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Malformations in a Chernobyl-Impacted Region

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Malformations in a Chernobyl-Impacted Region



WHAT'S KNOWN ON THIS SUBJECT: No other population-based birth defects surveillance data applying international standards concerning rates in Ukraine are known. Furthermore, no other reports on chronic low-dose ionizing radiation exposure population effects related to Chernobyl expressed as malformations are known.



WHAT THIS STUDY ADDS: Population-based rates of NTDs and other malformations in Ukraine that may reflect composite impacts of low-dose radiation, folate deficiencies, and prenatal alcohol teratogenesis are provided. This study provides a baseline for prospective investigations.

abstract



OBJECTIVE: One of the populations most exposed to chronic low-dose radiation from Chernobyl (Chernobyl in Russian) lives in Polissia, the region representing the northern half of Rivne Province (Oblast) in Ukraine. Here the patterns and population rates of malformations are reported and possible etiologic factors and regional contrasts are explored.

PATIENTS AND METHODS: Malformations, as defined by international standards, noted among all 96 438 births in Rivne between 2000 and 2006, were analyzed statistically. Contrasts of rates in Polissia compared with the rest of Rivne also were investigated.

RESULTS: The overall rate of neural tube defects in Rivne is among the highest in Europe (22.2 per 10 000 live births). The rates of conjoined twins and teratomas also seem to be elevated. In Polissia, the overall rates of neural tube defects are even higher (27.0 vs 18.3, respectively; odds ratio: 1.46 [95% confidence interval: 1.13–1.93]), and the rates of microcephaly and microphthalmia may also be elevated.

CONCLUSIONS: The malformation patterns observed suggest early disruptions of blastogenesis, manifesting as alterations of body axes, twinning, duplications, laterality, and midline formation. The results are sufficiently compelling to justify continuing and expanding this investigation of malformations in chronic low-dose radiation-impacted regions of Ukraine. *Pediatrics* 2010;125:e836–e843

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KEY WORDS

alcohol, anencephaly, Chernobyl, Chernobyl, conjoined twin, fetal alcohol syndrome, folate, gender, ionizing, malformation, microcephaly, microphthalmia, monozygotic, neural tube defects, nutrition, omphalocele, radiation, sex, spina bifida, teratoma, twin, Ukraine

ABBREVIATIONS

NTD—neural tube defect
EUROCAT—European Surveillance of Congenital Anomalies Organization
OR—odds ratio
CI—confidence interval
ABCC—Atomic Bomb Casualty Commission

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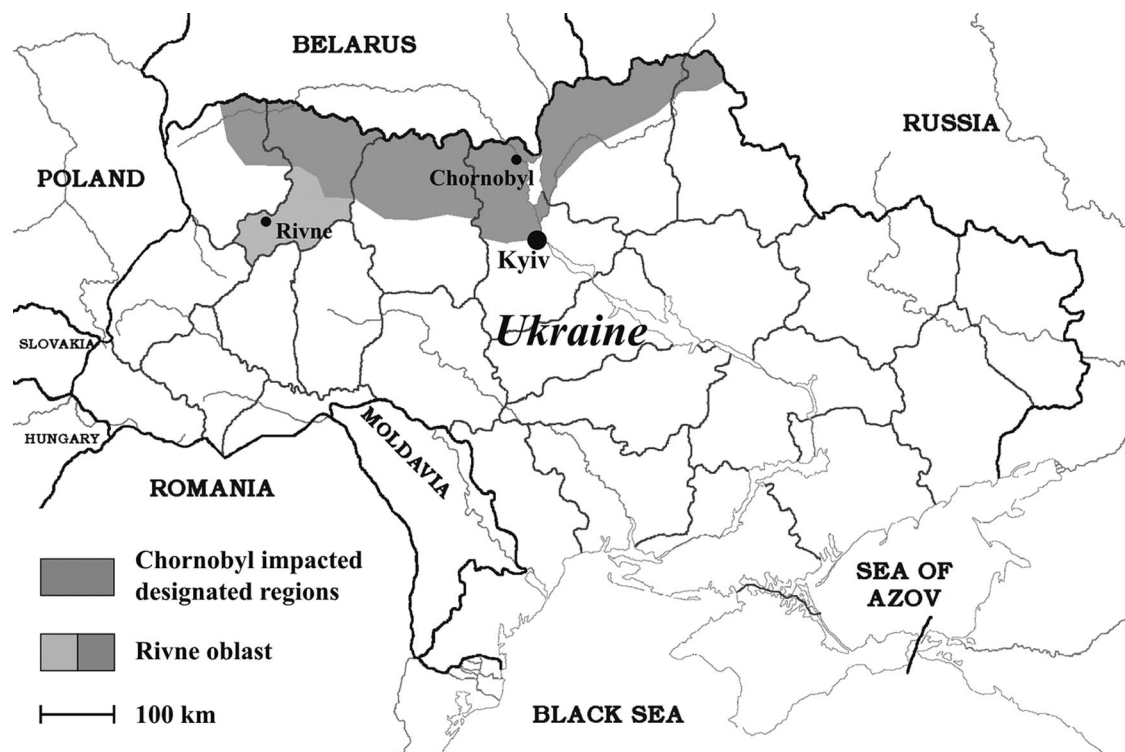


FIGURE 1
Outline of Ukraine, its provinces (Oblasts), and its waterways and coastlines.

In 1999, a Ukrainian population-based malformations surveillance system was established in Rivne and other provinces.¹ The Rivne Province is located nearly 250 km west of the Chornobyl atomic power plants, and its northern half is a region known as Polissia. The Chornobyl explosion and fire started on April 26, 1986, and caused ionizing radiation-contamination across northwestern Ukraine. In Rivne, all Polissia counties (raions) were officially designated as significantly impacted (Fig 1). In addition, the Polissian radiation-contaminated soils have one of the highest known transfer rates of Cs¹³⁷ from soil to the food chain known in Ukraine.² Recent radiation surveys confirmed that ingestion of Cs¹³⁷-contaminated foods, in particular milk and related products, is the main source of radiation exposures.³ Since recorded history, Polissia has been inhabited by “Polishchuks” (forest dwellers), whose culture has characteristics in common with those of

other isolated populations. Most Polishchuks inhabit small villages and primarily subsist on homegrown vegetables, animal products, home-produced milk, and dietary supplements gathered in nearby forests (from wild berries and wild mushrooms, as well as by hunting and fishing). Polissia also extends to adjoining provinces in Ukraine and Belarus.

The current investigation was prompted by persisting public concerns about the impact of Chornobyl-related chronic radiation exposure on pregnancy outcomes and lack of population-based malformations data collected according to international standards. After 2 years of malformations monitoring, rates of neural tube defects (NTDs) including anencephaly, iniencephaly, rachischisis, spina bifida, and encephaloceles in Northwestern Ukraine (Volyn and Rivne provinces) were noted to be elevated.⁴ In addition, recurrent births of conjoined-twin sets were noted in Rivne,

with none in 2 adjoining provinces (Volyn and Khmelnytsky).

The goal of this report is to present population rates of selected malformations noted during a 7-year period of standardized data collection and to compare and contrast these rates in the Polissian and non-Polissian regions of the Rivne Province. The specific malformations selected for comparison were NTDs; malformations related to twinning including conjoined twins, teratomas, and also microcephaly; and microphthalmia, all of which are malformations that may be due to prenatal exposure to ionizing radiation and the last two (microcephaly and microphthalmia) can also be due to prenatal exposure to alcohol.⁵

PATIENTS AND METHODS

In this report, the following conventions apply: “Rivne,” unless specified otherwise, means Rivne Province, the capital of which is likewise named

Rivne; Kostopil County represents a transition zone (the soils are characteristic of Polissia, but the inhabitants are not Polischuks); Kostopil is included in the non-Polissia category; and “rates in Europe” refer to those reported by the European Surveillance of Congenital Anomalies Organization (EUROCAT) for 2000–2006 (excluding instances because of chromosomal abnormalities).⁶

The malformation data presented were derived from virtually all 96 438 infants born in Rivne between 2000 and 2006, including from pregnancy terminations, pregnancy losses, stillbirths, and live births ascertained up to the age of 1 month. The methods used to ascertain and classify malformations conformed to the standards of the EUROCAT as described elsewhere.⁶ Infants with malformations

are computed into a single category in a priority order reflected in data presentation. Data for infants with disorders of established etiology or pathogenesis are included in Table 1 and excluded from calculation of rates presented in Table 2. Microcephaly is defined as an occipitofrontal circumference at least 3 SDs below the norm for gestational age and gender of the infant using standard growth curves. Mi-

TABLE 1 Individuals With Selected Malformations in Polissia and Non-Polissia Regions of Rivne, Ukraine

	Polissia, <i>n</i>			Non-Polissia, <i>n</i>				All Rivne, <i>n</i>			
	Total	Case	M	F	Total	Case	M	F	Total	M	F
All births (2000–2006)	43 392		22 346	21 028	53 046		27 391	25 624	96 438	49 737	46 652
NTD ^a	118		42	56	99		34	34	217	76	90
Craniocervicothoracic	55		20	25	43		13	15	98	33	40
Isolated	45		18	19	38		13	12	83	31	31
Anencephaly ^b	23	a	9 ^c	10	25	m	8 ^d	8	48	17	18
Cranio-rachischisis ^e	14	b	4	8 ^c	10		2	4	24	6	12
High spina bifida ^f	8		5	1	3		3	0	11	8	1
Not isolated	10	c	2	6 ^d	5	n	0	3	15	2	9
Lumbo-sacral spina bifida ^g	43		19	18	39		17	16	82	36	34
Isolated low spina bifida	39		17	17	34	o ^c	14	15 ^c	73	31	32
Not isolated	3	d	2	0	5	p	3	1	8	5	1
Syndromes ^h	1	e	0	1	0		0	0	1	0	1
Spina bifida isolated site undefined	11		2	8	4		0	1	15	2	9
Encephaloceles	9		1	5	13		4	2	22	5	7
Isolated	7		0	5	9		2	2	16	2	7
Not isolated	2	f	1	0	2	q	1	0	4	2	0
Syndromes ^h	0		0	0	2	r	1	0	2	1	0
Omphaloceles ⁱ	9		6	1	15		5	3	24	11	4
Isolated	4		4	0	10		4	2	14	8	2
Not isolated	3	g	0	1	4	s ^c	0	1	7	0	2
Syndromes ^h	2	h	2	0	1	t	1	0	3	3	0
Conjoined twins	2	i	0	1	3	u	0	3	5	0	4
Teratomas ^j	5		1	1	2		0	2	7	1	3
Microcephaly	21		9	12	14		7	7	35	16	19
Isolated	8		2	6	6		3	3	14	5	9
Not isolated	8	j	3	5	1	v	0	1	9	3	6
Syndromes ^h	5	k	4	1	7	w	4	3	12	8	4
Microthalamos ^k	8		2	6	2		2	0	10	4	6
Isolated	2		0	2	1		1	0	3	1	2
Not isolated	6	l	2	4	1	x	1	0	7	3	4
All	163		60	77	135		48	49	298	108	126
Isolated	123		44	59	107		37	40	230	81	99
Not isolated	32		10	16	18		5	6	50	15	22
Syndromes ^h	8		6	2	10		6	3	18	12	5

Unique individuals (singleton, twin, or conjoined twins) of male, female, or unknown gender are included in the “total” categories.

^a Individuals with NTDs are computed first, followed by those with omphalocele, those who are conjoined twins, teratomas, microcephaly, and microphthalmia, other concurrent malformations are described in the Appendix (cases a–x). Appendix is published as supplemental information at www.pediatrics.org/content/full/125/4/e836.

^b Acrania and exencephaly are included.

^c Inclusion of individuals who are a twin.

^d Inclusion of individuals who are a member of a conjoined-twin set.

^e Includes iniencephaly.

^f Includes cervical or thoracic spinal schises.

^g Includes spinal schises distal to the 11th thoracic vertebra.

^h Instances likely to be due to mutations, chromosomal defects and exposures to alcohol.

ⁱ Excludes gastroschisis.

^j All were isolated sacrococcygeal teratomas.

^k Includes anophthalmia and microphthalmia.

TABLE 2 Individuals With Malformations and Rates Per 10 000 Births Excluding Instances of Likely Mutations, Chromosomal Defects or Prenatal Exposures to Alcohol

	Polissia			Non-Polissia			All Rivne			Polissia vs Non-Polissia		
	All, <i>n</i>	Rate, per 10 000	M/F	All, <i>n</i>	Rate, per 10 000	M/F	All, <i>n</i>	Rate, per 10 000	M/F	<i>P</i> ^a	OR ^b	CI ^c
All births (2000–2006)	43 392	NA	1.06	53 046	NA	1.07	96 438	NA	1.07	NA	NA	NA
NTDs	117	27.0	0.76	97	18.3	0.97	214	22.2	0.84	0.003	1.46	1.13–1.93
Isolated	102	23.5	0.76	85	16	0.97	187	19.4	0.84	0.006	1.47	1.09–1.96
Omphalocele	7	1.6	NA	14	2.6	NA	21	2.2	NA	0.28	0.61	0.21–1.62
Conjoined twins	2	NA	NA	3	NA	NA	5	NA	NA	0.59	0.82	0.07–7.12
Teratomas	5	1.2	NA	2	0.4	NA	7	0.7	NA	0.15	3.06	0.50–32.1
Microcephaly	16	3.7	0.45	7	1.3	0.75	23	2.4	0.53	0.02	2.8	1.15–6.79
Microphthalmos	8	1.8	NA	2	0.4	NA	10	1.0	NA	0.03	4.89	1.04–23.03
All	155	35.7	0.72	125	23.6	0.91	280	29.0	0.79	0.0003	1.52	1.20–1.91
Isolated	123	28.3	0.75	107	20.2	0.93	230	23.8	0.82	0.006	1.41	1.08–1.82
Not isolated	32	7.4	0.63	18	3.4	0.83	50	5.2	0.68	0.005	2.17	1.22–3.87

M/F indicates male/female ratio; NA, not applicable (small number of observations).

^a *P* value of Fisher's exact test.

^b Odds ratio.

^c 95% confidence interval.

crophthalmia and anophthalmia were merged into a single category, a distinction that otherwise would require autopsy studies. Statistical comparisons between specific malformation rates were made between Polissian and non-Polissian regions by using χ^2 or Fisher's exact test as appropriate, and the unadjusted odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated.

RESULTS

Table 1 lists the number of individuals with selected malformations according to gender, region, and overall for 2000–2006. Table 2 lists the rates per 10 000 births after exclusion of instances likely to be because of mutations, chromosomal defects, and exposures to alcohol.

The overall rate of NTDs in Rivne was 22.2 per 10 000 births. This rate is nearly identical to the rate of 21 in Northwestern Ukraine (provinces of Rivne and Volyn) reported for 2000–2002.⁴ The overall NTD rates in Polissia were significantly higher than in non-Polissia (27.0 vs 18.3) and higher than the rates reported during the same period in Europe by monitoring systems with at least 50 recorded instances of NTD. The average rate in Europe was

9.43, and the highest was 15.34, recorded in Wales.⁶ The proportions of isolated NTDs in Polissia versus non-Polissia were similar (86%) as were NTD subcategories. Early detection of NTDs (before the 28th week of gestation) was less frequent in Polissia (69%) compared with 77% in non-Polissia (data not shown). The overall NTD male/female ratio was 0.84 (Table 2). Among those of known gender, 5 of 6 of the conjoined-twin sets and 3 of 4 of those with teratomas were girls (Table 1 and Appendix).

The association of NTDs with omphaloceles was noted in 9 of 217 (4.1%) individuals with NTDs compared with the overall omphalocele rate of 0.04% (all instances) or 0.015% (isolated instances). There were 7 individuals with an NTD-omphalocele association. Among those of known gender, 4 of 6 were girls from Polissia, and 1 of 2 was a boy from non-Polissia (Appendix). In Europe, the omphalocele rates reported by the EUROCAT during the same period (based on at least 25 instances) are similar (0.02%).

Concerning twinning, 6 of 217 individuals with NTDs were twins, and another was a co-twin member of a craniothoracopagus set with a large lumbosa-

cral spina bifida, and an omphalocele, whereas her co-twin was malformation-free (Table 1 and Appendix). In addition, there were 5 other conjoined-twin sets (a thoracopagus set with 1 co-twin with bilocular heart, 2 thoracophalopagi, and single instances of craniothoracopagus and omphalopagus sets). The Rivne rate of conjoined twins was 0.62 compared with 0.18 in Europe and 0.12 in the metropolitan Atlanta area.^{6,7} The rates of conjoined twins were similar in the Polissian and non-Polissian areas, but the numbers were very small. Regarding nonconjoined twins, there were 757 pairs of known gender. As shown in Table 3, 34 twins were malformed, and their co-twins were malformation-free, 25 of whom were of the same gender. There were 6 twins with NTDs, 5 of the co-twins were of the same gender, and all were malformation-free. There were 7 sacrococcygeal teratomas for an overall rate in Rivne of 0.73, although published rates have been within the range of 0.25 to 0.50.⁸

As shown in Table 2, rates of microcephaly and microphthalmia of unknown etiology were 2.4 and 1.0, respectively, and were significantly higher in Polissia than in non-Polissia

TABLE 3 Malformations Among 1514 Twin Individuals of Known Gender and Members of Nonconjoined Twin Pairs

	Polissia, <i>n</i>		Non-Polissia, <i>n</i>		Rivne Oblast, <i>n</i>	
Like-gender	260	12 ^a	282	13	542	25
Male-male	141	9 ^b	133	9 ^d	274	18
Female-female	119	3 ^c	149	4 ^e	268	7
Unlike-gender	92	5 ^f	123	4 ^g	215	9
All twin pairs	352	17	405	17	757	34

^a Number of twin individuals with malformations (excluding first-degree hypospadias); all co-twins were malformation-free.

^b Anencephaly, microtia-atretic ear canal, esophageal atresia and tetralogy of Fallot, 3 instances of ventricular septal defect, undefined cardiac malformation, Down syndrome, and balanic hypospadias.

^c Craniorachischisis, cardiac malformation, and polycystic kidney.

^d Two instances of anencephaly, ventricular septal defect, 3 instances of balanic hypospadias, jejunal atresia, penoscrotal hypospadias, and right upper limb reduction anomalies.

^e Dandy-Walker syndrome, single cardiac ventricle, ventricular septal defect, and low spina bifida.

^f A male with congenital hydrocephalus, a male with ventricular septal defect, a female with an abdominal wall defect, a male with severe left ureterohydronephrosis, and a male with amniotic band syndrome.

^g A male with cardiac malformation; a female with low spina bifida; a male with Down syndrome; and a female product of in vitro fertilization with an absent shoulder, forearm, femur, and cystic hygroma.

(3.7 vs 1.3, respectively; OR: 2.8 [95% CI: 1.15–6.79] and 1.8 vs 0.4; OR: 4.89 [95% CI: 1.04–23.03]). The combined frequency of microcephaly and microphthalmia (which can result from ionizing radiation) was likewise significantly higher in Polissia versus non-Polissia (5.5 vs 1.7, respectively; OR: 3.3 [95% CI: 1.52–7.02]).⁵

DISCUSSION

The risk factors in Rivne manifested as malformations include, among others, low-dose ionizing radiation, prenatal alcohol exposure, and, in view of the high prevalence of NTDs, probably folate deficiency. These factors can disrupt embryonal development before the third week after fertilization.

A report by the Committee on the Biological Effects of Ionizing Radiations, focused on health effects of low-level exposures, summarized prevalent

views.⁹ Authors of the report noted that “the estimates of genetic risks in humans are based primarily on experimental data obtained with laboratory animals.”⁹ Authors of another report by the International Atomic Energy Agency, which coordinates United Nations and World Health Organization policies on Chernobyl health effects, asserted that “because of the relatively low doses to residents of contaminated territories [in Ukraine, that there is] no evidence or likelihood [of detecting effects] . . . on the number of stillbirths, adverse pregnancy outcomes . . . or overall child health.”¹⁰ This position statement may have had a chilling effect on initiatives focused on investigations of malformation patterns and rates in Chernobyl-impacted regions and may reflect a reliance on interpretations of data collected in Japan by investigators sponsored by the Atomic Bomb Casualty Commission (ABCC). Other reports, also based on ABCC data, described the association of ionizing radiation exposure with microcephaly, and some of them have stressed that similar studies are desirable in Chernobyl-impacted areas.¹¹ Such recommendations were not included among those endorsed by the International Atomic Energy Agency. However, several Chernobyl-related investigations have pointed toward its impact on human health and the genome.^{12,13} With respect to human malformations, 2 ABCC reports are of interest.¹⁴ The first provided details of the methods and population studied, and the second report was focused on the array of malformations noted among children of nonconsanguineous parents, neither of whom were exposed to significant doses of radiation. The aim of the investigation was to provide normative malformations data for Japan for comparison with other countries. The overall conclusion was that “the biological impact of congenital malformations is very similar in all

populations.” However, the report also noted that “the frequency of malformed infants was significantly higher ($P < .05$) in Hiroshima and Nagasaki than in Kure (a control site). It should be noted that the array of malformations in Hiroshima-Nagasaki was similar to that in Rivne. Specifically, among 26 012 children from Hiroshima, 30 240 from Nagasaki, and 7544 children from Kure, there were conjoined twins (Hiroshima-Nagasaki, 1; Kure, 0), situs inversus (Hiroshima-Nagasaki, 2; Kure, 0), teratoma (Hiroshima-Nagasaki, 3; Kure, 0), NTD (Hiroshima-Nagasaki, 46; Kure, 5), omphalocele (Hiroshima-Nagasaki, 5; Kure 1), microcephaly (Hiroshima-Nagasaki, 3; Kure, 0), anophthalmia (Hiroshima-Nagasaki, 15; Kure, 0), and atresia ani (Hiroshima-Nagasaki, 13; Kure, 0). Comparisons of low-dose radiation exposures and dosimetry in Japan and in Ukraine are complex; in Japan exposures were acute and in Ukraine exposures are chronic.¹⁵

With respect to Chernobyl, investigations in Belarus of pregnant women and newborns residing in the most severely impacted regions by radiation suggested an increase of the frequency of dicentric and ring chromosomes. Also noted was an increase in frequency of multiple congenital malformations and limb defects.¹⁶ A comprehensive investigation of nearly half a million Swedish children born between 1983 and 1988 demonstrated that those in utero exposed at ~8 to 25 weeks of gestation during the Chernobyl accident had worse school outcomes than other birth cohorts. The impact was greatest in the 8 municipalities with the highest level of fallout.¹³ Such findings are consonant with the view that the higher microcephaly rates noted in Polissia may also be because of chronic exposures to ionizing radiation.

Two investigations focused on areas in proximity to atomic nuclear plants,

Hanford, California, and Sellafield, United Kingdom, are of interest. The first investigation found a significant association with NTDs, which was dismissed by the authors primarily because it contradicted conclusions based on ABCC data mentioned earlier.¹⁷ The second investigation showed a significant increased risk for stillbirths with congenital anomalies, in particular NTDs, most of which were anencephaly.¹⁸ Taking into account these and other similar investigations, the question of a low-dose radiation NTD association remains extant.^{19–21} In addition, the concurrent higher frequency of NTDs, microcephaly, and microphthalmia in Polissia, a region significantly exposed to low-dose radiation, is a finding sufficiently compelling to call for additional study.

Concerning the teratogenesis of alcohol, it is beyond dispute that prenatal exposures give rise to fetal alcohol spectrum disorders, which include microcephaly and microphthalmia. The relatively high proportion of microcephaly in combination with fetal alcohol spectrum disorders noted in Rivne underscores the importance for prospective investigations of microcephaly to include a focus on alcohol teratogenesis. Furthermore, high NTD rates in Rivne also suggest that folate deficiency may be prevalent, a factor that also may negatively affect DNA stability and repair, in a manner similar to exposures to low-dose radiation.²² To what extent synergistic effects of low-dose radiation, alcohol consumption, and folate deficiency are expressed in Rivne as NTDs, microcephaly-microphthalmia, and perhaps conjoined twins and teratomas remains unknown. However, the circumstances in Rivne are unique and favorable for concurrent investigations of these risk factors.

Regarding micronutrient deficiencies, apparently none of the population sur-

veys in Ukraine focused on folates. On the other hand, worldwide experience shows that in a variety of areas with high NTD rates, folic acid consumption significantly reduces the occurrence of these malformations.²³ Likewise, and irrespective of a micronutrient survey, programs to increase folic acid consumption in Rivne are expected to reduce NTD rates and should be implemented without delay. However, a nutrition survey in Rivne offers a unique opportunity to assess to what degree consumption of folic acid affects rates of NTDs and other malformations.

Investigations in Rivne of associations of NTD with non-NTD malformations and with twinning are of interest because such associations may suggest shared mechanisms.^{24–27} Probably among the first to stress the NTD-omphalocele association was McKeown, who in 1953 stated that “the frequency of association of anencephalus with exomphalos is striking (20%).”²⁵ He also noted the association with other midline malformations and noted that “the incidence of diaphragmatic hernia, ectopia vesicae, and severe genital malformations also seems to be unduly high.” In Europe, among patients with NTDs, the association with omphaloceles was noted in between 3% and 22% of instances.²⁶ A large international investigation of NTDs demonstrated an association with twin members of like-gender pairs, particularly in girls.²⁷

Classification notions affect categorizations of malformations and formulation of unifying hypotheses. For example, some regard hemihypertrophy as a minimal form of twinning, whereas in Rivne, NTDs-omphaloceles could be viewed as disruptions of body-wall formation.²⁸ Applying the latter sense, 6 additional observations of lethal thoraco-abdominoschisis, among which 4 also had ectopia cordis (a sev-

enth instance is case “n” in Table 1), could be added to this report.

It is generally accepted that monozygotic twins arise near the time of inactivation of an X chromosome in excess of 1 at the time when expression of batteries of maternal effect genes are inducing the formation of the cephalocaudal gradient and body-plan formation. The occurrence of conjoined twins and sacrococcygeal teratomas, as noted in Rivne, can be viewed as forms of embryonal duplications.^{29,30} Early malformations in monozygotic twins and conjoined twins are more common and tend to affect only 1 member of the twin set.³¹ In Rivne, the concordance rate for malformations in like-gender co-twins is near 0. Studies of conjoined twins also showed that malformations preferentially affect the right-side co-twin, whereas the left co-twin was malformation-free.³² Hypothetically, the lack of concordance for malformations in twins may reflect alterations of “nodal flow” of extracellular fluid containing morphogens and regarded to be among the first left-right symmetry-breaking embryonal events.^{33,34} Also of interest are observations of left-isomerism sequence associated with maternal type 1 diabetes, also noted in insulin-dependent diabetes mellitus mouse models.³⁵ Observations of monozygotic discordant twins with Wiedemann-Beckwith syndrome, preferentially in females, prompted the suggestion that a mechanism similar to X-chromosome inactivation may result in genomic imprinting, causing the malformation complex.³⁶ In summary, additional investigations in Rivne concerning early malformations associated with twinning and female preference are indicated.

CONCLUSIONS

The NTD rates in Rivne are persistently elevated, and the rates of conjoined

twins and teratomas also seem to be elevated. The rates of NTDs in Polissia are higher than in non-Polissia, and rates for microcephaly and microphthalmia likewise seem to be elevated. The malformation patterns observed suggest early disruptions of blastogenesis, manifesting as alterations of body axes, twinning, sacrococcygeal teratomas, midline, laterality, and duplication anomalies with attention to gender preference. We admit that the limitations of this study include a lack of data regarding levels of low-dose radiation, consumption of micronutrients, degrees of consanguinity, and other data that may further define con-

trasts of Polissian and non-Polissian regions. However, these and other risk factors, including chronic low-dose radiation and alcohol effects on the unborn, can be clarified by concurrent prospective investigations. Existing local resources and the expressed interest by Rivne authorities to nurture partnerships with national and international teams will facilitate such initiatives.

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