Epidemiology of Pediatric Tuberculosis in Kenya and Risk Factors for Mortality during Treatment: A National Retrospective Cohort Study

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Objectives To describe the epidemiology of childhood tuberculosis (TB) in Kenya, assess the magnitude of TB/human immunodeficiency virus (HIV) co-infection and identify risk factors for mortality during TB treatment.

Study design We conducted a retrospective analysis of the Kenyan national TB program data for patients enrolled from 2013 through 2015. A total of 23 753 children aged less than 15 years were included in the analysis. Survival analysis was performed with censorship at 9 months and mortality was the main outcome. We used Cox proportional hazards regression for assessing risk factors for mortality.

Results Childhood TB accounted for 9% (n = 24 216) of all patients with TB; 98% of the notified children (n = 23 753) were included in the analysis. TB/HIV co-infection was 28% (n = 6112). Most TB cases (71%; n = 16 969) were detected through self-referral. Treatment was successful in 90% (n = 19 088) and 4% (n = 1058) died. Independent risk factors for mortality included being HIV infected but not on antiretroviral therapy (adjusted hazard ratio [aHR], 4.84; 95% CI, 3.59-6.51), being HIV infected and on antiretroviral therapy (aHR, 3.69; 95% CI, 3.14-4.35), children aged less than 5 years (aHR, 1.25; 95% CI, 1.08-1.44), and being diagnosed with smear negative pulmonary disease (aHR, 1.68; 95% CI, 1.27-2.24).

Conclusions Most childhood TB cases in Kenya were detected through passive case finding. TB/HIV co-infection is high among children on treatment for TB, and HIV is associated with an increased risk of death. There is a need to intensify active case finding among children. TB prevention interventions among HIV-infected children, early diagnosis of HIV, and early antiretroviral therapy initiation among children on TB treatment should be strengthened. *(J Pediatr 2018;201:115-21).*

According to the World Health Organization (WHO), tuberculosis (TB) is the leading infectious cause of death globally and is thought to be an important cause of mortality in children.[1] The incidence and epidemiology of pediatric TB is poorly characterized globally; challenges in diagnosis mean that most cases are never detected or treated.[2] TB control programs have historically ignored pediatric TB because it was believed to be of less public health importance than adult disease owing to the low risk of transmission of TB by children. This neglect has contributed to a lack of focused global targets.[3,4] However, TB in children should be a priority area of focus for TB control programs, because infection with *Mycobacterium tuberculosis* progresses rapidly to disease in young children[5] and young children are predisposed to severe or disseminated forms of TB.[6] Although the true burden of TB mortality in children is unknown, the WHO estimates that 210 000 children died of TB globally in 2015[7]; 17% of these deaths occurred among HIV-infected children.[8] Risk factors for mortality among children on TB treatment in high-burden settings have not been well-characterized.

Kenya is currently experiencing the twin epidemics of TB and HIV. The country is categorized among the WHO high TB and high TB/HIV burden countries.[9] Despite an overall decrease in TB incidence, the incidence among those who are HIV positive has remained persistently high.[10] The TB epidemic among adults puts children at risk of acquiring the disease. Although childhood TB remains a serious public health problem in Kenya, its epidemiology has been described for 2 provinces only.[11] This analysis seeks to describe the epidemiology of childhood TB in Kenya at a national level, assess the magnitude of TB/HIV co-infection in children, and identify factors associated with mortality during TB treatment.

aHR	Adjusted hazard ratio
ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
TB	Tuberculosis
TIBU	Electronic TB surveillance system
WHO	World Health Organization

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Methods

We conducted a retrospective cohort analysis of routine programmatic data from 3837 health facilities reported to the Ministry of Health in Kenya. We included all patients less than 15 years old who started their TB treatment between January 1, 2013, and December 31, 2015.

Kenya's population in 2016 was estimated to be 47 million, of whom children aged less than 15 years made up 41%. By age group, 7.25 million children were aged 0-4 years, 6.62 million of them were aged 5-9 years, and 5.81 million were aged 10-14 years.[12] Childhood TB is managed according to the national treatment guidelines for management of TB in children adopted from WHO recommendations.[13] The National TB Control Program coordinates all aspects of TB management in the country. The diagnosis of pediatric TB is based on clinical evaluation in addition to laboratory investigations when possible. Tuberculin skin test, chest radiography, and sputum smear examination support clinical evaluation. The Xpert MTB/RIF assay was introduced in 2011, and implementation was scaled up in 2014; its use is currently being scaled up for both adults and children. Treatment regimens and duration follow national guidelines.[13] All children on TB treatment are offered HIV counseling and testing. Bacille Calmette-Guerin vaccine is administered to all newborns at birth as part of the Kenya Expanded Program on Immunization.

This study used data from the electronic TB surveillance system (TIBU) that was introduced in Kenya in 2012. All public, faith-based, and private treatment centers in the country enter individual-level data for children and adults into this system. The system captures data from nearly 100% of all treated patients with TB according to an assessment in 1 district conducted in 2013.[14] It includes information on demographic factors, diagnostic tests performed, and treatment outcome. We obtained anonymized TIBU data from the National Tuberculosis Control Program.

Definitions

Children were classified as having either pulmonary TB alone or having any extrapulmonary TB, which included children with both pulmonary and extrapulmonary TB. Children who completed treatment or achieved cure were considered to have successful outcomes and children who died during treatment, failed treatment, or defaulted from treatment were considered to have poor outcomes. Cure was defined as at least 2 negative sputum tests in a patient who had a positive sputum smear or culture at treatment initiation. Patients with a positive sputum smear at month 5 were considered to have failed treatment. Patients missing more than 2 appointments during the intensive phase or missing for more than 1 month during continuation was considered as loss to follow-up. Patients with negative or unavailable sputum smears at baseline who completed a full course of anti-TB treatment were considered to have completed treatment. Death was considered to be mortality from any cause during treatment.

Statistical Analyses

We excluded from analysis children with missing outcomes or a missing outcome date, and children whose recorded treatment outcome date was earlier than the treatment start date. We calculated TB notification rates per 100 000 people by age groups (0-4, 5-9, and 10-14 years); we divided notified cases by yearly populations projected from the 2009 Population and Housing Census.[15] For survival analysis, time to death or censoring was defined as the time between treatment initiation and outcome date. We evaluated the proportional hazards assumptions by testing the significance of time-dependent interaction terms for each covariate. If the outcome was death, the outcome date was assumed to be the date of death. Patients who were lost to follow-up or who had their treatment classified as transferred out, failure, success, or cure were censored at the outcome date. Patients with a follow-up time beyond 9 months were censored at 9 months regardless of the eventual outcome.

To determine risk factors for mortality, we conducted bivariate and multivariable analyses using Cox proportional hazards regression with death as the outcome of interest. Variables with *P* values of .2 or less on bivariate analysis were eligible for inclusion in a multivariable model, and the final model was constructed using a backward elimination approach. Robust standard errors that take into account the potential effect of clustering by health facility were calculated. Patients who transferred out were excluded from the risk factor analysis. Data were analyzed using R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) and Stata version 12 (Stata Corp, College Station, Texas).

Ethical Considerations

This analysis involved the use of de-identified data that were collected as part of a routine program monitoring. Approval to use TIBU data was obtained from the National Tuberculosis Control Program. This analysis was approved by Jaramogi Oginga Odinga Teaching and Referral Hospital ethical review board.

Results

From January 2013 through December 2015, Kenya notified 263 201 patients with TB, 9% (n = 24 216) of whom were children aged less than 15 years. Among children, the highest case notification rates were among children aged 0-4 years (**Table I**). In total, 98% of the notified children (n = 23 753) were included in the analysis; 0% (n = 11) were excluded from analysis because they had unknown outcomes, 1% (n = 273) because they had missing outcome dates, and 1% (n = 179) because the outcome date was before the treatment start date. A total of 8554 children were notified in 2013, 8477 in 2014, and 6722 in 2015. Children aged 0-4 years accounted for 47% of the children treated for TB (n = 11 160; **Table II**). Most cases of childhood TB (67%; n = 15 955) were detected through self-referral (ie, presenting to the clinic with symptoms).

Table I. TB Case Notification Rate per 100 000 Population in Kenya (n = 23 753)

Age Groups (y)	2013 Population (millions)	2013 Notified TB Cases	2013 Case Notification Rate per 100 000 population	2014 Population (millions)	2014 Notified TB Cases	2014 Case Notification Rate per 100 000 population	2015 Population (millions)	2015 Notified TB Cases	2015 Case Notification Rate per 100 000 population
0-4	6.97	4025	57	7.07	3922	55	7.17	3244	45
5-9	6.21	2178	35	6.36	2097	33	6.49	1619	25
10-14	5.29	2356	45	5.47	2485	45	5.65	2099	37
≥15	25.21	82 036	325	25.96	81 575	314	26.75	75 380	282
Total	43.68	90 595	207	44.86	90 079	201	46.06	82 342	179

TB/HIV Co-Infection

Overall, 93% of the children treated for TB (n = 22 081) were tested for HIV. Of those tested, 28% (n = 6112) were HIV infected. HIV positivity was highest among children tested in the 5- to 9-year-old age group (35%; n = 2044). Among HIV-infected children, 92% (n = 5606) were on antiretroviral therapy (ART). Among children on ART, 42% (n = 2402) had a recorded date of ART initiation. Of these, ART was initiated before TB diagnosis in 65% (n = 1552) and after TB diagnosis in 35% (n = 851). The probability of survival up to 9 months (270 days) during treatment was greatest among HIV-negative patients (survival probability, 0.97; 95% CI, 0.96-0.97) and least among HIV-infected patients who were not on ART (survival probability, 0.81; 95% CI, 0.65-0.90).

TB Diagnosis

In total, 12% of children (n = 2877) had TB disease that was bacteriologically confirmed by smear, GeneXpert, or culture (Table III). Overall, 32% of the children (n = 7578) had sputum smear examination performed; of these, 36% (n = 2755) tested positive for *M tuberculosis*. One-quarter of the children (n = 5874) were diagnosed with extrapulmonary TB majority of whom had lymphadenitis (45%; n = 2641). GeneXpert was performed for 2% of all children (n = 454), 63% of whom (n = 285) tested positive. Among 353 children who had both GeneXpert and sputum smear microscopy performed, 65% (n = 231) had a positive GeneXpert result and 52% (n = 182) had a positive smear result.

Table II. Sociodemographic and clinical characteristics of children treated for TB in Kenya (n = 23 753)

Sociodemographic/Clinical Characteristics	n	%
Age category (y)		
0-4	11 160	47
5-9	5799	24
10-14	6788	29
Sex		
Female	11 403	48
Male	12 350	52
Year		
2013	8554	36
2014	8477	36
2015	6722	28
Ownership of health facility where child was registered		
Public	18 432	78
Private	4769	20
Prisons	143	<1
Other faith based	409	2
Means of identification		
Self-referral	15 955	67
HIV clinics	2861	12
Contact investigation	2374	10
Other*	2563	11

*Antenatal clinics, community health workers, chemists/pharmacies, voluntary counseling and testing centers, and private clinics that do not provide TB services.

Treatment Outcomes

Of the 23 753 children, 80% (n = 19 088) completed treatment and 10% (n = 2405) were cured. Poor outcomes were reported for 8% of children (n = 1833), including 4% (n = 1058) who died, 3% (n = 760) who were lost to follow-up, and 1% (n = 15) who experienced treatment failure; 2% (n = 427) transferred out of the facility where they initiated treatment, so their final treatment outcome is unknown. Among children with meningitis, military, skeletal, and abdominal TB, which are more serious forms, the case fatality was higher (5%; 171 of 3233) than among children with lymphadenitis (3%; 81 of 2641) or children with pulmonary TB (4%; 830 of 17 873).

Risk Factors for Mortality

Among children with known treatment outcomes, age, type of TB, type of health facility attended, the means of identification, and HIV and ART status were significantly associated with mortality in bivariate analysis (Table IV). HIV-infected children who were not on ART had almost 5 times the likelihood of death (hazard ratio [HR], 4.80; 95% CI, 3.59-6.43) as HIV-negative children. HIV-infected children on ART had more than 3 times the likelihood of death (HR, 3.51; 95% CI, 3.04-4.05) as HIV-negative children. By age group, children aged less than 5 years had a 12% higher risk of death (HR, 1.12; 95% CI, 0.98-1.27) than children aged more than 5 years. The likelihood of death was twice as high among children with sputum smear-negative TB (HR, 2.21; 95% CI, 1.67-2.94) compared with those with smear-positive disease. Children treated in public health facilities had a 28% increased likelihood of death (HR, 1.28; 95% CI, 1.03-1.58) compared with children treated in private or faith-based facilities. Children who were identified through contact investigation had a 24% lower risk of death (HR, 0.76; 95% CI, 0.59-0.97) than children identified through self-referral. Sex violated the proportional hazards assumption, but male sex was associated with decreased odds of death (OR, 0.86; 95% CI, 0.77-0.99).

Table III. Diagnostic characteristics of children treated for TB in Kenya

Characteristics	Age 0-4 y (n = 11 160)	Age 5-9 y (n = 5799)	Age 10-14 y (n = 6788)	Total (n = 23 753)
Sputum smear microscopy				
Smear microscopy performed	1103 (10)	2128 (37)	4347 (64)	7578 (32)
Smear positive, out of those with smear performed	181 (16)	512 (24)	2062 (47)	2755 (36)
GeneXpert				
GeneXpert performed	91 (1)	131 (2)	232 (3)	454 (2)
Xpert positive, out of those with Xpert performed	57 (63)	71 (54)	157 (69)	285 (63)
Any microbiological confirmation				
Yes	218 (2)	548 (9)	2111 (31)	2877 (12)
No	10 942 (98)	5251 (91)	4677 (69)	20 870 (88)
Chest radiograph				
Performed	6261 (56)	3068 (53)	2737 (40)	12 066 (51)
Not performed	4899 (44)	2731 (47)	4051 (60)	11 681 (49)
Type of TB				
Pulmonary	8764 (79)	4101 (71)	5008 (74)	17 873 (75)
Lymphadenitis	1100 (10)	807 (14)	734 (11)	2641 (11)
Pleural effusion	277 (3)	266 (5)	303 (4)	846 (4)
Miliary TB	194 (2)	134 (2)	140 (2)	468 (2)
TB meningitis	101 (1)	59 (1)	72 (1)	232 (1)
Abdominal	33 (<1)	31 (1)	56 (1)	120 (<1)
Skeletal	85 (1)	87 (2)	132 (2)	304 (1)
Others	606 (5)	314 (2)	243 (4)	1263 (5)

Values are n (%).

In a sex-stratified multivariable model, age, type of TB, type of facility attended, means of identification, and HIV and ART status were significant predictors of death (Table IV). The greatest increases in likelihood of death were observed for children who were HIV infected but not on ART (adjusted HR [aHR], 4.84; 95% CI, 3.59-6.51) and children who were HIV infected and on ART (aHR, 3.69; 95% CI, 3.14-4.35). Children aged less than 5 years had 25% higher likelihood of death (aHR, 1.25; 95% CI, 1.08-1.44) than children aged more than 5 years. The risk of death among children with smear-negative pulmonary disease was 68% higher (aHR, 1.68; 95% CI, 1.27-2.24) than children with sputum smear-positive disease; children with extrapulmonary disease had a similar risk of death as those with smear-negative disease. The likelihood of dying was 39% higher (aHR, 1.39; 95% CI, 1.13-1.14-1.69) among children treated in public health facilities than those treated in private or faith-based facilities. Children who were identified through contact investigation had 25% lower risk of death (aHR, 0.75; 95% CI, 0.57-0.98) than children identified through self-referral.

Table IV. Bivariate and multivariable analysis of risk factors for mortality among children treated for TB in Kenya (n = 23 654)

Characteristics	Deaths, n/N (%)	HR (95% CI)	aHR (95% CI)
Sex*			
Male	586/12 105 (5)	1	
Female	472/11 221 (4)	0.86 (0.77-0.99)	
Age group (y)			
<5	514/10 920 (5)	1.12 (0.98-1.27)	1.25 (1.08-1.44)
≥5	544/12 406 (4)	1	1
Type of TB			
Smear positive pulmonary	60/2722 (2)	1	1
Smear negative pulmonary	221/4472 (5)	2.21 (1.67-2.94)	1.68 (1.27-2.24)
Smear not done pulmonary	525/10 351 (5)	2.32 (1.78-3.03)	1.87 (1.41-2.47)
Extrapulmonary	252/5781 (4)	1.94 (1.47-2.56)	1.65 (1.24-2.19)
HIV infection			
Negative	415/15 705 (3)	1	1
Positive on ART	513/5500 (9)	3.51 (3.04-4.05)	3.69 (3.14-4.35)
Positive not on ART	59/491 (12)	4.80 (3.59-6.43)	4.84 (3.59-6.51)
Unknown	71/1630 (4)	1.64 (1.27-2.12)	1.57 (1.22-2.02)
Ownership of health facility			
Private or faith based	187/5069 (4)	1	1
Public	871/18 257 (5)	1.28 (1.03-1.58)	1.39 (1.14-1.69)
Means of identification			
Contact investigation	69/2332 (3)	0.76 (0.59-0.97)	0.75 (0.57-0.98)
Self-referral	729/18 184 (4)	1	1
HIV clinic	260/2810 (9)	2.32 (2.02-2.68)	1.00 (0.98-1.19)

*Sex violated the proportional hazards assumptions so an OR is presented instead of HR. The multivariable model was, therefore, stratified by sex.

Discussion

Our analysis of nationally representative data collected over 3 years reveals a high TB/HIV co-infection rate among children with TB in Kenya. Although treatment outcomes are good for children with TB, children with HIV are at an increased risk of death, especially if they are not receiving ART. As is to be expected, most TB diagnoses in children are not bacteriologically confirmed. GeneXpert testing coverage was low. Furthermore, most children are being diagnosed with TB through passive case finding rather than through active case-finding strategies, such as contact investigation and screening of HIV-infected children.

The case notification rate for childhood TB decreased from 2013 to 2015. This finding may be a result of gains made in controlling TB in Kenya, because adult case notification has also decreased. In addition, early initiation of ART among HIV-infected children may have prevented new cases. However, active case-finding strategies are necessary to improve case detection and the timeliness of TB diagnoses. Contact investigation is a WHO-recommended intervention that involves health worker visits to homes of new TB cases, especially sputum smear-positive patients, screening close contacts and referral of high-risk contacts to health facilities for diagnostic tests.[16,17] The lower mortality among children identified through contact investigation that we observed in this study may reflect the benefit of early case detection. However, although Kenya has adopted contact investigation guidelines in line with current WHO recommendations, implementation remains weak. Another WHO-endorsed active case-finding recommendation is intensified TB case finding among people living with HIV, which involves screening for TB symptoms at every clinic encounter.[18] Intensified case finding is one of the key TB/HIV collaborative activities implemented in Kenya; HIV-infected children are routinely screened using a questionnaire at every clinic visit. However, our data suggest that the yield of the 2 active case-finding strategies may be suboptimal in children because the majority of children are still diagnosed through passive case finding. There is a need to intensify the use of community health workers in contact investigation and improve the monitoring of these investigations through a case investigation register. Similarly, efforts at intensified case finding among HIV-infected children should be enhanced to improve the timeliness diagnosis of TB.

We found that more than one-quarter of children with TB in Kenya were HIV infected, which is slightly lower than the 31% co-infection rate among adults with TB in Kenya and the 32% co-infection rate reported in a sample of Malawian children with TB,[19,20] but still substantial. Prevention of TB among HIV-infected children is a key priority in Kenya. Isoniazid preventive therapy, cotrimoxazole preventive therapy, and ART are known to prevent TB among HIV-infected children.[21,22] Although the coverage of cotrimoxazole preventive therapy and ART were commendably high among pediatric patients with TB, 1 in 3 children had ART initiated after TB diagnosis. Furthermore, because TIBU does not record information of isoniazid preventive therapy, the coverage of this intervention is unknown. TB/HIV collaborative activities should be enhanced to ensure early diagnosis of HIV, early initiation of ART, and use of cotrimoxazole and isoniazid preventive therapies to prevent TB in children.

Although the treatment success rate was higher than the WHO target of 85%, nearly one-tenth of children experienced poor outcomes, and death accounted for close to 60% of children with poor outcomes. The strongest predictor of death among children in our study was HIV infection. HIV-infected children experience faster disease progression and are predisposed to poor treatment response.[23-26] The increased risk of mortality among HIV-infected children being treated for TB has been documented in other settings, with a study from South Africa reporting that HIV-infected children with TB were almost 7 times more likely to die than HIV-negative children.[27] However, unlike a study from Malawi, we did not find that children on ART at the time of starting TB treatment were more likely to die than children who initiated ART after being diagnosed with TB.[20] The use of ART among TB/HIV co-infected children reduces morbidity and mortality.[22,28] Our observation that HIV-infected children on ART still had nearly 4 times the likelihood of death as HIV-negative children could be due to early mortality among children who were started on ART when their disease was already advanced, virologic failure, immune reconstitution syndrome, or poor adherence to ART.[29,30] Improving the coverage of HIV interventions for children and the coordination between TB and HIV services is essential to reducing TB-associated mortality in children. A study from Malawi, a similarly high HIV burden country, reported a 13% decrease in TB-associated mortality as a result of improvement in HIV interventions.[31]

The difference in the risk of mortality between children treated in public compared with private health facilities could be explained by the differences in healthcare-seeking behavior of their respective clientele. Clients of public health facilities generally belong to a lower wealth quintile, which often contributes to a delay in seeking healthcare for their respiratory symptoms. Our observation that children with pulmonary smear-negative disease had an increased risk of death compared with children with smear-positive disease could be explained by the nature of this diagnosis. TB symptoms in children are nonspecific, and diagnosing TB without bacteriologic confirmation may involve first putting children on antibiotics to treat pneumonia and diagnosing TB only after other possible diagnoses are excluded. Thus, children with bacteriologically unconfirmed disease may experience delayed initiation of TB treatment.[32] In addition, because the clinical diagnosis of TB is quite often a diagnosis of exclusion, it is possible that some of the observed mortality may result from misdiagnosis, because the true cause of illness was not treated. Timely diagnosis of TB in children can be promoted by training doctors in clinical diagnostic algorithms, expanding access to radiography, and using more sensitive bacteriological confirmation methods such as the GeneXpert,[33] the use of which is currently being expanded in Kenya.

In this study, a substantial proportion of children treated for TB were not subjected to any diagnostic testing. This finding may be attributed to difficulty in obtaining sputum specimen for testing in children and limited availability of radiography services. Consequently, these children were diagnosed clinically. A clinical diagnosis of TB relies on scoring systems and the acumen of clinicians, which is not standardized.[34] This is a potential cause of bias, because children on treatment for clinically diagnosed TB may actually have other diseases that could drive mortality, or they could have simpler nonfatal conditions that could cause an underestimation of TB case fatality ratios.

Our study was subject to several limitations. This study used routine data, which suffer from limitations of missing information and occasionally inconsistent data. Consequently, a small fraction of patients had to be excluded from the analysis. ART initiation dates were missing for most of the patients; thus, the timing of ART initiation could not be used in the mortality analysis. There was no variable indicating the basis of TB diagnosis and radiographic findings were not captured, limiting our capacity to comprehensively assess diagnostic practices. The role of malnutrition as a potential confounder could not be assessed because data on nutritional status are not captured in Kenyan TB registers. Finally, because we only evaluated notified cases, we are limited in the conclusions we can make about the true epidemiology of childhood TB in Kenya, including undiagnosed patients.

In conclusion, most childhood TB cases in Kenya are being detected through passive case finding. TB/HIV co-infection is high among children on treatment for TB, and HIV is associated with increased risk of death. There is a need to intensify active case finding among children. TB/HIV collaborative activities should be strengthened by implementing TB-preventive interventions among HIV-infected children, ensuring early diagnosis of HIV and early ART initiation among children on TB treatment. ■

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50 Years Ago in *The Journal of Pediatrics*

Maternal Phenylketonuria: Implications for Growth and Development

Frankenburg WK, Duncan BR, Coffelt RW, Koch R, Coldwell JG, Son CD. J Pediatr 1968;73:560-70.

By 1963, several women diagnosed with phenylketonuria (PKU) by urine ferric chloride testing as adults were noted to have children with intellectual disability; these children did not have the metabolic defect, thus, the cause of intellectual disability was hypothesized to be high levels of phenylalanine (a potent teratogen) circulating in the maternal blood.[1] Five years later, Frankenburg et al reported 8 children without PKU born to 3 women with untreated PKU, 6 of whom had intrauterine growth retardation (IUGR) and all of whom were developmentally delayed. (Interestingly, 2 of the 3 untreated women had graduated from high school and held jobs.) They also reported growth data on an additional 13 offspring without PKU of mothers with PKU and noted that all had a degree of IUGR. Finally, they reviewed 69 offspring without PKU of mothers diagnosed as having elevated phenylalanine blood levels and a positive urine ferric chloride reaction, and found that only 1 had a measured IQ above 90.

Of course, these cases were only the tip of the iceberg. With the adoption of newborn screening, many young women would be diagnosed as infants and treated through early childhood; the diet was usually discontinued, and subjects would not necessarily be aware of their own health history or even remember the name of the disease for which they had been treated.[2] Yet, the women's high levels of blood phenylalanine at conception and throughout pregnancy could harm their offspring. Unknown in 1968 was whether resumption of the PKU diet early in pregnancy or before conception would prevent harm.[2] The Maternal Phenylketonuria Collaborative Study, begun in 1984, prospectively evaluated the efficacy of dietary treatment in reducing congenital anomalies, IUGR, and intellectual disability in infants born to women with PKU. The Maternal Phenylketonuria Collaborative Study would demonstrate that adherence to a low-phenylalanine diet, although especially arduous during pregnancy, could indeed prevent fetal brain damage.

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