UDC 616-053.36- 092.11-036: 618.177-089.888.11
DOI: 10.21668/health.risk/2017.1.07.eng

RISK FACTORS AND PREDICTING HEALTH DISORDERS IN INFANTS BORN FROM MONOCYESIS AFTER IN VITRO FERTILIZATION

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Issues of health state and factors determining it in infants born due to in vitro fertilization (IVF) have been frequently discussed over recent years. The question yet to be answered is whether health disorders are related to burdened pre-morbid state of a mother as per extragenital and obstetric-gynecologic pathology or they are caused by IVF. Selective transfer of only one embryo has tended to increase recently, and, given this trend, specialists all around the world, and in our country as well, face a problem of detecting risk factors which cause health disorders in children born in monocyesis after IVF. Prognostic algorithm for most frequent pathologies is being worked out and it will help to implement targeted and differentiated approach to their prevention. We have completed clinical examination of infants during the first year of their life; all these infants were born in monocyesis after IVF (n=121). We have also questioned and interviewed their parents and analyzed data taken from infants' development records over a year as well. We have applied Wald sequential mathematical analysis to determine risk factors and create prognostic tables comprising most frequent somatic health disorders such as congenital abnormalities, iron-deficiency anemia, atopic dermatitis, absence of perinatal CNS damage compensation. We have detected that factors related to a mother's and newborn's health (extragenital morbidity, obstetric-gynecologic case history, pregnancy course) exert their influence on health disorders evolvement in such children during their first year of life; we have also shown that social factors and factors associated with IVF procedure don't have any statistical significance.

Key words: *risk factors, health disorders prediction, children from monocyesis, IVF, congenital abnormalities, iron-deficiency anemia, atopic dermatitis, perinatal CNS damages.*

There have recently been a lot of discussions on health state and factors determining it in children born due to in-vitro fertilization (IVF) [1, 2, 4, 6, 7, 8, 17, 24, 28, 29]. As per data given by various authors, IVF programs efficiency varies from 20 to 40%, number of born children from this group doesn't exceed 6-25% of all implanted embryos and 56-78% of occurred pregnancies [5, 8, 25]. We should point out that conception, fetus development and maturation due to application of auxiliary reproductive technologies takes place under conditions which differ from physiological standards rather substantially [4, 10, 21]. Embryo sensitivity to environment factors at pre-implantation stage is considerably high and it can cause fetus pathologies evolvement depending on its gestation stage [9, 10, 12, 16].

As per data taken from the recent

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domestic and foreign literature, there are several factors in a mother causing pathological course of neonatal period in children from IVF group. Such factors include burdened obstetric-gynecological case history, late reproductive age, ovary activity stimulation, pre-term delivery, multiple pregnancy, comcomitant somatic pathology, social status, education, and etiology of infertility [2, 5, 7, 8, 11, 12, 14, 15, 18, 22]. As per results presented by E.V. Vartanyan [2], risk factors are inflammatory diseases of reproductive system, menstrual function disorders, infertility duration, miscarriages and abortions in case history, surgeries performed on abdominal cavity organs and small pelvis organs, and sexual diseases.

In A.N. Plaksina's opinion [20], health of a child born after IVF pregnancy is determined by the following factors in a mother: missed miscarriage (20.3%), miscarriages at various terms (28.6%), multiple pregnancy (11.1%), and threat of miscarriage (48.3%). The author states that women who are older than 30 and have secondary infertility run increased risk for giving birth to a baby with low birth weight and low gestation term.

Some authors say that a method invasiveness is the basic burdening factor which influences infants from IVF group [2, 14]. Other believe that high morbidity and deviations in development of such children are related only to abnormal pregnancy and delivery course [18, 19]. Influence exerted by different superovulation stimulation schemes in IVF programs on health of a future baby is not sufficiently studied and described in contemporary scientific research [8]. At the same time there are data in literature on higher risks for congenital malformations of genitals in boys whose mothers underwent superovulation stimulation procedure and took progestin during pregnancy [12].

Infertility related to endometriosis is known to be hardly curable, and even IVF application in patients suffering from endometriosis has very low efficiency. Influence exerted by this factor on health of a future baby is not studied sufficiently [10].

Some scientists assume that unfavorable perinatal outcomes are related only to multiple pregnancy after IVF [16]. However some latest research prove that risk of giving birth to a sick infant even in case of monocyesis due to IVF is growing. But we couldn't find enough information on the matter [6, 9, 13, 24, 27].

Several reasons determining reproductive technologies application still exist and later they influence pregnancy course, delivery, and health of a future baby [4, 7, 9, 15, 17, 21, 25, 31].

There are practically no scientific works which deal with issues of combined impacts exerted by biological and social factors on somatic health formation in children born due to IVF depending on a number of transferred embryos [13, 22, 26, 27, 30].

Selective transfer of only one embryo has recently tended to increase in many countries, including Russia. And it becomes really essential to study factors causing health disorders risks in order to work out mechanisms of their prediction in children born from monocyesis after IVF. It will allow to apply differentiated and targeted approaches to prevention of most frequent pathologies and reduce risks of their evolvement [23, 30].

Our research goal was to highlight risk factors and work out predictive tables for most frequent health disorders (congenital malformations, iron-deficiency anemia, atopic dermatitis, absence of perinatal central nervous system (CNS) damage compensation) in one-year old children born from monocyesis after in-vitro fertilization.

Data and methods. We examined one-year old children born from monocyesis after IVF ($n = 121$). Their health was assessed in early neonatal period and after their one-year birthday as per clinical examinaiton results. We assessed morbidity as per appealability to a polyclinic and via dynamic observation over infants including functional methods of examination (according to Order No. 1346n dated December 21, 2012). We collected biological and social case history by copying data from patients' individual cards used at applying to auxiliary reproductive technologies

(form No. 111-1/u-03); data from a newborn development history (form No. 097/u) and from a child development history (form No. 112/u, form No. 003/u). Certain factors were clarified during questioning and interviewing parents with the use of a specially designed "Questionnaire on detecting social-biological risk factors".

We processed the obtained results statistically using MS Excel XP and Statistica 6.0 software. Discrepancies in relative indices were studied as per Pierson χ^2-criterion with Yates correction. Discrepancies were considered authentic at $p<0.05$. We detected correlations between studied indices via calculating Spearmen correlation coefficient (R). We calculated odds relations (OR) and relative risk (RR) for various factors in OpenEpi program with defining 95% confidence interval (RR, 95% DI). To detect risk factors for most frequent health disorders and working out a predictive table, we used Wald sequential mathematic analysis [3]. Having proved validity of discrepancy in frequency with which an examined factor occurred in children groups with health disorders and without them ($p<0.05$), we calculated predictive coefficients (PC) for each factor level. Predictive coefficients were calculated as per formula: $PC = 10 \lg (P_1/P_2)$ when a factor occurred, $PC = 10 \lg (1 – P_1/1 – P_2)$ when a factor was absent, where P_1 and P_2 was a frequency of a factor occurrence in compared groups. If an obtained value was positive it was an evidence of a factor negative influence.

Results and discussion. We detected that overall morbidity level in children from the basic group during the first year of their life was 1.3. times higher than in the control group (214.9 and 171.1 per 100 people correspondingly), due to higher occurrence frequency of perinatal central nervous system damage (P CNS D) (66.1 and 39.7 % correspondingly; $\chi^2 = 12.97$, $p = 0.000$), congenital malformations, mostly due to minor heart malformations (MHM) (33.1 and 17.4 % correspondingly; $\chi^2 = 7.91$, $p = 0.005$), iron-deficiency anemia (14.0 and 5.8 % correspondingly; $\chi^2 = 4.13$, $p = 0.042$), atopic dermatitis (8.3 and 2.5 % correspondingly; $\chi^2 = 3.16$, $p = 0.046$), thymus hyperplasia (7.4 and 1.7 % correspondingly; $\chi^2 = 4.67$, $p = 0.031$).

We detected significant factors for evolvement of most frequent health disorders in children basing on the analysis of the following data: biological case history (extragenital morbidity, obstetric-gynecological case history, mothers' reproductive function, a child's health state), and social case history (education, social status, occupational hazards of parents, family wealth, and family relations) of children born from monocyesis after IVF, as well as factors related to IVF procedure (IVF protocol duration, a number of IVF attempts, IVF techniques, and embryo quality).

We detected that risk factors causing:

– *congenital malformations* were: a mother suffering from chronic inflammatory diseases of urinary system (RR 4.4; 95 % CI 2.29–8.37), missed miscarriage in case history (RR 4.4; 95 % CI 2.29–8.37), spontaneous miscarriages in case history (RR 4.0; 95 % CI 2.03–7.88), male infertility (RR 3.3; 95 % CI 1.23–8.79), fetoplacental insufficiency (FPI) (RR 3.3; 95 % CI 1.60–6.96), threat of miscarriage (RR 3.2; 95 % CI 1.59–6.62), colpitis during pregnancy (RR 3.2; 95 % CI 1.59–.,26);

– *iron-deficiency anemia* were*:* birth after gestation period shorter than 37 weeks (RR 5.1; 95 % CI 2.04–12.60); birth after the third and more pregnancy (RR 4.7; 95 % CI 2.05–10.62); anemia of pregnant (RR 4.3; 95 % CI 1.88–9.93); fetoplacental insufficiency (RR 4.0; 95 % CI 1.70–9.41); intraventricular hemorrhages (IVH) (RR 3.2; 95 % CI 1.33–7.78);

– *atopic dermatitis* were*:* burdened allergic case history (RR 8.6; 95 % CI 2.95–25.20), preeclampsia (RR 8.5; 95 % CI 1.70–9.41), birth after gestation period shorter than 37 weeks (RR 7.0; 95 % CI 1.97–25.44), artificial nutrition since the very birth (RR 3.9; 95 % CI 1.19–12.93);

– *absence of perinatal CNS damage compensation by one-year birthday* were*:* birth after gestation period shorter than 37 weeks

(RR 3.3; 95 % CI 1.90–5.84), fetus growth retardation (RR 3.1; 95 % CI 1.94–5.17), gestational arterial hypertension (RR 3.1; 95 % CI 1.95–5.16), chronic adnexa inflammation in case history (RR 2.8; 95 % CI 1.46–5.34), neurocirculatory dystonia (NCD) in a mother (RR 1.9; 95 % CI 1.40–2.70), fetus growth retardation (RR 1.9; 95 % CI 1.34–2.66), intraventricular hemorrhages of the 2nd degree in neonatal period (RR 2.7; 95 % CI 1.57–4.60), iron-deficiency anemia in a child (RR 1.9; 95 % CI 1.09–3.53).

We detected that the greatest influence on evolvement of most frequent health disorders in children born from monocyesis after IVF was exerted by biological factors related to health of a mother and a newborn. Social factors had no statistic significance.

We analyzed factors influencing evolvement of most frequent health disorders in examined children related to IVF procedure (table 1).

We detected that factors determined by the very procedure had no statistically significant influence on evolvement of most frequent health disorders in children born from monocyesis after IVF.

Basing on the highlighted biological risk factors for children born from monocyesis after IVF, we worked out formalized tables for predicting congenital malformations evolvement, iron-deficiency anemia, atopic dermatitis, absence of perinatal central nervous system damage compensation by one-year birthday (table 2).

Table 1

Factors, related to IVF procedure, for most frequent health disorders in children born from monocyesis, abs. (%)

Index	Factor							
	Congenital malformations		Congenital malformations		Congenital malformations		Congenital malformations	
	yes	no	yes	no	yes	no	yes	no
	n = 21	*n* = 84	*n* = 16	*n* = 89	*n* = 10	*n* = 95	*n* = 12	*n* = 93
IVF protocol:								
short	2 (9,5)	13 (15,5)	4 (25,0)	11 (12,4)	1 (10,0)	14 (14,7)	1 (8,3)	14 (15,1)
long	19 (90,5)	71 (84,5)	12 (75,0)	78 (87,6)	9 (90,0)	81 (85,3)	11 (91,7)	79 (84,9)
Number of IVF attempts:								
1st	14 (66,7)	61 (72,6)	11 (68,8)	64 (71,9)	7 (70,0)	68 (71,6)	6 (50,0)	61 (65,6)
More than 2	7 (33,3)	23 (27,4)	5 (31,3)	33 (37,1)	3 (30,0)	35 (36,8)	6 (50,0)	32 (34,4)
IVF techniques:								
IVF	8 (38,1)	31 (36,9)	8 (50,0)	31 (34,8)	2 (20,0)	37 (38,9)	3 (25,0)	36 (38,7)
IVF + ICSI	13 (61,9)	53 (63,1)	8 (50,0)	58 (65,2)	8 (80,0)	58 (61,1)	9 (75,0)	57 (61,3)
Quality of embryos:								
excellent, A type	15 (71,4)	63 (75,0)	10 (62,5)	68 (76,4)	5 (50,0)	73 (76,8)	6 (50,0)	72 (77,4)
good, B type	6 (28,6)	19 (25,0)	6 (37,5)	19 (23,6)	5 (50,0)	20 (23,2)	6 (50,0)	21 (22,6)

Table 2

Predictive table for health disorders in children born from monocyesis after IVF during the first year of their life

Risk factors	Predictive coefficients (PC)			
	Congenital malfor-mations	Congenital malformations	Congenital malfor-mations	Congenital malformations
1	2	3	4	5
Extragenital pathology in a mother				
Chronic inflammatory diseases of urinary system:				
yes	+7,00	–	–	–
no	–0,75	–	–	–
Burdened allergic case history:				
yes	–	–	+4,93	–
no	–	–	–2,61	–
NCD (VNS somatoform disorder):				
yes	–	–	–	+7,24
no	–	–	–	–0,78
Obstetric-gynecological case history				
Chronic adnexa inflammation in case history:				
yes	–	–	–	+2,83
no	–	–	–	–2,13
Endometriosis in case history:				
yes	+2,98	–	–	–
no	–0,99	–	–	–
Spontaneous miscarriages in case history:				
yes	+5,09	–	–	–
no	–1,23	–	–	–
Missed miscarriage in case history:				
yes	+7,00	–	–	–
no	–0,75	–	–	–
Male infertility:				
yes	+3,01	–	–	–
no	–1,63	–	–	–
This pregnancy course				
Fetoplacental insufficiency:				
yes	+4,89	+3,74	–	–
no	–0,68	–1,63	–	–
Fetus growth retardation:				
yes	–	–	–	+5,08
no	–	–	–	–0,54
Preeclampsia:				
yes	–	–	+5,12	–
no	–	–	–1,70	–
Threat of miscarriage:				
yes	+4,21	–	–	–
no	–0,97	–	–	–
Gestational arterial hypertension:				
yes	–	–	–	+6,09
no	–	–	–	–0,39
Anemia of pregnant:				
yes	–	+5,22	–	–
no	–	–0,96	–	–
Colpitis during pregnancy:				
yes	+3,36	–	–	–
no	–1,01	–	–	–

Continuation of table 2

A child's health state				
Birth after gestation period shorted than 34 weeks:				
yes	+4,22	–	–	–
no	–2,44	–	–	–
Birth after gestation period shorted than 37 weeks:				
yes	–	+3,79	+3,93	+2,66
no	–	–2,38	–3,52	–0,86
Birth after the 3rd or more pregnancy:				
yes	–	+5,82	–	–
no	–	–2,39	–	–
Artificial feeding since the very birth:				
yes	–	–	+4,55	–
no	–	–	–5,68	–
Non-traumatic intraventricular hemorrhages of the 2nd degree in case history:				
yes	–	+7,60	–	+6,09
no	–	–1,99	–	–0,39
Iron-deficiency anemia:				
yes	–	–	–	+6,88
no	–	–	–	–0,53

An individual forecast is determined by a sum of predictive coefficients (PC). We used Wald's formula to determine predictive threshold (PT) value which allows to assess validity of health disorders evolvement in children born from monocyesis after IVF during the first year of their life (congenital malformations, iron-deficiency anemia, atopic dermatitis, perinatal central nervous system damage compensation) [17]. We considered not more than a 5% probability of an error in a forecast to be acceptable and determined that predictive threshold (PT) for a possibility of these health disorders evolvement was equal to +13, and their absence, –13.

If the predictive coefficients sum is equal or more than +13, than the forecast is unfavorable, and one can predict evolvement of congenital malformations (as per PC sum in the second column); iron-deficiency anemia during the first year of their life (as per PC sun in the third column); atopic dermatitis (as per PC sum in the fourth column); absence of perinatal CNS damage compensation by one-year birthday (as per PC sum in the fifth column).

If the PC sum is equal or less than –13, the forecast is favorable, and one can predict absence of such health disorder evolvement.

If the PC sum is within +12 to –12 range, than the forecast is uncertain, and we don't have enough data to make a decision on it (attention group).

We recommend pediatricians to include children with unfavorable forecasts into a risk group as per such health disorders evolvement and assign preventive activities which can lower such risks evolvement.

Conclusions. So, in the course of our research we detected biological risk factors for most frequent disorders in somatic health of children born from monocyesis after IVF during the first year of their life; such disorders include congenital malformations, iron-deficiency anemia, atopic dermatitis, consequences of perinatal CNS damage. We detected that somatic health formation in children born from monocyesis after IVF during the first year of their life is greatly influenced by factors related to a mother's health (extragenital morbidity, obstetric-gynecological case history, pregnancy course). and a newborn's health. Here social factors and factors determined by IVF procedure itself don't exert any statistically significant influence.

We worked out predictive tables which can help to predict evolvement of health disorders in a child born from monocyesis

after IVF just after its birth; we hope these tables will be suitable for practical use by neonatologists, district pediatricians, and family doctors.

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Received: 13.01.2017
Accepted: 10.03.2017
Published: 30.03.2017