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Intrauterine Growth Retardation in Africa

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In 1979, some 21 million low birthweight babies (<2,500 g) were born in the world. This represents about 17% of all births in that year (1). In those countries where the proportion of low birthweight is the highest and where action is needed, data on birthweight are scarce or even non-existent. The relative influences of genetic factors and environmental factors (socioeconomic, cultural, health) are still poorly elucidated.

Morbidity and neonatal mortality are higher in low birthweight babies than in those of normal weight, and among survivors, there is a higher incidence of neurological handicaps and mental retardation. Infections occur more frequently and are more severe and longer lasting after intrauterine growth retardation (2). In countries with high rates of low birthweight, there is an urgent need to promote measures aimed at reducing the environmental causes of intrauterine growth retardation, such as maternal diseases, chronic undernutrition, and poor socioeconomic conditions. However, effects and side effects of specific preventive interventions such as food supplements, chemoprophylaxis of malaria, etc., have not been thoroughly investigated so far. Therefore, no consensus can exist on health and social programs to be initiated. A prerequisite for any further progress is that birthweight should be more systematically measured.

EPIDEMIOLOGY

Low birthweight (<2,500 g) is a public health concern in Africa. It is, however, difficult to obtain an accurate evaluation of the incidence of low birthweight babies in this part of the world, since only a rather small number of babies born in Africa are weighed. Most data on birthweight available in Africa are from hospitals (3), but the majority of mothers are not delivered in hospital. In Nigeria, for example, most deliveries take place at home assisted by elder multiparous women, traditional birth attendants, or by herbalists; or in church dispensaries or private maternity homes (3). In Lagos, 46% of babies are born in hospitals while in the Kainji Lake area this figure falls to 2.6% (4). Average birthweights often tend to increase from teaching hospitals, through non-teaching hospitals and health centers, to homes. For exam-

TABLE 1. *Mean birthweight, rates of low birthweight, and rates of low birthweight for gestational age > 37 weeks in Africa*

Country	Region or city	Year	Number	Mean weight (g)	Percent < 2500 g or < 37 weeks	Percent < 2500 g and > 37 weeks
Western Africa						
Guinea-Bissau		1977	3,239	3,229	8.0	
Ivory Coast	Abidjan	1975	7,154	2,950	14.1	
Nigeria	Ibadan	1968–72	10,839	2,920	19.2	60
	Ibadan	1973–74	1,290	3,053	24.9	43
	Ibadan	1968–72	20,651	2,940	15.3	60
	Igbo-Ora	1971–75	4,334	—	11.0	
	Katsina	1975–76	1,460	3,030	15.8	
	Lagos	1966	9,104	3,230	13.1	
	Benin	1970–71	4,821	3,033	10.8	
Senegal	Dakar	1959	8,409	3,115	9.9	
Eastern Africa						
Ethiopia	Addis Ababa	1964–68	8,469	3,132	8.8	
	Addis Ababa	1971	3,144	3,139		
Kenya	Nairobi	1971	3,160	3,345	13.6	34
	Nairobi	1974	3,700		18.9	34
	Nairobi	1975	1,595		17.5	
	Nairobi	1971	14,326	3,143		
Rwanda		1971	7,929	2,890	17.0	
Tanzania	Dar es Salaam	1964	8,139	2,950	11.0	
	Dar es Salaam	1973	2,070	3,117		
	Dar es Salaam	1975–76	16,532	2,991	15.2	
	Dar es Salaam	1976–77	2,828	2,906	22.3	
	Moshi	1960–63	2,166	3,040	10.1	
	Moshi	1971–72	1,251	3,151	2.0	
	Tanga	1955–60	3,355	2,970		
	Tanga	1966	1,000		11.2	56
	Nzega	1955–60	2,007	2,900		
Zambia	Kitwe	1971–72	2,401		14.2	
Middle Africa						
Central African Republic		1973	19,496	2,873	23.0	
Chad		1965	3,000	3,114	10.5	
Gabon		1970–72	7,032	2,979	13.0	
Cameroun		1971–73	8,071	3,119		
Zaire	Lubumbashi	1969	5,206	3,163	12.6	
	Rutshuru	1983	1,121	2,850	16.6	
	Kabare	1983	1,224	2,940	13.6	
	Bagira	1983	806	3,020	6.7	
Southern Africa						
South Africa	Capetown	1964–65	4,657	3,050	14.9	42
	Capetown	1964–65	2,045	3,300	8.2	38
	Johannesburg	1971–72	1,800	883	19.5	73

Data from ref. 1 and ref. 6 for series of more than 1,000 deliveries.

ple, mean birthweight in Oluyoro Hospital, a mission hospital in Ibadan (Nigeria), is significantly higher than that of babies born in the University College Hospital (UCH) (5). This can be expected, since the University Hospital delivers more women with abnormal obstetric cases. There are fewer low birthweight babies in urban areas (6.7%) than in rural areas (13.5%–19.6%), as seen in Kivu (Table 1) (6). Data collected in only one hospital or only one health center are therefore rarely representative of the region where the hospital is located, and even less of the entire country.

Another difficulty is that in most cases the date of the last menstrual period is not available. This makes it difficult to differentiate between preterm deliveries and cases of intrauterine growth retardation (IUGR). As the date of the last menstrual period is generally not known, the maturity of the newborn has been evaluated in recent studies with reference to a scale of maturity (7). Unknown menstrual period is associated with high rates of low birthweight and with low socio-economic and socio-demographic status: these characteristics are themselves associated with a high rate of preterm deliveries (8). Thus, deleting the group of women with unknown last menstrual period may bias epidemiological studies on low birthweight and the consequences of such a choice must be carefully checked.

In Africa, the rates of low birthweight (<2,500 g) vary greatly from one study to another, sometimes within the same country (Table 1). They range between 8% and 25%. The average value estimated in 1980 for the continent was 15% (1). Average values estimated for Northern (13%), Western (17%), Eastern (14%), Middle (15%), and Southern (15%) Africa were fairly uniform (1). The mean birthweight in Africa is about 3,000 g, in comparison with 3,100 g in Latin America, and 3,200 g in Europe and Northern America (1).

ETIOLOGY

Olowe reported on the relation between birthweight and gestational age (from 26 weeks) in 436 newborn African infants delivered by healthy Nigerian mothers from middle to high socio-economic social classes, living at sea level and taking prophylactic antimalarial drugs, iron, and folic acid routinely throughout pregnancy (9). The growth curve based on these data is identical to the curves reported for newborns delivered by healthy mothers in industrialized countries (10,11).

The proportion of low birthweight babies with gestational age of >37 weeks is less frequently recorded. It appears to range from 34% to 74% of low birthweight babies in Africa. In a group of 250 low birthweight babies from Baragwanath Hospital (Johannesburg, South Africa) Stein and Ellis (12) observed that 73% were small-for-gestational age. Toxaemia (9%) was not a very important factor. "When the incidence of low birthweight is higher than 10%, it is almost exclusively due to the increase of intrauterine growth retardated low birthweight infants, while prematurity remains almost unchanged" (13).

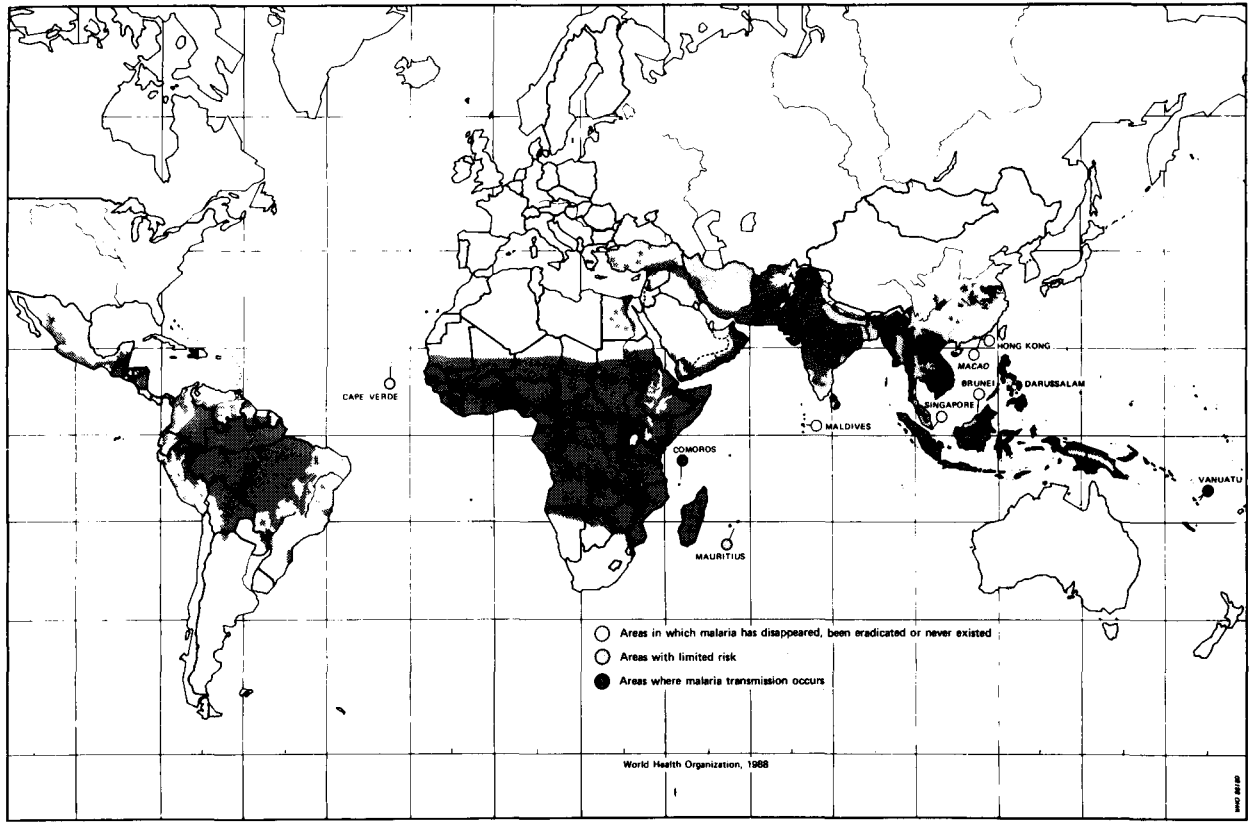

FIG. 1. Geographic distribution of the areas where malaria transmission occurs and of the areas where the risk of transmission is limited: world situation in 1986. (From ref. 14.)

MALARIA

Malaria remains one of the last plagues of mankind. Half of the world population is confronted with Plasmodium. Extensive successes have been obtained by antimalarial campaigns based on eradication of the anopheline vectors and on the reduction of the human source of Plasmodium by chemoprophylaxis (14). However, a new expansion of the disease has been observed in Asia, South America, and to a lesser extent, in Africa. This derives from the selection of strains of anopheline vectors resistant to insecticides and strains of *Plasmodium falciparum* resistant to quinine derivatives (14).

The malaria areas are located between the tropics of Cancer and Capricorn where almost half of the world population lives. Africa is the continent where the malarial endemic is of the greatest concern: Some 39 million people live in hypoendemic areas, about 115 million in mesoendemic zones, and 231 million in areas where malaria is hyperendemic to holoendemic (Fig. 1). About 1 million children die every year as a direct consequence of the disease. As children and pregnant women represent the high-risk groups for malaria, this results in an excess of low birthweight babies and of neonatal and infantile morbidity and mortality (15).

In epidemic conditions, in a population with a rather low level of immunization, such as that reported from Ceylon in 1934–35 (16), Saigon (17), and Malaysia (18), malaria is highly virulent, leading to frequent maternal death, high rates of abortion, stillbirth, and premature deliveries. In these conditions, *in utero* infection of the fetus and congenital malaria are frequent, too. Where malaria is endemic and where adult women have acquired protective immunity through repeated prior infections, it is agreed that during pregnancy women show an increased prevalence and density of malaria. But the effects of the disease on pregnancy are less apparent and not yet completely understood. This situation prevails in most parts of tropical Africa. Clark (19) and Blacklock and Gordon (20) were the first to report that placental malaria is a common feature at parturition in endemic conditions, and that it is asymptomatic in most cases. This has since been largely confirmed throughout tropical Africa, with incidences of placental malaria varying from 15% to 85%, and usually higher than those of peripheral parasitemia found in the same women (21).

PARASITEMIA AND PLACENTAL INFECTION

Placental infections are sometimes substantially heavier than suggested by the density of parasites in peripheral blood: the placenta may contain a large number of infected red blood cells (up to 65%) while the peripheral blood is free from parasites (21). Erythrocytes infected by *Plasmodium falciparum*, which in Africa is the most common cause of pregnancy malaria, are sequestered in the human placenta (22). Erythrocytes containing *Plasmodium falciparum* develop electron-dense excrescences at the cell surface, called knobs (23). These knobs adhere to endothelial cells

and form focal junctions with the endothelial cell membrane. This phenomenon is likely to contribute to the observed sequestration of mature erythrocytic forms of *Plasmodium falciparum* in the deep organs (24).

Placental malaria occurs more frequently (27%) in residents of rural communities than in those of urban ones (12%). Furthermore, in some areas there are seasonal variations in the prevalence of the parasitemia. It is highest in the 3 months following the end of the rainy season and lowest in the second half of the dry season (25).

It has been suggested that the higher prevalence of malaria during gestation is due to a decrease in the immune response of pregnant women. However, there have been several observations which do not support this idea. For example, the specific tetanus antibody response (IgG) in pregnant women is comparable to that in non-pregnant healthy adults. No apparent influence of gestational age on the immune response to the absorbed tetanus toxoid has been observed during pregnancy (26). Field studies in an area of stable malaria showed that mean serum levels of IgG and IgA were depressed during pregnancy, the lowest levels being observed during the last weeks of gestation (27). However, although protective antibodies against malaria are of the IgG type, assays of specific malarial antibodies in relation to pregnancy have failed to yield consistent results, and most authors have not found any significant difference in anti-malarial antibody titers between pregnant and non-pregnant women when aparasitemic, even in primigravidas (25,28,29). In Gambia, during the wet season of August, the prevalence and the density of parasitemia and also the specific antibody levels increase in pregnant women, just as in other adults and in children (28). This also favors the concept that the immune response to malaria is not impaired during pregnancy. Furthermore, the extreme rarity of congenital malaria in newborns throughout regions in which the disease is highly endemic seems to argue against any serious breakdown of anti-malarial immunity during pregnancy. Malarial antibodies are readily demonstrable in sera from Gambian newborns. They are responsible for the "relative freedom that the infant born in highly endemic areas appears to enjoy over the early weeks of life" (25). Finally, the increased prevalence and severity of malarial infection takes place early in pregnancy, with progressive recovery to non-pregnant levels close to delivery (21). This development bears no relationship to changes in immunoglobulin concentrations, since IgG declines progressively to reach the lowest levels at the time of delivery or even during the postpartum period (30).

An alternative explanation would be that a pregnancy-specific factor enhances the virulence of the Plasmodium. The trophoblastic origin of such a factor and its local production would explain the high density of parasites seen in the intervillous spaces: The idea of the pregnant uterus acting as a haven of safety for the parasite is not new, since Clark (19) proposed it in one of his earliest papers describing placental malaria. Studies conducted in areas of perennial transmission revealed that the prevalence of parasitemia increases rather early in pregnancy, with a calculated peak at around day 100 of gestation (21). Thereafter the prevalence of infection pro-

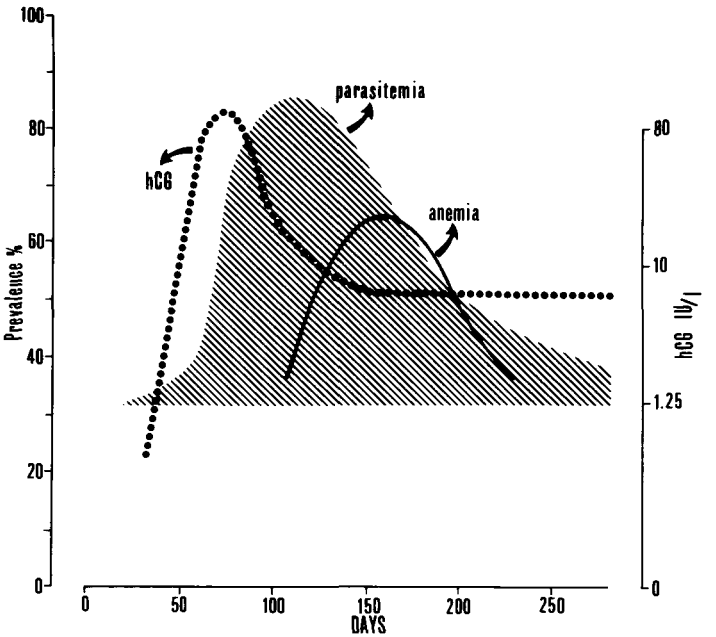

FIG. 2. Prevalence of malaria infection (parasitemia) and hemolytic anemia associated with splenomegaly in primigravidas, together with the development of human chorionic gonadotrophin (hCG) in urine during pregnancy. Day 1 = first day of last menstrual period. (From ref. 21.)

gressively declines and at the end of pregnancy it is only slightly higher than the level seen in non-pregnant women. The curve published by Brabin (21) runs parallel to that of the blood concentration of human chorionic gonadotrophin (hCG) during early pregnancy (Fig. 2).

The concept of pregnancy-induced immunosuppression also does not satisfactorily explain why primigravidas are much more susceptible than multigravidas to malarial infection during pregnancy, the prevalence of both parasitemia and placental infection being twice as high (21). Densities of infections are also higher in primigravidas (28). The significance of such differences is not known. However, the lower prevalence of parasitemia during pregnancy in multigravidas may simply be the consequence of the development of the age-dependent immunity against the parasite. In Africa, at the time of their first pregnancy, almost all women are below 20 and may not have yet acquired the optimal immune protection. If one considers the first pregnancy as a challenge due to an increased virulence of the infection under the influence of some specific pregnancy factors, then the difference in prevalence between primigravidas and multigravidas can be interpreted as the result of the higher degree of immunity developed in response to malarial infection in the first pregnancy (21).

PLACENTAL LESIONS

Galbraith et al. (31) and Walter et al. (32) produced a detailed histological and ultrastructural study of placentas from mothers infected with malaria. They developed techniques for the recognition of hemozoin, the brown malarial pigment, and parasites in the placenta. Thickening of the trophoblastic basement membrane is seen in all infected placentas. Monocytes containing phagocytosed pigment are found in the intervillous spaces. In heavily infected placentas, monocytes form aggregates or pseudo-inflammatory masses in the intervillous spaces, together with fibrin and parasitized erythrocytes. In these cases, malarial pigment is also observed in the cytoplasm of the trophoblast. This is associated with focal syncytial necrosis and cytotrophoblastic proliferation. The ultimate stage of villous necrosis is the formation of clumps of fibrinoid. In most placentas, a few deposits of pigment are apparent within the Hofbauer cells and within the stroma of scattered healthy villi. Even in placentas with dense parasitemia in the intervillous spaces, no plasmodias are seen in the placental tissue (32). Parasites are seldom found in cord blood, as congenital malaria is exceptional in areas of endemic malaria (33,34).

In practice in regions where malaria is endemic, malarial pigment and thickening of the basal membrane of the trophoblast are often seen in the absence of peripheral and placental parasitemia. Infected maternal erythrocytes were found in only some 40% of the placentas with malarial lesions (32). Conversely, parasitemia in maternal peripheral blood at the time of delivery is not necessarily associated with malarial lesions of the placenta: Only some 50% of parturient women with peripheral parasitemia had typical lesions in the placenta (32). Similar observations were reported by Watkinson and Rushton (35) in a study on the outcome of pregnancy in West African mothers. In 9 out of the 12 women with parasitemia but unpigmented placentas, however, malarial parasitemia had been last detected before 20 weeks of gestation. Thus when infection takes place early in pregnancy, the pigment may be "cleared" from the placenta, at least in some cases. The fact that the peak of monthly incidence (October–November) of placental pigmentation was synchronous with the peak incidence of parasitemia provides further evidence that pigmentation is associated with a relatively recent infection. According to Watkinson and Rushton (35), microscopic examination of biopsy specimens, even full-thickness slices of the placenta, may not always detect focal placental lesions. This could help to explain some of the discrepancies between the rate of placental lesions and the prevalence of parasitemia.

BIRTHWEIGHT

It has been consistently reported that the birthweights of infants born of mothers with infected placentas were lower than those of infants born from non-infected mothers: The differences in weights vary from 55 g to 310 g (34–46) (Table 2). There is a slight excess of female births (n = 150) over males (n = 120) in the series

TABLE 2. *Influence of placental malaria on birthweights in Africa (1952–1983): Positive mothers are mothers with placental malaria*

Ref.	n	Placental malaria (%)	Mothers positive for placental malaria: Mean birthweight (g)	Mothers positive for placental malaria: < 2500 g (%)	Mothers negative for placental malaria: Mean birthweight (g)	Mothers negative for placental malaria: < 2500 g (%)	Difference in weight
Bruce-Chwatt (36)	310	23.5	2,903	20.5	3,048	11.0	145
Archibald (37)	463	14.7	2,722	29.4	2,892	16.5	170
Archibald (38)	440	14.1	2,776	21.0	3,076	8.2	298
Cannon (39)	392	33.2	2,610	36.9	2,920	12.2	310
Spitz (40)	576	23.6	—	41.2	—	27.0	89
McLaren and Ward (41)	400	21.5	3,037	14.0	3,092	7.3	55
Jelliffe (42)	570	16.1	2,085	19.6	3,063	10.0	263
Jilly (43)	50	43.7	2,855	—	3,033	—	178
Kortmann (44)	413	34.1	2,945	—	3,020	—	75
Reinhardt et al. (45)	198	33.7	2,960	—	3,080	—	120
Walter et al. (46)	115	34.7[a]	2,770	—	2,920	—	220
Watkinson and Rushton (35)	65	41.5[a]	2,580	—	3,150	—	570[b]

[a]Placentas with malarial lesions.
[b]Difference calculated only for first-born babies.

of babies with infected placentas reported by McLaren and Ward (41) and by Jelliffe (42): The sex ratio (male/male + female) was 0.44 when it is classically over 0.50 at birth. It should be remembered that during the last trimester of pregnancy, the trophoblast of female fetuses produces more hCG than that of males (47). In areas of endemic malaria, there is no clear association between placental malaria and stillbirth or maternal death (34).

Chandra (48) has reported impaired T-cell function in infants who are small for their gestational age, a feature widely accepted as evidence of fetal malnutrition. This impaired T-cell function persists during the first months and even years of life and may adversely influence the infant's prospects for survival. To date, no studies have determined whether infants with low birthweight resulting from placental malaria show similar immunologic defects.

Reduction in birthweight associated with placental infection is greater in primigravidas, with mean reported values of 321 g (42) and 636 g (49). In some studies, it is even statistically significant only in first born infants (34). Dense placental infection is also more frequent in primigravidas. Birthweight deficits tend to be the

greatest in association with the highest parasite density and this is particularly true for first born children (34). In order to understand the relation between placental malaria *(Plasmodium falciparum)* and impaired fetal growth, McGregor and Avery (50) investigated the consequences on birthweight of a malaria eradication campaign initiated in the British Solomon Islands. The main antimalarial measure employed was spraying DDT in order to kill as many adult female anopheline mosquitoes transmitting malaria as possible. Birthweights rose substantially within a few months after starting the antimalarial operations. The average increase between 1969 and 1971 was 165 g for all babies and 252 g for the first born babies. The rate of low birthweight babies (<2,500 g) declined from 21% to 12% for all newborns and from 41% to 21% for first borns. During this period, the consumption of antimalarial drugs did not increase.

Taking biopsy specimens from 65 placentas in a region where *Plasmodium falciparum* malaria is endemic and where pregnant women traditionally receive only curative treatment for parasitemias and no chemoprophylaxis, Watkinson and Rushton (35) reported a 40% rate of pigmented placentas, i.e., with macrophages containing phagocytosed malarial pigment in the intervillous spaces. Parasitemias had been diagnosed antenatally in only 18% of these women despite frequent antenatal follow-up. Primigravidas had the highest incidence (67%) of pigmented placenta and of parasitemia. Mean birthweight of babies with pigmented placentas was lower than that of babies with non-pigmented placentas: The difference was the greatest for first born babies (570 g). All babies weighing less than 2,500 g at birth had pigmented placentas. The mean gestational age and the rate of preterm babies were the same whether the placenta was pigmented or not. The presence of malarial pigment did not influence the weight of the placenta (35).

In the same group of mothers, Watkinson et al. (51) also reported lower plasma estradiol levels in those who delivered babies with pigmented placentas. This was significant from the 32nd week of pregnancy. The plasma progesterone levels also tended to be lower. More recently, similar results have been obtained for estriol (52) and for human placental lactogen (53). All these endocrine changes seen during late pregnancy in mothers with pigmented placentas indicate that malarial infection causes damage to the trophoblast. These are likely to be responsible for intrauterine growth retardation. However, peripheral parasitemia is not a good marker of the morbidity of the fetoplacental unit. "As pigmented placentas were related to low birthweights and weights for gestational age whereas non-pigmented placentas, even in women with early parasitemias, were not, it may be only the later parasitemia and later placental infection that cause major morbidity for the feto-placental unit" (35).

Since, in the Gambian study, less than half of the women with pigmented placentas had parasitemia detected and treated during pregnancy, many of the malarial episodes must have caused either trivial symptoms or no symptoms at all. Neither the easily accessible daily clinic nor regular antenatal clinics ensured diagnosis and adequate protection against the morbidity of placental infection (35). Thus in regions of Africa where malaria is endemic, curative treatment for parasitemia is ineffective in preventing placental lesions and fetal growth retardation.

Since malarial lesions of the placenta cannot be predicted by detection of peripheral parasitemia, all pregnant women in endemic malarial areas should be given antimalarial chemoprophylaxis. This should start early and at least during the second trimester of pregnancy: the crucial period for protection of the feto-placental unit is, according to Watkinson and Rushton (35), the last trimester of pregnancy. The limited number of studies that have been undertaken so far show that chemoprophylaxis of malaria produces a fall in malaria antibody levels in protected populations and that the magnitude of the fall is related to the efficiency of the control program. It is unlikely, however, that pregnant women with established immunity to malaria will lose this immunity as a result of taking chemoprophylaxis for only a few months during pregnancy, although the situation may be different in children (54). Therefore, effective antimalarial measures result in reduced rates of parasitemia, anemia, fetal and maternal morbidity, and intrauterine growth retardation.

UNDERNUTRITION

Data on the influence of maternal malnutrition on birthweight came from observations made in Europe during the Second World War. The siege of Leningrad (55) and the Dutch situation in 1944–45 (56) are usually quoted as examples of a significant decrease of birthweight, by 500 g and 250 g, respectively, resulting from acute starvation. It was also reported that birthweight was reduced more when the restriction took place during the last trimester of pregnancy: The mean birthweight of infants born 9 weeks after the end of the starvation period was higher than that of infants born at the end of this period (56). In Ethiopia, the absence of further intrauterine growth of the fetus observed between the 36th and 40th week of gestation is considered to be the consequence of poor nutrition of the mother (57). However, altitude might also be a factor since the population investigated lives 2,500 m above sea level (58). A diet deficiency in all nutrients during the third trimester of pregnancy in healthy young non-privileged primigravidas results in the delivery of babies 470 g lighter than those delivered from similar women of the privileged group (59). In some regions of Africa, such as Ethiopia and Kenya, pregnant women purposely reduce their diet for fear of having big babies and difficult deliveries (60).

Seasonal variations in food supply influence the birthweight as well. The lowest mean birthweights were recorded in Ethiopia during the pre-harvest season when staple foods were scarce and prices at a maximum and when this period coincided with pregnancies in the third trimester (58). In Nigeria the mean birthweight of babies born from primiparas during the months of May–August, which corresponded to the rainy season, was significantly lower than for the other months of the year. However, this period of May–August is also a period of high malaria parasitemia in addition to food shortage (61).

The growth rate of the fetus is not only influenced by the energy supply to the mother but also by her energy consumption. Indeed, heavy physical labor during pregnancy affects the birthweight when mothers have energy intakes below WHO/FAO-recommended standards (62). In this study, the low energy and protein intakes

were not entirely due to limited family income. Full-term infants of mothers engaged in heavy physical labor had a mean birthweight (3,060 g) significantly lower (3,270 g) than that of infants born from less physically active mothers on a similar low energy diet. Physically active mothers gained less body weight during pregnancy (3.3 kg) than the less active mothers (5.9 kg). Thus, in a situation of borderline energy balance, such as in chronic undernutrition, the mother still continues to gain weight during pregnancy, even if weight gain is reduced to a minimum and even if this results in a significant although limited decrease in birthweight.

Change in third trimester skinfold measurements is a good predictor of birthweight. Changes in skinfold thickness reflect changes in maternal fat stores (63). In well-nourished women, 3 kg of fat are stored before the 30th week of gestation (64). Part of this is supplied to the fetus during the last trimester, when fetal growth rate is at its highest. Fat storage correlates with an increase in triceps skinfold thickness during the first two trimesters of pregnancy, and a progressive decrease of the skinfold during the last 3 months (63). Deficit in energy intake both limits the normal increase of skinfold thickness during pregnancy and reduces birthweight. In Ethiopia, women with very thin triceps skinfold in early gestation gave birth to infants weighing less than 2.9 kg. Women with large triceps skinfold and whose skinfold decreases during the third trimester produce heavy neonates (>3.2 kg).

ANEMIA

In many tropical areas, anemia is caused or aggravated by parasitic diseases, mainly malaria and intestinal parasites such as the hookworm (>2,000 eggs per g of feces). During pregnancy the hemoglobin iron of the mother increases by 500 mg. The total iron needed during the whole of pregnancy is about 1,000 mg. The daily requirements are six times greater during the last trimester than in non-pregnant women. In normal conditions, half the total requirement of iron comes from the iron stores. Abortions, premature births, low birthweight, and postpartum hemorrhage are associated with low hemoglobin levels during pregnancy (65). Anemia is more frequent in mothers giving birth to low birthweight babies. In Togo (66), 24% of such mothers are anemic in contrast to 10% in the group of mothers delivering babies weighing more than 2,500 g Kessel et al. (67) reported that the duration of pregnancy is independent of the anemia status. Thus, anemia is an important correlate of intrauterine growth retardation.

Anemia related to malaria in pregnancy is common. It is usually hemolytic. There is however no direct association between the hemoglobin level and the prevalence of parasitemia during pregnancy. In children, the peak incidence of anemia and splenomegaly follows the period of acute malarial infection. In pregnancy, patients with hemolytic anemia and splenomegaly are observed between the 16th and 24th week, coinciding with the peak of acute infection (21) (Fig. 2). Immunological factors seem to play an important role in the etiology of anemia associated with malaria: A reduction in red blood cell life span persists for several weeks after the acute

infection (68). Secondary megaloblastic anemia may occur, but later in pregnancy. This may have important consequences for the child. The peak of the prevalence of anemia before the 24th week of pregnancy is not suppressed by the sole administration of antimalarials at this time. Indeed, antimalarials given after 20 to 28 pregnancy weeks do not correct established anemia unless folic acid is given as well. However, chemoprophylaxis initiated from early pregnancy was successful in preventing pregnant women developing hemolytic anemia.

Iron is essential for the development of *Plasmodium falciparum*. It seems that in erythrocytes, parasites do not take iron from hemoglobin. There is no metabolism of the iron-containing moiety of hemoglobin. No parasite enzymes that degrade hemin have been identified. Hemin is even toxic to parasite carbohydrate metabolism. How then is it that iron is sequestered in infected red cells as hemozoin, the characteristic malarial pigment? The answer is that *Plasmodium falciparum* synthesizes a transferrin receptor and localizes it at the surface of the infected erythrocyte, allowing iron transfer to the parasite: Red cells lose their own transferrin receptor during erythrocyte maturation (68).

High frequencies of α-thalassemia and of sickle cell disease are the result of natural selection by malaria (69). However, in areas of high transmission, antimalarial immunity acquired by adult women is sufficient for the sickle cell trait to confer no advantage. The situation is different for children: Individuals with the sickle cell gene are more resistant to attacks of severe malaria. Parasite invasion of red cells and parasite growth within these cells are decreased when they contain sickle hemoglobin, but only under low oxygen tension as in deep tissues (70). Peak prevalence of parasitemia occurs before 24 weeks of gestation in women with the sickle cell trait as in women without the gene (71). Its amplitude is the same for the two types of pregnant women. Sickle cell anemia is seldom encountered during pregnancy in Africa, since most homozygous subjects do not reach adulthood as a result of the high mortality due to malnutrition and associated infectious diseases (72). The presence of the sickle cell trait, encountered in 20 to 25% of people from West Africa, is largely an asymptomatic condition and is not of great hazard in pregnancy for either mother or child (73). However, urinary tract infections and hematuria are more frequent in pregnant women with the trait. In the West Indies, the mean birthweight of babies born from women with the sickle cell trait was found significantly lower than that of a matched population without the trait (74). A similar observation has been made by Hoff et al. (75) in a population of black pregnant women in Alabama (USA). Mean femur lengths were found to be reduced at each gestational period when compared with similar measurements in women with normal hemoglobin (74).

TEENAGERS

In the Nairobi Birth Survey, conducted from June to August 1981, teenage mothers, aged 19 and below, were 19% of the total group. The rate of low birthweight

among teenagers was 18% (76). In a large series of deliveries in Nigeria, the incidence of low birthweight rate among the Hausa was 27% in mothers aged less than 15, 26% in mothers aged 15 to 19, 20% in those aged 20 to 24, and 18% in the 25 to 29 year age group (77).

The mean birthweight increases with parity up to the third (78), fourth (77), or fifth (44) pregnancy and with maternal age up until 34 to 36 years (57,77).

TWINS

The high rate of twins in some populations of Africa sometimes contributes importantly to the high rates of low birthweight babies. Among the Yorubas in Nigeria and in Ethiopians, twins represent about 5% of all births (57,79,80). In Togo, among 888 newborn babies with low birthweight (<2,500 g) investigated by Bégué et al. (81), 165 were twins (18.2%). Babies from multiple pregnancies represented 22% of all low birthweight infants in Hausa, Northern Nigeria (77) and 25% in Yoruba, Western Nigeria (5,82). In a group of 250 low birthweight babies, Stein and Ellis (12) found 26% were twins. This represented 32% of the babies who were small for their gestational age.

REFERENCES

1. World Health Organization, Division of Family Health. The incidence of low birthweight. A critical review of available information. *World Health Stat Q* 1980;33:197–224.
2. Xanthou M. Immunologic deficiencies in small-for-date neonates. *Acta Paediatr Scand* 1985;319:143–9.
3. Ransome-Kuti O. Intra-uterine growth, birthweights and maturity in the African newborn. *Acta Paediatr Scand* 1985;Suppl. 319:95–102.
4. Morley D, Knox G. The birthweights of Yoruba babies. *J Obstet Gynecol* 1960;67:975–80.
5. Effiong CE, Laditan AAO, Aimakhu VE, Ayeni O. Birthweight of Nigerian children. *Nigerian Med J* 1976;6:63–8.
6. CEMUBAC. Rapport pour l'année 1983 concernant les activités de la mission médicale CEMUBAC en République du Zaire, notamment auprès du Département Médical de l'IRS et des hôpitaux ruraux de Kirotshe, Masisi et Rutshuru. *Lwiro* 1983;60.
7. Dubowitz L, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr* 1970;77:1–10.
8. Buekens P, Delvoye P, Wollast E, Robyn C. Epidemiology of pregnancies with unknown last menstrual period. *J Epidemiol Community Health* 1984;38:79–80.
9. Olowe SA. Standards of intrauterine growth for an African population at sea level. *J Pediatr* 1981;99:489–95.
10. Rooth G, Meirik O, Karlberg R. Estimation of the normal growth of Swedish infants at term. *Acta Paediatr Scand* 1985; Suppl. 319:76–9.
11. Pecorari D, Costa L, Barbone F. Practical application of the Bristol perinatal growth chart to Mediterranean populations. *Acta Paediatr Scand* 1985;Suppl. 319:80–3.
12. Stein H, Ellis U. The low birthweight African baby. *Arch Dis Child* 1974;49:156–9.
13. Villar J, Belizan JM. The relative contribution of prematurity and fetal growth retardation to low birthweight in developing and developed societies. *Am J Obstet Gynecol* 1982;143:793–8.
14. World Health Organization. World malaria situation 1984. *World Health Stat Q* 1988;41:64–73.
15. Meuris S, Mavoungou D, Polliotti P. Malaria: la fin d'un règne multimillénaire. *Pathol Biol* 1986;34:886–92.
16. Wickramasuryia GAW. Clinical features of malaria in pregnancy. In: Wickramasuryia GAW, ed. *Malaria and ankylostomiasis in the pregnant woman*. London: Oxford University Press, 1937;5–90.

17. Le Van Hung. Paludisme et grossesse à Saigon. *Rev Paludisme Med Trop* 1951;83:75–112.
18. Menon R. Pregnancy and malaria. *Med J Malaysia* 1972;27:115–9.
19. Clark HC. The diagnostic value of the placental blood film in aestivo-autumnal malaria. *J Exp Med* 1915;22:427–45.
20. Blacklock DB, Gordon RM. Malaria infection as it occurs in late pregnancy: its relationship to labour and early infancy. *Ann Trop Med Parasitol* 1925;19:327–65.
21. Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bull WHO* 1983;61:1005–16.
22. Bray RS, Sinden RE. The sequestration of plasmodium falciparum infected erythrocytes in the placenta. *Trans R Soc Trop Med Hyg* 1979;73:716–9.
23. Trager W, Rudzinska MA, Bradbury P. The fine structure of Plasmodium falciparum and its host erythrocytes in natural malarial infections in man. *Bull WHO* 1966;35:883–92.
24. Perrin LH, Mackey LM, Miescher PA. Hematology of malaria in man. *Semin Hematol* 1982;19:70–81.
25. McGregor IA. Epidemiology, malaria and pregnancy. *Am J Trop Med Hyg* 1984;78:1–8.
26. Brabin BJ, Nagel J, Hagenaars AM, Ruitenberg E, Van Tilborgh AMJC. The influence of malaria and gestation on the immune response to one and two doses of adsorbed tetanus toxoid in pregnancy. *Bull WHO* 1984;62:919–30.
27. McGregor IA, Rowe DS, Wilson ME, Billewicz WZ. Plasma immunoglobulin concentrations in an African (Gambian) community in relation to season, malaria and other infections and pregnancy. *Clin Exp Immunol* 1970;7:51–74.
28. Bray RS, Anderson MJ. Falciparum malaria and pregnancy. *Trans R Soc Trop Med Hyg* 1979;73:427–31.
29. Gilles HM, Lawson JB, Sibelas M, Voller A, Allan N. Malaria, anaemia and pregnancy. *Ann Trop Med Parasitol* 1969;63:245–63.
30. Maroulis GB, Buckley RH, Younger JB. Serum immunoglobulin concentrations during normal pregnancy. *Am J Obstet Gynecol* 1971;109:972–6.
31. Galbraith RM, Faulk WP, Galbraith GMP, Holbrook TW, Bray RS. The human materno-foetal relationship in malaria: 1. Identification of pigment and parasites in the placenta. *Trans R Soc Trop Med Hyg* 1979;74:52–62.
32. Walter P, Garin Y, Blot P. Placental pathologic changes in malaria: a histologic and ultrastructural study. *Am J Pathol* 1982;109:332–44.
33. Covell G. Congenital malaria. *Trop Dis Bull* 1950;47:1147–67.
34. McGregor IA, Wilson ME, Billewicz WZ. Malaria infection of the placenta in the Gambia, West Africa: its incidence and relationship to stillbirth, birthweight and placental weight. *Trans R Soc Trop Med Hyg* 1983;2:232–44.
35. Watkinson M, Rushton DI. Plasmodial pigmentation of placenta and outcome of pregnancy in West African mothers. *Br Med J* 1983;287:251–4.
36. Bruce-Chwatt LJ. Malaria in African infants and children in Southern Nigeria. *Ann Trop Med Parasitol* 1952;46:173–200.
37. Archibald HM. Influence of malarial infection of the placenta on the incidence of prematurity. *Bull WHO* 1956;15:842–5.
38. Archibald HM. Influence of maternal malaria on newborn infants. *Br Med J* 1958;2:1512–4.
39. Cannon DSH. Malaria and prematurity in the Western Region of Nigeria. *Br Med J* 1958;2:877–8.
40. Spitz AJW. Malaria infection of the placenta and its influence on the incidence of prematurity in Eastern Nigeria. *Bull WHO* 1958;21:242–4.
41. McLaren DS, Ward PG. Malaria infection of the placenta and foetal nutrition. *East Afr Med J* 1962;39:182–9.
42. Jelliffe EFP. Low birthweight and malarial infection of the placenta. *Bull WHO* 1968;38:69–78.
43. Jilly P. Anaemia in parturient women, with special reference to malaria infection of the placenta. *Ann Trop Med Parasitol* 1969;63:109–11.
44. Kortmann HFCM. Malaria and pregnancy. M.D. Thesis, University of Amsterdam. Utrecht: Drukkerij Elinkwijk, 1972.
45. Reinhardt MC, Ambroise-Thomas P, Cavallo-Serra R, Meylan C, Gautier R. Malaria at delivery in Abidjan. *Helv Paediatr Acta* 1978;33:65–84.
46. Walter P, Garin JF, Blot Ph. Placenta et paludisme: étude morphologique, parasitologique et clinique. *J Gynecol Obst Biol Reprod* 1981;10:535–42.
47. Brody S, Carlström G. Immuno-assay of human chorionic gonadotropin in normal and pathologic pregnancy. *J Clin Endocrinol* 1962;22:564–74.

48. Chandra RK. Fetal malnutrition and postnatal immunocompetence. *Am J Dis Child* 1975;129: 450–4.
49. McLaren DS. Records of birth weight and prematurity in the Wasukuma of Lake Province Tanganyika. *Trans R Soc Trop Med Hyg* 1959;53:173–8.
50. McGregor JD, Avery JG. Malaria transmission and fetal growth. *Br Med J* 1974;3:433–6.
51. Watkinson M, Rushton DI, Lunn PG. Placental malaria and foetoplacental function: low plasma oestradiol associated with malarial pigmentation of the placenta. *Trans R Soc Trop Med Hyg* 1985;79:448–50.
52. Mavoungou D, Walter P, Gass R, Billiault X, Meuris S, Collet M, Roth-Meyer C, Polliotti B. Umbilical serum levels of steroid hormones in relation to spontaneous labour and vaginal delivery: influence of malaria. In: Proceedings of the 5th World Congress on Human Reproduction, 1985.
53. Polliotti B, Meuris S, Mavoungou D, Walter P. Influence of placental malarial lesions on maternal serum levels of human chorionic gonadotrophin, placental lactogen and estriol. *Placenta* 1986;7:490.
54. Taufa T. Malaria and pregnancy. *Papua New Guinea Med J* 1978;21:197–206.
55. Antonov NA. Children born during the siege of Leningrad, 1942. *J Pediatr* 1947;30:250–5.
56. Smith CA. Effect of wartime starvation in Holland upon pregnancy and its product. *Am J Obstet Gynecol* 1947;53:599–608.
57. Gebre-Medhin M, Gurovsky S, Bondestam L. Association of maternal age and parity with birth weight, sex ratio, still birth and multiple births. *J Trop Paediatr Environ Child Health* 1976;22: 99–102.
58. Gebre-Medhin M, Sterky G, Taube A. Observation on intrauterine growth in urban Ethiopia. *Acta Paediatr Scand* 1978;67:781–9.
59. Gebre-Medhin M, Gobezie A. Dietary intake in the third trimester of pregnancy and birth weight of offspring among non-priviledged women. *Am J Clin Nutr* 1975;28:1322–9.
60. Naeye RL, Dozer A, Tafari N, Ross SM. Epidemiological features in perinatal death due to obstructed labour in Addis Ababa. *Br J Obstet Gynaecol* 1977;84:747–50.
61. Morley D, Knox G. The birth weights of Yoruba babies. *J Obstet Gynaecol* 1960;67:975–80.
62. Tafari N, Naeye RL, Gobezie A. Effects of maternal undernutrition and heavy physical work during pregnancy on birthweight. *Br J Obstet Gynaecol* 1980;87:222–6.
63. Naeye RL, Tafari N. Biologic bases for international fetal growth curves. *Acta Paediatr Scand* 1985; Suppl. 319:164–9.
64. Taggart NR, Holliday RM, Billewicz WZ, Hytten FE, Thompson AM. Changes in skinfold thickness during pregnancy. *Br J Nutr* 1967;21:439–51.
65. Royston E. The prevalence of nutritional anaemia in women in developing countries: a critical review of available information. *World Health Stat Q* 1985;38:52–75.
66. Bégué P, Capochichi D. Les nouveaux-nés de petit poids de naissance au Togo. I. Classification en fonction de l'âge gestationnel, à partir de 888 cas. *Ann Pediatr* 1979;26:639–51.
67. Kessel E, Sastrawinata S, Mumford SD. Correlates of fetal growth and survival. *Acta Paediatr Scand* 1985;Suppl. 319:120–7.
68. Rodriguez MH, Jungery M. A protein on plasmodium falciparum-infected erythrocytes functions as a transferrin receptor. *Nature* 1986;324:388–91.
69. Flint J, Hill AVS, Bowden DK, et al. High frequencies of alpha-thalassaemia are the result of natural selection by malaria. *Nature* 1986;321:744–50.
70. Pasvol G. The interaction between sickle haemoglobin and the malarial parasite plasmodium falciparum. *Trans R Soc Trop Med Hyg* 1980;74:701–5.
71. Brabin BJ, Perrin L. Sickle-cell trait and plasmodium falciparum parasitaemia in pregnancy in Western Province, Kenya. *Trans R Soc Trop Med Hyg* 1985;79:733.
72. van Dongen PWJ, van't Hof. Sickle cell trait, malaria and anaemia in pregnant Zambian women. *Trans R Soc Trop Med Hyg* 1983;77:402–4.
73. Serjeant GR. Sickle haemoglobulin and pregnancy. *Br Med J* 1983;287:628–30.
74. Roopnarinesingh S, Ramsewak S. Decreased birthweight and femur length in fetuses of patients with the sickle-cell trait. *Obstet Gynecol* 1986;68:46–8.
75. Hoff C, Wertelecki W, Dutt J, Hernandez R, Reyes E, Sharp M. Sickle-cell trait, maternal age and pregnancy outcome in primiparous women. *Human Biol* 1984;55:763–70.
76. Bwibo NO. Birthweights of infants of teenage mothers in Nairobi. *Acta Paediatr Scand* 1985;Suppl. 319:89–94.

77. Rehan NE, Tafida DS. Low birthweight in Hausa infants. *Nigerian Med J* 1976;6:324–6.
78. Latham MC, Robson JRK. Birthweight and prematurity in Tanzania. *Trans R Soc Trop Med Hyg* 1960;60:791–6.
79. Fadahunsi O. Low birthweight and maturity in the Nigerian infant. *Nigerian Med J* 1976;6:324–6.
80. Nylander PPS. Perinatal mortality in Ibadan. *Afr J Med Sci* 1971;2:173–8.
81. Bégué P, Assimadi K, Capochichi D. Les nouveau-nés de petits poids de naissance au Togo. II. Essai d'appréciation de différents facteurs étiologiques. *Ann Pediatr* 1979;26:647–51.
82. Adelusi B, Lapido OA. Preterm and other babies with low birthweights in Ibadan. *Trop Geogr Med* 1976;28:316–22.