

¹A.M. Kalimagambetov , ¹A.A. Dyusembaeva ,
²I.A. Khalelova , ¹Z.G. Aitasheva , ³B.N. Kudryavtsev 

¹Al-Farabi Kazakh National University, Kazakhstan, Almaty,

e-mail: aitkali.kalimagambetov@kaznu.kz

²Regional Perinatal Center, Kazakhstan, Aktau

³Institute of Cytology, Russia, St. Petersburg

CHROMOSOMAL DISORDERS IN THE FETUS OF PREGNANT WOMEN FROM AKTAU

Abstract. The article presents the data of cytogenetic study on the fetal karyotype of 310 pregnant women from the city Aktau in 2013–2015. Chorionic biopsy and placental biopsy were carried out for 248 pregnant women with amniocentesis in 18 cases and cordocentesis in 44 cases. Clinical indicators imposing invasive procedures to pregnant women at risk were maternal age factor, fetal ultrasound markers, serum blood markers determined in pregnant women, the presence of children with multiple congenital malformations, chromosomal pathologies, etc. Distribution frequencies of fetal chromosomal abnormalities have been determined based on clinical and laboratory studies. The highest frequency of chromosomal abnormalities of the fetus was indicated in pregnant women with three salient indicators: the factor of the age of the pregnant woman, parameters of biochemical screening, and ultrasound markers. Chromosomal abnormalities of the fetus were detected in 94 (30.3%) pregnant women including 92 cases (97.9%) represented by numerical chromosome disorders and 2 cases (2.1%) of structural disorders. Disorders of the autosome system were observed 9.4 times more often comparing to abnormalities in the sex chromosome system. Of the numerical chromosome abnormalities, a high specific weight is occupied by trisomy of the 21-st chromosome which has reached 65.1%. A comparative analysis of the frequencies of chromosomal abnormalities of the fetus of two port cities has demonstrated a 1.7-fold increase in the city of Aktau (Kazakhstan) compared with the city of Murmansk (Russia), and the average frequencies of fetal karyotype anomalies have made up 19.6% and 11.6%, respectively. Higher level of frequencies for fetal karyotype anomalies in Aktau is possibly associated with unfavorable environmental conditions in this city caused by the allocation of the oil and gas industry, the repository for tailing toxic and radioactive wastes, and abandoned uranium mines.

Key words: karyotype, fetus, prenatal diagnosis, fetal chromosome disorders, ecological state of urban agglomerations.

¹А.М. Калимагамбетов, ¹А.А. Дюсембаева,
²И.А. Халелова, ¹З.Г. Айташева, ³Б.Н. Кудрявцев

¹Ал-Фараби атындағы Қазақ ұлттық университеті, Қазақстан, Алматы қ.,

e-mail: aitkali.kalimagambetov@kaznu.kz

²Облыстық перинаталдық орталығы, Қазақстан, Ақтау қ.

³Цитология институты, Ресей, Санкт-Петербург қ.

Ақтау қаласындағы жүкті әйелдер ұрығының хромосомалық бұзылыстары

Аңдатпа. Мақалада 2013–2015 жылдар аралығында Ақтау қаласындағы 310 жүкті әйелдің ұрық кариотиптерінің цитогенетикалық зерттеу нәтижелері келтірілген. Хориониопсия және плацентобиопсия 248 жүкті әйелге, амниоцентез – 18 және кордоцентез – 44-не жүргізілді. Қауыпты тобындағы жүкті әйелдерге арналған инвазивті процедуралардың клиникалық көрсеткіштері: аналық жас факторы, ұрықтың ультрадыбыстық маркерлері, жүкті әйелдердің қан сарысуындағы маркерлері, көптеген туа біткен ақаулары, хромосомалық патологиялары бар балалардың болуы. Ұрықтың хромосомалық аномалияларының таралу жиілігі клиникалық және зертханалық зерттеулерді ескере отырып анықталады. Ұрықтың хромосомалық ауытқуларының ең жоғары жиілігі пренатальды диагностиканың үш көрсеткіші бар жүкті әйелдерде анықталды, яғни, жүкті әйелдің жас факторы, биохимиялық скрининг параметрлері және ультрадыбыстық маркерлер бойынша. Ұрықтың хромосомалық ауытқулары 94 (30,3%) жүкті әйелдерде анықталды, олардың ішінде 92 жағдай (97,9%) хромосомалардың сандық бұзылыстарымен және

2 жағдай (2,1%) құрылымдық бұзылыстармен сипатталды. Жыныстық хромосомалар жүйесіндегі ауытқулармен салыстырғанда аутосомалық хромосомалар жүйесіндегі бұзылыстар 9,4 есе жиі байқалды. Хромосомалардың сандық бұзылыстарының ішінде жоғары үлес 21 хромосоманың трисомиясы бойынша байқалды, оның жиілігі 65,1% құрады. Екі теңіз жағалауындағы қалаларда ұрықтың хромосомалық аномалияларының жиілігі Мурманск (Ресей) қаласымен салыстырғанда Ақтау қаласында (Қазақстан) 1,7 есе рет өскенін көрсетті, ұрықтың кариотиптік ауытқуларының орташа жиілігі сәйкесінше 19,6% және 11,6%, байқалды. Ақтаудағы ұрықтың кариотиптік ауытқуларының жиілік деңгейінің жоғарылауы Ақтаудағы қолайсыз экологиялық жағдайға, яғни мұнай-газ өнеркәсіптерінің болуына, токсиндік және радиобелсенді қалдықтарға арналған қалдық қоймасы мен тасталған уран шахталарына байланысты болуы мүмкін.

Түйін сөздер: кариотип, ұрық, пренатальды диагноз, ұрықтың хромосомасының бұзылыстары, қалалық агломерацияның экологиялық жағдайы.

¹А.М. Калимагамбетов, ¹А.А. Дюсембаева,
²И.А. Халелова, ³З.Г. Айгашева, ³Б.Н. Кудрявцев

¹Казахский национальный университет имени аль-Фараби, Казахстан, г. Алматы,
e-mail: aitkali.kalimagambetov@kaznu.kz

²Областной перинатальный центр, Казахстан, г. Ақтау

³Институт цитологии, Россия, г. Санкт-Петербург

Хромосомные нарушения у плода беременных женщин г. Ақтау

Аннотация. В статье приведены результаты цитогенетического исследования кариотипа плода у 310 беременных женщин г. Ақтау за 2013–2015 гг. Хориониобиопсия и плацентобиопсия проведены у 248 беременных женщин, амниоцентез – у 18 и кордоцентез – у 44. Клиническими показателями для проведения инвазивных процедур беременным женщинам группы риска были: материнский фактор возраста, УЗИ маркеры плода, сывороточные маркеры крови беременных женщин, наличие детей с множественными врожденными пороками развития, хромосомной патологией и др. Определены частоты распределения хромосомных нарушений у плода с учетом клинко-лабораторных показателей. Наибольшая частота хромосомных нарушений плода установлена у беременных женщин при наличии трех показателей: фактора возраста беременной женщины, параметров биохимического скрининга и УЗИ маркеров. Хромосомные нарушения плода выявлены у 94 (30,3%) беременных женщин, из них 92 случая (97,9%) представлены численными нарушениями хромосом и 2 случая (2,1%) – структурными нарушениями. Нарушения в системе аутосом наблюдались в 9,4 раза чаще по сравнению с нарушениями в системе половых хромосом. Из численных нарушений хромосом высокий удельный вес занимает трисомия по 21 хромосоме, что составило 65,1%. Сравнительный анализ частоты хромосомных нарушений у плода двух портовых городов показал ее увеличение в 1,7 раза в г. Ақтау (Казахстан) по сравнению с г. Мурманском (Россия), средняя частота аномалий кариотипа плода составила соответственно 19,6% и 11,6%. Более высокий уровень частоты аномалий кариотипа плода в г. Ақтау, вероятно, связан с неблагоприятной экологической обстановкой в городе, наличием предприятий нефтегазовой промышленности, хвостохранилища токсичных и радиоактивных отходов, заброшенных урановых рудников.

Ключевые слова: кариотип, плод, пренатальная диагностика, хромосомные нарушения плода, экологическое состояние городских агломераций.

Introduction

Currently, due to the intensification of all spheres of human economic activity, a large-scale environmental pollution is observed to be evoked by environmentally hazardous factors, many of which have genotoxic, mutagenic and carcinogenic properties. These factors include heavy metals, pesticides, drugs, wastes from mining, nuclear, oil extraction, refinery and other industries. All these pollutants threaten human health increasing the risk of hereditary pathologies. This is especially

dangerous for the development of embryos and the fetus.

In this regard, one of the priority areas of modern medical genetics is the prevention of congenital malformations and chromosomal pathologies at the stage of fetal development. In this direction, methods of prenatal diagnostics are widely used. The main purpose of prenatal diagnostics is the selection of pregnant women into the high-risk groups of the birth of children with congenital and hereditary pathologies, which require in-depth additional investigations including special

laboratory studies (biochemical, cytogenetic, molecular genetic) on the fetal material [1-4]. According to the data “National Genetic Register of the Republic of Kazakhstan” (NGR) of 2012, 3,500-4500 children with congenital malformations (CDF, or *Congenital Disorders of the Fetus*) are born in the Republic of Kazakhstan annually, out of which 350 with chromosomal pathology, 130 neural tube defects, 270 multiple malformations. Annually, 1000-1200 lethal CDFs are revealed by the program of genetic screening of pregnant women at the stage of fetal development, 140-150 of which display chromosomal pathology. According to the NGR data of the Republic of Kazakhstan, the share of CDFs in the layout of the causes of perinatal mortality makes up 10-15%, and it does not tend to decrease [5].

The aim of this work was cytogenetic investigation on metaphase cells of the fetal biomaterial obtained by chorion- and placentiopsy, amniocentesis and cordocentesis from pregnant women of Aktau.

Materials and methods

In the period from 2013 to 2015, a cytogenetic study of the fetal karyotype across 310 pregnant women at risk was carried out in the Medical-Genetic Department of the State-Owned Enterprise “Regional Perinatal Center”, Aktau. Under these conditions the maternal age factor, ultrasound markers of the fetus, biochemical markers of the peripheral blood serum of pregnant women, the birth of children with multiple CDFs, chromosomal

pathologies, and etc. have been taken into account. Metaphase cells of chorionic and placental villi, amniotic fluid cells, fetal cord blood lymphocytes served as the material for investigation after being obtained by the biopsy from pregnant women aged from 18 to 45 years. Biopsy material for cytogenetic studies was obtained by transabdominal puncture under the control of ultrasound examination.

In order to obtain chromosomal preparations from metaphase cells of chorionic and placental villi, the assay on “direct” preparations was implied. Metaphase chromosome preparations from cord blood lymphocytes were obtained by cultivation *in vitro*, in accordance with standard methods. For differential staining of chromosome preparations, the GTG method was used [6, 7].

Metaphase cells were analyzed using an AxioLabA1 light microscope (Zeiss, Germany) and VideoTest – Cario 3.1 computer software (St. Petersburg, Russia) [8].

Results and discussion

The frequency of fetal chromosomal abnormalities has been estimated depending on various factors: maternal age, fetal ultrasound markers, biochemical markering indices of a woman’s serum, the presence of children with chromosomal abnormalities in the family, etc. [9]. The data on cytogenetic study taking into account clinical and laboratory parameters of invasive prenatal diagnostics are presented in Table 1.

Table 1 – Frequency of distribution of chromosomal disorders of the fetus of pregnant women based on various clinical and laboratory parameters for 2013-2015

№	Indicators	Number of pregnant women		Frequency of chromosomal abnormalities of the fetus	
		n	%	n	%
1	Age factor	45	14.5	42	93.3
2	Age factor + ultrasound markers	16	5.2	6	37.5
3	Age factor + biochemical markers	115	37.1	10	8.7
4	Age factor + ultrasound markers + biochemical markers	6	1.9	6	100.0
5	Biochemical markers	90	29.0	19	21.1
6	Ultrasound markers	28	9.0	7	25.0
7	Ultrasound markers + biochemical markers	10	3.2	4	40.0
10	Total	310	100.0	94	30.3

As it can be seen from Table 1, chromosomal abnormalities of the fetus were detected in 94 pregnant women, which made up 30.3%. Chromosomal disorders of the fetus in pregnant women were represented by trisomy for autosomes, monosomy and polysomy for sex chromosomes, as well as structural abnormalities.

Analysis of the frequency of occurrence of chromosomal abnormalities depending on clinical and laboratory parameters revealed their ranging from 8.7% to 100%. Moreover, in 93.3% of cases, the presence of fetal chromosomal abnormalities was detected in pregnant women with an age factor,

and in 100% cases, fetal karyotype disorders were established using a triple combination of indicators – maternal age, deviation from normal biochemical markers in the blood serum of a woman and fetal ultrasound markers. A comparative study revealed a higher impact of the age factor (by 4.4 and 3.7 times) and triple combination indicators (by 3.7 and 4.0 times) in comparison with a single effect of biochemical markers and ultrasound markers (sonography markers), respectively. Analytical data on the frequency and spectrum of chromosomal abnormalities of the fetal karyotype are indicated in Table 2.

Table 2 – Frequency and spectrum of chromosomal abnormalities of the fetal karyotype

Chromosomal abnormalities	Fetal karyotype	n	%
numerical			
Trisomy 13 chromosome	47,XX+13, 47,XY+13	6	6.4
Trisomy 18 chromosome	47,XX,+18; 47,XY+18	22	23.4
Trisomy 21 chromosome	47,XX,+21; 47,XY+21	54	57.4
Trisomy on chromosome 21 and an additional marker chromosome	48,XX,+21,+mar	1	1.1
X chromosome monosomy	45,X	4	4.2
X chromosome polysomy in a fetus with a male karyotype	47,XXY	5	5.3
structural			
Robertson translocation between chromosomes 15 and 21	46,XY,t(15/21)	1	1.1
Duplication of the long arm of chromosome 13	46,XY,dup(13)(q)	1	1.1
Total		94	100
Note: n – is the number of cases; + mar – additional marker chromosome			

As seen from Table 2, out of 94 detected chromosomal abnormalities, 92 cases (97.9%) are referred to occur numerical abnormalities and 2 cases (2.1%) may be attributed to structural abnormalities. Disturbances in the autosome system were observed 9.4 times more often than disorders of the sex chromosome system. In reference of the numerical chromosome abnormalities, a specifically high percentage was determined for the trisomy of the chromosome 21 which achieved 65.1%. Table 3 shows the outputs of a comparative analysis of the frequency of annual chromosomal disorders of the fetus in 2013, 2014 and 2015.

As it follows from Table 3, among fetal chromosomal abnormalities, the highest frequency of occurrence may be ascribed to trisomy of the 21-st chromosome. If in 2013 this indicator made up 50.0%, then in 2014 – 68.4% and 2015 – 73.7%. That means that there is an evident trend of growing frequency of trisomy on chromosome 21 of the fetus. Considering other chromosome disorders of the autosome and the sex chromosome systems, a random occurrence of these disorders has been marked. Table 4 demonstrates the data on the frequency of fetal chromosomal abnormalities depending on the gender with taking into account the invasive procedures conducted.

Table 3 – Comparative analysis of the frequency of annual chromosomal abnormalities (2013-2015)

Indicators		2013		2014		2015	
		n	%	n	%	n	%
Total number of pregnant women with fetal chromosomal abnormalities		56	100	19	100	19	100
Of them:	Trisomy 13 chromosome	5	8.9	1	5.3	-	-
	Trisomy 18 chromosome	18	32.1	1	5.3	3	15.7
	Trisomy 21 chromosome	28	50.0	13	68.4	14	73.7
	X chromosome monosomy – 45,X	2	3.6	1	5.3	1	5.3
	X chromosome polysomy – 47,XXY	2	3.6	2	10.4	1	5.3
	Structural disturbances	1	1.8	1	5.3	-	-

Table 4 – Numerical ratios of female and male fruits with normal and abnormal karyotype

Invasive diagnosis	Число беременных женщин	Количество плодов в зависимости от пола		Нормальный кариотип плода		Аномальный кариотип плода	
		♀	♂	♀	♂	♀	♂
Chorionbiopsy	114	57	57	31	37	26	20
Placental biopsy	134	74	60	53	40	21	20
Amniocentesis	18	11	7	9	5	2	2
Cordocentesis	44	30	14	29	12	1	2
Total	310	172	138	122	94	50	44

As given in Table 4, there is a susceptibility (by 6.4%) to violations of the fetal karyotype among female and male fetuses (53.2% and 46.8%, respectively). Similar data have been obtained in the study of Russian researchers [10]. In particular, in the group of women with a history of undeveloped pregnancy, the embryo and fetus had a pathological karyotype in 34 cases (77.1%). Female karyotype was identified to occur more often than that one of the males by 7.4%: 29 cases (53.7%) versus 25 cases (46.3%). Another investigation emphasizes that the sex ratio in the first trimester of pregnancy is shifted towards the male gender due to conspicuous elimination of female embryos [11]. The authors suggest that one of the reasons for this phenomenon may be a violation of the process of inactivation of the X chromosome. Thus it may be assumed that such a growing elimination of female embryos also includes the presence of inner embryonic chromosomal abnormalities in result of the combinatorial effect of environmental stresses explained by a long-lasting residence in ecologically unfavorable areas. According to the WHO, exposure of the maternal body to certain pesticides and other chemicals, as well as certain drugs, alcohol, tobacco, psychoactive agents or radiation during pregnancy, may increase the risk

of congenital malformations in the fetus or newborn. Living or working in the neighbourhood or directly at the spot of test sites, metallurgical plants or mines can also be a risk factor, especially when the mother's body is exposed to supplementary environmental risk factors or in case of malnutrition [12, 13]. One of the significant environmental factors endangering human health is the air pollution of urban agglomerations. According to the WHO recommendation, air pollution level (together with air quality index, AQI) in cities should not be more than $10 \mu\text{g} / \text{m}^3$, and the average daily level should not exceed $25 \mu\text{g} / \text{m}^3$. However, in large megacities, air pollution level is exceeded many times. Excessive air pollution level is a risk to human health. It is known that chemical compounds and heavy metals of atmospheric air in the city exhibit carcinogenic, mutagenic and toxic effects [14]. This, of course, can cause an accelerated frequency of birth of children with gene and chromosomal diseases.

In this regard, we carried out a comparative analysis of the data obtained to the data of the scientific literature on the most frequent numerical violations of fetal chromosomes in the population. The data on cytogenetic studies of the fetal karyotype of pregnant women living in various regions of Kazakhstan and

Russia were analyzed (Aktau, Almaty, Kazan and Murmansk). The main comparative background was the similarity of the ecological state of urban agglomerations. Almaty and Kazan are the largest megacities with a population over 1 million people. Aktau and Murmansk are referencing port cities with a population of nearly 300 thousand people.

According to local meteorological services, Almaty and Kazan are classified as cities with a high level of air pollution, whereas Aktau and Murmansk as those with a low level. Table 5 presents comparative study on the average incidence of numerical disorders among fetal chromosomes in the cities of Aktau, Almaty, Kazan, and Murmansk.

Table 5 – Frequency of numerical violations of fetal chromosomes

Chromosomal abnormalities	Frequency of chromosomal abnormalities, %			
	Kazan [15]	Murmansk [16]	Almaty [17]	Aktau (own data)
Trisomy 13 chromosome	4.5	1.0	5.0	6.0
Trisomy 18 chromosome	19.0	7.0	15.0	23.0
Trisomy 21 chromosome	51.0	39.0	46.5	60.0
X chromosome monosomy – 45,X	17.0	9.0	5.0	4.0
X chromosome polysomy – 47,XXY	-	2.0	8.3	5.0
Average frequency	18.3	11.6	16.0	19.6

As indicated in Table 5, the average frequency of numerical violations of fetal chromosomes in cities of Almaty and Kazan is approximately the same – 16.0% and 18.3%, respectively. However, significant increase of the average frequency of numerical abnormalities of fetal chromosomes in pregnant women in the city of Aktau (19.6%), when compared with the city of Murmansk (11.6%), is 1.7 times higher, though the air pollution level in both cities, Aktau and Murmansk, are equally low. There is also a noticeable elevation of average frequency of fetal chromosomal abnormalities in the city of Aktau by 1.2 times, comparing to Almaty. In this regard, distinctive environmental features of Aktau should be mentioned. Aktau is the center of the oil and gas industry of Kazakhstan. The oil industry has undoubtedly put a serious environmental burden on the city. There are also adjacent radiologically hazardous facilities: the Koshkar-Ata tailing repository concluding toxic and radioactive wastes, neglected uranium mines and the “dead lake” Little Oymasha (Malaya Oymasha). All this in general can lead to the strengthening environmental load and, accordingly, may affect the state of human health, including the development of the fetus.

There is a statistically reliable increase of the frequency of abortions due to genetic disorders in the fetus and congenital malformations of newborns in the Zhytomyr Region contaminated with Chernobyl radionuclides [18]. The negative effect

of air and water pollutants due to oil and natural gas production on the development of the embryo and fetus has been manifested [19]. It was established that seasonal differences in the incidence of trisomy of chromosome 21 in the fetus correlated with levels of nitric oxide and ozone fluctuations in the environment [20].

It should be mentioned that the solution of the problem of air pollution in urban agglomerations will certainly facilitate reduced frequency of birth of children with hereditary pathology to improve the gene pool of the population.

Conclusion

1. The combination of three indicators of prenatal diagnostics, namely the maternal age, sonography markers and deviations from the parameters of maternal blood biochemical markers, indicate a high probability of fetal chromosomal abnormalities.

2. Chromosomal abnormalities in the autosome system are observed 9.4 times more often than abnormalities in the sex chromosome system – 97.8% and 2.2%, respectively.

3. Among the numerical chromosome disorders of the autosome system, trisomy of chromosome 21 is prevailing with a high proportion reaching 65.1%.

Thus, cytogenetic methods are able to confirm or exclude fetal chromosomal pathology and are considered as essential tool for prenatal diagnostics.

References

- 1 Nussbaum R.L., McInnes R.R., and Willard H.F. *Tompson & Tompson Genetics in Medicine* 7th ed. ELSEVIER, 2007.
- 2 Hixson L., Goel S., Schuber P., Faltas V., Lee J., Narayakkadan A., Leung H., Osborne J. "An Overview on Prenatal Screening for Chromosomal Aberrations" *J Lab Autom.* 20, no. 5 (2015): 562–573.
- 3 Baer R.J., Currier R.J., Norton M.E., Flessel M.C., Goldman S., Towner D., Jelliffe-Pawlowski L.L. "Outcomes of pregnancies with more than one positive prenatal screening result in the first or second trimester." *Prenat Diagn.* 35, no. 12 (2015): 1223–1231.
- 4 Levy B., Stosic M. "Traditional Prenatal Diagnosis: Past to Present." *Methods Mol Biol.* 1885, (2019): 3–22.
- 5 Prikaz Ministra zdravookhraneniya Respubliki Kazakhstan ot 19 marta 2012 goda № 183 «Ob utverzhdenii «Dorozhnoy karty» po organizatsii prenatal'nogo skrininga v Respublike Kazakhstan», st.5. [Order of the Minister of Health of the Republic of Kazakhstan dated March 19, 2012 No. 183 "On approval of the Roadmap for the organization of prenatal screening in the Republic of Kazakhstan", Article 5.]. (In Russian).
- 6 Plaseska-Karanfilska D. *Human Genetic Diseases*. InTech. Croatia, 2011.
- 7 Vorsanova S.G., Yurov Yu.B., Chernyshev V.N. *Meditinskaya tsitogenetika [Medical cytogenetics]*. M.: ID MEDPRAKTIKA-M, 2006. (In Russian).
- 8 Programs for cytogenetics Videotest-Kario 3.1. Last modified October 21, 2018. <http://www.microscope-plus.ru/videotest-karyo.html>
- 9 Ozawa N., Ogawa K., Sasaki A., Mitsui M., Wada S., Sago H. "Maternal age, history of miscarriage, and embryonic/fetal size are associated with cytogenetic results of spontaneous early miscarriages." *J Assist Reprod Genet.* 36, no. 4 (2019): 749–757.
- 10 Spiridonova N.F., Kalinkina O.B., Gil'miyarova F.N., Meleshkina O.I. "Vzaimosvyaz' nerazvivayushchey beremennosti s khromosomnoy patologiyey ploda." ["The relationship of undeveloped pregnancy with chromosomal pathology of the fetus"]. *Kazanskiy meditsinskiy zhurnal* 94, no. 5 (2013): 748–751. (In Russian).
- 11 Tolmacheva E.N., Vasil'ev S.A., Sazhenova E.A., Zhigalina D.I., Grigorovich E.I., Nikitina T.V., Mel'nikov A.A., Zhabina E.S., Ivanova T.V., Evtushenko I.D., Lebedev I.N. "Asimmetrichnaya inaktivatsiya Kh-khromosomy u vnutritrobno pogibshikh embrionov cheloveka." ["Asymmetric inactivation of the X chromosome in prenatally dead human embryos."]. *Tsitologiya*, no. 11 (2015): 808–812. (In Russian).
- 12 World Health Organization. Congenital anomalies. Last modified September 7, 2016 <https://www.who.int/ru/news-room/fact-sheets/detail/congenital-anomalies>
- 13 Mattison D.R. "Environmental exposures and development." *Curr Opin Pediatr.* 22, no. 2 (2010): 208–218.
- 14 Agudelo-Castañeda D.M., Teixeira E.C., Schneider I.L., Lara S.R., Silva L.F.O. "Exposure to polycyclic aromatic hydrocarbons in atmospheric PM1.0 of urban environments: Carcinogenic and mutagenic respiratory health risk by age group." *Environ Pollut.* no. 224 (2017): 158–170.
- 15 Abuseva A.V., Teregulova L.E., Vafina Z.I., Toktarova O.A., Tukhbatullin M.G. "Prenatal'naya diagnostika khromosomnykh anomalii u plodov, voshedshikh v gruppuy srednego i nizkogo riska po rezul'tatam kombinirovannogo prenatal'nogo skrininga I trimestra po modulyu FMF." ["Prenatal diagnosis of chromosomal abnormalities in fetuses that are in the medium and low risk group according to the results of combined prenatal screening of the first trimester according to the FMF module."]. *Prakticheskaya meditsina* 2, no 3. (2014): 112–117. (In Russian).
- 16 Peretruchina I.V., Kazeeva D.O. "Laboratornaya diagnostika khromosomnoy patologii v Murmanske i Murmanskoj oblasti (2006-2011 gody)." ["Laboratory diagnosis of chromosomal pathology in Murmansk and the Murmansk region (2006-2011)."] *Vestnik MGT* 16, no. 4 (2013): 777–782. (In Russian).
- 17 Kalimagambetov A.M., Rustembekov N.Zh., Ayapova S.K., Abdresheva G.K., Myrzabekova G.T. "Rezul'taty tsitogeneticheskogo issledovaniya v prenatal'noy diagnostike." ["The results of cytogenetic studies in prenatal diagnosis."]. *Vestnik KazNU. Seriya biologicheskaya* 57, no 1 (2013): 139–142. (In Russian).
- 18 Timchenko O.I., Linchak O.V., Protsiuk O.V., Pol'ka E.A., Benedichuk Iu.V., Marinich A.V. "Birth defects on Chernobyl radionuclide polluted territories." *Radiats Biol Radioecol.* 54, no. 5 (2014): 507–521.
- 19 Webb E., Bushkin-Bedient S., Cheng A., Kassotis C.D., Balise V., Nagel S.C. "Developmental and reproductive effects of chemicals associated with unconventional oil and natural gas operations." *Rev Environ Health.* 29, no. 4 (2014): 307–318.
- 20 Chung M.K., Lao T.T., Ting Y.H., Wong T.W., Leung T.Y. "Seasonality of fetal trisomy 21—have ambient air pollutants played a role?" *J Matern Fetal Neonatal Med.* 28, no. 5 (2015): 552–557.