Intrauterine Infection, Fetal Growth and Mental Development*

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Introduction

Excellent reviews on intrauterine infections (IUI) have been published. In particular, these papers have shed light on the teratogenic effect of IUI and about its influence on human abortion and fetal death rates (Eichenwald and Shinefield, 1962; Mims, 1968; Blattner and Heys, 1961; Hardy, 1965; Miller, *et al.* 1949; Monif, 1969; Rennert, 1969). In addition, a review of relevant animal studies have been recently provided by Mims (1968). Nonetheless, no integrated attempt has been published to define the magnitude of the problem, to quantify the damage produced on fetal growth and mental development, and to identify areas needing further research. The present report constitutes an effort to answer these questions from a public health point of view. The term intrauterine infection will be employed to mean the invasion, by a microorganism, of the fetus, the placenta, and/or its membranes.

Epidemiology of Intrauterine Infection

Infectious Agents

Several techniques, none of which is devoid of problems, have been employed to demonstrate the presence of fetal infection.

Cases detected through clinical investigations have usually been those in which the infection was severe (Eichenwald, 1966; Hughes, 1970; Davies, 1971), since mild or moderate infections are very difficult to detect clinically (Birnbaum *et al.*, 1969; Stern, 1968; Montgomery and Stockdell, 1970; Eichenwald, 1966).

Microbiological techniques have also been employed in diagnosis. Though microbiological diagnosis, which involves isolation of the causal agent, is highly reliable (Hanshaw, 1969), it is frequently a complicated and expensive technique. Furthermore, the percentage of false positives may be too high, particularly when the sample is obtained by umbilical catheterization (Davies, 1971). It is also difficult to define whether the infection was acquired *in utero* or during the first hours of the neonatal period. In some cases of infection by enterovirus and bacteria (Banker, 1968), the germ isolated in the newborn may have been acquired during the first hours of postnatal life, especially when the mother presented simultaneously the same infection or when epidemics by the same agent developed in neonate wards. In addition, microbiological diagnostic techniques are less effective when infection occurs early in gestation and the fetus recovers before birth.

Diagnostic methods based on the measurement of fetal immune response, such as determination of IgM and IgM antibody titers are relatively simple, cheap and permit one to know the history of infection (Weller, Alford and Neva, 1964; Alford, Jr., 1971). However, reliable techniques for determination of IgM antibodies have been developed only for syphilis (Alford *et al*, 1969b), rubella (Alford, 1965), *Toxoplasma* (Peetoom and Mulder, 1969; Remington, 1971), and cytomegalovirus (Hanshaw, Steinfield and White, 1968). In addition, there exists high variability in the results according to the antisera and standards used, which makes difficult the establishment of normal values (Sever, 1969; Buckley, Dees and O'Fallon, 1968; Buckley, Younger and Brumley, 1969; McCracken *et al.*, 1969a,b; Hardy, 1969a,b; Janeway, 1969; Lechtig, Mata and Arroyave, 1970; Stiehm, Amman and Cherry, 1966; McCracken and Shinefield, 1956; Miller, Sunshine and Remington, 1969; Alford *et al.*, 1969a,b; Ackerman, 1969; Birnbaum *et al.*, 1969; McCracken *et al.*, 1969 a,b,c; Gottoff *et al.*, 1971; Sever *et al.*, 1969; McKay, Thom and Gray, 1967). Furthermore, IgM indicators are difficult to interpret since the fetus can produce IgM in response to noninfectious antigenic fractions (Bellanti and Jackson, 1967); cord blood may be "contaminated" with the mother's blood (Miller, Sunshine and Remington, 1969), and IgM levels vary according to gestational age (Rothberg, 1969; Thom, McKay and Gray, 1967; Ackerman, Taylor and Loughlin, 1969). The fact that a variable proportion of antibodies produced by the fetus are 7S

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IgM (Pershalsk, Clem and Small, Jr., 1968; Peetoom and Mulder, 1969), adds new technical difficulties, since the specificity of the antisera varies according to the spatial distribution of the heavy chains (Peetoom and Mulder, 1969). Because of these problems, the determination of IgM may have better diagnostic value during the first 6 or 12 months of life than at birth (McCracken *et al.*, 1969c,d; Dudgeon, Marshall and Soothill, 1969; Korones *et al.*, 1969; Blankenship *et al.*, 1969). It is generally accepted that IUI is present when the titer of antibodies at birth is maintained or increased. Regarding measurement of antibody titers in pregnant women, it is assumed that a sudden increase indicates maternal exposure to an infectious agent. Nevertheless, high variability exists in the frequency with which maternal infection during gestation leads to fetal infection.

Other techniques employed to diagnose IUI infections include placentography (Ramsey, 1970); histological study of placenta and umbilical cord (Overbach, Daniel and Cassady, 1970); analysis of amniotic fluid (Brosens and Gordon, 1966; Lucey, 1970; Ostergard, 1970, Nadler, 1970) and determination of leukocytes in swabs from the external auditive conduct. The usefulness of most of these techniques must still be demonstrated.

Cytomegalovirus (Smith, 1956; Weller *et al.*, 1957; Weller and Hanshaw, 1962), rubella virus (Gregg, 1944, 1945; Korones *et al.*, 1965; Selzer, 1963; Bellanti *et al.*, 1965; Heggie and Weir, 1964; Kay *et al.*, 1964), *Coxsackie* B. (Delaney and Fukunaga, 1958; Kibrick and Bernirshke, 1956, 1958); polio virus (Barsky and Beale, 1957; Swarts and Kercher, 1954; Shelokov, 1956; Winsser, Pfaff and Seanor, 1957) and ECHO virus (Cherry, Soriano and Jahn, 1968) have been shown to cause IUIs. Transplacental infection produced by arbor virus has also been shown, especially by agents of western equine encephalitis (Copps and Giddings, 1959; Shinefield and Townsend, 1953), herpes virus (Sieber, Fulginiti and Brazie, 1966; Epstein and Crouch, 1954; Nahmias, Josey and Naib, 1967; Nahmias, Alford and Korones, 1970) and vaccinia virus (McArthur, 1952; Wielenga *et al.*, 1961; Entwistle, Bray and Laurence, 1962). Evidence is less convincing regarding infections caused by measles virus (Kugel, 1957), mumps (Caughey, Jr. 1959; Greenberg and Beilly, 1949), influenza (Wilson *et al.*, 1959; Coffey and Jessop, 1959; Hardy *et al.*, 1961), chickenpox (Middlekamp, 1953; Shuman, 1939) and hepatitis (Krainin and Lapan, 1956; Peterman, 1957; Aterman, 1963; Cassady, Morrison and Cohen, 1964). Finally, no data are available on fetal infection caused by the "slow viruses" whose neurotropism may lead to damage of the central nervous system (Koprowski, 1968).

Among other bacteria, IUI has been produced by *Treponema pallidum* (Rasmussen, 1970; Woody, Sistrunk and Platou, 1964; Hill, Platou and Kometani, 1947) and the Koch bacillus (McGregor, 1960; Smith, 1968). Gram-negative bacteria (Barrett-Connor, 1969; Davies, 1971), *Listeria monocitogenes* and *Vibrio fetus* can also infect the fetus (Davies, 1971). Recently, there has been indirect evidence of a similar phenomenon with the I strain of mycoplasma (Braun *et al.*, 1971; Miller and Enbom, 1971).

Among the protozoa, *Toxoplasma gondii* has been definitely established as an agent of fetal infection (Wolf, Cowen and Paige, 1939; Eichenwald, 1957, Frenkel, 1968), and *Plasmodium* has been frequently observed in placentas of populations where malaria is endemic (Jelliffe, 1967). The information on fetal infection produced by fungi is still contradictory and requires further verification.

Estimations of Prevalence

Industrialized countries. Approximately 5% of a sample of 30,000 pregnant American women studied between 1959 and 1962 exhibited clinically one or more viral infections during the gestation period. Of these, 58% were diseases of the upper respiratory tract (Sever and White, 1968).

The prevalence of antibodies against cytomegalovirus in several British samples fluctuated from 21 to 54% for adults (Stern and Elek, 1965). In adult Australian populations, the prevalence of antibodies for anti-cytomegalovirus varied between 24 and 58% (Jack and McAuliffe, 1968). The frequency of vaginal infection by cytomegalovirus varies according to socioeconomic conditions, from 3 to 18% for pregnant mothers (Feldman, 1969; Hilderbrandt *et al.*, 1967; Medearis, Jr., Montgomery and Youngblood, 1970; Alexander, 1967), and the virus has been isolated in 0.6 to 3% of newborns during the first 24 hours of life (Birnbaum *et al.*, 1969; Starr and Gold, 1968; Stern 1968). In Japanese populations the virus has been isolated from the vagina in 23% of the women during the third trimester of pregnancy (Numazaki *et al.*, 1970).

The frequency of maternal infection by rubella in pregnant mothers has been estimated to be between 0.1 and 10%, and that of fetal infection between 0.07 and 0.7% of live births, depending on the point in the epidemic wave (Sever, Nelson and Gilkeson, 1965; Sever, 1968; Alford, Jr., 1971; Weller, Alford, Jr. and Neva, 1965). The frequency of perinatal infection by *Herpes simplex* has been estimated between 0.003 and 0.03% of newborns (Nahmias, Josey and Naib, 1971). In a group of 4930 mothers of low socio-economic level in the United States, 2.4% presented positive seroconversion for influenza, herpes virus, mumps and cytomegalovirus during gestation (Korones *et al.*, 1970). In a study performed in East Germany, 337 cases of fetal infection by *Listeria monocytogenes* were detected, with a

mortality of 37% (Ortel, 1971). In a group of 2600 U.S. women, 14% presented antibodies for *Toxoplasma* (Feldman, 1965). Studies conducted recently in the United States have shown that 38% of a group of pregnant women had antibodies for *Toxoplasma*, and 0.1% showed serological evidence of the infection during gestation (Sever, 1968). Studies made in different parts of France have reported a prevalence of antibodies to *Toxoplasma* of 75%. The frequency of congenital toxoplasmosis in France is estimated to be between 0.1 and 0.15% (Couvreur and Desmonts, 1962; Desmonts, Couvreur and Rachid, 1965). The rate of fetal infection by *Toxoplasma* for the North American population probably varies from 0.1 to 0.4% according to the geographic location and the sanitary conditions (Sever, 1970; Alford, Jr., 1971).

Recently, the determination of levels of IgM in cord blood has been used as a screen test to detect children with a high risk of fetal infection (Alford *et al.*, 1969a). The prevalence of high values of IgM in umbilical cord blood varies, depending on the socio-economic level, from 0.8 to 8% for North American populations (Miller, Sunshine and Remington, 1969; McCracken, 1969a; Alford *et al.*, 1969a). Under the assumption that up to 40% of the infants with elevated values of cord IgM suffer some types of IUI (Alford, Jr., 1971; Korones *et al.*, 1970), the estimated prevalence in industrialized countries is from 0.3 to 5% of live births.

Less developed countries. In a prospective study of 88 mothers from rural Guatemala, 66% showed one or more days of sickness during gestation, a proportion 13 times greater than that reported for North American populations (Sever and White, 1968). Most of the illnesses were infections of the respiratory, genito-urinary, and digestive tracts (Lechtig *et al.*, 1972b; Mata, Urrutia and Lechtig, 1971). A study of malaria in Uganda has reported that of 570 pregnant women, 16% showed histological evidence of infection by *Plasmodium* (Jelliffe, 1967). The prevalence of *Toxoplasma* antibodies has been reported as varying from 60 to 94% in adult populations of Guatemala and Costa Rica (Gibson and Coleman, 1958).

Studies made in Latin American countries have shown that the levels of IgM in cord blood are frequently high in rural or urban populations with deficient sanitary conditions. In these groups the proportion of children with high levels of IgM is approximately 50%, as compared to 5% in Latin American populations with satisfactory environmental conditions (Lechtig *et al.*, 1974). This prevalence is similar to that of children who have had clinical suspicion of intrauterine infection (Stiehm, Amman and Cherry, 1966), and ten times greater than that of black children coming from the lower socio-economic classes of Birmingham, Alabama (Alford *et al.*, 1969a). In children who have had intrauterine infection, the prevalence of high cord IgM is 85% (Alford *et al.*, 1967). Taking into account these observations, the estimated prevalence of IUI in pre-industrial populations is probably as high as 10% of all live births.

Effects of Intrauterine Infection on Physical Growth

Low birth weight for gestational age is frequently associated with intrauterine infection (Hughes, 1970; Krech and Jung, 1971). This association is particularly evident in infections caused by rubella virus; the average weight of newborns with congenital rubella is less than 2500 g (Sever, Nelson and Gilkeson, 1965; Siegel and Fuerst, 1966; Siegel and Greenberg, 1960; Cooper *et al.*, 1965; Lundstrom, 1962), in comparison to 3300 to 3500 g for normal newborns from the same populations (Meredith, 1970). Furthermore, a linear relationship exists between increase of weight during the first nine months of postnatal life and the duration of virus excretion (Rawls and Melnick, 1966). Children who have died from rubella acquired *in utero* show a decrease in weight of all the organs, including the brain. Although the mass of each cell tends to be normal, the number of cells of each organ is consistently reduced (Naeye and Blanc, 1965).

Other viral agents have been associated with fetal growth retardation. From 30 to 100% of the children with cytomegalovirus infection (Levinsohn *et al.*, 1969; Weller and Hanshaw, 1962) and all those infected by herpes virus (Nahmias, Alford and Korones, 1970) have been reported to be underweight for their gestational age. Fetal infection by polio virus is probably a cause of prematurity and low birth weight, especially if it occurs during the first trimester and if it is clinically severe (Siegel and Greenberg, 1956; Horn, 1955). A similar observation has been made concerning antivariolic vaccination (Wielenga *et al.*, 1961).

Available data are contradictory regarding the relationship between fetal growth retardation and fetal infection by influenza (Campbell, 1953; Wilson *et al.*, 1959), mumps (Siegel and Greenberg, 1960; Korones *et al.*, 1970; Siegel and Fuerst, 1966), smallpox (Berendes, 1968), chickenpox (Middlekamp, 1953; Shuman, 1939; Siegel and Fuerst, 1966) and measles (Siegel and Fuerst, 1966). An association has also been reported between bacteriuria during pregnancy and fetal growth retardation (Stuart, Cummins and Chin, 1965; Patrick, 1967; Wren, 1969; but other reports (e.g. Gower *et al.*, 1970; Bryant *et al.*, 1964; Dixon and Brant, 1967; Williams, Campbell and Davies, 1969) have not confirmed this association. Also, the presence of T strains of mycoplasma in the cervix or in the urine of pregnant women has been associated with low birth weight (Braun *et al.*, 1971). Body weight of children with congenital syphilis has also been found to be slightly reduced (Naeye, 1971).

Table 1
Intrauterine infection (IUI) and Low Birth Weight (LBW 2.5 kg) in U.S.A. Populations

Agent	Prevalence, % Newborns	Prevalence, % Mothers	% of infected babies with LBW	% of all newborn who have IUI and LBW
Cytomegalovirus	1.10[a]		37[b]	0.408
Herpes simplex	0.03[c]		60[d]	0.018
Rubella 1st trimester		0.8[e]	17.5[f]	0.140
Bacteriuria		5.00[g]	13.3[h]	0.665
Measles		0.04[i]	17[j]	0.007
Total				1.238[k]

* Equivalent to 46,800 babies with IUI and LBW or 12% of all LBW babies born in U.S.A. during 1975 (assuming 10% of LBW for U.S.A.: Lechtig *et al.*, 1977).

[a] Hanshaw 1971; Alford, Jr., 1971; Sever, 1968; Alexander, 1967; Stern, 1968, Starr and Gold, 1968.

[b] Stern, 1968; Starr and Gold, 1968; Birnbaum *et al.*, 1969, Weller and Hanshaw, 1962.

[c] Nahmias, Josey and Naib, 1971.

[d] Epstein and Crouch, 1954; South *et al.*, 1969.

[e] Sever, Nelson and Gilkeson, 1965.

[f] Lundstrom, 1962; Sever, Nelson and Gilkeson, 1965; Siegel and Greenberg, 1960; Siegel and Fuerst, 1966.

[g] Dixon and Brant, 1967.

[h] Patrick, 1967; Dixon and Brant, 1967; Stuart, Cummins and Chin, 1965.

[i] Sever, 1968

[j] Siegel and Fuerst, 1966.

An association between low birth weight and positive sero-conversion for *Toxoplasma* during pregnancy has been reported as well (Sever, 1970). Likewise, the birth weight of a group of children with toxoplasmosis was found to be an average of 600 g less than that of a control group (Alford *et al.*, personal communication). In Uganda, the mean weight of newborns with placental infection by *Plasmodium* was 260 g lower than that of a control group (Jelliffe, 1967).

Table 1, based upon data from U.S.A. populations, presents the principal agents that have been found able to produce intrauterine infections and fetal growth retardation. It appears that IUI induced by these agents may be the cause of up to one-quarter of all low birth-weight babies born in U.S.A. It thus appears that IUI may be an important determinant of LBW in industrialized countries. Given the high prevalence of IUI in developing countries its role as a determinant of LBW may also be very important.

In conclusion, the data reviewed strongly suggest that bacteriuria and IUI produced by rubella virus, *Toxoplasma*, cytomegalovirus, herpes virus, and *Plasmodium*, exert unfavorable effects on fetal growth. Because of the continuing high prevalence of malaria in many areas of the world, the effect of *Plasmodium* on fetal growth retardation may be a major public health problem, for other infections reviewed here, particularly syphilis, the evidence for an effect on fetal growth is doubtful.

Effects of Intrauterine Infection on Central Nervous System (CNS) Damage and on Mental Development

Studies of infection by cytomegalovirus have indicated a 20 to 100% presence of microcephaly (Daurelle, Smith and Reimer, 1958; Weller and Hanshaw, 1962; McCracken *et al.*, 1969d; Wolf and Cowen, 1959; Hanshaw, 1971). In 10 to 70% of these cases of cytomegalovirus, mental retardation was detected (Weller and Hanshaw, 1962; McCracken *et al.*, 1969d; Hanshaw, 1971; Kreeh and Jung, 1971; Feldman, 1969), generally at one year of age or later (Birnbaum *et al.*, 1969; Alford *et al.*, 1969a; Stern, 1968). Convulsions and mental retardation have been observed in fetal infection by western equine encephalitis virus (Finley *et al.*, 1955), Coxsackie B (Kibrick and Bernirschke, 1958; Delaney and Fukunaga, 1958) and polio virus. In addition, psychomotor retardation has been reported in 50 to 100% of cases of fetal infections by herpes virus (Epstein and Crouch, 1954; South *et al.*, 1969), and in 70 to 100% of those caused by rubella (Lundstrom, 1962; Weller, Alford, Jr. and Neva, 1965). In a group of 139 children with congenital deafness, 6% suffered from intrauterine infection by rubella (Gumpel, Hayes and Dudgeon, 1971). In contrast, no significant difference was found in the intellectual development of children with infection by influenza, cytomegalovirus, herpes virus, and mumps, occurring during the last trimester of pregnancy (Korones *et al.*, 1970).

Pleocytosis in the cerebrospinal fluid has been demonstrated in 45% of cases with congenital syphilis (Wolf and Cowen, 1959). It has been shown that more than half of the cases with congenital syphilis were clinically normal at birth and only began to show signs of mental retardation at 15 to 20 years of age (e.g. Wolf and Cowen, 1959). In a group of mentally retarded patients under institutional attention, approximately half of the cases whose retardment was due to infection, were children with congenital neurosyphilis (Poskanzer and Salam, 1968). The reported proportions of mentally retarded children that show positive serological tests for syphilis range from 3.8 to 9.2% (Wolf and Cowen, 1959). Elevated frequency of high titers of *Listeria* antibodies was demonstrated in a group of children with cerebral lesions (Lang, 1955), and in a series of 18 cases of congenital tuberculosis, 10 presented clinical signs of meningeal inflamation (Wolf and Cowen, 1959). From 21 cases of meningitis by gram negative bacteria acquired *in utero* 33% showed mental retardation (Ziai and Haggerty, 1958).

Fetal infections by *Toxoplasma* have been related to central nervous system damage since the first studies of Wolf, Cowen and Paige (1939). The five cases these investigators described from 1937 to 1939 suffered convulsions, and 3 of them presented choroidoretinitis and changes in the cerebrospinal fluid. At autopsy they showed disseminated granulomatous lesions where protozoa was identified. Eichenwald (1957) reported mental retardation and neurological alterations in 90% of a group of 115 cases observed until 5 years of age. Similar results have been notified by other authors (Frenkel, 1968; Sever, 1970).

In a cohort of 17 cases with subclinical congenital toxoplasmosis, all presented an increase in lymphocytes and proteins in the cerebrospinal fluid (Alford, Jr., 1971). The frequency of antitoxoplasma antibodies was 3 to 20 times greater in children with clinical evidence of mental retardation or neurological lesions, than in control groups (Frenkel, 1968; Thalhammer, 1962). The studies reviewed herein report two categories of damage due to IUI: lesions of the central nervous system evident from clinical, histological, electroencephalographic, and biochemical investigation (Wolf and Cowen, 1959; Gibbs, 1968), and mental retardation as estimated through clinical examinations, psychomotor tests, or IQ tests. Probably, less is known about the relationship of IUI to retardation, since techniques for detection of the latter are mostly effective when such retardation is severe. Furthermore, these techniques generally fail to provide information on the specific areas of intellectual function affected (Klein, Habicht and Yarbrough, 1973).

In addition, performance on IQ tests is intimately associated with non-intellectual characteristics of behavior. For example, the solution to test problems that require analysis of visual stimuli is influenced by the degree of impulsivity of the child (Kagan, 1966; Garcia-Romero, 1969). Other non-intellectual factors such as motivation to do well on the tests are also important determinants of IQ test performance (e.g. Anastasi, 1971), for all methods of diagnosis of a functional alteration are related to age, treatment, and the interacting effect of intellectual and social stimulation available to the child (Williams and Scarr, 1971).

Since the most complete data available for IUI agents implicated in CNS damage or mental retardation come from U.S. populations, we will first focus on these data to estimate the relative importance of IUI as determinant of fetal growth retardation. We will then examine their implications for developing countries.

Table 2 summarizes data for U.S. populations on the principal agents which produce intrauterine infection and alterations in the central nervous system. The total prevalence of infected newborns by these agents is around 1.4%. Although the information on said agents is heterogeneous and incomplete, the weight of evidence suggests that mental retardation appears to be more frequently associated with deafness in rubella, with microcephaly in cytomegalovirus and with convulsions and retinochoroiditis in toxoplasmosis.

The number of newborns with mental retardation due to cytomegalovirus, rubella and *Toxoplasma* are computed in Table 2. It appears that approximately 13.3% of all cases of mental retardation which occur in the United States are due to intrauterine infections produced by these three agents. Thus, we estimate that IUI due to these agents may have been responsible for about 15,000 mentally retarded children born in U.S.A. during 1975. Cytomegalovirus and *Toxoplasma* are probably the most important in terms of proportion of cases. This value of 13.3% is probably an underestimate because not all infections have been detected and because in most studies only cases of severe mental retardation have been identified. In spite of these limitations, available data suggest that in the U.S.A. a significant proportion of the mental retardation observed in children may be due to intrauterine infection.

The number of children with mental retardation due to intrauterine infection is probably 3 or 4 times higher in developing countries than in the United States, as a consequence of the higher intrauterine infection rates in preindustrialized countries to which we have previously referred.

In consequence, surveillance of infections produced by citomegalovirus, *Toxoplasma* and rubella may help to prevent, or at least, permit treatment of 13.3% of the cases of mental retardation occurring in the United States. Because of the great potential benefit of this approach, comprehensive action pro-

Table 2
Prevalence of Intrauterine Infection (IUI) Associated with Mental Retardation in U.S.A. Populations*

	(A)	(B)	(C)	(D)
Agent	Prevalence in newborns %	Prevalence of mental retardation in those infected, %	% of all newborns with IUI and mental retardation†	% of all mentally retarded children with IUI‡
Cytomegalovirus	1.10[a]	25[d]	0.275	9.2
Rubella virus	0.10[b]	4[e]	0.004	0.1
Toxoplasma	0.15[c]	80[f]	0.120	4.0
Total	1.35		0.399	13.3§

* Average estimates from prospective studies.
† Computed: A × B = C.
‡ Assuming that prevalence of mental retardation is 3%:
computed: $D = \frac{C \times 100}{3}$
§ Equivalent to 15,561 babies born during 1975.
[a] Hanshaw, 1971; Alford, Jr., 1971; Sever, 1968; Alexander, 1967; Stern, 1968; Starr and Gold, 1968.
[b] Alford, Jr., 1971.
[c] Alford, Jr., 1971; Couvreur and Desmonts, 1962; Sever, 1968.
[d] Hanshaw, 1971; Stern, 1968; Starr and Gold, 1968; Feldman, 1969; Birnbaum *et al.*, 1969; Weller and Hanshaw, 1962; McCracken *et al.*, 1969 d.
[e] Lundstrom, 1962.
[f] Couvreur and Desmonts, 1962; Frenkel, 1968; Eichenwald, 1957; Wolf, Cowen and Paige, 1939.

grams aimed towards the solution of this problem should be strongly considered.

Routes of Infection and Mechanisms

In most reported cases, IUI was produced through maternal blood and the placenta (Bernirschke, 1968; Overall and Glasgow, 1970; Flamm, 1968; Medearis, 1964). In other cases, particularly those infections produced by herpes virus and bacteria, the infection was produced through the vaginal route (Nahmias, Josey and Naib, 1967; Nahmias, Alford and Korones, 1970; South *et al.*, 1969), originating the "syndrome of amniotic infection" (Overall and Glasgow, 1970; Bernirschke, 1968). There are other possible routes of infection, including transmission through maternal ovaries (Mims, 1968).

A major mechanism of fetal growth retardation is probably the reduction of placental blood flow (Wigglesworth, 1964, 1969; Bernirchke and Hoefinagel, 1970) due to damage of the placental endothelium (Driscoll, 1969). Another important mechanism is inhibition of cellular multiplication, which results in hypoplasia (Rawls and Melnick, 1966; Plotkin and Vaheri, 1967; Boue and Boue, 1969; Fogh, Fogh and Ramos, 1971).

High frequency of chromosome ruptures have also been described in cases of intrauterine infection (Boue and Boue, 1969), leading to greater number of nonviable cells and therefore to lower growth rates. In addition, increase of catabolic rate (Beisel *et al.*, 1967; Feigin, 1970) and tissue hypoxia (Jelliffe, 1967) may play a role as mechanism of the effect of IUI on fetal growth retardation. In contrast, cellular necrosis is not an important mechanism of fetal growth retardation (Nacye, 1971).

Factors that Influence the Effect of Intrauterine Infection

An obviously important factor that influences the effect of intrauterine infection is the identity of the infectious agent itself. Thus, infection by rubella is consistently associated with growth retardation, whereas that produced by cytomegalovirus shows association with mental retardation, independent of physical growth. In the case of infections by *Plasmodium*, low placental and fetal weight frequently occur in the absence of mental retardation, whereas in toxoplasmosis; psychomotor retardation and low birth weight are associated.

Gestational age at which injury occurs is also of importance in determining the magnitude of the damage, its nature and reversibility. The infection is more dangerous if it occurs during the first months of pregnancy, since at this age many human organs, including the brain, are in the hyperplastic phase of growth (Winick, 1968, 1970; Winick[e] and Rosso, 1969). For example, in order to compromise the periventricular zone, as happens in infections by *Toxoplasma* and cytomegalovirus, the infection must take place around the 3rd or 4th month of gestation,

the stage at which this tissue is proliferating actively (Haymaker *et al.*, 1954).

Differences observed in fetal growth between children with congenital syphilis and those with rubella are probably due to the different age at which the fetus became infected (Naeye, 1971).

Another factor is severity of the infection, defined by the extension involved, duration, and localization of the lesions. Thus, generalized infections may produce greater damage than others affecting only the urinary tract. On the other hand, a lesion of functional areas of the brain will be more damaging in terms of later mental development than one localized in the relatively "silent" areas. Lastly, under similar conditions of extension and localization, processes of longer duration appear to cause more profound effects on fetal growth and development than short episodes.

Factors that modify fetal physiological status such as nutrition, are also important. If the diet of the mother or her placental circulation are not adequate, as occurs in malnourished mothers, IUI will probably aggravate the fetal nutritional deficit producing greater damage than might have been observed had the fetal nutritional status been adequate. Thus, the interrelationship between infection and nutrition during fetal life may be similar to that observed in postnatal life (Scrimshaw, Taylor and Gordon, 1968).

The magnitude and efficiency of the host immune response, may also influence effects of IUI. After the third month of gestation the fetus is able to produce immunoglobulins (Berg and Nilsson, 1969; Van-Furth, Schutt and Hymans, 1965; Gitlin and Biasucci, 1969), and components of the hemolytic complement system (Gitlin and Biasucci, 1969; Adinolfi and Gardner, 1967). At birth, it is able to show delayed hypersensitivity reactions (Uhr, Dancis and Neumann, 1960; Fowler, Jr., Schubert and West, 1960) and phagocytosis activity (Horman and Stiehm, 1969) similar to the adult. The efficiency of these mechanisms is enough to protect most newborns living in environments with a high risk of infection (Altemeier and Smith, 1965; Silverstein, Prendergast and Parshall, 1970; Rothberg, 1969; Evans and Smith, 1963).

In most IUI immunologic reactions of fetal origin have been demonstrated (Eichenwald and Shinefield, 1963; Alastair *et al.*, 1969; Huntley *et al.*, 1969; Serra *et al.*, 1967). Nevertheless, in some cases (Singer *et al.*, 1969; Epstein and Crouch, 1954, Hardy, Sever and Gilkeson, 1969b) the reactions have appeared late or have not been detected, which implies alteration of the ability to identify the infectious agent as foreign to the host organism. This observation has been reported in some infections produced during the first trimester of gestation (Soothill, Chandra and Dudgeon, 1969; Schimke, Bolano and Kirpatrick, 1969; Hardy *et al.*, 1969a) and it has important implications for immunological theory.

Maternal mechanisms of defense also play an important role in influencing the effect of IUI. Most of the antibodies produced by the mother are IgG type and therefore pass to the fetus (Kohler and Farr, 1966; Connell, Connell and Tidd, 1967; Osborn, Dancis and Rosenberg, 1956; Gitlin *et al.*, 1964; Gitlin and Koch, 1968). In many reported cases, maternal viremia or bacteremia occurred due to the lack of previous contact of the mother with the agent. In infections via the vagina, the passage of antibodies and other factors from the mother to the fetus may also be important in the protection of the fetus (Davies, 1971).

Other variables may produce retarded fetal development as well. In chronically malnourished populations, maternal protein-calorie nutrition exerts a definite effect on fetal growth (Lechtig, *et al.*, 1971b, 1972a, 1975) and probably also on mental development (Klein *et al.*, 1976). Maternal thyroid hormone level may affect as well fetal mental development with thyroid deficiency clearly resulting in cretinism (e.g. Stanbury *et al.*, 1974) Maternal characteristics such as size, parity and birth interval, affect fetal growth (Thomson, 1970; Lechtig *et al.*, 1972c; Lechtig *et al.*, 1975). Toxemia of pregnancy (Buck *et al.*, 1969) can affect physical growth as well as the mental development of the child. Lesions produced as a consequence of abnormal delivery can result in sequelae to the central nervous system (James, 1970; Méndez-Bauer *et al.*, 1970).

In populations of low socioeconomic level, the risk of intrauterine infection (Alford *et al.*, 1969a; Lechtig and Mata, 1971, 1972) is as great as the prevalence of maternal malnutrition (Arroyave, Méndez and Ascoli, 1970; Naeye and Blanc, 1970a,b; Lechtig *et al.*, 1971a; Béhar, 1968; Gordon, 1968; Terris and Gold, 1969; Baird, 1947; Eisenberg, 1968; Birch and Cravioto, 1966; Naeye and Blanc, 1970a,b; Cravioto *et al.*, 1969). Due to the lack of medical care, the frequency of dystocias in such populations may also be much greater than in industrialized societies (Föllmer, 1964).

Comments

Problems are encountered in the interpretation of the literature reviewed particularly because study designs are not often appropriate. For example, in most studies control groups were not adequate or simply did not exist, and the number of subjects investigated was very small. It is thus difficult to draw reliable conclusions from these data, useful for public health policies (Katz, 1968).

In the past, insufficient attention has been paid to the problem of effects of intrauterine infections. However, important questions from a public health point of view arise: What is the prevalence of infections *in utero* by socioeconomic group and

etiological agent? What proportion of growth and what proportion of mental retardation in a specific population are attributable to intrauterine infections? What preventive measures should be taken?

In order to obtain more precise answers to these questions, it is advisable that future studies satisfy the following conditions:

(1) The methodology employed should be adequate to the task of obtaining information on intrauterine infection, and on evaluation of fetal growth and psychological development.

(2) The population under study must include a sufficient number of subjects both in the experimental and control groups.

(3) Data analysis should include comparisons to control groups whose only significant difference from the experimental group is the absence of intrauterine infection.

(4) In order to have reliable information on the cause-effect nature of this relationship, children must be studied since conception in a longitudinal design developed prospectively.

Satisfaction of these conditions requires long-term and relatively costly studies. However, their expense is justified given their promise of making possible more efficient utilization of public health resources.

Summary

A review of the effects of intrauterine infection on fetal growth and mental development in human populations is presented. The evidence suggests that infections caused by *Toxoplasma*, rubella, cytomegalovirus, *herpes simplex* and syphilis retard fetal development principally by decreasing placental blood flow and diminishing mitotic rate in fetal organs.

The estimated prevalence of intrauterine infection (IUI) oscillates between 0.3 and 5.0% for industrialized countries, and may be as high as 10% for less developed countries (LDCs). The degree of injury depends on the type of infectious agent, fetal age, severity of the infection, nutritional status of the fetus and efficiency of the immune response. Furthermore, in developed countries such as the U.S.A., intrauterine infections may be responsible for about a quarter of low birth weight (LBW) babies, and approximately 13 percent of all cases with mental retardation. The absolute number of LBW babies and mentally retarded children produced by IUI in developing nations may be much higher.

Because of its implications for better use of public health resources, it is recommended that further studies in this area be carried out with adequate design and methodology.

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