

Special Opinion on the Dependence of the Birth of Children with down Syndrome on the Age of Their Parents

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Abstract: The problem of prenatal diagnosis of Down syndrome is one of the most urgent problems in modern obstetrics. The paper analyzes and studies the effectiveness of prenatal diagnosis of Down syndrome in Uzbekistan, cities in West Africa, North and South America, Eastern and Western Europe, Southeast Asia and South Asia for 2008-2011, taking into account the age of women who gave birth to healthy children and children with Down syndrome. In contrast to developed countries, in developing countries, the peak birth rate is at the age of 22-26 years, the birth rate for women under 35 years is higher and on average is 80% compared to women over 35 years – 20%. The number of registered fetuses with trisomy 21 in women under 35 years of age is 4 times higher than in older women. When computation the risk of having a child with Down syndrome in a woman over 35 years of age increases significantly, compared with women under 35 years of age. Our research confirms that the highest percentage of births of children, both with Down syndrome and children without genetic pathology, occur in the age period from 20 to 35 years. Therefore, the expediency of complex use of biochemical and ultrasound screening in the first and second trimesters of pregnancy, regardless of age, for the purpose of effective prevention of chromosomal diseases and, above all, Down syndrome, is noted.

Keywords: biochemical screening, ultrasound screening, age-related risk, down syndrome, prenatal diagnosis.

Introduction

Aneuploidies are the main causes of perinatal mortality, among which Down syndrome is one of the most common forms of chromosomal abnormalities [1,2,3]. Every year, the number of births of children with Down syndrome increases by an average of 0.9% of cases per year, compared to the previous year. The average birth rate of children with Down syndrome is 1:800 [1,2,4,5,6].

The method of screening for Down syndrome not so long ago was screening for the age of a pregnant woman, above 35 years of age, all performed invasive diagnostics, in which it was possible to identify fetuses with Down syndrome only in 30-35% of cases [7].

Most authors in 70% of cases associate the risk of having children with trisomy 21 with maternal age and in 30% with the age of the father, as well as with the age of the maternal grandmother [8,9,10,11,12]. Thus, at the age of a mother under 30 years, the probability of having a child with Down syndrome is 1:2500, at 31-34 years, the risk of birth increases and is 1:1200, the greatest risk of birth occurs at 35-39 years-1:200 [1,8,11,16].

However, the data presented by the authors indicate that the development of the risk scale for the birth of children with Down syndrome was based on the ratio of already born children with trisomy 21 to the total number of newborns [13].

When compiling the risk of having children with Down syndrome, the number of miscarriages, abortions and intrauterine fetal death, the risk of which in trisomy 21 starting from 12 weeks of pregnancy, is about 30%, was not taken into account. For comparison, the risk of intrauterine death of the euploid fetus is only 1-2% [13].

In the early 70s, the number of pregnant women over 35 years old was only 5%, among which 30% of the total number of fetuses was with trisomy 21- chromosomes. In subsequent years, in developed countries, the number of pregnant women over 35 years of age increased

to 20%, and in this regard, the number of fetuses with trisomy 21-chromosome also increases [14,15,16].

It should also be noted that all complete trisomies occur only on autosomes rich in heterochromatin, which are located on 8-, 9-, 13-, 18- and 21- chromosomes, in most cases (90%) trisomies occur due to non-divergence of chromosomes in meiosis. It can be assumed that the frequency of occurrence of trisomies on chromosomes (8, 9, 13, 18 and 21) in all cases will occur in the same way. Although trisomies of chromosome 18 and 13 are relatively rare (1:7000-1: 14000), but the relationship with respect to the age of a woman is less strict, compared to trisomy on 21-chromosome [11,17,18,19,21]. For comparison, the risk of having a child with Edwards syndrome, for women over 45 years of age, is only 0.7 % compared to Down syndrome over the age of 45, the probability of which is 3-5% [11,17,18,22].

The absence of the age factor is indicated by the data of Ferguson-Smith (1983), according to which the risk of having children with Down syndrome at the age of 35 and 39-47 years is higher, compared with women older than 47 years. The data of Mattei J. F. et al also revealed the absence of age as a factor of non-divergence of chromosomes in meiosis. The failure of the theory of age-related risk is also indicated by the low sensitivity of the Down syndrome diagnosis method for age-related risk [19,20].

This analysis examines the effectiveness of prenatal diagnosis without taking into account the age risk of the mother, as well as the relationship between the age of the parents.

Purpose of the research: Evaluation, comparison and study of the effectiveness of prenatal diagnosis of Down syndrome depending on the age of the parents.

Materials and methods of the research: This study is the result of studying the effectiveness of demographic indicators of Uzbekistan, cities in West Africa, North and South America, Eastern and Western Europe, Southeast Asia and South Asia, as well as ultrasound and biochemical indicators in the physiological course of pregnancy and Down syndrome.

Questionnaire data on pregnant women who gave birth to children without genetic pathology and questionnaires of children with Down syndrome were collected in the Republican "Screening Center for Mother and Child" from January 1, 2008 to December 31, 2011.

Consent to this study was obtained from the administration of the Republican "Screening Center for Mother and Child", as well as from pregnant women who agreed to undergo prenatal diagnosis.

As a result of the study, we retrospectively analyzed 516448 questionnaires of women who gave birth to children without genetic pathology, 386 questionnaires of children with Down syndrome. The division by ethnic group was not carried out, as this data is not available in the questionnaires of pregnant women.

Maternal and paternal age were studied as continuous and categorical variables. Age was divided into 7 groups as categories, divided by a five-year interval (up to 19 years, 20-24, 25-29, 30-34, 35-39, 40-44 and over 45 years old), and two age categories under 35 and over 35 years old. We used seven and two age categories to identify possible non-linear trends in the relationship between the age of parents, the prevalence of Down syndrome and the number of births.

Biochemical screening was carried out to calculate the risk of giving birth to a child with Down syndrome using test systems on the DELFIA - A067 - 101 device. Blood was taken according to generally accepted standards on an empty stomach from the brachial vein in the elbow joint. The biochemical parameters of alphafetoprotein and chorionic gonadotropin were studied.

Statistical research methods: All calculations were performed using the statistical packages SPSS and Microsoft Excel 2010. The use of the data was in accordance with the obligations to protect confidentiality, as a result of which the identity cannot be determined from the data provided for analysis.

Results of the research: According to the results of studies conducted from 2008 to 2011, among 516448 pregnant women who gave birth to children without genetic pathology, the largest number of births occurred at the age of 20 to 24 years, and on average amounted to 38.8%. The average age of pregnant women who gave birth to children without genetic pathology was 26 years. The largest percentage of births in women without genetic pathology occurs in the age range from 16 to 34 years (90.02%), women over 35 years give birth to only 9.98% (table 1).

Table 1
Number of newborns without genetic pathology of the Republic of Uzbekistan (2008-2011)

Mother's age	2008		2009		2010		2011		Total	
	№	%	№	%	№	%	№	%	№	%
<19	6048	4,52	5353	5,25	10645	6,27	6547	5,89	28593	5,54
20-24	49066	36,70	37148	36,44	73859	43,54	42918	38,61	202991	39,31
25-29	37526	28,07	31816	31,21	49026	28,90	32014	28,80	150382	29,12
30-34	25051	18,74	16713	16,39	23459	13,83	17708	15,93	82931	16,06
35-39	13450	10,06	9251	9,07	10566	6,23	10186	9,16	43453	8,41
40-44	2486	1,86	1652	1,62	2049	1,21	1771	1,59	7958	1,54
unknown	80	0,06	20	0,02	40	0,02	0	0	140	0,03
Total	133707		101953		169644		111144		516448	
%	25,89	4,52	19,74	5,25	32,85	6,27	21,52	5,89		

When studying the birth rate among women who gave birth to children with Down syndrome, the largest number of births from 2008 to 2010 occurred at the age of 20 to 24 years, in 2011 the largest number of births occurred from 25 to 29 years. The average age of pregnant women who gave birth to children with Down syndrome was 30 years (table 2).

Table 2
Number of newborns with Down syndrome (2008-2011)

Mother's age	2008		2009		2010		2011		Total	
	№	%	№	%	№	%	№	%	№	%
<19	1	1,43	1	1,05	2	1,67	4	3,33	8	1,72
20-24	21	30	21	25,26	25	20	27	24,17	94	23,1
25-29	12	17,14	14	14,74	23	20	29	22,50	78	19,16
30-34	11	15,71	13	15,79	21	17,50	20	16,67	65	15,48
35-39	12	17,14	11	17,89	20	16,67	17	14,17	60	17,2

40-44	5	7,14	8	10,53	8	6,67	13	10,83	34	9,34
unknown	8	11,43	8	14,74	21	17,50	10	8,33	47	14
Total	70	100	76	100	120	100	120	100	386	100

The greatest number of children with Down syndrome was registered in fathers aged 25 to 29 years, the average number of which was 21.4% (table 3). The median paternal age was 33 years. In 99 children with Down syndrome, the age of the father was not included due to lack of data.

Table 3
Number of newborns with Down syndrome (2008-2011), depending on the age of the father

Mother's age	2008		2009		2010		2011		Total	
	N₂	%	N₂	%	N₂	%	N₂	%	N₂	%
<19	0	0	0	0	0	0	0	0	0	0
20-24	7	9,09	7	7,78	7	6,36	11	9,91	32	8,25
25-29	17	22,08	19	21,11	20	18,18	27	24,32	83	21,39
30-34	12	15,58	14	15,56	21	19,09	15	13,51	62	15,98
35-39	7	9,09	14	15,56	20	18,18	15	14,41	56	14,69
40-44	11	14,29	8	8,89	7	7,27	14	12,61	40	10,57
unknown	23	29,87	28	31,11	34	30,91	28	25,23	113	29,12
Total	77	100,00	90	100,00	109	100,00	110	100,00	386	
%	19,85		23,20	0	28,35	0	28,61	0		

The inverse average correlation between the age of parents and the birth of children with Down syndrome was obtained. Thus, the dependence on maternal age was ($r = -0.56$), on paternal age ($r = -0.61$). Similar correlations are found among children without genetic pathology, so the correlation between the number of births and the age of pregnant women was ($r = -0.62$). This relationship between the age of the parents and the number of births without genetic pathology and the birth of children with Down syndrome indicates a decrease in the number of births with an increase in the age of the parents.

The prevalence of births of children with Down syndrome in all age groups in the Republic of Uzbekistan during the period from 2008 to 2011 was from 0.51 to 0.79 cases per 1000 newborns. On average, the birth of a child with Down syndrome is 1 case per 625 newborns without a genetic pathology (figure 1).

Figure 1
The frequency of birth of children with Down syndrome from 2008 to 2011

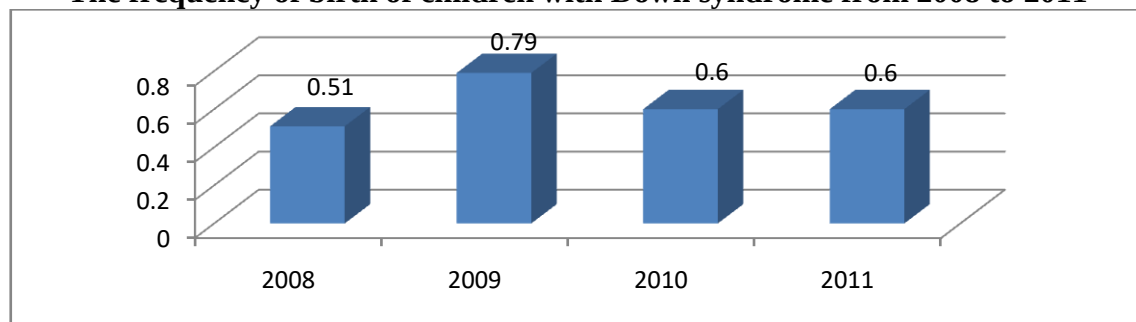


Table 4
The number of children born with Down syndrome in women under 35 and 35 years and older

Countries	год	<35	%	>35	%
USA [8]	1979	1318	67,83	625	32,17
USA [8]	1979	51	76,12	16	23,88
USA [8]	1979	125	77,16	37	22,84
Nigeria [18]	1982	304	78,76	82	21,24
Brazil [19]	1996	132	66,00	68	34,00
USA [8]	2005	353	59,53	240	40,47
Czech [21]	2005	219	87,25	32	12,75
India [22]	2006	64	92,75	5	7,25
Uzbekistan	2011	99	82,5	21	17,5

Data on the total birth rate, conducted in both developed and developing countries, show the greatest prevalence of births in women under 35 years of age (88.16% - 95.23%) and amounted to an average of 90.9%. The birth of older children without a genetic pathology over 35 years old ranged from 4.77% to 13.99%, with an average of 9.1%.

Table 5
The number of children born without genetic pathology in women under 35 and 35 years older

Countries	год	<35	%	>35	%
Sweden [14]	1989	306151	92,53	24708	7,47
Wales[14]	1989	42854	93,07	3192	6,93
Hong Kong [14]	1989	102164	92,53	13779	11,88
Kuala Lumpur [14]	1989	30436	88,16	4086	11,84
Brazil [19]	1996	1460	94,10	92	5,90
California [8]	2005	444272	86,01	72290	13,99
Czech [21]	2005	453118	95,23	22716	4,77
Uzbekistan	2011	464897	90,02	51551	9,98

The number of children with Down syndrome also prevails in women under 35 years of age (59.53% - 92.75%), with an average of 74.95%, and the highest number of births of children with Down syndrome was registered in India and amounted to 92.75%.

The birth of children with Down syndrome in mothers over 35 years of age ranged from 7.25% to 40.47% , and the average was 25.05%, which is almost 3 times less than in women under 35 years of age (table 5).

Table 6
The number of newborn children with no genetic disease and down syndrome

Country	without genetic pathology		with Down syndrome		Prevalence 1 000
	№	%	№	%	

England 2010 [13]	811759	99,44	4559	0,6	5,65
USA 2005[20]	516562	99,89	593	0,11	1,15
Czech 2005[21]	475834	99,95	251	0,05	0,53
Uzbekistan 2008-2011	516448	99,91	386	0,07	0,88

Conclusions and practical recommendations:

Our study confirms that the highest percentage of births of children, both with Down syndrome and children without genetic pathology, occur in the age period from 20 to 35 years. Although according to numerous authors, the risk of having children with Down syndrome increases significantly with increasing maternal and paternal age, the number of births to parents aged 35 and older ranges from 4.77% to 13.99%.

Prenatal diagnostic tactics to prevent the birth of children with Down syndrome are of paramount importance and need timely diagnosis of all pregnant women, regardless of age.

In screening testing to identify the risk of having children with Down syndrome, exclude age-related risk as a method of diagnosing chromosomal pathology in women over 35 years of age. When making a diagnosis, it is necessary to rely on the presence of ultrasound chromosomal markers present in this pathology. This strategy can be one of the most effective methods in reducing the number of chromosomal abnormalities, thereby reducing the number of diagnostic errors in this pathology.

The main focus is to compare the ethnic characteristics of the birth of children with Down syndrome in different populations. In general, the prevalence of children with Down syndrome per 10,000 population ranges from 0.88 to 1.15 cases.

Our statistical analysis once again proves that there is no age factor as a risk for the birth of children with Down syndrome, and the increase in the birth of children with Down syndrome in mothers aged 19 to 35 years is directly related to the increase in the number of births. The exclusion of the mother's age as one of the main factors equalizes the chances of drawing up high-risk groups for the birth of children with Down syndrome in all age groups, therefore, reducing the percentage of false negative results of this syndrome in women from 19 to 34 years old.

From this it follows that in the future it is necessary to look for other etiological factors that affect the occurrence of Down syndrome, which will allow us to reasonably form a high-risk group for the birth of children with Down syndrome.

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