



Multidirectional Changes in the Blood Cholesterol in Mammals of Different Species during Pregnancy and Lactation

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Abstract

The aim of this review is to summarize the data on cholesterol variations in animals of different species during pregnancy and lactation period. The physiological hypercholesterolemia of late pregnancy in many species, including rats, heterozygous Watanabe heritable hyperlipidemic rabbits, dogs, sheep, goats, deer and pregnant women are not common. The concentration of serum cholesterol in some mammals (e.g. rabbits, guinea pigs, buffaloes, cows, baboon and monkey) gradually decreased to the end of pregnancy. Why cholesterol is increased in some mammals during pregnancy and it decreases in other animals? Its changes are necessary or not for female organism? In this review, we have demonstrated the need for physiological changes of cholesterol in animals during the breeding season. We have tried to summarize the factors that are responsible for the cholesterol level fluctuations in females of different species at certain stages of the reproductive cycles.

Keywords: Blood Cholesterol; Mammals; Pregnancy; Lactation.

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1. Introduction

Cholesterol is an important sterol in mammals. It participates in many physiological processes, including the formation of cell membranes and regulates signal transduction in the cells. Cholesterol is required for normal cell function and it is essential for the structural integrity of the cell membranes. Increasing concentration of cholesterol decreases the membrane fluidity and thereby controls or regulates the permeability of the cell membrane. Cholesterol is also required for differentiation of cells, their proliferation and interaction, development of the embryo and fetus. It is essential for the synthesis of progesterone and estradiol, hormones that actively participate to sustain pregnancy. It is known that the level of total cholesterol (T-chol) may have important long-term regulatory effect on steroidogenesis in the ovaries [1].

Physiological and metabolic adaptations in organism of animals have place during reproductive cycle. Internal redistribution of substrates under hormonal control is the main characteristic of metabolic adaptations to pregnancy or lactation. The concentration of cholesterol in the blood can be regulated by the following processes: its absorption from food, endogenous synthesis in the liver, excretion of neutral steroids and bile acids from the body and/or its absorption and release from tissues. The dynamics of cholesterol in mammals of different species depends on the stage of the reproductive cycle [2-9]. It is considered that the achievement of the necessary levels of cholesterol is essential to maintain pregnancy and optimal fetal development [10-13]. The results of studies of various mammalian species, including humans, during pregnancy showed an increase T-chol in blood serum of some mammals in late pregnancy compared with the beginning [9-15].

The concentration of T-chol in rabbits, guinea pigs, cows, non-human primates decreases gradually toward the end of pregnancy [5, 16-25] and rises during postpartum (lactation) period. All of these differences may be related to the level of metabolism in the body of different animals and with necessary changes of the metabolic demands of the fetus. Changes in the level of cholesterol in females in the postpartum period may be due to its direct participation in the reproductive processes and intensive use in the synthesis of milk. Mechanisms by which some factors increase T-chol in blood of different animals during pregnancy or lactation period are not well understood.

The purpose of this review is to summarize data on multidirectional fluctuations of cholesterol in animals of different species during pregnancy or lactation and identify conditions that may contribute to the increase or decrease in blood cholesterol levels.

1.1. Pregnancy-induced hypercholesterolemia in some mammals at the end of pregnancy

Hyperlipidemia is defined as an excessive concentration of cholesterol or triglyceride or both in blood. It is considered that changes in lipid metabolism during pregnancy should contribute to the accumulation of fat reserves in the body of the female in the first half and increase the mobilization of these reserves at the end of pregnancy [8, 26-28]. Cholesterol plays a key role in the development of the embryo and fetus, therefore, the demand for it during pregnancy and, especially in late pregnancy is relatively high. Hyperlipidemia in some animals during normal pregnancy reflects metabolic requests at this stage of life [8, 12].

Pregnant rats had a high cholesterol concentration on 18-19 days of gestation [29]. An elevation of serum lipids in rats McKay and Kaunitz [30] observed on the 21st day of pregnancy (their gestational length). Dannenburg and his colleagues [31] showed that this hyperlipemia of pregnancy disappears rapidly in postpartum non-lactating rats.

Pregnancy in heterozygous Watanabe heritable hyperlipidemic (WHHL) rabbits (an animal model of human lipoprotein disorders, these rabbits exhibit strong hypercholesterolaemia), like in human beings may induce hyperlipidemia, which is opposite to the effects observed in normal rabbits or homozygous WHHL rabbits [32].

T-chol concentration in blood plasma of the dogs is markedly increased in later stages of pregnancy, as compared to non-pregnant animals [9].

Some researchers reported that serum T-chol and triglyceride concentrations were higher in pregnant compared to non-pregnant sheep [33-34]. Pregnancy had a significant impact on the T-chol in Iranian fat-tailed sheep: its level increased from 0.60 ± 0.12 to 1.51 ± 0.25 mmol / L in the end of pregnancy [35]. A week before parturition, its concentration was higher than after it. The lowest cholesterol was observed 2-3 weeks after parturition during lactation [35]. This data is in agreement with results of studies of Rawal and his colleagues [36], Krajnicáková and his colleagues [37] and Ozpinar and Firat [38].

The concentration of T-chol was higher in pregnant goats compared to non-pregnant animals: marked increase its level is in the second trimester at the 9-10th week of the pregnancy [39]. A low level of T-chol in goats noted on the 10th day after delivery: 0.95 ± 0.21 mmol / L compared to 1.65 ± 0.42 mmol / L in 7 days before delivery [40].

It is shown the highest concentration of T-chol in healthy ponies in late pregnancy [41]. After foaling, its quantity in their blood plasma remains high. T-chol concentration in the blood of females red deer similar results Knox and his colleagues [42] and Marco and Lavin [43], and these serum levels of female fallow deer corresponds to parameters for adult fallow deer [44]. The cholesterol concentrations were significantly higher in pregnant females of red, *Cervus elaphus*, and fallow deer, *Dama dama*, than in animals from non-pregnant group [45].

It is possible that high cholesterol is needed to maintain the increased production of hormones during pregnancy. The observed higher cholesterol during pregnancy can also be secondary to an increase of hormones associated with pregnancy.

1.2. Decreasing cholesterol in the blood of some mammals during second part of pregnancy

Study the dynamic of cholesterol in the blood of rabbits during pregnancy performed Baumann and Holly [16], who noted a marked decrease in its concentration in these animals during the second part of pregnancy, in contrast to mammalian species listed above. During lactation cholesterol gradually is elevated to values that determined in non-pregnant or non-lactating animals [22]. Ho and his colleagues [19] reported a very low concentration of serum cholesterol in rabbits at the end of pregnancy. The concentration of cholesterol in New

Zealand white rabbits decreased gradually to 25-28 day gestation. Cholesterol at the 28th day of pregnancy of these animals was lower by 91% in comparison with its level in the blood of non-pregnant rabbits [24].

These data were confirmed Zilversmit and his colleagues [4], who showed that other types of plasma lipids were decreased in maternal plasma, and even in rabbits fed a cholesterol additive noted manifestation of hypolipidemic effect to the end of pregnancy. Popjak [46] rejected the hypothesis Baumann and Holly [16] that lower concentration of maternal serum lipids depends on of its use by the growing fetus. Instead, he suggested that hormonal or some other factor associated with pregnancy is responsible for the transfer of cholesterol from the blood into the tissues of animals. Possible mechanisms to explain the difference in the values of T-chol changes in pregnant rabbits may be related to its increased accumulation in the tissues, transporting cholesterol of mother in fetuses, increased excretion in the feces [47] or the high activity of the thyroid gland [48-49].

T-chol concentration in blood plasma of guinea pigs decreased markedly at day 25 of pregnancy and remained low until the end [23]. This hypolipidemia of pregnancy in the guinea pig may appear due to the increased turnover of plasma lipoprotein and it is very different from well-characterized hyperlipidemia during pregnancy in rats and women [23].

In principle, the reduction of plasma cholesterol in pregnant animals may result from:

- 1) hemodilution,
- 2) reduce the secretion of lipoproteins from the liver and other organs that normally produce them,
- 3) transport of cholesterol from the body to the female fetus,
- 4) increased use of cholesterol for biosynthesis of steroid hormones,
- 5) accumulation of cholesterol in the tissues of the female body,
- 6) increased excretion of sterols or bile acids in the feces,
- 7) decreased absorption of cholesterol from food [4], in the case of inclusion of cholesterol in the animal feed.

For both New Zealand white and heterozygous WHHL rabbits, progressive hypocholesterolemia of gestation was associated with parallel changes in the lipid transfer activity (LTA) [6, 50]. Blood plasma of rabbit and human contains lipid-protein complexes that transporting cholesterol esters and triglycerides, as well as taking part in the transport of lipids into and out of cells. Furthermore, a rapid rise in plasma cholesterol of postpartum animals is accompanied by increased activity of LTA in white and heterozygous rabbits. The results of these studies show that the concentration of plasma cholesterol and LTA activity in the rabbit are closely linked, and this dependence can be determined not only by coordinated secretion of cholesterol and LTA in the liver [6, 50].

Differences in the concentration of cholesterol in rabbits and women during pregnancy can not be explained only the using of a vegetarian diet. Mullick and his colleagues [26] showed an increase in the concentration of cholesterol in women on a vegetarian diet at the end of pregnancy. A slight reduction in cholesterol observed in the baboons during pregnancy [51]. Decrease cholesterol in pregnant monkey (*Macaca mulatta*) has been reported by Wolf and his colleagues [17] and by Martin and his colleagues [18]. Cholesterol in the blood of African green monkeys (*Cercopithecus aethiops*) reaches a minimum level during pregnancy [20]. Results of Kessler and Rawlins [5] show a reduction in T-chol during pregnancy in the Cayo Santiago rhesus macaques.

It was observed a decrease of cholesterol concentration in serum blood of buffalo during the last months of pregnancy compared with its level in lactating non-pregnant animals [52-53]. T-chol concentration in serum was minimal at parturition and then increased during lactation.

The changes of the concentration of serum cholesterol in the blood of cows during the reproductive cycle were determined [25, 54-55]. Its maximum values we observed before fertilization and in early pregnancy (30th days), and minimum values - in the last months of pregnancy, closer to parturition (Table 1.). Concentrations of cholesterol in cows before calving were higher than the values reported by Skotnicka and his colleagues [40] in goats and Nazifi and his colleagues in sheep [35].

A large number of researchers have reported about fluctuations of metabolites circulating in blood of females during gestation, in most cases, these changes are regarded as indicators of the total amount of metabolites in circulation flow.

It is considered that the volume of the biological fluid in which the metabolites are diluted is constant during pregnancy. However, the results on the T-chol concentration in ruminants during the last stage of pregnancy could have been attributed to the hemodilution effect resulting from an increase in plasma volume. This phenomenon was also observed in pregnant Danish landrace goats [56] and Baladi goats during late pregnancy [57]. The observed increase in blood volume (hemodilution) in ruminants during late gestation has physiological importance since it reduces the viscosity of the blood and significantly increases blood flow in small blood vessels [58]. Thus, hemodilution may improve the blood flow through placental blood vessels, especially in late pregnancy to increase the transfer of nutrients and oxygen to the fetus.

As blood volume increases during pregnancy moderate decrease in the concentration of some hematological and biochemical parameters are normal. Increased blood volume in females serves two purposes.

First, it is necessary for additional blood flow to the uterus, to meet elevated metabolic demands of the fetus and increase the perfusion of other organs, especially the kidneys. Second, it reduces the impact of the female blood loss on the organism during parturition.

The average increase in blood volume in women at the end pregnancy is 45-50% [59]. Zilversmit and his colleagues [4] reported an increase in plasma volume of 40% in rabbits on day 28 of pregnancy. With an increase in blood volume by the end of pregnancy in rabbits cholesterol did reduced, and for women it reaches the maximum values.

Table 1: Total cholesterol in serum blood of Kholmogorus cows at certain stages of reproductive cycle

Study period	Examined animals	Total cholesterol, mmol/L
Before calving	10	3.14±0.17
Postpartum period, 10 days	14	3.88±0.23*
Postpartum period, 35 days	31	5.34±0.19**
Before fertilization	39	5.83±0.18
Pregnancy, 30 days	20	6.42±0.24*

*Note: * $p < 0.05$ and ** $p < 0.001$ compared with the cholesterol level in cows during previous stage of reproductive cycle*

1.3. Conclusion

It's possible to conclude from this review that the profile of T-chol in the blood of mammals of different species at certain stages of the reproductive cycle indicates the differences between species and within species. Passage of pregnancy and lactation of females accompanied by complex metabolic rearrangements that affect cholesterol metabolism and its concentration. We must take into account the fact the cholesterol is practically absent in food of all herbivorous mammals. This means that the specificity of its metabolism in these animals is determined mainly by changing its endogenous synthesis. Despite the significant differences in the level of cholesterol in the blood of various animals during pregnancy and the postpartum period, which have been studied in details, many questions remain unanswered, including the peculiarities of its metabolism, as well as the relevance of significant fluctuations in cholesterol level during pregnancy or lactation.

Finally, for the accurate interpretation of results for the cholesterol concentration in the blood of females, which are used as animal models in research laboratories, should be considered clinical norm of its concentrations at certain stages of the reproductive cycle. This can be the basis for the early prediction of possible changes and the use of measures for the timely prevention of diseases. It is important to determine the physiological mechanisms of cholesterol changes in different animals during the breeding season, and the reasons for significant fluctuations in its level during pregnancy or lactation. We hope that this will be the subject of future research.

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