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Incidence of Major Congenital Malformations in a Region of Bosnia and Herzegovina Allegedly Polluted with Depleted Uranium

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Objectives. To determine the prevalence of major congenital malformations in West Herzegovina, a part of Bosnia and Herzegovina, immediately and five years after 1991-1995 military activities, which allegedly included the use of weapons with depleted uranium.

Methods. The study included all live-born and stillborn neonates and excluded all aborted fetuses in two one-year cohorts (1995 and 2000) of neonates in the Maternity Ward of the Mostar University Hospital. Malformations were recorded according to the recommendations of the EUROCAT protocol.

Results. Major malformations were found in 40 (2.16%) out of 1,853 neonates in 1995 (95% confidence interval [CI], 1.49–2.82%) and in 33 (2.26%) out of 1,463 neonates five years later (95% CI, 1.50–3.01%), ie, at comparable prevalence. In both cohorts, anomalies of the musculoskeletal system were the most common, followed by anomalies of the digestive system (in 1995) and the cardiovascular system (in 2000). The prevalence of malformations and the organ systems involved were essentially comparable with those in other populations not affected by military activities.

Conclusion. Despite alleged environmental pollution in some regions of the former Yugoslavia, which was attributed to military activities and the presence of depleted uranium (the "Balkan syndrome"), there was no significant postwar increase in the prevalence of congenital malformations.

Key words: *abnormalities; Bosnia and Herzegovina; environmental exposure; environmental pollution; uranium; war*

In the last decade, West Herzegovina, a southwest part of Bosnia and Herzegovina, has suffered substantial demographic, social, cultural, economic, and ecological turbulences as direct or indirect consequences of the 1991-1995 war. It was also the area where international peace-keeping forces and their weapons were deployed after the war was over (1).

Public attention worldwide has been drawn to an apparently increased incidence of malignant diseases in the areas of military activities in former Yugoslavia. This increase was associated with alleged radioactive and/or chemical contamination by military equipment and weapons and the conditions was dubbed "Balkan syndrome" (2-5). Although a lot has been written about it (*http://www.balcansyndrome.com; http://www.ratical.org/radiation/vzajic*), sound quantitative data either on the level of environmental contamination or at the (increased) signs of adverse effects on health have never been published. The aim of our study was to assess whether the alleged contamination of Bosnia and Herzegovina with depleted uranium affected the prevalence and/or spectrum of congenital malformations in our region, as malformations could be used as objective indicators of environmental contamination with mutagenic agents and, compared with neoplastic disease, could yield relevant information more readily (6,7).

Participants and Methods

We compared the prevalence and organ-site of major congenital malformations in two one-year cohorts of neonates born at the Maternity Ward of the Mostar University Hospital in 1995, immediately after the war (8), and in 2000, after a relatively peaceful period. All migration changes occurred before 1995, so the demographic structure remained essentially unchanged in the 1995-2000 period. The 1995 cohort was followed up in a prospective study, and the 2000 cohort was analyzed retrospectively.

West Mostar is a town in the southern part of Bosnia and Herzegovina and the capital of two cantons with about 200,000 inhabitants. Deliveries usually take place in the Maternity Ward of the Mostar University Hospital, occasionally in smaller local hospitals in the region. All live-born neonates were physically examined during the first three days after delivery and the malformations were noted if present. Stillborn fetuses were only physically examined, but autopsy was not performed.

Malformations were most often recorded in the early neonatal period, although some were also noted later during the first year of life. A few malformations were registered at regular medical checkups of children born in local hospitals during their first year of life. Newborns with more complex problems were admitted to the Children's Department of the Mostar University Hospital for additional examination. Chromosomopathies were cytogenetically confirmed in laboratories of the University Hospitals in Split and Zagreb, Croatia.

Malformations were registered according to the recommendations of the EUROCAT Protocol (9). Their prevalence was analyzed with respect to the organ system involved, gestational age, and sex. Data on prenatal and perinatal complications in the 1995 cohort were obtained from both the interviews with the mothers and medical documentation, and on the 2000 cohort only from the medical documentation. Perinatal complications were defined as any departure from the normal pregnancy, delivery, or both, and they included infections, gestosis, metabolic complications, epilepsy, neurosis, bleeding in pregnancy, medically maintained pregnancy, shortened or prolonged gestation (less than 37 or more than 42 weeks), prolonged delivery, obstetrical complications in mother or child, heavy anemia of mother or child, Rh-incompatibility with hyperbilirubinemia, perinatal hypoxia, perinatal infections, and other problems of adaptation. Uneventful pregnancies and puerperium were included into the category of "negative anamnesis".

Aborted fetuses were excluded from detailed analysis of malformations due to technical and organizational problems.

Statistical Analysis

Statistical methods of sample distribution and chi-square test with Yates' correction were used. All statistical analyses were performed using SPSS Version 11 for Windows (SPSS Inc., Chicago, IL, USA). Significance was accepted at $p < 0.05$.

Results

In 1995, 40 out of 1,853 neonates (1,836 live-born and 17 stillborn) had major malformations, yielding an average prevalence of 2.16% (95% confidence interval [CI], 1.49–2.82%). In 2000, out of 1,463 neonates (1,451 live-born and 12 stillborn), 33 (2.26%) had major malformations (95% CI, 1.50–3.01%). No gross anomalies were found in the stillborn fetuses in either cohort (Table 1). There was no increase recorded in the spontaneous or artificial abortion rates attributable to an environmental pollution or to the fear of it. The infant mortality rates and the incidence of death of infants with major malformations were comparable in the pre- and post-war periods (Table 1).

In 1990, 53 (1.53%) out of 3,452 newborns died; 8 (15.09%) among them had major malformations. In the 1995 cohort, 32 (1.73%) out of 1,853 neonates died, and 3 (9.4%) among them had major malformations. In the 2000 cohort, 5 (0.34%) out of 1,463 newborns died and none had any malformation. There were no stillborns with malformations in the 1995 and 2000 cohorts. In other cohorts – 1990, 1991, 1994, and 1999, there were 3, 3, 2, and 1 stillborn neonates with malformations, respectively. All malformations affected the central nervous system. Autopsies of stillborn neonates or aborted fetuses were not performed.

Anomalies of the musculoskeletal, digestive, and cardiovascular systems were the most frequent (Table 2). Cardiovascular and central nervous system anomalies were significantly higher in the 2000 cohort than in the 1995 cohort.

In the 1995 cohort, four cases of chromosomal anomalies were recorded: three children with Down syndrome (all regular types of trisomy 21) and a child with mosaicism 46,XX/46,XX,der (15). In the 2000 cohort, there were three cases of Down's syndrome of regular type. Multiple anomalies were noted in two girls in the 1995 cohort and in a boy in the 2000 cohort. The anomalies in the two girls included thoracic

Table 1. Yearly vital statistics from the Maternity Department of West Mostar University Hospital, 1990-2000

			No. of neonates			
Year	total	stillborns	stillborns with MM*	aborted	infant deaths	deaths with MM
1990	3,452	30	3	367	53	8
1991	2,642	35	3	348	43	4
1992	1,196	–†	–	140	15	3
1993	961	–	–	103	16	0
1994	1,609	13	2	109	11	1
1995	1,853	17	0	67	32	6
1996	1,764	24	0	111	25	4
1997	1,618	23	0	125	18	2
1998	1,556	19	0	170	17	2
1999	1,518	23	1	200	9	1
2000	1,463	12	0	166	5	0

*Major malformations.
†Missing data.

Table 2. Major malformations (MM) in neonates by organ systems and sex

	No. of malformations in year						Prevalence* in year	
	1995			2000				
System	girls	boys	total	girls	boys	total	1995	2000
Musculoskeletal	9	6	15	6	5	11	8.09	7.52
Digestive	5	5	10	3	2	5	5.39	3.42
Genitourinary	0	5	5	0	0	0	2.69	0
Chromosomal anomalies	2	2	4	3	0	3	2.16	2.05
Cardiovascular	1	2	3	6	3	9	1.62	6.15
Multiple	2	0	2	0	1	1	1.08	0.68
Metabolic	0	1	1	0	0	0	0.54	0
Central nervous	0	0	0	2	2	4	0	2.73
Total	19	21	40	21	12	33	21.57	22.55

*Per 1,000 neonates.

Table 3. Major malformations (MM) in relation to the gestational age

	No. of newborns in year			
	1995		2000	
Maturity	No.	with one or more MM (%)	No.	with one or more MM (%)
Mature, eutrophic	1,734	30 (1.73)	1,388	29 (2.09)
Premature	65	2 (3.07)	42	3 (7.14)
Mature, hypotrophic	54	8 (14.81)	33	1 (3.03)
Total	1,853	40 (2.16)	1,463	33 (2.26)
95% confidence interval		1.49–2.82		1.50–3.01

Table 4. Number (%) of obstetrical complications (OC) accompanying pregnancies and/or deliveries of children with major malformations (MM)

Complications and malformations	No. in year	
	1995	2000
MM	40	33
OC	34	18
% MM with OC	85.0 (83.38-86.63)*	54.5 (51.95-57.05)

*95% confidence intervals.

deformity, unspecified cardiac defect, and feet syndactylia in one girl; and esophageal atresia, unspecified cardiac defect, and bilateral aplasia of the 1st finger in the other. The boy had Pierre-Robin syndrome and unspecified cardiovascular anomaly.

Major malformations in the 1995 cohort occurred at comparable frequencies in girls and boys (19 vs 21), and more frequently in girls in the 2000 cohort (21 vs 12), but not significantly (Table 2).

Malformations in the 1995 cohort were noted in hypotrophic neonates more often than in mature and premature ones (chi-square, 42.721; d.f. = 2; $p < 0.001$; Table 3). In the 2000 cohort, that correlation was not found (chi-square, 4.814; d.f. = 2; $p = 0.090$).

In the 1995 cohort, pre- and perinatal complications were recorded in 85.0% pregnancies with or deliveries of malformed children. The corresponding prevalence in the 2000 cohort was 54.5% (Table 4). Unfortunately, data about the occurrence of complications accompanying the pregnancies with and/or deliveries of normal (non-malformed) newborns were not available. Thus, it was not possible to determine the statistical correlation between the prevalence of obstetrical complications and presence or absence of malformations in the offspring, but observed percentages associated with the presence are compelling. Apparently higher percentage of complications in the 1995 cohort then in the 2000 cohort could be ascribed to the differences to data acqusition.

Discussion

The region of Bosnia and Herzegovina covered by this study was involved in armed conflicts that resulted in destruction of private and state properties, military and civil victims, refugees, and displaced persons. Fortunately, there were no epidemics. After 1995, the international peace-keeping troops (SFOR) and their weapons were deployed in the area.

Despite NATO's assurance that there was "no link between depleted uranium (DU) ammunition and negative healthy effects in Bosnia and Herzegovina" (*http://www.nato.int.du*), fear of pollution and unknown radiation is still present. The newest data from the United Nations Environment Program (UNEP) have confirmed contamination with depleted uranium at two sites near Sarajevo, around the points of military impacts (10). However, in contrast to widespread contamination after Chernobyl accident and Hiroshima and Nagasaki disasters, the worst human exposures to radioactive material (11), this contamination in Bosnia and Herzegovina has been localized, with concentrations of depleted uranium in soil varying from 0.01 to 100 ppm (mg/kg). At this level of contamination, radiological risks should be insignificant, whereas the ingestion of heavily contaminated material might cause heavy metal toxicity. Earlier UNEP missions in the Balkan region, UNEP 2001 and UNEP 2002, found traces of uranium (U-236) and plutonium (Pu-239/240) (10). The respective concentrations were 0.003 mass % and about 20 Bq/kg, but these levels of radioactive contamination are considered low.

Nevertheless, there is fear of the "Balkan syndrome" in whole Bosnia and Herzegovina. We therefore tried to analyze the prevalence of major malformations in newborn children as an indicator of pathological morphogenesis that might be associated with the alleged pollution from depleted uranium. For logistic reasons, data were recorded for two cohorts of newborns: the first cohort born immediately after the military actions, ie, in 1995, and the second one born five years later, ie, in 2000. Available statistical data for the pre-war period were also taken into consideration. Prevalence of major malformations in the two cohorts did not differ and was not higher than the average prevalence of congenital malformations in the EUROCAT centers (2.16% in the 1980-1984 period) (12).

An insignificantly higher prevalence of major malformations (2.71%) was recorded in Pleven, Bulgaria, in the 1993-1997 period, whereas in Beirut, Lebanon, the prevalence was lower (1.65%) than that in our cohorts (13,14). On Hawaii, USA, the prevalence of major malformations in newborns born in the 1989-1993 period and parented by veterans from the Gulf War corresponded to the EUROCAT average (15).

The Chernobyl nuclear disaster increased the prevalence of major malformations in children conceived in contaminated regions immediately after the fallout (16-20). On the other hand, no increased risk of congenital malformations was recorded in other parts of Europe at that time (21-24).

Studies on Japanese survivors of nuclear bombing revealed that the relative risks of cancer and congenital malformations decreased with increasing time since the exposure (25-27). Experimental studies re-

vealed a significant correlation between the radiation doses and increased occurrence of congenital malformations in laboratory conditions (28-30). Nevertheless, it has been propounded that "humans were not as sensitive to the genetic effects of radiation as projected from the mouse paradigm" (31). In Japan, population risks from the past radiation exposures are still being studied as an important epidemiological and clinical problem (32).

The prevalence of major congenital malformations has not been studied in Herzegovina before the 1991-1995 war. Some crude data were obtained (by personal contact) from the Federal Agency for Public Health of Bosnia and Herzegovina. In 1990, 34 cases were reported for the population of 560,954 children in the age group from 0 to 6 years (0.006%). In the canton of Sarajevo, the capital of Bosnia and Herzegovina, located in Bosnia, 42 (0.84%) anomalies were recorded in the cohort of 4,995 neonates born in 2000 (33). This study, however, did not meet stringent criteria. Prevalence of major malformations in neonates born in 1979 in Split, a coastal city in Croatia (150 kilometers from Mostar) was 1.42% (personal communication). In another Croatian town, Pula, the prevalence before the war, in 1987, was 1.98% (34).

Analysis of the involvement of the organ systems in our study revealed some differences between the 1995 and the 2000 cohorts with regard to the cardiovascular, central nervous, and urogenital systems. The most frequent major malformations in both our cohorts involved musculoskeletal system, which is similar to other studies (35-37), followed by malformations of the digestive tract in the 1995 cohort (5.39 per 1,000 newborns, ie, 0.539%), and cardiovascular malformations in the 2000 cohort (0.615%). This corresponded to their incidence in five Croatian communities in the 1986-1987 period (34). In Hungary, in the 1973-1982 period, the musculoskeletal malformations occupied the fifth place (37). In our cohort from 1995, anomalies of the genitourinary system were the third most frequent (5 cases, or 0.269%), and not registered at all in the 2000 cohort. On the other hand, incidence of genitourinary malformations in Hungary was 3.5 times higher (37), whereas in Zagreb, Croatia, it was more than four times lower (36).

The diminishing trend of urogenital anomalies was partly outweighed by an increasing incidence of anomalies involving the cardiovascular and central nervous systems. Major malformations of central nervous system were not registered in the 1995 cohort, whereas in the 2000 cohort, they were found in 4 (0.273%) children. In some countries, e.g., Northern Ireland, the incidence of the central nervous system anomalies in the same period was even higher (35). In the Beirut study, anomalies of the central nervous system were on the third place, after anomalies of the skeletal and the genitourinary systems, occurring at a frequency of 3.10 per 1,000 births (14).

In our study, anomalies of the cardiovascular system were found in 3 children in the 1995 cohort, and 9 in the 2000 cohort. In Croatia, these anomalies were the most frequent in Istria in the 1986-1987 period, and the second most frequent in the city of Varaždin in the 1982-1984 period (38).

The anomalies of central nervous and cardiovascular systems showed an increasing trend, and the anomalies of the urogenital system a decreasing trend. It should be noted that detection of genitourinary anomalies depends on an active search (prenatal ultrasound, postnatal follow-up), but in view of good maternal and pediatric care in West Herzegovina, our study was not biased in that respect. However, small numbers and short time interval do not permit any generalizations.

In the 1995 cohort, there were three children with inguinoscrotal hernia, one child with bilateral cryptorchism, and one case of familial agenesis of the right kidney (found in the mother and two brothers of the newborn). Similar results were recorded in Hungary (37).

There were three examples of Down syndrome in the 2000 cohort, and four in the 1995 cohort, which is an average incidence. All cases were regular types of trisomy 21 and all were offsprings of parents over 35 years of age. A girl with the Williams syndrome was discovered in the 2000 cohort. This rare syndrome (2-5 cases per 100,000) is caused by a microdeletion on 7q11.23 (39).

In the 1995 cohort, both sexes were almost equally affected by the anomalies, but in the 2000 cohort, anomalies predominated in girls. The difference, however, was not statistically significant. A comprehensive study by Stevenson et al (35) showed a higher incidence of the anomalies in boys. That was also true for a sample of Croatian children (36). The observed preponderance of anomalies in the girls in our 2000 cohort remains unexplained, requiring further observation and clarification.

In the last decade (1990-2000), the infant mortality rate and the mortality rate attributable to malformations were both essentially stable and even decreasing. In 1995, the infant mortality was 1.73% and mortality attributable to major malformations 18.75%. This mostly corresponds with data from other countries (13-15,34). In 2000, no deaths attributable to malformations were recorded and infant mortality decreased to 0.34%, reflecting recent advances in pediatric neonatal care.

Analysis of the prevalence of anomalies in relation to the gestational age showed the highest relative frequency of malformations in small-for-date neonates in the 1995 cohort (14.81%). In the 2000 cohort, the malformations were most frequent in the group of premature neonates (7.14%). Higher scores of malformations in premature and hypotrophic neonates are in agreement with data reported in the literature (34,38-42).

Obstetricians and pediatricians often share an impression that "something is wrong" with pregnancies harboring malformed fetuses, as if the nature "announces" birth of an aberrant creature. Analysis of the available data showed correlation between obstetrical complications and major malformations. In the

1995 cohort, a "pathological trait" was recorded in 85.0% of pregnancies and/or deliveries of children born with major malformations, and in the 2000 cohort, in 54.5% newborns. However, the difference between the two cohorts might be ascribed to different methods of data acquisition. The 1995 cohort was studied prospectively and the data were collected from medical documentation as well as by interviewing the mothers according to the EUROCAT protocol. For logistic reasons, the 2000 cohort was studied retrospectively and the data were extracted from medical documentation.

In conclusion, we may say that the prevalences of major malformations in two cohorts of neonates born in 1995 and in 2000 were similar. The overall prevalence was comparable to that in geographically and demographically related regions before the war. Malformations of the musculoskeletal system were the most frequent ones. Boys and girls were equally affected in the 1995 cohort, whereas in the 2000 cohort, the anomalies were more frequent in girls, but not significantly. A correlation between prenatal and perinatal obstetrical complications and major malformations in the offspring was noted in both cohorts.

Rather scarce, localized, and low radiation contaminations detected in Bosnia and Herzegovina that could be associated with the military use of depleted uranium ammunition in 1995, together with our present finding of no change in prevalence of neonatal malformations, suggests that the danger from this type of environmental pollution in Bosnia and Herzegovina is insignificant.

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