BOOTS FOR ACHILLES: PROGESTERONE'S REDUCTION OF CHOLESTEROL IS A SECOND-ORDER ADAPTATION

Dorsa Amir

Center for Behavior, Evolution, and Culture, Department of Anthropology,
University of California, Los Angeles
Los Angeles, California 90095-1553 USA

e-mail: dorsaamir@gmail.com

Daniel M. T. Fessler

Center for Behavior, Evolution, and Culture, Department of Anthropology,
University of California, Los Angeles
Los Angeles, California 90095-1553 USA

e-mail: dfessler@anthro.ucla.edu

abstract

Progesterone and cholesterol are both vital to pregnancy. Among other functions, progesterone downregulates inflammatory responses, allowing for maternal immune tolerance of the fetal allograft. Cholesterol, a key component of cell membranes, is important in intracellular transport, cell signaling, nerve conduction, and metabolism. Despite the importance of each substance in pregnancy, one exercises an antagonistic effect on the other, as periods of peak progesterone correspond with reductions in cholesterol availability, a consequence of progesterone's negative effects on cholesterol biosynthesis. This arrangement is understandable in light of the threat posed by pathogens early in pregnancy. Progesterone-induced immunomodulation entails increased vulnerability to infection, an acute problem in the first trimester, when fetal development is highly susceptible to insult. Many pathogens rely on cholesterol for cell entry, egress, and replication. Progesterone's antagonistic effects on cholesterol thus partially compensate for the costs entailed by progesterone-induced immunomodulation. Among pathogens to which the host's vulnerability is increased by progesterone's effects, approximately 90% utilize cholesterol, and this is notably true of pathogens that pose a risk during pregnancy. In addition to having a number of possible clinical applications, our approach highlights the potential importance of second-order adaptations, themselves a consequence of the lack of teleology in evolutionary processes.

Introduction

CHOLESTEROL and progesterone each play a vital role in pregnancy. Intriguingly, despite the importance of each, the latter exercises an antagonistic effect on the availability of the former. Here, we ar-

gue that this puzzling arrangement reflects an evolved second-order adaptation, that is, an adaptation that addresses an adaptive challenge that is itself a consequence of the effects of another adaptation. Consider the following: it is well documented that cholesterol plays an important role in fetal development (Brizzi et al. 1999; Innis 2005; Woollett 2011). Although maternal triglycerides cannot directly cross the placental membrane, free fatty acids and ketones produced from those trigylcerides can cross the barrier, and are utilized by the fetus as both fuels and lipogenic substrates (Brizzi et al. 1999). It has been shown that when maternal plasma cholesterol is low (<160 mg/dL), birthweights are lower than normal, and there is a trend for microcephaly (Edison et al. 2007), suggesting that, although the fetus can also metabolize its own cholesterol, its capacity in this regard is limited and, hence, inadequate transfer of maternal cholesterol components negatively impacts fetal growth (Woollett 2011). Correspondingly, low intakes of specific fatty acids by the mother during gestation can result in decreased neural growth cones in the fetal brain, liver, and the placenta (Innis 2005). Paralleling the importance of cholesterol, the ovarian hormone progesterone, vital for the success of pregnancy, is unequivocally required in all mammals for maternal support of conceptus survival and development (Spencer and Bazer 2002). Progesterone is essential to several important events in the establishment of pregnancy, including ovum transport, endometrial cell proliferation, differentiation, decidualization, and the process of implantation. It is also vital for the maintenance of pregnancy, and a loss of progesterone is causally associated with miscarriage in early pregnancy (Macdonald 1989). It is therefore striking that a characteristic action of progesterone is its reduction of cholesterol. Progesterone has been shown to inhibit the esterification of cholesterol derived from low-density lipoproteins (LDLs), preventing its delivery to cellular enzymes (Metherall et al. 1996). Treatment of cholesterol with progesterone also causes the accumulation of sterol precursors, implying that cholesterol pro-

duction pathways are disrupted (Lindenhall et al. 2001). Indeed, progesterone disrupts pathways involved in both cholesterol biosynthesis and the processing of LDL-derived cholesterol (Lindenhall et al. 2001).

Why would a hormone that is intimately linked to successful pregnancy cause a reduction in the availability of a building block needed for fetal development? Although seemingly paradoxical, we suggest that this relationship constitutes a compromise solution to a problem that arises due to tradeoffs inherent in pregnancy. We review the respective roles of cholesterol and progesterone, describe the effects of progesterone on cholesterol availability, delineate the potential costs of this interaction, and then outline the benefits (in the form of reduced vulnerability to pathogens) that we hypothesize outweigh these costs.

THE FUNCTIONS OF CHOLESTEROL AND ITS ROLE IN FETAL DEVELOPMENT

Cholesterol, a lipid molecule with a characteristic four-ring steroid structure (Yoshida and Wada 2005), is vital to life. It is required as the structural component of mammalian cell membranes, helping to maintain proper permeability and fluidity (Yeagle 1985). Cholesterol also functions in intracellular transport, cell signaling (Maxfield and Tabas 2005), and nerve conduction (Saher et al. 2011). It is a fundamental mediator of metabolism through the propagation of signaling cascades and is essential to both the activation and propagation of hedgehog signaling (Woollett 2005). Additionally, cholesterol is the precursor for other necessary compounds, such as steroid hormones, bile acids, and vitamin D (Lecerf and de Lorgeril 2011), and is a significant component of lipid rafts in the plasma membrane, which serve as organizing centers for the assembly of signaling molecules (Rosenberger et al. 2000). Lipid rafts themselves play multiple functions, including polarized secretion, membrane transport, transcytosis across epithelial monolayers, and the generation of cell polarity (Rosenberger et al. 2000). Two types of lipoproteins are associated with cholesterol: high-density lipoproteins (HDLs) and low-density lipoproteins

(LDLs). These function in the transport of cholesterol throughout the body. LDLs assist in the transport of cholesterol out of the liver, while HDLs act as acceptors of cholesterol and are believed to bring fat and cholesterol back to the liver (Grummer and Carroll 1988; Assmann and Gotto 2004). Regulation of synthesis, influx, and efflux keeps cellular cholesterol levels tightly controlled (Simons and Ikonen 2000).

Reflecting its many important functions in the body, cholesterol is a vital factor in development. Cholesterol's relationship to the Sonic hedgehog (Shh) group of proteins entails an essential role in embryonic development, as these proteins are required for morphogenesis; cholesterol modulates the function of the Shh group by binding a functional Shh fragment and thereby restricting the distribution and activity of the Shh signal on the cell membrane (Yoshida and Wada 2005). Correspondingly, cholesterol deficits during embryogenesis cause severe abnormalities (Kolejáková et al. 2010). To take one example, Smith-Lemli-Opitz syndrome, caused by an inherited defect in a specific enzyme in the cholesterol biosynthesis pathway, is characterized by abnormal development and poor function, especially in cognition (Salen et al. 1996). This is further supported by evidence showing correlations between statin use in pregnancy and fetal neurological damage, and impaired placental implantation and function (Kenis et al. 2005; Pollack et al. 2005; Lockshin 2010).

Consonant with the above, reflecting the substantial need for cholesterol during this time of rapid growth, fetal sterol synthesis rates are greater than those in other extra-hepatic tissues (Woollett 2005). Importantly, however, although the fetus is able to synthesize its own cholesterol, because demand generally outstrips supply—such that maternal contribution is a limiting factor in fetal growth (Gluckman and Hanson 2004)—the fetus is dependent on maternal supply. Maternal cholesterol, in the form of lipoproteins, can enter into fetal circulation through uptake by the placenta and trophoblasts, via both receptor-mediated and receptor-independent transport (Wool-

lett 2005). Correspondingly, studies consistently reveal an intimate relationship between maternal cholesterol levels and healthy fetal development (Brizzi et al. 1999; Innis 2005; Woollett 2011).

PROGESTERONE-MEDIATED REDUCTIONS IN CHOLESTEROL DURING PREGNANCY, THE LUTEAL PHASE, AND MENOPAUSE

Early pregnancy is associated with a nadir in the mean value of serum cholesterol (Darmady and Postle 1982; Basaran 2009). Although cholesterol rises steadily through gestation, early in the first trimester there is an initial decrease in plasma lipids (Basaran 2009; Sep et al. 2011). Cholesterol levels eventually climb dramatically, but recovery from the initial decline is gradual, such that LDL levels at the end of the first trimester are often still within normal ranges (Brizzi et al. 1999); it is generally only by the beginning of the second trimester that cholesterol levels rise substantially above the pre-pregnancy baseline (Basaran 2009).

Importantly, the first-trimester decline in maternal cholesterol levels is not a consequence of utilization of maternal cholesterol by the conceptus, as total conceptus cell mass is small during the first-trimester cholesterol nadir and, moreover, the general pattern of cholesterol decline is not dependent on conception, as it also occurs during the luteal phase of menstrual cycles in which conception has not taken place. During the follicular phase of the menstrual cycle, total cholesterol levels peak (Kim and Kalkhof 1979; Ahumada Hemer et al. 1985; Jones et al. 1988), as do levels of LDL (Ahumada Hemer et al. 1985; Tikkanen et al. 1986). During the luteal phase, in which the endometrium is prepared for implantation, levels of both total serum cholesterol and triglycerides decline (De León et al. 1992). The luteal phase constitutes preparation for pregnancy and, correspondingly, pregnancy can be conceptualized as a continuation of changes present mid-luteally—declines in cholesterol thus occur in anticipation of, rather

than as a consequence of, the presence and growth of a conceptus.

Progesterone is the principal candidate for the cause of the decline in cholesterol in the luteal phase and the early first trimester. Progesterone remains at a relatively low level throughout the follicular phase and during ovulation, but increases sharply during the luteal phase (De León et al. 1992). In the event of conception and implantation, progesterone continues to climb across the first trimester (Tay and Lenton 2002). Importantly, progesterone's cholesterol-reducing effects are well established. Studies have shown that progesterone inhibits the delivery of LDL-derived cholesterol to processing enzymes such as acetyl-Coenzyme A acetyltranferase (ACAT; Metherall et al. 1996). Progesterone inhibits the movement of LDL-derived cholesterol from lysosomes to the plasma membrane (Plemenitas et al. 1990), and the movement of cholesterol from the plasma membrane to the endoplasmic reticulum (Lange 1994). This movement of sterols from the plasma membrane to the endoplasmic reticulum is required for cholesterol biosynthesis (Metherall et al. 1996); thus, progesterone's impediment of LDL-derived cholesterol movement in turn impedes cholesterol biosynthesis. Consistent with the disruption of cholesterol production pathways, treating tissue with progesterone leads to an accumulation of sterol precursors (Lindenhall et al. 2001). At the organismic level, exogenous progesterone has been shown to reduce HDL cholesterol both when administered through progestin-only oral contraceptives (Wynn and Niththyananthan 1982) and when administered through hormone-replacement therapies in postmenopausal women (Lamon-Fava et al. 2006).

Menopause is accompanied by a dramatic decline in progesterone levels and, consistent with the above portrait, across diverse populations, there is a corresponding increase in serum cholesterol during this period independent of the effects of age (Wu et al. 1990; Akahoshi et al. 1996; Matthews et al. 2009); correspondingly, surgical menopause has a similar effect (Akahoshi et al. 1996).

We are thus faced with the apparent contradiction that a hormone that is central to pregnancy causes a reduction in lipids that, being vital to cellular activity and cell division, are crucial to successful fetal development. To date, this question has not been explored. Several authors (Butte 2000; Toescu et al. 2002) have noted in passing that low cholesterol levels early in pregnancy correspond to an anabolic phase during which fat deposition is enhanced in anticipation of late pregnancy, when rapid fetal growth will require maternal catabolism. In this view, the initial reduction in gestational cholesterol levels is simply a side effect of the need to lay in energy stores for later. However, the ratio of cholesterol to triglycerides in fat cells is both constant and largely independent of cell size, indicating that both are likely deposited simultaneously in a fixed ratio (Kovanen et al. 1975)—a feature inconsistent with progesterone's disruption of cholesterol production. Hence, while there is conclusive evidence of a patterned shift from anabolism to catabolism across pregnancy, this pattern provides neither proximate nor ultimate explanations of the antagonistic effects of progesterone on cholesterol synthesis. Rather, we propose that the solution to this puzzle lies in the intersection of the effects of progesterone on the immune system and the role of cholesterol in infection.

PROGESTERONE-INDUCED IMMUNOMODULATION AND COMPENSATORY PROPHYLAXIS

With half of its genome being paternally derived, from the perspective of the maternal immune system, the conceptus constitutes a genetically incompatible allograft. As a consequence, changes must occur in the maternal immune system in order to prevent maternal lymphocytes from attacking the conceptus (Szekeres-Bartho et al. 1983). Pregnancy is facilitated by a shift in the Th1/Th2 balance in maternal immune functioning, a move away from those inflammatory responses that pose the greatest danger to the invasive blastocyst and the subsequently semiparasitic embryo (reviewed in Fessler 2002; Doyle et al. 2007;

Fleischman and Fessler 2011). Importantly, progesterone plays a central role in the immunomodulation necessary to tolerate the half-foreign conceptus (Siiteri et al. 1977). The downregulation of maternal inflammation is achieved through decreased levels of proinflammatory cytokines and natural killer cells. These changes are the downstream consequence of progesterone-induced blocking factor (PIBF), which shifts the maternal immunological balance toward anti-inflammatory signals (reviewed in Fessler 2001; see also Szekeres-Bartho et al. 1995; Doyle et al. 2007). Hence, progesterone is essential to pregnancy in part because it commands an immunomodulatory cascade that allows for tolerance of the half-foreign parasitic conceptus.

Maternal immune tolerance of the conceptus comes at a price as, by lowering host defenses, it increases the chances of infection (reviewed in Fessler 2001, 2002; Doyle et al. 2007). PIBF alters the cytokine secretion profile by increasing the production of Th2 cytokines and decreasing the production of Th1 cytokines (Faust et al. 1999). PIBF has also been shown to inhibit natural killer cell activity, through a blockade of degranulation (Faust et al. 1999). Both of these changes increase vulnerability to infection by lowering defenses in regard to both the detection and elimination of pathogens. Indeed, some pathogens may have evolved the ability to exploit this temporary weakening of host defenses; for example, progesterone not only increases the probability of infection by cytomegalovirus but, moreover, actually increases the pathogen's virulence (Chong and Mims 1984). Furthermore, increased maternal susceptibility to infection comes at a particularly dangerous time. Later in pregnancy the fetus eventually develops some autonomous defenses against pathogens, but these are absent early in development (Holt and Jones 2000). Moreover, the early first trimester is a critical period in fetal development, as organogenesis, concentrated during this phase, is a process that is especially vulnerable to insult (Arnold 1990) and, correspondingly, infection during the first trimester often can have drastic consequences (Wright 1966).

Progesterone's effects on the immune system clearly constitute an adaptation that serves to allow for gestation. Yet, this adaptation comes at the cost of increased susceptibility to infection during a particularly vulnerable period. Importantly, natural selection is not a teleological process—innovations that solve one problem can create another. Moreover, the liabilities entailed by one trait can, in turn, constitute a source of selective pressure leading to the evolution of new traits that mitigate the costs of these liabilities. Such second-order adaptations have been variously referred to as adaptive workarounds (Eastwick 2009) or the product of compensatory mutations (Maisnier-Patin and Andersson 2004). Of relevance to the matter at hand, recent evidence suggests that changes in other systems adaptively mitigate the vulnerability to pathogens entailed by progesterone's effects on the immune system. Specifically, alterations in behavior provide one avenue for such mitigation. The compensatory prophylaxis hypothesis holds that, because prophylactic behavior entails time, energy, attention, and opportunity costs, rather than remaining constant, prophylactic behavior should be enhanced during periods of increased susceptibility to infection, when the greater benefits obtained merit increased expenditures (Fessler and Navarrete 2003). Hence, because progesterone regulates a cascade of physiological events that result in increased vulnerability to infection, progesterone can be expected to also mediate increased behavioral prophylaxis (Fessler and Navarrete 2003). Consonant with this hypothesis, studies have shown increases in disgust sensitivity (a proximate mechanism subserving disease avoidance) during the vulnerable first trimester (Fessler et al. 2005). More specifically, disgust sensitivity, disease-avoidance behaviors, and related perceptions and attitudes all increase as a function of progesterone levels (Conway et al. 2007; Navarete et al. 2007; Fleischman and Fessler 2011; but see also Fessler and Navarrete 2003). Likewise, preferences for healthy over un-

healthy faces (a cue of disease risk) are elevated during periods of elevated progesterone (Jones et al. 2005). Although compensatory prophylaxis is behavioral, we believe that a similar logic explains the effects of progesterone on cholesterol, as the latter plays a central role in infection.

Cholesterol and Infection

Critically, cholesterol plays a key role in infection. Lipid rafts are sites of entry and exit for a wide variety of viruses (Medigeshi et al. 2008). Lipid rafts can be exploited by pathogens in a number of ways. Some viruses, such as human immunodeficiency virus type 1, coxsackievirus, simian virus 40, and severe acute respiratory syndrome coronavirus, depend on lipid rafts for binding to and entry into the host cell; other viruses, such as rotavirus, Newcastle disease virus, influenza virus, Ebola virus, and Marburg virus, utilize raft-mediated pathways for assembly and egress (Chazal and Gerlier 2003; Mañes et al. 2003; Ono and Freed 2005; Pelkmans 2005).

A number of bacteria similarly exhibit cholesterol dependence, including *Anaplasma phagocytophilum* (Xiong et al. 2009), *Escherichia coli* (Goluszko and Nowicki 2005), *Mycobacterium* (Gatfield and Pieters 2000), *Staphylococcus aureus* (Liu et al. 2008), *Salmonella* (Hayward et al. 2005), and *Shigella* (Hayward et al. 2005), among others. Some, such as *Mycobacterium tuberculosis*, utilize cholesterol as a primary carbon source throughout the course of infection, such that degradation of this sterol is crucial for bacterial persistence (Miner et al. 2009). In other cases, in species such as *Staphylococcus aureus* that do not use cholesterol as a significant energy source (Shine et al. 1993), disruption of cholesterol biosynthesis nevertheless blocks bacterial virulence (Liu et al. 2008), as cholesterol is a key component of the cytoplasmic membrane (Yeagle 1985). Cholesterol dependency can be a distinguishing feature of the pathogenic adaptations of bacteria; indeed, an entire family of bacterial cytolysins is referred to as cholesterol-dependent cytolysins (CDCs) because they can only function effectively in the presence of host cholesterol. These pore-forming toxins are produced by more than 20 species from the genera *Clostridium, Streptococcus, Listeria, Bacillus,* and *Arcanobacterium* (Tweten 2005). Cholesterol-dependent cytolysins function both as simple hemolysins and as general cell-lytic agents that are crucial in bacterial infection (Tweten 2005). Conversely, bacterial sepsis causes decreases in the concentrations of total cholesterol, HDL, and apoproteins A and B of patients; the return of serum lipids to more normal concentrations parallels the recovery from sepsis (Alvarez and Ramos 1986). Although at present there is no consensus as to why this correlation exists, it may be that hypocholesterolemia in cases of sepsis is a component of defensive responses (Das et al. 2011).

Consonant with the thesis that the availability of cholesterol is a determinant of the ability of pathogens to proliferate, intriguing indications are emerging regarding a relationship between statin therapy, which decreases cholesterol, and a lower incidence of severe sepsis (Almog 2003). Statins display antimicrobial effects in many studies. Both in vivo and in vitro, statins reduce the intracellular growth of a subspecies of *Salmonella enterica* (Catron et al. 2004), while simvastatin has shown a significant antimicrobial effect against MSSA and, to a lesser extent, against MRSA (Jerwood and Cohen 2008).

Given that cholesterol plays a role in infectious disease, it is tempting to ask whether epidemiological studies reveal a link between cholesterol and infection. However, before reviewing this evidence, it is important to note that it is difficult to predict in advance how such correlations will play out. On the one hand, pathogens' dependence on cholesterol suggests that we might expect a straightforward positive correlation between the host's systemic cholesterol levels and morbidity and mortality due to infection. On the other hand, if the body is able to facultatively adjust cholesterol levels as a function of the individual's capacity to resist infection, then the opposite pattern may obtain, as individuals who are vulnerable to pathogens for reasons other than cholesterol availability may both exhibit lower cholesterol

levels (reflecting an attempt to reduce vulnerability) and suffer higher rates of morbidity and mortality due to infection (reflecting the incomplete success of such efforts). Lastly, complicating the picture still further, it may be important to distinguish between different affordances of cholesterol from the perspective of the host. Although cholesterol facilitates infection and pathogen proliferation, once infection is established, cholesterol may sometimes benefit the host by reducing the destructive effects of endotoxins produced by some bacterial pathogens (Feingold et al. 1995; Ravnskov 2003). Accordingly, among individuals who are able to mount a robust immune response to infection, those having high cholesterol levels may suffer less pathogen-driven morbidity and mortality than those having low cholesterol levels.

Hospital studies reveal that low levels of HDL increase the probability of nosocomial infections (Delgado-Rodríguez et al. 1997; Canturk et al. 2002), and are predictors of in-hospital death and length of stay (Delgado-Rodríguez et al. 2002). These patterns are consistent with the thesis that cholesterol availability directly determines risk of infection, as HDL functions to transport excess cholesterol from the periphery to the liver for excretion into bile (Zhang et al. 2003), hence lower HDL levels equate to less reverse cholesterol transport and organ clearance, which, in turn, could conceivably lead to an increase in the amount of cholesterol available to pathogens elsewhere in the body. Conversely, however, outside of the hospital, among men, total cholesterol is inversely related to urinary tract, venereal, musculoskeletal, and all infections and, among women, to urinary tract, all genitourinary, septicaemia, bacteraemia, miscellaneous viral site unspecified, and all infections (Iribarren et al. 1998). Given the role of cholesterol in infection, the latter pattern strongly suggests that individual differences in cholesterol levels may reflect underlying differences in immunologic robustness, such that more vulnerable individuals maintain lower cholesterol levels in an incompletely successful

effort to compensate for their vulnerability to pathogens.

A less direct route to exploring the relationship between cholesterol levels and infection is to consider cholesterol's effects on overall mortality. One difficulty in interpreting such patterns is the question of how to evaluate the respective effects of cholesterol on susceptibility to infection and cardiovascular disease. Although conventional wisdom holds that cholesterol contributes directly to cardiovascular disease, consonant with the view advanced here, Ewald (2008) presents a strong case that this correlation actually reflects the role of cholesterol in facilitating infection by pathogens such as Chlamydia that, in turn, damage blood vessels. Nevertheless, given that this remains a minority view, it is conservative to evaluate the contributions of cholesterol to mortality independent of deaths due to cardiovascular disease. Although a number of studies have sought to elucidate the relationship between cholesterol and noncardiovascular mortality, at present there is no consensus in the literature in this regard. Age may be an important factor. In adults over the age of 85, high total cholesterol concentrations are associated with longevity, seemingly from lower mortality due to cancer and infection (Weverling-Rijnsburger et al. 1997). A similar pattern of the protective effects of cholesterol has also been found among adults older than 55, who evince an inverse relationship between total cholesterol and several infectious diseases (Iribarren et al. 1998). Conversely, studies of younger adults reveal that the effect of total cholesterol on noncardiovascular mortality is neutral (Kronmal et al. 1993; Krumholz et al. 1994; Gould et al. 1995). Another study finds a trend of increased noncardiovascular mortality with decreased LDL, in both placebo and treatment groups (Razzolini et al. 2008). However, at each given LDL cholesterol level, noncardiovascular mortality is lower in patients treated with statins (Razzolini et al. 2008).

To summarize the above, at the cellular level, there is substantial evidence that cholesterol can play a key role in infection. At

TABLE 1

Summary of survey of pathogens with regard to limiting and exacerbating cytokine responses, threat posed during pregnancy, and utilization of cholesterol

Pathogen	Limiting cytokine response	Exacerbating cytokine response	Threat during pregnancy	Cholesterol utility/ dependence?
Toxoplasma gondii	Th1: IL-12, IL-6, TNF-alpha (1, 2)	Th2: IL-4 (1, 2)	Early pregnancy (3)	Yes (4)
Escherichia coli	Th1: IL-1, IL-2, IFN-gamma (5)	Th2: IL-10 (6)	Early pregnancy (7)	Yes (8)
Brucella abortus, *Brucella* *melitensis*	Th1: IL-12, IFN-gamma, TNF-alpha (9)	Th2: IL-10, IL-4 (10)	Early pregnancy (83)	Yes (11)
Shigella dysenteriae	Th1: IL-8, IL-2 (12)		Early pregnancy (64)	Yes (13)
Campylobacter *jejuni*	Th1: TNF-alpha, IL-8 (14)		Early pregnancy (15)	Yes (16)
Mycobacterium	Th1 (19)	Th2 (19)		Yes (17)
Coxsackievirus B	Th1: IFN-gamma (20)	Th2 (20)	Early pregnancy (54)	Yes (35)
Lassa virus	Th1: IL-6, IL-1beta (29)		Third trimester (53)	Yes (18)
Poliovirus	Th1: IL-6, IL-8 (21), IFN response (24)			Yes (23)
CVB4	Th1: IFN-gamma (25)			Yes (26)
Helicobacter pylori	Th1: IFN-gamma (27)	Th2: IL-4 (28)		Yes (36)
Leishmania *donovani*	Th1: IFN-gamma, IL-12 (30)	Th2: IL-4, IL-5, IL-10 (30)		Yes (31)
Plasmodium *falciparum*	Th1: IFN-gamma (32), TNF-alpha (33)			Yes (37)
Ehrlichia *chaffeensis*	Th1: IFN-gamma (34)			Yes (38)
Salmonella enterica	Th1: IFN-gamma, TNF-alpha (39)	Th2: IgG1/IgE (40, 41)		Yes (42)
Semliki Forest virus	Th1 (44)	Anti-Th1: decreases in IL-12, IFN-gamma cause increased and prolonged infection (43)		Yes (45)
Epstein-Barr virus	Th1: IFN-gamma (46)	Th2 (47)		Yes (48)
Vesicular stomatitis virus	Th1 (49)			Yes (50)
Dengue virus	Th1: IFN-gamma (51)			Yes (52)
Varicella (Chickenpox)	Th1: IL-6 (57), IFN-gamma, IL-10, IL-12 (58)		Early pregnancy (59)	Yes (56)
Parvovirus	Th1: IL-10, IFN-gamma (60)		Early pregnancy (59)	Yes (61)
Rubella	Th1: IL-2, TNF-alpha (62)		Early pregnancy (59)	Yes. May depend on macropinocytosis for entry (69), which requires cholesterol (70)
Influenza virus	Th1: IL-6 (63)	Th2: IL-4 (64)	Early pregnancy (66)	Yes, decrease in infectivity when cholesterol depleted (65)

continued

TABLE 1
Continued

Pathogen	Limiting cytokine response	Exacerbating cytokine response	Threat during pregnancy	Cholesterol utility/ dependence?
Seasonal Influenza A (H1N1)	Mixed response: TNF-alpha, IL-6, IL-8, IL-15 (87)		Early pregnancy (86)	
Adenoviruses	Th1: IL-6, IL-8, TNF (67)		Early pregnancy (72)	Yes (71)
Respiratory Syncytial Virus	Th1 (68)	Th2: IL-4 (73)		Yes (74)
Anaplasma phagocytophilum	Th1: IFN-gamma (77)	Th2 (76)		Yes (75)
Listeria monocytogenes	Th1: IL-12 (79)		Early pregnancy (80)	Yes (78)
Clostridium perfringens	Th1: IL-10 (82)			Yes (81)
Leptospira	Th1: IL-12, TNF-alpha, IFN-gamma (85)			
Borna Virus	In acute infections, Th1: TNF-alpha, IL-2, IL-6, IFN-gamma (88) In chronic, switches to Th2 (88)			Yes (84)
Cytomegalovirus			Can damage fetus at any stage in pregnancy (55)	

References cited: (1) Thouvenin et al. 1997. (2) Suzuki 1999. (3) Beazley and Egerman 1998. (4) Portugal et al. 2008. (5) Chopra et al. 1997. (6) Zimmer et al. 1996. (7) Sechser et al. 1976. (8) Goluszko and Nowicki 2005. (9) Oliveira et al. 1998. (10) Fernandes et al. 1996. (11) Watarai et al. 2002. (12) Sansonetti et al. 1999. (13) Lafont et al. 2002. (14) Pancorbo et al. 1999. (15) Simor and Ferro 1990. (16) Wooldridge et al. 1996. (17) Gatfield and Pieters 2000. (18) Schlie et al. 2010. (19) Zhang et al. 1995. (20) Sepúlveda et al. 2005. (21) Dodd et al. 2001. (23) Danthi and Chow 2004. (24) Ida-Hosonuma et al. 2005. (25) Varela-Calvino et al. 2002. (26) Triantafilou and Triantafilou 2004. (27) Lindholm et al. 1998. (28) Smythies et al. 2000. (29) Hensley et al. 2011. (30) Murphy et al. 2001. (31) Pucadyil et al. 2004. (32) Hensmann and Kwiatkowski 2001. (33) Fievet et al. 2001. (34) Dumler et al. 2000. (35) Wong et al. 2006. (36) Niemelä et al. 1996. (37) Lauer et al. 2000. (38) Lin and Rikihisa 2003. (39) Lalmanach and Lantier 1999. (40) VanCott et al. 1998. (41) Raupach and Kaufmann 2001. (42) Nawabi et al. 2008. (43) Peltoniemi et al. 2002. (44) Fleeton et al. 1999. (45) Phalen and Kielian 1991. (46) Andersson 1996. (47) Jin et al. 2012. (48) Katzman and Longnecker 2003. (49) Oxenius et al. 1999. (50) Wang et al. 2009b. (51) Chaturvedi et al. 1999. (52) Martínez-Gutierrez et al. 2011. (53) Price et al. 1988. (54) Ornoy and Tenebaum 2006. (55) Morgan-Capner 1991. (56) Hambleton et al. 2007. (57) Wang et al. 2005. (58) Jenkins et al. 1998. (59) Ely et al. 2000. (60) Franssila and Hedman 2004. (61) Avrahami et al. 2008. (62) Dhiman et al. 2010. (63) Conn et al. 1995. (64) Moran et al. 1996. (65) Barman and Nayak 2007. (66) Lieberman et al. 2011. (67) Mistchenko et al. 1994. (68) Martinez-Sobrido et al. 2006. (69) Mercer and Helenius 2009. (70) Grimmer et al. 2002. (71) Imelli et al. 2004. (72) Arechavaleta-Velasco et al. 2008. (73) Hoebee et al. 2003. (74) Gower and Graham 2001. (75) Xiong et al. 2009. (76) Ogden et al. 2002. (77) Pedra et al. 2007. (78) Gekara et al. 2005. (79) Hsieh et al. 1993. (80) Wing and Gregory 2002. (81) Heuck et al. 2010. (82) Karlsson et al. 2002. (83) Khan et al. 2001. (84) Clemente et al. 2009. (85) Kimpel et al. 2003. (86) Lieberman et al. 2011. (87) Hagau et al. 2010. (88) Gluckman and Hanson 2004.

the population level, the picture is more mixed, possibly reflecting both complex relationships between cholesterol levels and immunological robustness and the effects of cholesterol on other aspects of health. Here, we are concerned with the possibility that patterned changes in systemic cholesterol can adaptively mitigate vulnerability to infection entailed by pro-

gesterone's effects on the immune system. Given the extent to which pathogens are dependent on cholesterol, if humans have indeed evolved mechanisms capable of such compensatory adjustment, then we should expect to find evidence of an evolutionary arms race between human hosts and a variety of pathogens, as each seeks to gain control of cholesterol availability in

order to determine the outcome of infection.

ARMS RACES BETWEEN HOST AND PATHOGENS OVER CHOLESTEROL REGULATION/SYNTHESIS

There appears to be a correlation between innate immune signaling processes and the regulation of sterol metabolism (Castrillo et al. 2003; Ogawa et al. 2005; Zelcer and Tontonoz 2006; Wang et al. 2009a). In keeping with the role of cholesterol in infection and the corresponding strategic value of its regulation, a relationship has been demonstrated between the cholesterol-metabolic pathway and protection against, or susceptibility to, infection (Blanc et al. 2011). Specifically, mammalian hosts produce high levels of interferons after infection with a range of viruses; in turn, via interferon receptors, high levels of interferons lower enzyme levels on the cholesterol pathway, resulting in a net reduction in cholesterol availability (Blanc et al. 2011). Host reduction of cholesterol as a defense mechanism is also observed in conjunction with the hepatitis C virus (HCV) (Walters et al. 2006). However, in keeping with the advantages to the pathogen of cholesterol abundance, HCV counters this move by impairing lipid metabolism and causing an unregulated increase in cholesterol and fatty acid synthesis (Nakamuta et al. 2009). In response, infected cells catalyze rate-limiting steps in the cholesterol pathway to reduce the amount of cholesterol produced, while increased expression of genes associated with peroxisomes, which are capable of breaking down cholesterol, suggests attempts to prevent the pathogen from utilizing previously produced cholesterol (Walters et al. 2006). Thus, it appears that the host is engaged in an arms race with HCV to regulate the production and availability of cholesterol. The same is likely true of other pathogens as well as, in a variety of viral pathogens, there is a correlation between increased virulence and increase in fatty acid supply and synthesis. Human cytomegalovirus has been shown to alter fatty acid biosynthesis pathways to increase fatty acid supply, which is essential for optimal viral growth (Munger et al. 2008). West Nile virus acts similarly, modulating host cell cholesterol homeostasis by upregulating cholesterol biosynthesis and redistributing cholesterol to viral replication membranes (Mackenzie et al. 2007); the same pattern has been shown in both Dengue virus (Heaton et al. 2010) and HIV (Taylor et al. 2011). It is thus quite likely that natural selection has favored host mechanisms that reduce or sequester cholesterol as a means of combating pathogens.

THE CONJUNCTION OF PROGESTERONE-DRIVEN RISK OF INFECTION AND CHOLESTEROL DEPENDENCE IN PATHOGENS

In order to test our hypothesis that progesterone's effects on cholesterol constitute a second-order adaptation that reduces the costs of progesterone's immunomodulatory effects, we turn to an examination of the postulated selection pressures at issue. Specifically, if cholesterol reduction is a preemptive defensive maneuver aimed at decreasing the threat posed by those pathogens that stand to benefit from progesterone's immunomodulatory effects—most notably including those pathogens that pose a substantial risk to mother and conceptus—then it should be the case that a majority of such pathogens are importantly dependent on host cholesterol for their success. We therefore conducted an extensive literature search to identify such pathogens, then explored the extent to which they are known to be dependent on cholesterol. Table 1 presents our findings.

As evident in Table 1 and illustrated in Figure 1, a wide range of pathogens utilize cholesterol for maximal infectivity. As illustrated in Figure 2, almost all of these are best countered by a Th1 cytokine response in the host and, as illustrated in Figure 3, a large number are exacerbated by a Th2 cytokine response. Progesterone shifts the Th1/Th2 balance toward the latter; therefore, it follows that progesterone increases the susceptibility of the host to the pathogens listed. As evident in Figure 4, many of these pathogens also pose a substantial risk during early pregnancy, a period charac-
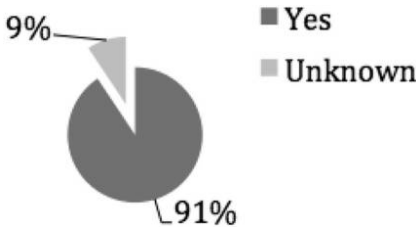
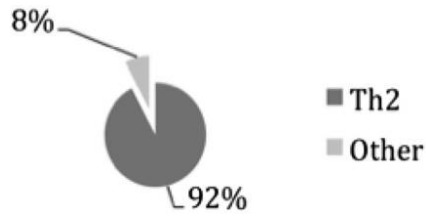FIGURE 1. FRACTION OF PATHOGENS EXAMINED THAT UTILIZE CHOLESTEROL (N = 32).

FIGURE 3. PATHOGENS FOR WHICH THE INFECTION CYCLE IS MAXIMALLY ENHANCED BY TH1 OR TH2 RESPONSES (N = 13).

terized by a "perfect storm" of minimal immunological capacities and maximal susceptibility to perturbation. Progesterone's general reduction of cholesterol, and the first-trimester nadir in maternal cholesterol in particular, thus appears to reflect a beneficial adaptation that helps protect both mother and conceptus from pathogenic infection.

CHOLESTEROL DURING PREGNANCY

Despite progressive increases in progesterone levels, cholesterol levels increase during gestation; plasma concentration increases about 50% on average, the major increase occurring during the second trimester (Potter and Nestel 1979; Basaran 2009), while plasma triglyceride concentration reaches a peak in the third trimester (Potter and Nestel 1979; Basaran 2009). In regard to both LDLs and HDLs, the ratio of triglycerides to cholesterol rises throughout the course of pregnancy (Potter and Nestel 1979). At the proximate level, the increase in maternal cholesterol is likely due to the effects of estrogens, which elevate cholesterol significantly (Schaefer et al. 1983).

Estrogen increases progressively throughout pregnancy (Hassiakos et al. 1991). Levels of LDL parallel this rise, and the same is true of HDL through mid-pregnancy (maternal HDL levels fall late in pregnancy, possibly due to the onset of insulin resistance, glucose intolerance, and enhanced fatty acid mobilization; Ordovas et al. 1984). At the ultimate level, these increases can be correlated to the increased need for cholesterol by the fetus. Fetal cholesterol is very high at the end of the second trimester, a period vital to the neural and vascular growth of the developing organism (Herrera and Amusquivar 2000). Cholesterol accessibility in the second and third trimesters helps enhance basic fetal metabolism and function via normalized membrane integrity and cell signaling (Woollett 2005). Cholesterol is used by the placenta for steroid synthesis and fatty acids are used for placental oxidation and membrane formation (Mankuta et al. 2010). The third trimester is also marked by body fat accretion in the fetus, a process fundamentally dependent on maternal cholesterol (Herrera and Amusquivar 2000).
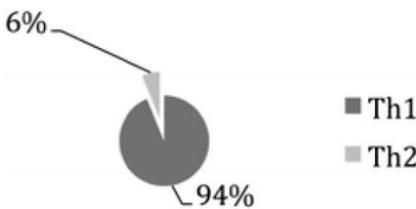

FIGURE 2. PATHOGENS FOR WHICH THE INFECTION CYCLE IS MAXIMALLY LIMITED BY TH1 OR TH2 RESPONSES (N = 32).
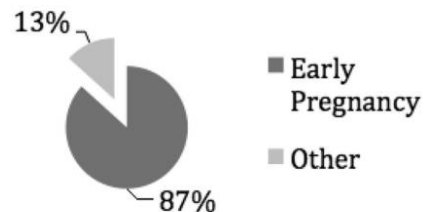

FIGURE 4. PERIOD OF MAXIMAL NEGATIVE IMPACT OF INFECTION AMONG PATHOGENS KNOWN TO AFFECT THE COURSE OF PREGNANCY (N = 15).

Importantly, as pregnancy progresses, the fetus becomes increasingly buffered from infection, and fetal development becomes increasingly less vulnerable to perturbation (reviewed in Profet 1992). Meanwhile, the fetal demand for cholesterol continues to climb throughout development, with the fetus matching any increase in maternal cholesterol intake with corresponding elevations in fetal cholesterol uptake (Burke et al. 2009). As reflected by the correlation between elevated maternal cholesterol and increased fetal growth rates (McConihay et al. 2000), just as vulnerability to infection and susceptibility to perturbation decline over the second and third trimesters, so too does the fetal need for cholesterol increase. Against this backdrop, the steady increase in cholesterol across the second and third trimesters is understandable as an adaptive pattern, reflecting a reduction in the immunological costs of cholesterol and an increase in the need for this vital building block.

Conclusion

Cholesterol modulation appears to be exquisitely timed over the course of pregnancy, closely matching the shifting importance of combating pathogens and building fetal tissue. The functionality of these changes is evident in the closeness of fit between the ability of pathogens to exploit progesterone-induced downregulation of inflammatory responses and their reliance on cholesterol. Taken together, these features indicate that the relationship between progesterone and cholesterol, although puzzling at first glance, most likely reflects a second-order adaptation selected for by the increased vulnerability to infection that is an inherent consequence of progesterone's role in maternal immune tolerance of the conceptus. Indeed, it is possible that this is but one in a suite of second-order adaptations serving this purpose. Progesterone may exercise a similar antag-

onistic effect on the availability of iron (see Fessler 2002), and there is evidence that estrogen has an antagonistic effect on the availability of tryptophan (Doyle et al. 2007). Like cholesterol, iron and tryptophan play critical roles in infection, suggesting the presence of evolved systems that compensate for the liabilities entailed by reproductive immunomodulation (Fessler 2002; Doyle et al. 2007).

The approach presented here has a number of possible implications for both clinical practice and basic research. First, if we are correct that cholesterol-dependent pathogens pose a substantial risk to the conceptus then, via pathways different from those recognized to date in the literature (e.g., Bartels and O'Donoghue 2011), chronically high cholesterol levels may constitute an underrecognized factor in both pregnancy loss and a variety of developmental abnormalities. Second, if, as seems plausible, multiple feedback mechanisms link progesterone production to cholesterol, then pharmacological manipulation of cholesterol levels may entail unintended consequences for progesterone production, with subsequent effects on fertility and other aspects of health. Third, in light of existing evidence that progesterone shapes behavioral disease avoidance in a manner that partially compensates for the immunomodulation effects of this hormone, if the thesis presented here is correct, this would constitute a case of two entirely independent compensatory mechanisms linked to a single proximate system. The latter suggests that evolutionary investigations of health and disease should attend carefully to the possibility of complex, and even multiple, second-order adaptations stemming from constraints on the optimality of individual adaptations.

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