Pathogenesis of Maternal-Fetal Syphilis Revisited

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Although congenital syphilis has been recognized for several centuries and an efficient treatment with penicillin became available more than a half-century ago, the disease is still with us. Inability to culture in vitro the causative agent, Treponema pallidum, and the lack of an adequate animal model have prevented exploration of the various immunopathological events affecting the natural course of congenital infection. The purpose of this review is to analyze the disease in the context of recent knowledge acquired from human and experimental animals, particularly from the guinea pig model of congenital and neonatal syphilis, and to describe how the infection interacts with the maternal-fetal unit and how it is further modulated by the conceptus’ ontogenic development. We also attempt to elucidate several old immunologic concepts and misconceptions that have remained unchallenged for too long.

Congenital syphilis results from transplacental infection with the spirochete Treponema pallidum subspecies pallidum. The disease has been recognized for ~500 years. Descriptions of the devastating early and late clinical and pathological manifestations of the disease have been reported in excellent treatises in the older literature [1–3]. A milder, less aggressive clinical presentation of the condition observed in the postpenicillin era is also the subject of several reports in the modern literature [4–7]. Despite the current availability and application of modern methodologies (reviewed in [8]) for evaluation of the maternal and neonatal humoral response, serodiagnosis continues to be a problem, because >50% of infected infants are asymptomatic at birth and syphilitic babies may even be born to seronegative mothers [9, 10].

The fact is that the nature and role of the maternal-fetal immune response, their mutual interaction, and their effect on the outcome of pregnancy and ontogenic development of the conceptus remain poorly understood. The scarcity of relevant animal models (reviewed in [11, 12]) has thwarted our understanding of the immunopathological events affecting the various presentations and the natural course of the disease. It has also prevented experimental verification and challenge of old immunologic concepts (quoted in [6, 7]), born mostly from empirical observations that were not (and still are not) clearly understood.

EFFECT OF SYPHILIS ON PREGNANCY OUTCOME

Congenital syphilis may occur when an infected woman becomes pregnant or when a pregnant woman becomes infected. For the sake of clarity, these sequences of events will be called A and B, respectively (figure 1). The human period of gestation normally is 9 months, which is approximately the duration of the most active primary, secondary, and early latent stages of maternal syphilis. Therefore, several combinations between stages of pregnancy and infection—and consequently, different outcomes—can be expected.

Sequence A. It has long been recognized that transmission of the disease to the fetus is largely dependent on the duration of the disease in the mother [3, 13–16], although there are controversial reports regarding the incidence of fetal morbidity and mortality (figure 1).
affected infants are those conceived in, not born to, mothers with primary or secondary syphilis, whereas the less affected are those conceived in mothers in the early-late or late stage of the disease [15]. Both situations relate exclusively to sequence A (figure 1).

On the basis of empirical observations in humans [2, 3, 23], it was long believed that reduction in transplacental infection with progression of maternal syphilis was related to evolution of maternal immunity, also known as Kassowitz’s law [23]. However, more recent observations in humans [2, 24] have demonstrated that the possibility of fetal infection is never eliminated. A classic example was provided by Fiumara in 1965 [24], in which an untreated syphilitic mother transmitted the disease to her children, although with decreasing frequency, during a period of 10 years. The most puzzling and as yet unexplained finding in this report, as in other reports [2], was the intermittence of the transmission, because normal offspring could be preceded and followed by an infected infant [24].

These findings are interesting in light of recent studies of the guinea pig model of congenital syphilis [25]. In the latter studies, controlled by more specific and sensitive techniques than those used by Fiumara in the human study, it was demonstrated that untreated syphilitic sows could consistently transmit the infection to their young; this infection would perpetuate itself through multiple pregnancies and up to the fourth generation. Whereas congenital infection in guinea pigs is asymptomatic, infection of most littermates examined was demonstrated by use of ≥1 specific and sensitive methods: the IgM test, PCR, and the rabbit infectivity test (RIT) [25].

It is interesting that in the animal studies, what seemed to decrease in successive progeny was not the maternal transmission but the load of transmitted microorganisms and/or their virulence. This assumption was in accordance with the expression of a milder humoral response in consecutive progeny and the extremely low infectivity displayed by their organs when injected into rabbit testes. Neither obvious local inflammation nor systemic seroconversion was observed, and yet T. pallidum DNA was repeatedly detected in the rabbit testes by PCR [25]. PCR detects T. pallidum regardless of its virulence or viability.

Changes in pathogenicity are not foreign to treponemal diseases and are due to multiple factors: nutritional, environmental, behavioral, and immunologic [26]. Furthermore, as demonstrated in the guinea pig model of neonatal and congenital syphilis [25, 27, 28], the pathogen’s virulence may be modulated by the maternal immune response but also by the conceptus’ genetic background, which is at least as important as, if not more important than, the traits of the bacterium [29]. This could explain why, in many situations, congenitally infected infants are asymptomatic at birth and remain so for variable periods of time, whereas other newborns present with full-blown disease [30]. In the untreated congenitally asymptomatic infant, the organisms apparently vegetate in a com-

![Figure 1. In congenital syphilis, the outcome of pregnancy depends on the stage of maternal syphilis at time of conception (sequence A) or the stage of gestation at the time of infection (sequence B).](image)
and RIT positive) was detected in only 4 (36%) of 11 amniotic
et al. [19] reported similar findings:

and umbilical cord) were positive by PCR (authors' unpub-

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8 of 8 fetuses obtained 24 h after maternal infection of 3 C4D

amined within 24–48 h of intravenous infection of C4D and

immunocompetence and an increased chance of finding trep-

bellum and Borrelia burgdorferi can induce the

TNF-α [34, 35], which has the potential for cell activation and

Apoptosis has been implicated in immune defense against several pathogens, including some of those that

cause congenital infection [37, 38], although the full mechan-

ism remains controversial and not clearly understood [39].

To our knowledge, apoptosis in congenital syphilis has not been

explored.

Alternatively, the completion of the sequence of the T. pal-

lidum genome [40] has provided clues regarding the pathogen’s

limited biosynthetic capabilities, which explain its full depend-

ence on the host for survival, propagation, and dissemination

by adhesion to cells, including endothelial cells and extracellular

matrix components [41–44]. Indeed, the survival of the patho-

gen should be highly restricted in the incipient embryo-fetal

microenvironment (figure 1). This could also explain why treat-

ment initiated early in pregnancy is highly effective.

In light of these new findings, how then can we explain the

high incidence of fetal death associated with pregnancy that

occurs immediately before or after infection? As indicated

above, one possibility is that resorption or fetal demise early
during pregnancy is caused by the infected fetal-maternal unit’s

immune reaction, due to an intense release of inflammatory
cytokines from activated leukocytes infiltrating the infected

membranes [45]. In recent years, extensive evidence has been

accumulated regarding the bidirectional interaction between

mother and fetus [46]. In fact, during gestation, cytokine pro-
duction not only precedes but is an active part of the process

of implantation, growth, and survival of the fetus. Cytokines

also contribute to the process of fetal lymphogenesis and or-

ganogenesis [47, 48].

More important, these cytokines are produced locally by

lymphoid and resident nonlymphoid cells of the decidua, choro-

ion, and trophoblasts [45, 47, 49]. Their main role is to dis-

criminate between 2 apparently contradictory requirements, to

protect the uterus from invading infectious agents while pre-

venting the rejection of the allotransplant. Under normal cir-
cumstances the fetoplacental unit itself spontaneously secretes

the anti-inflammatory cytokines IL-10, IL-4, and transforming

growth factor (TGF)–β to fend off any harmful effect of sys-
temic or local inflammation [50–52]. Increased production of the inflammatory cytokines IL-2, IFN-γ, and TNF-α and prostaglandins (Th1) induced by uterine infection has been associated with fetal demise, growth retardation, and preterm delivery at any stage of gestation [52–55], whereas a predominant Th2 response, although it will not prevent fetal infection, is unlikely to cause fetal damage [50, 51]. One may reason, therefore, that a detrimental Th1 immune response must be prevalent when a recently infected mother becomes pregnant or when maternal syphilis occurs in very early pregnancy, causing resorption or fetal death.

Although it is not totally eliminated, the risk of fetal loss should progressively diminish when infection occurs in later stages of gestation and ontogenic development, when the fetal-placental unit immune response is tilted toward preservation of the conceptus [47, 48, 50]. The report of Desmonts and Couvreur [56] on a prospective study of congenital toxoplasmosis is worth considering. The majority of congenital infections (65%) occurred following third-trimester maternal infection. However, the vast majority of the infants were asymptomatic. In contrast, only 17% of neonates who were born to mothers infected during the first trimester were congenitally infected, but the majority were severely damaged.

Dramatically depressed cellular responses to cytomegalovirus and herpes simplex infection, potential sources of gestational morbidity, have been observed during second-trimester and third-trimester human pregnancies [57, 58]. The relatively large percentage of congenitally infected but asymptomatic newborns with syphilis is consistent with the above hypothesis. None of the above immune mechanisms have been explored in cases of natural congenital syphilis.

**EFFECT OF PREGNANCY ON THE COURSE OF MATERNAL SYPHILIS**

Clinical and experimental studies have shown that several hormonal and immunologic changes that take place during pregnancy [47, 52, 59–61] are potential modulators of maternal susceptibility to infection. Various hormones made by the trophoblast have been shown to interfere with the induction of the immune response. These include progesterone and estrogen, which inhibit cytotoxic T cells and natural killer (NK) cells [60–62]. Progesterone is essential for the maintenance of pregnancy in several mammalian species, apparently because it affects the Th1/Th2 ratio and decreases cell-mediated responses [60]. NK activity is significantly lower during healthy human pregnancy than in nonpregnancy, whereas it is substantially increased in patients who experience spontaneous abortion or preceding parturition [63]. Parker and Wendel [64] reported that reduction of estrogen production may be associated with severe intrauterine stress in pregnancies complicated by syphilis.

In the prepenicillin era, when expression of the disease was much more dramatic [1–3] than it is today [4–7] and only few serological tests (of low sensitivity and specificity) were available, observations made by clinicians in the field of syphilis indicated that pregnancy affected the natural course of syphilis [65–68]. As early as 1922, Moore [67] wrote: “The fact that women who bear syphilitic children often give no history of syphilis and present no signs of the disease (except a positive Wasserman reaction) has long been a common knowledge.” and “a woman infected at or shortly after the time of conception usually does not develop a chancre or secondary syphilis. When infection takes place late in pregnancy, on the other hand, the usual course of events follow[s], but is often much delayed.” These observations, reassessed and confirmed 20 years later by Moore et al. [68], were consistent with those made earlier by Brown and Pearce [65] with regard to the rabbit model.

Although the aforementioned concepts are not shared by modern clinicians [4, 5, 69], one cannot but recognize how the prevailing diagnosis of congenital syphilis relies so heavily on maternal and neonatal serological tests (VDRL, RPR, FTA-Abs) and molecular tests (T. pallidum DNA), on neonatal clinical symptoms, and on radiological findings, because maternal clinical symptoms are often absent in pregnancy, even during active disease [10, 70]. In a retrospective study, Reyes et al. [33] reported that of 148 serologically (RPR, FTA-Abs) positive mothers who delivered either congenitally infected stillborn or liveborn infants, only 6 (4%) had a history of primary or secondary syphilis. The remaining 142 infected mothers (96%) were asymptomatic.

If implantation and survival of the fetus is associated with an altered Th1/Th2 balance, one might predict that the humoral response in pregnancy is increased, whereas cell-mediated responses are either ameliorated or seriously impaired. In fact, some clinical and experimental data [61, 71] support the concept that healthy pregnancy is characterized by a Th2-like phenomenon. Systemic lupus erythematosus, an antibody-mediated autoimmune disease, tends to flare up, especially in women with recently active disease, before conception [72, 73]. A noticeable temporary abatement of the symptoms of rheumatoid arthritis (a cell-mediated disorder) has been consistently observed in pregnancy [74], whereas a strong Th1 response against intracellular pathogens is known to compromise pregnancy, as demonstrated in the murine model of *Leishmania* infection [59] and infections with other intracellular pathogens such as *Toxoplasma* and *Plasmodium*, as well as HIV-associated infections (reviewed in [46]).

Fortuitously, we have observed what seems to be a Th2 phenomenon during the course of recent experimental studies directed toward elucidation of maternal transmission of syphilis through several litters and generations of guinea pigs [25]. In those studies, *T. pallidum*-infected multiparous females were bled for serological examination approximately every 23 days.
A dam that was congenitally infected (figure 3) and 5 consecutive litters, respectively, and in 1 multiparous does with acquired syphilis, which were the source of 3 females tested for a similar 12-month period (figure 3). The humoral response was not observed in nulliparous syphilitic infants [75] and guinea pigs [11].

rheumatoid factor commonly observed in congenitally infected in the fetal production of circulating immune complexes and IgM antibodies and positive, PCR positive, and RIT positive). It could also account shown by the obvious transmissibility to the fetuses (IgM pos-

As early as 18–20 weeks' gestation, the fetus has the potential to respond to infection with use of nonspecific host-resistant factors, such as phagocytic cells and NK cells, or with a relatively low level of specificity provided by the γδ T cells and B1 CD57 B cells [83]. The mammalian immune system, however, is not completely functional during fetal life or even at birth but undergoes a gradual maturation, which may be completed after

CONGENITAL SYPHILIS

Perinatal infection with *T. pallidum* exhibits a wide range of clinical manifestations. The general assumption that the outcome of pregnancy is determined by the time of gestational infection [15] and by fetal immunogenesis [31, 32] has been insufficient to define the various modalities and presentations of the disease. It cannot explain why the majority of congenitally infected newborns are free of symptoms at birth or why some of them develop early or late manifestations, whereas others remain asymptomatic for life. Indeed, there is a paucity of information about congenital syphilis with regard to the immunomodulatory role played by the fetal-maternal relationship, and changes associated with fetal ontogenic development and genetic background.

During pregnancy, the human placenta undergoes critical structural changes, which are synchronized with the development of the embryonic/fetal and maternal compartments [77]. Normally, the placenta is a main source of anti-inflammatory cytokines (IL-10, IL-4) and a variety of growth factors, including TGF-β. These factors not only stimulate or inhibit fetal growth, but they also participate in cellular and tissue differentiation, programmed cell death, metabolism, nutrient uptake, and angiogenesis [48, 77]. In the fetus, TGF-β plays a critical role in the differentiation of oligodendrocytes [78], in the integrity of the musculoskeletal system, and in the remodeling and mineralization of bone tissue [77]. Together with IL-10 and IL-4, the growth factors protect the fetus from systemic or local inflammation by inhibiting lymphokine-activated killer cells [79], allospecific cytotoxic T cells [80], antigen-presenting cells, and macrophage activation [81]. An additional property of IL-10 is its potent inhibition of osteoclast formation and prevention of bone resorption [82].

Thus, one may speculate that factors known to promote placental and fetal growth, as well as fetal survival as an allograft, may incidentally benefit and protect an invasive pathogen, such as *T. pallidum*, from an immune attack, while promoting asymptomatic infection. Following the same line of reasoning, *T. pallidum*-associated temporary or permanent damage to a variety of embryonic/fetal tissues and organs, including skin, brain, bones, liver, and pancreas, may be regarded as a failure of the fetal-maternal unit to prevent an inflammatory response triggered by the pathogen in a relatively immunocompetent fetal microenvironment.

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![Figure 2](https://academic.oup.com/cid/article-abstract/33/3/354/277468/Downloaded from https://academic.oup.com/cid/article-abstract/33/3/354/277468)
the neonatal or even adolescent life [84]. Although the normal newborn produces a large number of B cells with different specificities, the full array of antibody response is reached only postnatally by the gradual exposure to different bacteria and viruses and the acquisition of memory cells [83, 85, 86].

Furthermore, the immune response to a particular antigen remains constant for the individual animal within a particular strain but shows marked differences between different strains [87, 88], which suggests an important role for genetic factors in the evolution of the host’s immunocompetence. Several reports have shown genetic differences among mouse strains in their susceptibility to bacterial [88], viral [89], and protozoal infection [90]. It has also been shown that expression of resistance genes may not be equally distributed in different organs [91, 92] or at all stages of ontogenic development [27, 93]. We have shown strain-associated and age-associated differences in lymphocyte phenotypes and immune responsiveness to alloantigens and mitogens in 2 strains of guinea pigs: (1) C4D genetically associated with inbred strain 13 and (2) the Alb line haplotype identical to inbred strain 2 [94].

More interesting is that the ontogeny of the humoral response and cutaneous reaction to *T. pallidum* infection in these 2 strains follow a different time course in neonates and in adults [27]. C4D neonates (1–3 days old) are temporarily resistant (2–3 months) to intradermal infection but are highly susceptible as adults. The opposite occurs with Alb strain neonates. Ontogenic changes in susceptibility to cutaneous challenge with *T. pallidum* has also been demonstrated in the rabbit model [95] and in infection of mice with another pathogenic spirochete, *B. burgdorferi* [96].

There is little information about the role of the cellular arm of the immune response in congenital syphilis. Friedmann, in 1977 [97], reported that peripheral blood lymphocytes from 7 babies aged 2 months to 2 years with active disease responded to *T. pallidum* antigen with stimulation ratios significantly higher than those of normal age-matched control cells, whereas the cellular response of 16 asymptomatic, serologically positive newborns (24–48 h old) was not significantly different from that of controls. Samsom et al. [98] did not find any significant differences between 17 newborns (1–7 days old) with early congenital syphilis and 17 age-matched controls in response to phytohemagglutinin antigen (PHA). These authors found significantly increased levels of B cells and production of IgM and circulating immune complexes (CICs). Fitzgerald and Froberg [99] showed that congenitally infected rabbits have an elevated T cell proliferative response to mitogen and B cell function involving increased levels of antitreponemal antibodies.

We have shown that transplacental infection with *T. pallidum* in C4D and Alb dams occurs irrespective of their different genetic backgrounds and their susceptibility to cutaneous infection [11]. In these 2 strains, in utero infection elicits early and extended (2–4 months of age) production of IgM antitreponemal antibodies, IgM–rheumatoid factor, IgM–CIC, and a delayed switch to IgG antibodies [28]. Compared to those of normal control animals, spleen cells from congenitally infected pups aged 1–20 weeks showed a remarkably prolonged naïve-type of immune response, as reflected in the significantly higher response to both T cell mitogens concanavalin-A (ConA) and PHA and a weaker response to B cell mitogen.

Several studies [100–102] have indicated that T lymphocytes can be phenotypically divided into 2 different subsets of CD4+ T cells: naïve (CD45Rhi) and memory (CD45Rlo) T cells. Naïve T cells represent the suppressor-inducer subset [100]; they display an increased lymphoproliferative response to T cell mitogens but react poorly to antigen and are associated with a primary IgM immune response and induction of suppression of antigen-driven IgG production. Memory CD4+ T cells, on the other hand, represent the helper-inducer subpopulation for antigenic and mitogenic responses of B cells [101]. They have a relatively lower proliferative response to T cell mitogens but react strongly to antigens. Both subpopulations have different activation requirements and secretion of cytokines [102].
characteristics of naïve and memory T cells are consistent with the elevated response to T cell mitogens in asymptomatic congenitally infected rabbits [99] and guinea pigs [103] and the lower response to T. pallidum antigen in asymptomatic infants [97]. They also correlate with the abundant production of IgM polyclonal antibodies and IgM–rheumatoid factor, reflecting the activation of naïve B1-CD5⁺ B cells [28, 104, 105]. Indeed, delayed maturation of T cells and B cells will contribute to the dysfunction of the immune response with decreasing resistance to pathogens and increased production of autoantibodies, particularly of the IgM type [28, 75, 103, 105].

Whether the prolonged naïve-type of humoral immune response in asymptomatic congenital syphilis is associated with some mechanism of immunologic tolerance at the cellular level, as occurred in children congenitally infected with Toxoplasma gondii [21] and lymphocytic choriomeningitis virus [106], has remained unexplored. The presence of the pathogen at the critical stage of development could result in a lymphocyte population unable to distinguish between the microorganism and self. However, immunologic tolerance that results from an efficient process of clonal deletion of T cells capable of mounting an aggressive response to “self”–MHC molecules [107] may not play a major role in congenital syphilis, because such type of tolerance leaves the organism unable to induce an autoimmune response, a process commonly seen in patients with syphilis [108]. High levels of circulating immune complexes containing T. pallidum, creatine kinase (CK), fibronectin (Fn), and IgG1 and IgG3, in addition to IgM, have been found in serum samples of congenitally infected babies [104, 105]. Antibodies to host antigens, such as cardiolipin, CK, collagen, laminin, and Fn, are often present in serum samples obtained from T. pallidum–infected human and experimental animals (see review of literature in [104]). We are more inclined to believe that a process akin to clonal inactivation (1) by antigen presentation in the absence of costimulatory signals, due to the dominance of immature T and B cells early in ontogeny, or (2) by a state of “immunological ignorance,” where T cells that are able to recognize the antigen will be present in the mature host but will not normally be activated [109], may have some relevance in congenital syphilis.

Apparently, failure to maintain an appropriate balance between self-reactive naïve CD45Roha T cells and normally present antagonistic mature CD45Rhb T cells may result in an autoimmune response [110] ranging from a lethal wasting disease in the newborn, as shown in the rat model [111], to irreversible tissue damage. Indeed, a subtle but insidious inflammatory autoimmune response could explain why late manifestations of congenital syphilis, such as interstitial keratitis, Clutton’s joints, and sensorineural deafness, may respond to steroid treatment rather than to antibiotics.

THE GUINEA PIG MODEL

Although congenital syphilis causes no apparent disease in guinea pigs, this animal has been the source of valuable information on various immunologic and clinical aspects of perinatal syphilis that could not be explored in humans or other animal models. The guinea pig host has been instrumental in the addressing of 3 important but controversial clinical puzzles. The first relates to the possibility of transmission of congenital syphilis through several generations, also known as tertiary syphilis, which has been suspected since the end of the 19th century [1, 2]. The animal model demonstrated not only third-generation and fourth-generation syphilis but also an association between congenital transmission and pregnancy-related changes in the maternal humoral response and a decline in immune response in successive congenitally infected progeny [25].

Second, we have conclusively shown that despite its close genetic relationship with T. pallidum subspecies pallidum, T. pallidum subspecies pertenue, the causative agent of yaws, shows distinctive pathogenic properties, such as its inability to cross placenta and cause congenital infection [112]. Third, we addressed the question of whether infection occurring during delivery or immediately after birth differs from infections occurring during gestation. The results of these studies indicated that, as opposed to congenital infection, intracutaneous inoculation of 1–3-day-old neonates with T. pallidum did not induce IgM rheumatoid factor or IgM-CIC, which reflect a host’s naïve B1 (CD5⁺) B cell response to maternally transmitted IgG. The inclusion of both strains of guinea pigs in these studies of neonatal infection also served to demonstrate age-associated and genetically associated differences in the cutaneous response to T. pallidum [27].

CONCLUSION

Although in the past decade the number of new cases of congenital syphilis in the United States has substantially decreased, from a peak of 107 cases per 100,000 live-born infants in 1991 to 30 per 100,000 in 1996 [113], isolated outbreaks of infection with up to 10-fold higher rates have been reported [113–115]. This suggests that eradication of the disease cannot be taken for granted. The failure to eradicate the disease now and in the past should in part be attributed to our insufficient understanding of the immunologic mechanisms involved in the maternal-fetal interface that cause early fetal death, stillbirth, and early and late manifestations of congenital syphilis. Adequate knowledge of immunity is essential to comprehend the natural history of the disease and how it relates to latency, clinical progression, and relapse and to properly evaluate therapeutic results.

Indeed, there is a need for new epidemiological, immuno-
logic [116], and clinical strategies, if not to fully eliminate the pathogen, then to at least keep it under control.

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