakis and Raoult, 2010). In unvaccinated flocks, where toxoplasmosis has been diagnosed, control can be instituted through feeding of prophylactic medications during pregnancy; administration of monensin at a dose rate of 16.8 mg per ewe daily has been shown to reduce losses (Buxton et al., 1988), whilst administration of decoquinate at a rate of 2 mg per kg bodyweight daily for the final 14 weeks of pregnancy can also lead to decreasing abortion risk caused by *T. gondii* (Buxton et al., 1996); finally, sulphadimidine administered in various dose rates, on its own or in combination with baquiloprim, trimethoprim or pyrimethamine, has also been found to be effective in controlling abortion risk due to toxoplasmosis (Buxton et al., 1993; Giadinis et al., 2011a).

7. Management of endoparasitic infections

Gastrointestinal parasites are important constrains on sheep production, responsible for significant losses (Jackson and Coop, 2007). Control of gastrointestinal parasitic infections largely relies on regular treatments with anthelmintics. On the other hand, treatments need to be carried out with minimum selection pressure, in order to delay development of anthelmintic resistant strains. A sustainable solution remains the application of targeted selective treatments of individual animals at risk, instead of the systematic treatment of the whole flock, approach which supports maintenance of a reservoir of susceptible worms within the parasite population. The benefits from the anthelmintic treatments can vary depending upon a number of factors, particularly the timing of treatments (Cringoli et al., 2008). Juste-Jordan and Garcia-Perez (1991) demonstrated that improved timing of treatment could yield up to 9% increase in milk production. In the temperate South European climates, sheep can acquire gastrointestinal parasitic infections almost throughout the year, as they are challenged with infective parasitic stages during the almost constant pasture grazing. Therefore, a strategic and sustainable anthelmintic protocol has to be designed for annual long-term protection and combined to animal production, in order to be flexible according to the different needs of sheep during the year.

A critical timing for anthelmintic treatment in ewes is before mating, i.e. beginning of summer in the para-Mediterranean countries. Any class of anthelmintics may be used at this point. Experimental results have shown that removal of helminthes before mating can improve reproductive efficiency. Garcia-Perez et al. (2002) observed that highest conception rates (>95%) were achieved among animals treated before mating and considered that to be the result of increased fecundity during the first 30 days after ram introduction into the flock; moreover, it seemed that pre-mating treatment had a positive effect on lamb bodyweight per ewe mated. Hence, control of helminthes during the pre-mating period can be considered to have an effect similar to 'flushing' (Section 4.1) (Venter and Greyling, 1994). In case the treatment has to be carried out during or soon after the mating period, the choice of nematocide anthelmintics to be used includes levamisole, macrocyclic lactones, monepantel (an amino-acetonitrile derivative) or derquantel (a spiroindole), if necessary combined with a trematocide. Obviously, at that period, benzimidazoles have to be excluded as a possible choice, as these compounds have documented embryotoxic properties, leading to teratogenesis (Braun, 1997); hence, there is a scope for avoiding their use during the peri-conception and early pregnancy period (Gibson, 1980; Gottschal et al., 1990; Navarro et al., 1998). The same precaution should also be maintained in flocks where rams are kept permanently with ewes, as some animals may be already at early pregnancy at the time of benzimidazole administration.

Antiparasitic treatment of pregnant ewes during the last month of pregnancy can be incorporated in flock health management, as animals are particularly susceptible to the effects of parasitism at that time (Coop and Jackson, 2000). The interaction of parasitism and reproductive activity in ewes is expressed with the periparturient rise in worm egg output, which has been attributed to a loss of resistance associated with late pregnancy and early lactation (Dunsmore, 1965). The findings of Houdijk et al. (2003) imply that, in lactating ewes, milk production takes a priority over reduction of helminth numbers. Therefore, treatment of pregnant ewes at this stage eliminates helminthes (thus, increasing production potential for ewes) and prevents the built-up of parasitic burdens in the environment (thus, reducing infection of lambs during their neonatal period). Effective treatment of pregnant ewes, using drugs with persistent activity, can also result in increased future birth bodyweight of their lambs and increased milk production (up to 44%) during the subsequent lactation (Juste-Jordan and Garcia-Perez, 1991; Fthenakis et al., 2005; Cringoli et al., 2008).

The choice of nematocide anthelmintics to be used at that time, includes benzimidazoles, macrocyclic lactones, monepantel (an amino-acetonitrile derivative) or derquantel (a spirondole), potentially combined with a trematocide

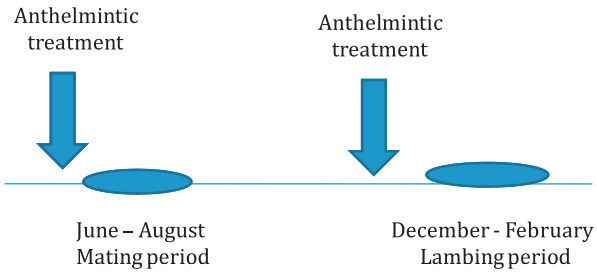

Fig. 1. Strategic timing for anthelmintic treatments of ewes reared in temperate climates in the para-Mediterranean areas.

drug (e.g., triclabendazole, closantel, rafoxanide or albendazole at a dose rate of 20 mg per kg bodyweight) if necessary. Certainly, choice of the drug to be prescribed, should also take into consideration the rotation of classes of anthelmintics, in order to minimise selection for resistance. Levamisole has been reported to potentially cause abortion if administered in late pregnancy (Braun, 1997), hence, it should better be avoided.

Finally, it is noteworthy that, as a general rule, in the temperate climates prevailing in para-Mediterranean countries, a course of two anthelmintic treatments annually (i.e., before mating and at the end of pregnancy) is the most effective option for strategic protection of ewes against helminthes (Fig. 1).

8. Vaccinations

Vaccinations of pregnant ewes aim to ensure health of these animals, as well as that of their offspring at the early stages of their life (Mobini et al., 2002).

Clostridial infections constitute a significant health problem in sheep and anti-clostridial vaccinations, most often carried out during the last month of pregnancy, will contribute significantly to protection of vaccinated ewes, as well as of their offspring (Lewis, 2011). Internationally, various anti-clostridial vaccines are licenced for use in sheep. Some of these are multivalent, whilst others are composed of few clostridial antigens, mainly *Clostridium perfringens*. Multivalent vaccines aim to protect, except for *Cl. perfringens* infections, also against *Cl. septicum*, *Cl. novyi* (types B and D), *Cl. tetani* and *Cl. chauvoei* (Lewis, 2011). In recent years, *Cl. sordellii* has also been identified as a cause of deaths in newborn lambs and adult animals, hence, some vaccines now include *Cl. sordellii* antigens (Vatn et al., 2000; Clark, 2003). Vaccination of pregnant ewes against clostridiosis should be carried out 20–40 days before the expected start of the lambing season, in order to achieve increased antibody titres in the colostrum of the vaccinated animals for protection of the newborn lambs, as the main immune mechanism in clostridial infections is humoral immunity. To note that ewes that had not lambed within three months after the last anti-clostridial vaccination should be revaccinated (Blackwell et al., 1983; Uzal et al., 1999; Giadinis et al., 2011b; Lewis, 2011).

Infections from *Manheimia haemolytica* can cause mortality in newborn lambs; therefore, vaccination of pregnant ewes can be useful, especially as many risk factors for the disease cannot be avoided. Vaccines incorporating iron-regulated proteins produced by the causative organisms are best for use and they confer cross-protection against all isolates of *M. haemolytica* and *Bibersteinia trehalosi* (Scott, 2011). It is noteworthy that vaccination of pregnant ewes confers immunity to their lambs up to the 5th week of their life, hence lambs maintained after that age need to be vaccinated for complete protection. Vaccination for protection against *M. haemolytica* infection can be combined with anti-clostridial vaccinations (Donachie, 2009; Sargison, 2009). Nevertheless, in order to maximise protection afforded by vaccination, predisposing factors of the disease (e.g., inappropriate ventilation, overcrowding in shed etc.) need also to be removed (Giadinis and Petridou, 2008; Donachie, 2009; Sargison, 2009).

Contagious ecthyma ("orf"), caused by *Orf virus*, can also be prevented by vaccination of pregnant ewes, especially in flocks with increased incidence risk of the disease in lambs or increased mortality rate of lambs due to secondary bacterial infections. In general, field studies have confirmed that annual vaccination of pregnant ewes one month before lambing by using an attenuated vaccine, affords adequate protection of newborn lambs (McKeever and Reid, 1987; Giadinis et al., 2007; Stampoulis et al., 2010), although vaccination failures may also occur (Buddle et al., 1984).

Contagious agalactia, caused by *Mycoplasma agalactiae* and other mycoplasmas is a common health problem in the para-Mediterranean countries (De la Fe et al., 2005). Excellent control of the disease can be achieved by combining hygiene, biosecurity measures and effective vaccinations (Madanat et al., 2001; Buonavoglia et al., 2010; Fragkou et al., 2011). Vaccination should be carried out during pregnancy, in order to confer immunity to the female animals, as well as to their lambs, as humoral immunity is important for contagious agalactia (Chessa et al., 2009).

Pregnant ewes cannot be vaccinated with attenuated vaccines, especially vaccines against abortifacient agents, e.g., *B. melitensis* (Stournara et al., 2007; Samadi et al., 2010), *C. abortus* (Aitken, 2000) or *T. gondii* (Giadinis et al., 2011), as this would lead to abortion. Therefore, only inactivated vaccines may be used. Inactivated whole cell vaccines are available to protect against *C. abortus* infections and may be administered to pregnant ewes, in view of an outbreak of the infection. The possibility of vaccinating pregnant ewes, in front of an abortion 'storm' is being discussed in another article in this special issue (Menzies, this issue), hence there is no need for elaboration here.

9. Prevention of metabolic disorders: pregnancy toxaemia, hypocalcaemia

9.1. Control of pregnancy toxaemia

Pregnancy toxaemia ("twin-lamb disease") is a metabolic disorder of pregnant ewes, caused by an abnormal metabolism of carbohydrates and fats, which occurs at the final stage of pregnancy. Treatment of pregnancy toxaemia, as well as management of flocks where cases of the disease have been diagnosed, were recently described in detail (Brozos et al., 2011).

In order to improve prevention of the disease, especially in farms with prevailing risk factors of the disease,

ewes should ideally be allocated into early and late lambing groups on the basis of mating records. Moreover, animals may be subdivided into ewes bearing one foetus and ewes bearing multiple foetuses (Sargison, 2007), as established in pregnancy diagnosis (Sections 3.2 and 3.3). This allows improved nutritional management during the last stage of pregnancy (Section 4.3), as well as administration of anthelmintic treatments (Section 7) and vaccinations (Section 8) at the most appropriate time-point.

A representative sample of ewes (around 20% of the animals) should be evaluated to assess their body-condition score. Ideally, body-condition score of ewes should be '2½' to '3½' one month before lambing and '2' to '2½' at lambing (Cannas et al., 2004). Thin ewes (body-condition score ≤'2') should be provided additional high-energy feeding and their condition should be re-evaluated every fortnight.

Animals at risk of developing pregnancy toxaemia can be identified by measuring β-hydroxybutyrate concentration in their blood during the last six to four weeks of pregnancy, especially as rapid measurement techniques are now available (Panousis et al., 2012). If the number of foetuses carried has not been identified, the value of 0.8 mmol L^{-1} should be considered to distinguish animals at risk to develop the disorder. Otherwise, if the number of foetuses carried had been determined, then β-hydroxybutyrate concentration should be measured only in the blood of animals carrying multiple foetuses; in this case, the cut-off value to be used for identifying animals at risk is 1.1 mmol L^{-1} (Sargison, 2007; Braun et al., 2010). If financial or labour constraints preclude examination of all animals as above, then examination of around 20% of animals will still provide a valuable overview of the flock situation. If blood measurement is not feasible, semi-quantitive measurement in urine by using dipsticks can be advocated, but results should be considered cautiously. Animals found to have increased concentration of β-hydroxybutyrate in blood or urine should be separated from other animals and monitored closely.

9.2. Control of hypocalcaemia

Hypocalcaemia ("parturient paresis", "lambing sickness") is an acute or subacute pathological condition, which occurs more often shortly before or after parturition. A detailed account of preventive measures for the disease has recently been published by Brozos et al. (2011). In general, an effective preventive strategy against the disease should include (i) control of body condition (Ostergaard et al., 2003), (ii) regulation of calcium (Sorensen et al., 2002), magnesium (Roche, 2003) and phosphorus (Lean et al., 2006) content in the feed, (iii) monitoring of cation/anion balance in the feed (Goff, 2004) and (iv) regular monitoring of calcium concentration in the animals' blood (Oetzel, 2004).

10. Husbandry practices before the start of the lambing season

Lambing is a crucial period in a sheep farm. Correct health management at that period significantly improves the overall financial performance of the flock, especially as, given the seasonality of sheep breeding, a large number of ewes may give birth over a relatively short period. In any sheep flock, husbandry interventions before the expected lambing are associated with the production system applied in the farm.

Good management practices require that personnel in charge of peri-parturient ewes are aware of the animals' needs and have the appropriate knowledge to control and manage potential problems. Moreover, personnel (even the most experienced) should update their skills on latest techniques and management practices.

Allocation of ewes into groups (as discussed above) will reduce workload in the farm, considering the variability in length of pregnancy in ewes. In general, one should focus on avoiding long, spread-out lambing periods, because this results in increased stress for ewes and more workload for the farm staff. Moreover, ewes in different lambing groups should lamb in separate areas of the shed, in order to minimise the risk for build-up of pathogens in the farm environment (Menzies, 2007b).

Regardless of the production system applied in the flock, stress to parturient ewes should be minimal, but still with maximum supervision. Availability of temporary individual lambing pens provides many advantages, such as significant reduction of newborn lamb losses and facilitation of animal marking. Specific measures should be taken to ensure that any purchased replacement ewes will lamb in a separate barn, away from the home flock, in order to avoid potential cross infections (Gelasakis et al., 2010). A similar management should apply to ewe-lambs lambing for the first time. Areas with pregnant ewes should allow a floor space of ≥2 m^2 per ewe, whereas clean straw bedding should be always available (Gelasakis et al., 2010). Shearing around the perineal area of parturient ewes and dirt removal from the udder and teats of ewes contributes to quick access of lambs to the mammary glands of their dams, as well as decreased incidence risk of *post-partum* genital infections of ewes and cryptosporidiosis of newborn lambs. Finally, an 'isolation' area should be available, where ewes with obstetrical problems or *post-partum* disorders may be isolated.

11. Induction and synchronisation of lambings

Synchronisation of lambings in sheep flocks is beneficial for optimising flock production, as it leads in correct management of peri-parturient ewes and newborn lambs. The method can also be used to ensure that newborn lambs are only artificially fed, as part of schemes for eradication of various infectious diseases (e.g., *Small Ruminant Lentivirus* infection). Induction of lambing in individual animals may be required as part of the therapeutic regime in *peri-partum* pathological conditions of ewes (e.g., pregnancy toxaemia) (Kastelic et al., 1996; Ingoldby and Jackson, 2001; Klobasa et al., 2004; Menzies, 2007b; Batista et al., 2008).

The procedure is not routinely applied in sheep flocks, but only in farms where it had been well planned in advance and where a cost/benefit study had been undertaken. In general, induction of lambing can be easily performed only if the mating date of the ewes is known within a three-day margin, which aids to avoid premature birth of lambs.

In practice, lambing may be induced by administration of corticosteroids, oestrogens or prostaglandin, depending on the stage of pregnancy and the overall treatment regime applied.

Synthetic corticosteroids (10–20 mg dexamethasone per ewe i.m., 10–12 mg betamethasone per ewe i.m. or 2 mg flumethasone per ewe i.m.) can be administered as early as the 137th day of a 144–149 day-long pregnancy. However, it may be better to induce lambing on or after the 142nd day, in order to ensure increased chances of newborn viability. In the above cases, lambing takes place within 30–75 h after start of the treatment (Harman and Slyter, 1980; Rommereim and Slyter, 1981; Edey et al., 1985; Menzies, 2007b; Rawlings and Bartlewski, 2007). Later in pregnancy (146th day of a 148–150 day-long pregnancy), induction of lambing may be achieved by administration of smaller doses of dexamethasone (1–2 mg i.m.) (Tsiligianni et al., 2008). To note that, in general, efficacy of dexamethasone-induced lambing can be affected by breed of the ewe and time of the year (Sir and Bartlewski, 2010).

Oestrogens (oestradiol benzoate 2–20 mg per ewe i.m.) can be administered 5 days before the expected end of pregnancy, leading to lambing after 30–45 h (Rawlings and Howell, 1988; Rawlings and Bartlewski, 2007). Specifically in ewes carrying in vitro-produced embryos, use of a combination of betamethasone and oestradiol benzoate, albeit expensive, is preferred, because it ensures increased percentages of newborn lamb viability (Ptak et al., 2002). Attempts to concentrate lambings during the day, after administration of synthetic corticosteroids have not been successful (Edey et al., 1985). In contrast to that, administration of oestradiol benzoate has proved to be more effective in improving synchronisations of lambing during the day (Rawlings and Howell, 1988).

Prostaglandins, alone or in combination with dexamethasone, have given poor results in inducing lambing (Harman and Slyter, 1980; Tsiligianni et al., 2008). Thus, these protocols appear insufficient for successful application under field conditions, in contrast to common practices for induction of parturition in heifers or goats.

In ewes with pregnancy toxaemia, in which induction of lambing is performed as part of the overall therapeutic regime, simultaneous administration of cloprostenol (0.375 mg per ewe) would increase the efficacy of the regime, as endogenous concentration of corticosteroids may be increased (Brozos et al., 2011). In these cases, induction should be followed by intravenous administration of 20% dextrose solution (dose: 200–300 mL per ewe) or 50% dextrose solution (dose: 80–120 mL per ewe) twice daily until parturition is completed.

In all cases, animals should be monitored at regular intervals after hormonal administration, because they can often develop dystocia, retention of foetal membranes and metritis.

12. Concluding remarks

This paper has provided, for the first time, a detailed account of health management of pregnant ewes, which is a multi-faceted very significant task for successful management of the flock within the annual production cycle. The paper provides guidelines for health management of pregnant ewes around the world. Fine-tuning of the procedures will need to be carried out in individual flocks, after taking into account their specific requirements.

Conflict of interest statement

The authors have nothing to disclose.

References

Agriculture and Food Research Council, 1993. Energy and Protein Requirements of Ruminants. CAB International, Wallingford, 159 pp.

Agriculture Research Council, 1980. The Nutrient Requirements of Ruminant Livestock. The Gresham Press, London, 351 pp.

Aitken, I.D., 2000. Chlamydial abortion. In: Martin, W.B., Aitken, I.D. (Eds.), Diseases of Sheep. , 3rd ed. Blackwell, Oxford, pp. 81–86.

Andrews, A., 1997. Pregnancy toxaemia in the ewe. In Pract. 19, 306–314.

Angelakis, E., Raoult, D., 2010. Review – Q Fever. Vet. Microbiol. 140, 297–309.

Barkema, H.W., Schukken, Y.H., Lam, T.J.G.M., Beiboer, M.L., Wilmink, H., Benedictus, G., Brand, A., 1998. Incidence of clinical mastitis in dairy herds grouped in three categories by bulk milk somatic cell counts. J. Dairy Sci. 81, 411–419.

Bartlewski, P.M., Baby, T.E., Giffin, J.L., 2011. Reproductive cycles in sheep. Anim. Reprod. Sci. 57, 67–88.

Batista, M., Nino, T., Alamo, D., Gonzalez, F., Santana, M., Rodriguez, N., Cabrera, F., Gracia, A., 2008. Use of luprostiol and cloprostenol for induction of parturition in pregnant goats. Reprod. Domest. Anim. 44, 83–87.

Bazer, F.W., Burghardt, R.C., Johnson, G.A., Spencer, T.E., Wu, G., 2008. Interferons and progesterone for establishment and maintenance of pregnancy: interactions among novel cell signaling pathways. Reprod. Biol. 8, 179–211.

Bhanu, T.P., Green, J.A., 2007. Comparative placentation. In: Schatten, H., Constantinescu, M.G. (Eds.), Comparative Reproductive Biology. Blackwell, Philadelphia, pp. 271–319.

Blackwell, T.E., Butler, D.G., Bell, J.A., 1983. Enterotoxemia in the goat: the humoral response and local tissue reaction following vaccination with two different bacterin-toxoids. Can. J. Comp. Med. 47, 127–132.

Blanchart, D., Sauvant, D., 1974. Consequences of pregnancy on the evolution of lactation. In: Proceedings of a Conference 'Information Day on the Feeding of the Dairy Goat', Paris, France, pp. 76–87.

Bloomfield, F.H., Bauer, M.K., van Zijl, P.L., Gluckman, P.D., Harding, J.E., 2002a. Amniotic IGF-I supplements improve gut growth but reduce circulating IGF-I in growth-restricted fetal sheep. Am. J. Physiol. 282, E259–E269.

Bloomfield, F.H., van Zijl, P.L., Bauer, M.K., Harding, J.E., 2002b. A chronic low dose infusion of insulin-like growth factor I alters placental function but does not affect fetal growth. Reprod. Fertil. Dev. 14, 393–400.

Bloomfield, F.H., Oliver, M.H., Hawkins, P., Holloway, A.C., Campbell, M., Gluckman, P.D., Harding, J.E., Challis, J.R., 2004. Periconceptional undernutrition in sheep accelerates maturation of the fetal hypothalamic–pituitary–adrenal axis in late gestation. Endocrinology 145, 4278–4285.

Bocquier, F., Guillouet, P., Barillet, F., 1995. Alimentation hivernale des brebis laitières: intérêt de la mise en lots. INRA Prod. Anim. 8, 19–28.

Braun, W., 1997. Non-infectious prenatal pregnancy loss in the doe. In: Youngquist, R.S. (Ed.), Current Therapy in Large Animal Theriogenology. Saunders, Philadelphia, pp. 548–550.

Braun, J.P., Trumel, C., Bézille, P., 2010. Clinical biochemistry in sheep: a selected review. Small Rumin. Res. 92, 10–18.

Brozos, C., Mavrogianni, V.S., Fthenakis, G.C., 2011. Treatment and control of peri-parturient metabolic diseases: pregnancy toxemia, hypocalcemia, hypomagnesemia. Vet. Clin. N. Am. Food Anim. Pract. 27, 105–113.

Buddle, B.M., Dellers, R.W., Schurig, G.G., 1984. Contagious ecthyma virus-vaccination failures. Am. J. Vet. Res. 45, 263–266.

Buonavoglia, D., Greco, G., Corrente, M., Greco, M.F., D'Abramo, M., Latronico, F., Fasanella, A., Decaro, N., 2010. Long-term immunogenicity and protection against *Mycoplasma agalactiae* induced by an oil adjuvant vaccine in sheep. Res. Vet. Sci. 88, 16–19.

Buxton, D., Blewett, D.A., Trees, A.J., 1988. Further studies in the use of monensin in the control of experimental ovine toxoplasmosis. J. Comp. Pathol. 98, 225–236.

Buxton, D., Brebner, J., Wright, S., Maley, S.W., Thomson, K.M., Millard, K., 1996. Decoquinate and the control of experimental ovine toxoplasmosis. Vet. Rec. 138, 434–436.
Buxton, D., Thomson, K.M., Maley, S., 1993. Treatment of ovine toxoplasmosis with a combination of sulphamezathine and pyrimethamine. Vet. Rec. 132, 409–411.
Cannas, A., 2004. Energy and protein requirements. In: Pulina, G. (Ed.), Dairy Sheep Nutrition. CAB Publishing, pp. 31–50.
Cannas, A., Tedeschi, L.O., Fox, D.G., Pell, A.N., Van Soest, P.J., 2004. A mechanistic model for predicting the nutrient requirements and feed biological values for sheep. J. Anim. Sci. 82, 149–169.
Cappio-Bornilo, A., Macciota, N.P., Pulina, G., 2004. Mathematical modeling of milk production patterns in dairy sheep. In: Pulina, G. (Ed.), Dairy Sheep Nutrition. CABI Publishing, Wallingford, pp. 13–30.
Chaffer, M., Leitner, G., Zamir, S., Winkler, M., Glickman, A., Ziv, N., Saranet, A., 2003. Efficacy of dry-off treatment in sheep. Small Rumin. Res. 47, 11–16.
Charlton, V., Johengen, M., 1985. Effects of intrauterine nutritional supplementation on fetal growth retardation. Biol. Neonate 48, 125–142.
Charlton, V., Johengen, M., 1987. Fetal intravenous nutritional supplementation ameliorates the development of embolization-induced growth retardation in sheep. Pediatr. Res. 22, 55–61.
Chessa, B., Pittau, M., Puricelli, M., Zobba, R., Coradduzza, E., Dall'Ara, P., Rosati, S., Poli, G., Alberti, A., 2009. Genetic immunization with the immunodominant antigen P48 of *Mycoplasma agalactiae* stimulates a mixed adaptive immune response in BALBc mice. Res. Vet. Sci. 86, 414–420.
Clark, S., 2003. Sudden death in periparturient sheep associated with *Clostridium sordellii*. Vet. Rec. 153, 340.
Clarke, L., Heasman, L., Juniper, D.T., Symonds, M., 1998. Maternal nutrition in early-mid gestation and placental size in sheep. Br. J. Nutr. 79, 359–364.
Commonwealth Scientific and Industrial Research Organisation, 1990. Feeding Standards for Australian Livestock – Ruminants. CSIRO, Melbourne, 266 pp.
Commonwealth Scientific and Industrial Research Organisation, 2007. Nutrient Requirements of Domesticated Ruminants. CSIRO, Collingwood, 270 pp.
Constable, P.D., Morin, D.E., 2003. Treatment of clinical mastitis: using antimicrobial susceptibility profiles for treatment decisions. Vet. Clin. N Am. Food Anim Pract. 19, 139–155.
Coop, R.L., Jackson, F., 2000. Gastrointestinal helminthosis. In: Martin, W.B., Aitken, I.D. (Eds.), Diseases of Sheep. , 3rd ed. Blackwell, Oxford, pp. 159–167.
Cringoli, G., Veneziano, V., Jackson, F., Vercruysse, J., Greer, A.W., Fedele, V., Mezzino, L., Rinaldi, L., 2008. Effects of strategic anthelmintic treatments on the milk production of dairy sheep naturally infected by gastrointestinal strongyles. Vet. Parasitol. 156, 340–345.
Croft, A., Duffield, T., Menzies, P., Leslie, K., Bagg, R., Dick, P., 2000. The effect of tilmicosin administered to ewes prior to lambing on incidence of clinical mastitis and subsequent lamb performance. Can. Vet. J. 41, 306–311.
De la Fe, C., Assunção, P., Antunes, T., Rosales, R.S., Poveda, J.B., 2005. Microbiological survey for *Mycoplasma* spp. in a contagious agalactia endemic area. Vet. J. 170, 257–259.
Deligiannis, C., Valasi, I., Rekkas, C.A., Goulas, P., Theodosiadou, E., Lainas, T., Amiridis, G.S., 2005. Synchronization of ovulation and fixed time intrauterine insemination in ewes. Reprod. Domest. Anim. 40, 6–10.
Devaskar, S.U., Anthony, R., Hay, W.J., 2002. Ontogeny and insulin regulation of fetal ovine white adipose tissue leptin expression. Am. J. Physiol. Regul. Integr. Comp. Physiol. 282, R431–R438.
Diskin, M.G., Morris, D.G., 2008. Embryonic and early foetal losses in cattle and other ruminants. Reprod. Domest. Anim. 43 (Suppl. 2), 260–267.
Donachie, W., 2009. Pasteurellosis. In: Aitken, I.D. (Ed.), Diseases of Sheep. , 4th ed. Blackwell, Oxford, pp. 224–231.
Drackley., J.K., Richard, M.J., Beitz, D.C., Young, J.W., 1992. Metabolic changes in dairy cows with ketonemia in response to feed restriction and dietary 1,3-butanediol. J. Dairy Sci. 75, 1622–1634.
Dunsmore, J.D., 1965. *Ostertagia* spp. in lambs and pregnant ewes. J. Helminthol. 39, 159–184.
Economides, S., 1981. The Energy Requirements of the Chios Sheep. 1. Requirements for Maintenance and Late Pregnancy. Agricultural Research Institute, Nicosia, 12 pp.
Economides, S., Louca, A., 1981. The effects of the quantity and quality of feed on the performance of pregnant and lactating goats. In: Proceedings of the International Symposium on Nutrition and Systems of Goats Feeding, Tours, France, pp. 319–326.
Edey, T.N., Thwaites, C.J., Baillie, N.D., Bremner, G.J., 1985. Dose rate, time of injection and litter size effects on dexamethasone-induced parturition in Border Leicester × Merino ewes. Aus. Vet. J. 62, 104–105.
Edmondson, M.A., Roberts, J.F., Baird, A.N., Bychawski, S., Pugh, D.G., 2002. Theriogenology of sheep and goats. In: Pugh, D.G., Baird, A.N. (Eds.), Sheep and Goat Medicine. , 2nd ed. Saunders, Philadlphia, pp. 150–230.
Edwards, L.J., McFarlane, J.R., Kauter, K.G., McMillen, I.C., 2005. Impact of periconceptional nutrition on maternal and fetal leptin and fetal adiposity in singleton and twin pregnancies. Am. J. Physiol. Regul. Integr. Comp. Physiol. 288, R39–R45.
Ehrhardt, R.A., Bell, A.W., 1995. Growth and metabolism of the ovine placenta during mid-gestation. Placenta 16, 727–741.
Ehrhardt, R.A., Bell, A.W., Boisclair, Y.R., 2002. Spatial and developmental regulation of leptin in fetal sheep. Am. J. Physiol. Regul. Integr. Comp. Physiol. 282, R1628–R1635.
Eremia, S.C., de Boo, H.A., Bloomfield, F.H., Oliver, M.H., Harding, J.H., 2007. Fetal and amniotic insulin-like growth factor-I supplements improve growth rate in intrauterine growth restriction fetal sheep. Endocrinology 148, 2963–2972.
Fleming, T.P., Kwong, W.Y., Porter, R., Ursell, E., Fesenko, I., 2004. The embryo and its future. Biol. Reprod. 71, 1046–1054.
Fleming, T.P., Velazquez, M.A., Eckert, J.J., Lucas, E.S., Watkins, A.J. Nutrition of females during the periconceptional period and effects on foetal programming and health of offspring. Anim. Reprod. Sci., doi:10.1016/j.anireprosci.2012.01.015, this issue.
Forhead, A.J., Thomas, L., Crabtree, J., Hoggard, N., Gardner, D.S., Guissani, D.A., Fowden, A.L., 2002. Plasma leptin concentration in fetal sheep during late gestation: ontogeny and effect of glucocorticoids. Endocrinology 143, 1166–1173.
Fragkou, I.A., Giadinis, N.D., Brozos, C., 2011. Contagious agalactia. In: Fthenakis, G.C. (Ed.), Small Ruminant Reproduction. Tziolas Publications, Thessaloniki, pp. 353–360.
Fthenakis, G.C., 1994. Prevalence and aetiology of subclinical mastitis in ewes of Southern Greece. Small Rumin. Res. 13, 293–300.
Fthenakis, G.C., Jones, J.E.T., 1990a. The effect of inoculation of coagulase negative staphylococci into the ovine mammary gland. J. Comp. Pathol. 102, 211–219.
Fthenakis, G.C., Jones, J.E.T., 1990b. The effect of experimentally induced subclinical mastitis on milk yield of ewes and on the growth of lambs. Br. Vet. J. 146, 43–49.
Fthenakis, G.C., Papadopoulos, E., Himonas, C., 2005. Effects of three anthelmintic regimes on milk yield of ewes and growth of lambs. J. Vet. Med. A. 52, 78–82.
Garcia-Perez, A.L., Hurtado, A., Oregui, L.M., Juste, R.A., 2002. Effects of a second annual strategic anthelmintic treatment in dairy sheep in Northern Spain. Small Rumin. Res. 43, 121–126.
Gardner, D.S., Pearce, S., Dandrea, J., Walker, R., Ramsay, M.M., Stephenson, T., Symonds, M.E., 2004. Peri-implantation undernutrition programs blunted angiotensin II evoked baroreflex responses in young adult sheep. Hypertension 43, 1290–1296.
Gardner, D.S., Van Bon, B.W., Dandrea, J., Goddard, P.J., May, S.F., Wilson, V., Stephenson, T., Symonds, M.E., 2006. Effect of periconceptional undernutrition and gender on hypothalamic–pituitary–adrenal axis function in young adult sheep. J. Encrinol. 190, 203–212.
Gelasakis, A.I., Valergakis, G.E., Fortomaris, P., Arsenos, G., 2010. Farm conditions and production methods in Chios sheep flocks. J. Hell. Vet. Med. Soc. 61, 111–119.
Giadinis, N.D., Filliusis, G., Lafi, S.Q., Panousis, N., Pourliotis, K., Bojkovski, J., Karatzias, H., 2007. Field evaluation of an orf vaccine in sheep and goat flocks with high neonatal mortality. Veterinar. Glasnik 61, 301–312.
Giadinis, N.D., Minas, A., Mavrogianni, V.S., Fthenakis, G.C., 2011a. Diseases of microbial or parasitic aetiology in neonatal lambs and kids. In: Fthenakis, G.C. (Ed.), Small Ruminant Reproduction. Tziolas Publications, Thessaloniki, pp. 487–504.
Giadinis, N.D., Petridou, E.J., 2008. Pasteurellosis of small ruminants in Greece. Vet. J. Repub. Srpska 6, 99–101.
Giadinis, N.D., Terpsidis, K., Diakou, A., Siarkou, V., Loukopoulos, P., Osman, R., Karatzias, H., Papazahariadou, M., 2011b. Massive toxoplasma abortions in a dairy sheep flock and therapeutic approach with different doses of sulfadimidine. Turk. J. Vet. Anim. Sci. 35, 207–211.
Gibson, T.E., 1980. Factors influencing the application of anthelmintics in practice. Vet. Parasitol. 6, 241–254.
Goff, J.P., 2004. Macromineral disorders of the transition cow. Vet. Clin. N. Am. Food Anim. Pract. 20, 471–494.
Gonzalo, C., Tardáguila, J.A., De La Fuente, L.F., San Primitivo, F., 2004. Effects of selective and complete dry therapy on prevalence of

intramammary infection and on milk yield in the subsequent lactation in dairy ewes. J. Dairy Res. 71, 33–38.
Gottschal, D.W., Theodorides, V.J., Wang, R., 1990. The metabolism of benzimidazole anthelmintics. Parasitol. Today 6, 115–124.
Gunn, R.G., 1967. Dietary Energy and Ovulation Rate in Sheep. HFRO 4th Report 1964–1967, HFRO, Edinburgh, pp. 57–58.
Hansen, P.J., 2007. Regulation of immune cells in the uterus during pregnancy in ruminants. J. Anim. Sci. 85, E30–E31.
Harding, R., Bocking, A.D., Sigger, J.N., Wickham, P.J., 1984. Composition and volume of fluid swallowed by fetal sheep. Comp. J. Exp. Physiol. 69, 487–495.
Harding, J.E., Evans, P.C., Gluckman, P.D., 1997. Maternal growth hormone treatment increases placental diffusion capacity but not fetal or placental growth in sheep. Endocrinology 138, 5352–5358.
Harman, E.L., Slyter, A.L., 1980. Induction of parturition in the ewe. J. Anim. Sci. 50, 391–393.
Harrison, J.L., Adam, C.L., Brown, Y.A., Wallace, J.M., Aitken, R.P., Lea, R.G., Miller, D.W., 2007. An immunohistochemical study of the localization and developmental expression of ghrelin and its functional receptor in the ovine placenta. Reprod. Biol. Endocrinol 5, 25.
Heasman, L., Clarke, L., Firth, K., Stephenson, T., Symonds, M., 1998. Influence of restricted maternal nutrition in early to mid gestation on placental and fetal development at term in sheep. Pediatr. Res. 44, 546–551.
Hendy, P.G., Pugh, K.E., Harris, A.M., Davies, A.M., 1981. Prevention of post weaning mastitis in ewes. Vet. Rec. 109, 56–57.
Henze, P., Bickhardt, K., Fuhrmann, H., Sallmann, H.P., 1998. Spontaneous pregnancy toxaemia (Îetosis) in sheep and the role of insulin. Zblatt. Vet. Med. A 45, 255–266.
Hill Farming Research Organisation, 1979. Science and Hill Farming HFRO 1954–1979. HFRO, Edinburgh.
Houdijk, J.G., Kyriazakis, I., Jackson, F., Huntley, J.F., Coop, R.L., 2003. Is the allocation of metabolisable protein prioritized to milk production rather than to immune functions in *Teladorsagia circumcincta*-infected lactating ewes? Int. J. Parasitol. 33, 327–328.
Hueston, W.D., Boner, J.B., Baertsche, S.L., 1989. Intramammary antibiotic treatment at the end of lactation for prophylaxis and treatment of intramamary infections in ewes. J. Am. Vet. Med. Assoc. 194, 1041–1044.
Ingoldby, L., Jackson, P., 2001. Induction of parturition in sheep. In Pract. 23, 228–231.
Jackson, F., Coop, R.L., 2007. Gastrointestinal helminthosis. In: Aitken, I.D. (Ed.), Diseases of Sheep. , 4th ed. Blackwell, Oxford, pp. 185–195.
Jainudeen, M.R., Hafez, E.S.E., 2000a. Gestation, prenatal physiology and parturition. In: Hafez, E.S.E., Hafez, B. (Eds.), Reproduction in Farm Animals. , 7th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 140–155.
Jainudeen, M.R., Hafez, E.S.E., 2000b. Reproductive failure in females. In: Hafez, E.S.E., Hafez, B. (Eds.), Reproduction in Farm Animals. , 7th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 261–278.
Juste-Jordan, R.A., Garcia-Perez, A.L., 1991. Effect of treatment with netobimin on milk production of sheep. Vet. Parasitol. 38, 173–183.
Kähn, W., 2004. Veterinary Reproductive Ultrasonography. Schlütersche Verlagsgesellschaft, Hannover.
Kastelic, J.P., Cook, R.B., McMahon, L.R., McAllister, T.A., McClelland, L.A., Cheng, K.J., 1996. Induction of parturition in ewes with dexamethasone or dexamethasone and cloprostenol. Can. Vet. J. 37, 101–102.
Kelly, R.W., Speijers, E.J., Ralph, I.G., 1992. Lambing performances and wool production of maiden and adult merino ewes fed different amounts of lupin seed in mid-pregnancy. Aus. J. Agric. Res. 43, 339–354.
Kimble, R.M., Breier, B.H., Gluckman, P.D., Harding, J.E., 1999. Enteral IGF-I enhances fetal growth and gastrointestinal development in oesophageal ligated fetal sheep. J. Endocrinol. 162, 227–235.
Kirkbride, C.A., 1993. Diagnoses in 1784 ovine abortions and stillbirths. J. Vet. Diagn. Invest. 5, 398–402.
Klobasa, F., Henning, M., Werhahn, E., 2004. Artificial rearing of lambs with bovine colostrum during a sanitation programme of a sheep flock. Zuchtungskunde 76, 75–84.
Lean, I.J., DeGaris, P.J., McNeil, D.M., Block, E., 2006. Hypocalcemia in dairy cows: meta-analysis and dietary cation anion difference theory revisited. J. Dairy Sci. 89, 669–684.
Lewis, C.J., 2011. Control of important clostridial diseases of sheep. Vet. Clin. N. Am. Food Anim. Pract. 27, 121–126.
Linklater, K.A., 1979. Abortion in sheep. In Pract. 1, 30–33.
McDonald, P., Edwards, R.A., Greenhalgh, J.F.D., Morgan, C.A., Sinclair, L.A., Wilkinson, R.G., 2011. Animal Nutrition, 7th ed. Ashford Colour Press, Gosport, 692 pp.
McGrab, G.L., Egan, A.R., Hosking, G.J., 1991. Maternal undernutrition during mid pregnancy in sheep- placental size and its relationship to calcium transfer during late pregnancy. Br. J. Nutr. 65, 157–168.
McGrab, G.L., Egan, A.R., Hosking, G.J., 1992. Maternal undernutrition during mid pregnancy in sheep. J. Agric. Sci. 118, 127–132.
McKeever, D.J., Reid, H.D., 1987. The response of the supramammary lymph node of the sheep to secondary infection with orf virus. Vet. Microbiol. 14, 3–13.
McLaughlin, S.M., Walker, S.K., Roberts, C.T., Kleemann, D.O., McMillen, I.C., 2005. Periconceptional nutrition and the relationship between maternal body weight changes in the periconceptional period and feto-placental growth in the sheep. J. Physiol. 565, 111–124.
Madanat, A., Zendulkova, D., Pospisi, Z., 2001. Contagious agalactia of sheep and goats, a review. Acta Vet. Brno 70, 403–412.
Martal, J., Chene, N., Camous, S., Huynh, L., Lantier, F., Hermier, P., L'Haridon, R., Charpigny, G., Charlier, M., Chaouat, G., 1997. Recent development and potentialities for reducing embryo mortality in ruminants: the role of INF-tau and other cytokines in early pregnancy. Reprod. Fertil. Dev. 9, 355–380.
Mavrogianni, V.S., Brozos, C., 2008. Reflections on the causes and the diagnosis of peri-parturient losses of ewes. Small. Rumin. Res. 76, 77–82.
Mavrogianni, V.S., Fthenakis, G.C., Brooks, H., Papaioannou, N., Cripps, P.J., Taitzoglou, I., Brellou, G., Saratsis, P., 2005. The effects of inoculation of *Mannheimia haemolytica* into the teat of lactating ewes. Vet. Res. 36, 13–25.
Mavrogianni, V.S., Menzies, P.I., Fragkou, I.A., Fthenakis, G.C., 2011. Principles of mastitis treatment in sheep and goats. Vet. Clin. N. Am. Food Anim. Pract. 27, 115–120.
Meinecke-Tillmann, S., Meinecke, B., 2007. Ultrasonography in small ruminant reproduction. In: Schatten, H., Constantinescu, M.G. (Eds.), Comparative Reproductive Biology. Blackwell, Philadelphia, pp. 349–376.
Menzies, P.I., 2007a. Abortion in sheep: diagnosis and control. In: Youngquist, R.S., Threlfall, W.R. (Eds.), Current Therapy in Large Animal Theriogenology. Saunders, Philadelphia, pp. 667–680.
Menzies, P.I., 2007b. Lambing management and neonatal care. In: Youngquist, R.S., Threlfall, W.R. (Eds.), Current Therapy in Large Animal Theriogenology. Saunders, Philadelphia, pp. 680–695.
Menzies, P.I., 2011. Control of important causes of infectious abortion in sheep and goats. Vet. Clin. N. Am. Food Anim. Pract. 27, 81–93.
Menzies, P.I. Vaccination programs for reproductive disorders of small ruminants. Anim. Reprod. Sci., doi:10.1016/j.anireprosci.2012.01.010, this issue.
Miller, D.R., Blache, D., Jackson, R.B., Downie, E.F., Roche, J.R., 2010. Metabolic maturity at birth and neonate lamb survival: association among maternal factors, litter size, lamb birth weight, and plasma metabolic and endocrine factors on survival and behavior. J. Anim. Sci. 88, 581–593.
Mobini, S., Wolf, C., Pugh, D.G., 2002. Flock health. In: Pugh, D.G. (Ed.), Sheep and Goat Medicine,. Saunders, Philadelphia, pp. 421–434.
Morand-Fehr, P., Sauvant, D., 1978. Nutrition and optimum performance of dairy goats. Liv. Prod. Sci. 5, 203–213.
Morand-Fehr, P., Sauvant, D., 1980. Composition and yield of goat milk as affected by nutritional manipulation. J. Dairy Sci. 63, 1671–1680.
Muhlhausler, B.S., Roberts, C.T., Yuen, B.S., Marrocco, E., Budge, H., Symonds, M.E., McFarlane, J.R., Kauter, K.G., Stagg, P., Pearse, J.K., McMillen, I.C., 2003. Determinants of fetal leptin synthesis, fat mass, and circulating leptin concentrations in well-nourished ewes in late pregnancy. Endocrinology 144, 4947–4954.
Navarro, M., Cristofol, C., Carretero, A., Arboix, M., Ruberte, J., 1998. Anthelmintic induced congenital malformations in sheep embryos using netobimin. Vet. Rec. 142, 86–90.
Noakes, D., 2003. Pregnancy and its diagnosis. In: Noakes, D.E., Parkinson, T.J., England, G.C.W. (Eds.), Arthur's Veterinary Reproduction and Obstetrics. Saunders, Philadelphia, pp. 167–189.
Oetzel, G.R., 2004. Monitoring and testing dairy herds for metabolic disease. Vet. Clin. N. Am. Food Anim. Pract. 20, 651–674.
Oliver, M.H., Harding, J.E., Breier, B.H., Gluckman, P.D., 1996. Fetal insulin-like growth factor (IGF)-I and IGF-II are regulated differently by glucose or insulin in the sheep fetus. Reprod. Fertil. 8, 167–172.
Oliver, M.H., Hawkins, P., Breier, B.H., Van Zijl, P.L., Sargison, S.A., Harding, J.E., 2001. Maternal undernutrition during the periconceptual period increases plasma taurine levels and insulin response to glucose but not arginine in the late gestational fetal sheep. Endocrinology 142, 4576–4579.
Oliver, M.H., Hawkins, P., Harding, J.E., 2005. Periconceptional undernutrition alters growth trajectory and metabolic and endocrine responses to fasting in late-gestation fetal sheep. Pediatr. Res. 57, 591–598.

Orskov, E.R., 1982. Very intensive systems. In: Coop, I.E. (Ed.), Sheep and Goat Production. Elsevier, Amsterdam, pp. 401–416.
Ostergaard, S., Sorensen, L.T., Houe, H., 2003. A stochastic model simulating milk fever in a dairy herd. Prev. Vet. Med. 58, 125–143.
Owens, J.A., Owens, P.C., Robinson, J.S., 1995. Experimental restriction of growth. In: Hanson, M.A., Spencer, J.A.D., Rodeck, C.H. (Eds.), The Fetus and Neonate,. Growth, vol. 3. Cambridge University Press, Cambridge, pp. 139–175.
Panousis, N., Brozos, C., Fthenakis, G.C., Karatzias, C., 2001. Pregnancy toxaemia of ewes. A literature review. J. Hell. Med. Vet. Soc. 52, 89–96.
Panousis, N., Brozos, C., Karagiannis, I., Giadinis, N.D., Lafi, S., Kritsepi-Konstantinou, M., 2012. Evaluation of Precision Xceed® meter for on-site monitoring of blood β-hydroxybutyric acid and glucose concentrations in dairy sheep. Res. Vet. Sci., doi:10.1016/j.rvsc.2011.06.019.
Parr, R.A., Cumming, I.A., Clarke, I.J., 1982. Effects of maternal nutrition and plasma progesterone concentrations on survival and growth of the sheep embryo in early gestation. J. Agric. Sci. 98, 39–46.
Petridis, I.G., Mavrogianni, V.S., Fragkou, I.A., Gougoulis, D.A., Tzora, A., Fotou, K., Amiridis, G.S., Brozos, C., Fthenakis, G.C., 2011. Effects of drying-off procedure of ewes' udder in subsequent mammary infection and development of mastitis. In: Proceedings of European Conference Small Ruminant Health Management, Athens, Greece, p. 37.
Phillips, J.D., Fonkalsrud, E.W., Mirzayan, A., Kim, C.S., Kieu, A., Zeng, H., Diamond, J.M., 1991. Uptake and distribution of continuously infused intraamniotic nutrients in fetal rabbits. J. Pediatr. Surg. 26, 374–378.
Pitkin, R.M., Reynolds, W.A., 1975. Fetal ingestion and metabolism of amniotic fluid protein. Am. J. Obst. Gynecol. 123, 356–363.
Ptak, G., Clinton, M., Tischner, M., Barboni, B., Mattioli, M., Loi, P., 2002. Improving delivery and offspring viability of in vitro-produced and cloned sheep embryos. Biol. Reprod. 67, 1719–1725.
Rassu, S.P.G., Enne, G., Ligios, S., Molle, G., 2004. Nutrition and reproduction. In: Pulina, G. (Ed.), Dairy Sheep Nutrition. CABI Publishing, Wallingford, pp. 109–128.
Rawlings, N.C., Bartlewski, P.M., 2007. Clinical reproductive physiology of ewes. In: Youngquist, R.S., Threlfall, W.R. (Eds.), Current Therapy in Large Animal Theriogenology. Saunders, Philadelphia, pp. 642–649.
Rawlings, N.C., Howell, W.E., 1988. The use of estradiol benzoate to manage lambing period in ewes bred at synchronized estrus. J. Anim. Sci. 66, 851–854.
Roche, J.R., 2003. The incidence and control of hypocalcaemia in pasture-based systems. Acta Vet. Scand. (Suppl. 97), 141–144.
Rommereim, D.N., Slyter, A.L., 1981. Effect of day of gestation on induction of lambing with flumethasone. J. Anim. Sci. 53, 564–566.
Rumball, C.W.H., Harding, J.E., Oliver, M.H., Bloomfield, F.H., 2008. Effects of twin pregnancy and periconceptional undernutrition on maternal metabolism, fetal growth and glucose–insulin axis function in ovine pregnancy. J. Physiol. 586, 1399–1411.
Sahin, O., Plummer, P.J., Jordan, D.M., Sulaj, K., Pereira, S., Hoffman, L.J., Zhang, O., 2008. Emergence of a tetracycline-resistant *Campylobacter jejuni* clone associated with outbreaks of ovine abortion in the United States. J. Clin. Microbiol. 46, 1663–1671.
Samadi, A., Ababneh, M.M., Giadinis, N.D., Lafi, S.Q., 2010. Ovine and caprine brucellosis (Brucella melitensis) in aborted animals in Jordanian Sheep and goat flocks. Vet. Med. Int., 458695.
Saratsis, P., Alexopoulos, C., Tzora, A., Fthenakis, G.C., 1999. The effect of experimentally induced subclinical mastitis on the milk yield of dairy ewes. Small Rumin. Res. 32, 205–209.
Saratsis, P., Leontides, L., Tzora, A., Alexopoulos, C., Fthenakis, G.C., 1998. Incidence risk and aetiology of mammary abnormalities in dry ewes in 10 flocks in Southern Greece. Prev. Vet. Med. 37, 1–4.
Sargison, N.D., 2007. Pregnancy toxaemia. In: Aitken, I.D. (Ed.), Diseases of Sheep,. , 4th ed. Blackwell, Oxford, pp. 359–363.
Sargison, N., 2009. Sheep Flock Health. Blackwell, Oxford, 465 pp.
Scott, P.R., 2011. Treatment and control of respiratory disease in sheep. Vet. Clin. N. Am. 27, 175–186.
Scott, P.R. Applications of diagnostic ultrasonography in small ruminant reproductive management. Anim. Reprod. Sci., doi:10.1016/j.anireprosci.2012.01.013, this issue.
Scott, P.R., Sargison, N.D., 2010. Ultrasonography as an adjunct to clinical examination in sheep. Small Rumin. Res. 92, 108–119.
Scwimmer, A., Keningswald, G., Van Straten, M., Lavi, Y., Merin, U., Weisblit, L., Leitner, G., 2008. Dry-off treatment of Assaf sheep: efficacy as a management tool for improving milk quantity and quality. Small Rumin. Res. 74, 45–51.
Shneider, H., 1996. Ontogenic changes in the nutritive function of the placenta. Placenta 17, 15–26.
Sir, C., Bartlewski, P.W., 2010. Analyses of parental and seasonal influences on the synchrony of dexamethasone-induced lambing and lamb characteristics. Liv. Sci. 131, 119–124.
Skjevdal, T., 1982. Nutrient requirements of dairy goats based on Norwegian research. In: Proceedings of the 3rd International Conference in Goat Production and Disease, Tuscon, USA, pp. 105–108.
Sorensen, J.T., Ostergaard, S., Houe, H., Hindhede, J., 2002. Expert opinions of strategies for milk fever control. Prev. Vet. Med. 55, 69–78.
Spanu, C., Berger, Y.M., Thomas, D.L., Ruegg, P.L., 2011. Impact of intramammary antimicrobial dry 1 treatment and teat sanitation on somatic cell count and intramammary infection in dairy ewes. Small Rumin. Res. 97, 139–145.
Spencer, T.E., Bazer, F.W., 2004. Uterine and placental factors regulating conceptus growth in domestic animals. J. Anim. Sci. 82, E4–E13.
Spencer, T.E., Johnson, G.A., Bazer, F.W., Burghardt, R.C., 2004. Implantation mechanisms: insights from the sheep. Reproduction 128, 657–668.
Spencer, T.E., Johnson, G.A., Bazer, F.W., Burghardt, R.C., 2007. Fetal-maternal interactions during the establishment of pregnancy in ruminants. Soc. Reprod. Fertil. (Suppl. 64), 379–396.
Spencer, T.E., Sandra, O., Wolf, E., 2008. Genes involved in conceptus–endometrial interactions in ruminants: insights from reductionism and thoughts on holistic approaches. Reproduction 135, 165–179.
Stampoulis, D., Giadinis, N.D., Papanastassopoulou, M., Kritas, S.K., 2010. Novel views upon the treatment and prevention of contagious ecthyma (orf) infection in small ruminants: with emphasis upon the problem in Greek sheep and goat production. J. Hell. Vet. Med. Soc. 61, 351–358.
Stournara, A., Minas, A., Bourtzi-Chatzopoulou, E., Stack, J., Koptopoulos, G., Petridou, E., Sarris, K., 2007. Assessment of serological response of young and adult sheep to conjunctival vaccination with Rev-1 vaccine by fluorescence polarization assay (FPA) and other serological tests for *B. melitensis*. Vet. Microbiol. 119, 53–64.
Strang, B.D., Bertics, S.J., Grummer, R.R., Armentano, L.E., 1998. Effect of long-chain fatty acids on triglyceride accumulation, gluconeogenesis and ureagenesis in bovine hepatocytes. J. Dairy Sci. 81, 728–739.
Tamasia, M., 2007. Pregnancy diagnosis in the ewe. In: Schatten, H., Constantinescu, M.G. (Eds.), Comparative Reproductive Biology. Blackwell, Philadelphia, pp. 337–342.
Taverne, M., Noakes, D.E., 2009. Pregnancy and its diagnosis. In: Noakes, D.E., Parkinson, T.J, England, G.C.W. (Eds.), Veterinary Reproduction and Obstetrics. , 9th ed. Saunders, Edinburgh, pp. 76–122.
Tedeschi, L.O., Cannas, A., Fox, D.G., 2010. A nutrition mathematical model to account for dietary supply and requirements of energy and other nutrients for domesticated small ruminants: the development and evaluation of the small ruminant nutrition system. Small Rumin. Res. 89, 174–184.
Thomas, L., Wallace, J.M., Aitken, R.P., Mercer, J.G., Trayhurn, P., Hoggard, N., 2001. Circulating leptin during ovine pregnancy in relation to maternal nutrition, body composition and pregnancy outcome. J. Endocrinol. 169, 465–476.
Todd, S.E., Oliver, M.H., Jaquiery, A.L., Bloomfield, F.H., Harding, J.E., 2009. Periconceptional undernutrition of ewes impairs glucose tolerance in their adult offspring. Pediatr. Res. 65, 409–413.
Tsiligianni, T., Ntovolou, E., Amiridis, G.S., 2008. Synchronization of lambing with low doses of dexamethasone in Chios ewes—Short Communication. Acta Vet. Hung. 56, 393–397.
Uzal, F.A., Wong, J.P., Kelly, W.R., Priest, J., 1999. Antibody response in goats vaccinated with liposome-adjuvanted *Clostridium* perfringents type D epsilon toxoid. Vet. Res. Commun. 23, 143–150.
Vatn, S., Tranulis, M.A., Hofshagen, M., 2000. Sarcina-like bacteria, *Clostridium fallax* and *Clostridium sordellii* in lambs with abomasal bloat, haemorrhage and ulcers. J. Comp. Pathol. 122, 193–200.
Venter, J.L., Greyling, J.P.C., 1994. Effect of different periods of flushing and synchronized mating on body weight, blood glucose and reproductive performance in spring-mated ewes. Small Rumin. Res. 13, 257–261.
Yuen, B.S., Owens, P.C., McFarlane, J.R., Symonds, M.E., Edwards, L.J., Kauter, K.G., McMillen, I.C., 2002. Circulating leptin concentrations are positively related to leptin messenger RNA expression in the adipose tissue of fetal sheep in the pregnant ewe fed at or below maintenance energy requirements during late gestation. Biol. Reprod. 67, 911–916.