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Hair Trace Element and Electrolyte Content in Women with Natural and In Vitro Fertilization-Induced Pregnancy

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Abstract The objective of the present study was to perform comparative analysis of hair trace element content in women with natural and in vitro fertilization (IVF)-induced pregnancy. Hair trace element content in 33 women with IVF-induced pregnancy and 99 age- and body mass index-matched control pregnant women (natural pregnancy) was assessed using inductively coupled plasma mass spectrometry. The results demonstrated that IVF-pregnant women are characterized by significantly lower hair levels of Cu, Fe, Si, Zn, Ca, Mg, and Ba at $p < 0.05$ or lower. Comparison of the individual levels with the national reference values demonstrated higher incidence of Fe and Cu deficiency in IVF-pregnant women in comparison to that of the controls. IVF pregnancy was also associated with higher hair As levels ($p < 0.05$). Multiple regression analysis revealed a significant interrelation between IVF pregnancy and hair Cu, Fe, Si, and As content. Hair Cu levels were also influenced by vitamin/mineral supplementation and the number of pregnancies, whereas hair Zn content was dependent on prepregnancy anthropometric parameters. In turn, planning of pregnancy had a significant impact on Mg levels in scalp hair. Generally, the obtained data demonstrate an elevated risk of copper, iron, zinc, calcium, and magnesium deficiency and arsenic overload in women with IVF-induced pregnancy. The obtained data indicate the necessity of regular monitoring of micronutrient status in IVF-pregnant women in order to prevent potential deleterious effects of altered mineral homeostasis.

Keywords In vitro fertilization · Iron · Copper · Deficiency · Arsenic

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Introduction

Multiple studies demonstrated that dietary factors, including vitamins [1] and trace elements [2], may have a significant effect on reproductive health. Deficiency of essential trace elements has been shown to be associated with impaired fertility [2]. In particular, it has been suggested that women with recurrent miscarriages have more selenium deficiency in comparison to healthy controls [3]. Experimental studies with animals demonstrated that dietary Zn deficiency is associated with impaired embryogenesis in animals conceived through in vitro fertilization (IVF) [4].

Correspondingly, adequate micronutrient intake may play a role in prevention of female infertility [5]. Vitamin D deficiency was observed to be rather common in infertile couples requiring assisted reproduction technologies [6]. Women undergoing IVF were also characterized by lower serum and follicle fluid selenium and zinc concentrations [7]. Increased vitamin C, E, and A intake has been associated with shorter time to pregnancy in couples being treated for unexplained infertility [8]. Dietary non-heme iron intake including iron supplements has been shown to reduce the risk of ovulatory

infertility [9]. At the same time, a review of the supplementation trials demonstrated that the effect of micronutrient supplementation on female fertility is rather unclear [10].

Micronutrient status has also been shown to contribute to the efficiency of assisted reproductive technologies. For example, a positive association between blood Zn and Mg concentrations with the probability of pregnancy has been demonstrated [11]. The normal level of folic acid is associated with successive IVF [12]. Higher folate intake has also been associated with higher live birth rates in women undergoing assisted reproduction [13]. However, data on essential trace element status in women undergoing IVF are insufficient and somewhat contradictory.

Toxic metal exposure (including occupational) also has a significant effect on reproductive system functioning [14]. In particular, the existing data indicate a significant negative influence of Pb exposure on female fertility [15]. Multiple studies have demonstrated that the effect of cadmium on ovaries, oogenesis, and embryogenesis (both in pre- and post-implantation periods) is mediated by Cd-induced oxidative stress, apoptosis, altered cell adhesion, interference with essential trace element metabolism, and DNA damage [16]. In addition, certain toxic metals including Cd, Hg, Pb, and As act as endocrine disruptors affecting endocrine and reproductive endocrine system signaling [17]. Moreover, it has been demonstrated that increased blood toxic trace elements (Pb, Hg, and Pb) levels may affect the outcome of IVF [11].

Therefore, the existing data demonstrate that monitoring of trace element status of women with reproductive problems is of particular importance in order to reveal deficiency of the essential trace elements and possible excess of the toxic ones. Moreover, simultaneous assessment of trace element status is also required as the interaction of essential and toxic trace elements may have a significant impact on fertility [18].

Hair is widely used for trace element status assessment due to non-invasiveness of sampling, simplicity of storage, irreversible binding of trace elements into the hair matrix, and high degree of mineralization [19]. Therefore, hair trace element content may be indicative of the nutritional status of the organism for a period of time, whereas blood, serum, and urinary trace element levels reflect current physiological state of the organism due to homeostatic regulation [20]. Hair may be also used for assessment of environmental exposure to trace elements [21]. At the same time, hair trace element content may vary in response to a number of factors including gender, age, geographical location, ethnicity, and living and dietary habits, as well as physiological state of the organism [22]. Therefore, appropriate reference values should be used in order to improve interpretation of the obtained hair trace element data [23].

Earlier studies demonstrated the dynamics of hair trace element content in pregnancy [24]. Our previous studies demonstrated that trace element levels in pregnant women may respond to certain lifestyle factors, such as alcohol consumption [25, 26]. Moreover, hair trace element analysis in pregnant women may be indicative of certain perinatal pathologies [27].

In vitro fertilization is the one of the most effective assisted reproductive technologies today. Briefly, it includes ovarian hyperstimulation for optimization of follicle development and egg production, subsequent egg retrieval, and in vitro fertilization by co-cultivation of eggs and sperms, embryo culture for 3–5 days, and, finally, transfer of the embryo into the uterus [28].

As the use of reproductive technologies is growing, it is important to identify factors of risk that may be characteristic of women undergoing IVF treatment. Therefore, the primary objective of the present study was to perform comparative analysis of hair trace element content in women with natural and IVF-induced pregnancy.

Materials and Methods

A total of 33 women with IVF-induced pregnancy were enrolled in the present investigation. The control group included 99 women with natural pregnancy who were matched to the cases for age, anthropometric parameters (weight, height, and body mass index (BMI)), and the place of habitation. The IVF and control groups consisted of women living in the Siberian Federal District of the Russian Federation (Tomsk, Novosibirsk, and Barnaul) in similar proportions. Only cases of normal pregnancy were included in the present study. In order to prevent the influence of the side factors on hair trace element status, the following exclusion criteria were used: (i) the presence of metal implants (including dental amalgam fillings), (ii) occupational exposure to heavy metals, (iii) the use of hormonal replacement therapy, (iv) smoking (both before and during pregnancy).

All pregnant women had filled in a questionnaire and provided personal information on age at menarche, age at first sex, marital status (and years married), and education. They have also specified whether the present pregnancy is the first one and planned. Information about the use of vitamin/mineral supplements, iron supplements, and the period of iron supplementation was also collected using the questionnaire.

Prepregnancy anthropometric parameters (height and weight) were registered. Prepregnancy BMI was calculated using the values of body height (m) and weight (kg) using the standard formula (BMI (kg/m^2) = body weight/height). Q1

Table 1 provides a summary of anthropometric and personal data of the examined women with natural and IVF-induced pregnancy.

Scalp hair samples were collected from the occipital region using ethanol-precleaned stainless steel scissors (0.05–0.1 g) in the third trimester of pregnancy from women with both normal and IVF-induced pregnancy. Only proximal parts of

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Table 1 Population description

Parameter	Natural pregnancy (n = 99)	IVF pregnancy (n = 33)	p value
Age, years	30.6 ± 3.7	31.8 ± 4.5	0.094
Prepregnancy height, cm	165.5 ± 6.3	166.2 ± 4.8	0.849
Prepregnancy weight, kg	63.1 ± 13.7	64.0 ± 14.3	0.722
Prepregnancy BMI	23.0 ± 4.6	23.1 ± 4.8	0.930
Age of menarche, years	13.2 ± 1.4	12.6 ± 1.2	0.065
Age of first sex, years	18.2 ± 2.4	18.4 ± 3.0	0.770
	Marital status		
Married, n	85/99	30/33	0.458
Cohabiting, n	12/99	2/33	0.132
Single, n	2/99	1/33	0.745
Years married	4.2 ± 3.5	5.5 ± 4.9	0.185
	Education (highest)		
Secondary school	2/99	1/33	0.744
College	12/99	3/33	0.543
University	78/99	28/33	0.476
PhD	–	2/33	–
Other (not specified)	7/99	–	–
	Pregnancy		
First pregnancy, n	30/9	19/33	0.005*
Planned pregnancy, n	80/99	33/33	0.025*
Use of vitamin/mineral supplements, n	92/99	24/33	0.002*
Use of Fe supplements, n	41/96	13/33	0.743
Fe supplementation, days	65 ± 70	100 ± 101	0.291

Data expressed as mean ± SD or n (n is indicative of the number of women with a particular characteristics from the total number of women in the group)

*Significant difference at $p < 0.05$ as assessed by the Mann-Whitney U test

the collected hair strands were used for chemical analysis. All women have washed their hair before sampling using usual commercial shampoos. It has been shown that the use of different shampoos does not significantly affect hair mineral content [29].

The obtained hair samples were washed with acetone and rinsed thrice with distilled deionized water (18 MΩ cm) with subsequent drying on air at 60 °C till air-dry condition [30]. The deionized water was obtained by an electric distiller with combined membrane set DVS-M/1HA-1(2)-L (Mediana-Filter, Podolsk, Russia). Acetone as a washing agent removes mechanical contamination (dirt, dust) but does not alter the level of trace elements externally bound to hair matrix [31]. After drying, 0.05 g of hair was introduced into Teflon tubes containing concentrated nitric acid (HNO_3) (Fluka, Sigma-Aldrich, Co.). Microwave digestion of the samples was performed in BerghofSW-4 DAP-40 (Berghof Products & Instruments, Germany) system at 170–180 °C for 20 min. After cooling the system, the obtained solutions were transferred into polypropylene test tubes. The liners were rinsed thrice by distilled deionized water, and the rinses transferred into the correspondent test tubes. Afterwards, distilled deionized water was added to the samples to a total volume of 15 ml and vigorously mixed manually. The obtained solution was used for chemical analysis.

Analysis of hair for trace elements was performed by inductively coupled plasma mass spectrometry (ICP-MS) at NexION 300D (PerkinElmer Inc., Shelton, CT 06484, USA) equipped with the 7-port FAST valve and ESI SC DX4 autosampler (Elemental Scientific Inc., Omaha, NE 68122, USA). The use of Dynamic Reaction Cell (DRC) technology allowed to remove the majority of interferences. The system was calibrated using standard solutions prior to the analysis. Briefly, trace element solutions with a final concentration of 0.5, 5, 10, and 50 ng/l were prepared from Universal Data Acquisition Standards Kit (PerkinElmer Inc., Shelton, CT 06484, USA) by dilution with distilled deionized water and acidification with 1% HNO_3. Internal standards containing 10 μg/l yttrium-89 and rhodium-103 were used. The standards were prepared from Yttrium (Y) Pure Single-Element Standard (PerkinElmer Inc., Shelton, CT 06484, USA) and Rhodium (Rh) Pure Single-Element Standard (PerkinElmer Inc., Shelton, CT 06484, USA) on a matrix containing 8% 1-butanol (Merck KGaA), 0.8% Triton X-100

(Sigma-Aldrich, Co.), 0.02% tetramethylammonium hydroxide (Alfa-Aesar, Ward Hill, MA 01835 USA), and 0.02% ethylenediaminetetraacetic acid (Sigma-Aldrich, Co). The obtained data on hair mineral content were expressed in micrograms per gram dry weight. The obtained levels of essential and toxic trace elements that were significantly different between the groups were compared to the existing Russian reference values for adult women [32–34].

Laboratory quality control was performed using the certified reference material (CRM) of human hair GBW09101 from Shanghai Institute of Nuclear Research, Shanghai (China). Analysis of CRM was performed both before and after analysis of the obtained hair samples. The recovery rate for all trace elements analyzed was within 90–110% during all measurements.

Statistical treatment of the data obtained was performed by using Statistica 10.0 (Statsoft, Tulsa, OK, USA). Analysis of data distribution using Shapiro-Wilk revealed non-Gaussian distribution for all trace elements studied. After exclusion of outliers (percentile two-sided) the group median and 25–75 percentile boundaries were calculated. Significance of group differences was assessed using the Mann-Whitney *U* test. Multiple regression analysis was used in order to assess the association of anthropometric and personal characteristics with hair levels of trace elements that were significantly different between the groups. The level of significance of $p < 0.05$ was used for all statistical analyses applied.

Results

The obtained data demonstrate that IVF-induced pregnancy was associated with significant variations in hair essential trace element content (Table 2). In particular, women with IVF pregnancy had 29, 46, 27, and 24% lower levels of hair Cu, Fe, Si, and Zn, when compared to the controls. Moreover, the incidence of low hair Fe content in the IVF-pregnant women (16 of 33) was significantly higher ($p < 0.001$) than that of the control group (16 of 99). Similarly, the prevalence of low hair copper (16 of 33) detected in the IVF group significantly ($p = 0.034$) exceeded that of the control group (28 of 99). In contrast, no significant difference in the incidence of Zn deficiency was observed between the groups. At the same time, 25 of 99 women from the control group had high hair Fe content, being significantly ($p = 0.050$) higher than the rate in IVF-pregnant women (3 of 33). No significant difference in the prevalence of high Cu and Zn content in hair was detected between the groups.

Significant group differences were also found for hair electrolytes (Table 2). In particular, women with IVF pregnancy had 30 and 32% lower hair Ca and Mg levels in comparison to the natural pregnancy group values, respectively. At the same time, hair K levels were on average higher in women with IVF pregnancy, although not significantly.

Similar to essential trace elements and electrolytes, the hair levels of toxic elements also differed between the study groups (Table 3). Women with IVF pregnancy were characterized by a significant 33% increase in hair As content in comparison to the control values. At the same time, the hair level of Ba in these women was 21% lower than that in women with natural pregnancy. Despite nearly twofold higher levels of tin in hair of IVF-pregnant women, the observed elevation was not significant due to a high variability of the data. No significant group difference in hair Al, B, Cd, Hg, Ni, Pb, and Sr was detected. In comparison to the Russian reference values [32], the prevalence of low (43 of 99 vs 11 of 33, $p = 0.310$) and high (1 of 99 vs 2 of 33, $p = 0.095$) hair As content was nearly similar in the control and IVF-induced pregnant women.

The results of multiple regression analysis demonstrated that the personal anamnestic and pregnancy characteristics are related to hair essential trace elements and electrolyte content (Table 4). In particular, the obtained data demonstrated that IVF-induced pregnancy is significantly associated with variations of hair Cu, Fe, and Si content. Hair copper levels were also significantly associated with the number of pregnancies (first pregnancy or not), and the use of vitamin/mineral supplements. Surprisingly, neither iron supplementation nor its duration had a significant impact on hair Fe content in women with both natural and IVF pregnancy. The results of multiple regression analysis demonstrated that type of pregnancy was not significantly associated with hair Zn content. Hair Zn levels were related to morphometric parameters (height, weight, and BMI). Despite the presence of significant group differences, multiple regression analysis failed to reveal any significant effect of the studied parameters on hair calcium content in pregnant women (data not shown). Only IVF-induced pregnancy was significantly associated with hair As levels out of all the parameters. Hair magnesium levels were significantly related to pregnancy planning. Hair Ba levels in the pregnant women were not related to the personal parameters (data not shown).

Discussion

The results demonstrate that women with IVF-induced pregnancy are characterized by altered hair trace element and electrolyte content. In particular, women with IVF-induced pregnancy had significantly lower levels of essential trace elements (Cu, Fe, Si, and Zn) and electrolytes (Ca, Mg) in comparison to women with natural pregnancy. Surprisingly, hair Ba, Au, Ga, and Li were also significantly lower in women with IVF pregnancy in comparison to the control values. In

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Table 2 Medians and 25–75 percentile boundaries of hair essential element content (μg/g) in women with natural and IVF-induced pregnancy

Element	Natural pregnancy		IVF pregnancy		*P* value	Reference range	References
	Median	25–75 percentile	Median	25–75 percentile			
Ca	2031	1400–3498	1429	902–2406	0.010*	494–1619	[34]
Zn	234	191–295	179	163–246	0.008*	140–315	[33]
P	173	149–199	171	153–178	0.545	135–181	[34]
Mg	155	101–228	105	57–191	0.030*	39–137	[34]
K	138	43–278	191	105–360	0.089	29–159	[34]
Na	86	55–171	102	41–187	0.749	73–331	[34]
Si	37	25–48	27	18–35	0.020*	11–37	[34]
Cu	16.8	11.5–27.3	11.9	9.8–14.9	0.002*	12.1–44.5	[33]
Fe	16.6	10.6–24.9	8.9	7.0–13.2	< 0.001*	8.9–25.6	[33]
Sr	8.2	5.0–12.7	6.4	3.2–10.9	0.141	1.6–15.2	[32]
Mn	1.1	0.7–2.2	0.8	0.5–2.4	0.191	0.3–2.1	[33]
I	0.364	0.265–0.569	0.314	0.201–0.597	0.243	–	
Se	0.356	0.280–0.456	0.381	0.332–0.451	0.552	0.094–0.504	[33]
Cr	0.078	0.05–0.158	0.070	0.047–0.126	0.373	0.060–0.400	[33]
Mo	0.021	0.016–0.026	0.022	0.019–0.027	0.446	–	
Co	0.019	0.011–0.044	0.015	0.007–0.035	0.104	0.011–0.085	[33]
Li	0.009	0.004–0.013	0.011	0.006–0.014	0.306	0.009–0.040	[32]
V	0.008	0.005–0.014	0.007	0.004–0.013	0.393	0.010–0.056	[33]

*Significant group difference at $p < 0.05$ as assessed by the Mann-Whitney *U* test.

contrast, women who underwent IVF had significantly elevated hair levels of As.

A previous study involving women following ovarian hyperstimulation demonstrated a significant decrease in iron status, as assessed by serum ferritin [35]. These findings correspond to the earlier data demonstrating the efficiency of dietary non-heme iron intake including iron supplements in reduction of the ovulatory infertility risk [9]. The role of iron supplementation in reducing the risk of adverse pregnancy outcome or infertility may be associated with increased requirements in pregnancy [36]. The results of both group comparisons and multiple regression analysis demonstrated that IVF-induced pregnancy is significantly interrelated with hair Fe content, whereas other factors including Fe supplementation did not affect the parameter. These findings are indicative of the possible low dietary iron intake in women with IVF pregnancy. The absence of a significant influence of iron supplementation on iron status in the estimated models is at least partially in agreement with the data by Ribot et al. [37] who demonstrated that iron supplementation does not significantly influence the adverse effect of iron deficiency without anemia in early pregnancy [37]. It has been also demonstrated that consumption of vitamin/mineral supplements did not affect serum Fe levels in IVF patients [7].

Table 3 Medians (25–75 percentile) of hair toxic trace element levels (μg/g) in women with natural and IVF-induced pregnancy

Element	Natural pregnancy		IVF pregnancy		*P* value	Reference range [32]
	Median	25–75 percentile	Median	25–75 percentile		
Al	3.9	2.4–6.2	3.7	2.3–5.9	0.670	2.8–10.5
Ba	3.8	2.3–6.2	3.0	1.0–4.4	0.007*	–
Pb	0.362	0.224–0.553	0.317	0.165–0.609	0.446	0.160–0.917
B	0.339	0.257–0.458	0.381	0.282–0.572	0.175	–
Ni	0.299	0.180–0.431	0.211	0.155–0.438	0.200	0.168–0.779
Hg	0.296	0.184–0.436	0.301	0.153–0.493	0.870	0.185–1.094
Sn	0.184	0.083–0.577	0.343	0.083–0.997	0.376	0.082–1.158
As	0.009	0.006–0.014	0.012	0.007–0.026	0.011*	0.008–0.062
Cd	0.009	0.004–0.016	0.008	0.006–0.015	0.427	0.005–0.042

*Significant group difference at $p < 0.05$ as assessed by the Mann-Whitney *U* test

t4.1 **Table 4** Multiple regression analysis for the association of anthropometric and personal data of pregnant women and hair trace element and electrolyte content as a dependent variable

t4.2 Element	Cu		Fe		Si		Zn		As		Mg	
t4.3 Parameter	β	p	β	p	β	p	β	p	β	p	β	p
t4.4 Age, years	−0.047	0.652	0.036	0.744	0.127	0.277	−0.028	0.804	−0.119	0.271	0.080	0.470
t4.5 Age at menarche, years	0.074	0.388	0.113	0.209	−0.046	0.621	−0.010	0.914	0.018	0.838	−0.057	0.526
t4.6 Age at first sex, years	0.001	0.992	−0.123	0.208	0.045	0.660	0.050	0.610	−0.060	0.505	−0.122	0.217
t4.7 First pregnancy	0.311	0.002*	−0.008	0.939	−0.015	0.887	0.025	0.804	−0.075	0.438	−0.011	0.916
t4.8 Planned pregnancy	−0.077	0.393	0.109	0.244	0.096	0.320	−0.091	0.335	0.025	0.781	−0.214	0.024*
t4.9 Prepregnancy height, cm	0.171	0.711	−0.054	0.910	−0.169	0.736	−1.065	0.030*	0.091	0.845	0.412	0.402
t4.10 Prepregnancy weight, kg	−0.211	0.875	0.032	0.982	0.552	0.704	−3.185	0.022*	0.128	0.925	−1.281	0.378
t4.11 Prepregnancy BMI	0.354	0.776	−0.178	0.891	−0.529	0.695	−3.037	0.019*	−0.088	0.944	1.160	0.385
t4.12 Pregnancy type	−0.306	0.003*	−0.308	0.005*	−0.268	0.018*	−0.138	0.205	0.405	< 0.001 *	−0.088	0.416
t4.13 Use of V/M supplements	−0.241	0.012*	−0.076	0.446	−0.050	0.625	0.153	0.124	0.078	0.413	0.050	0.616
t4.14 Use of Fe supplements	0.009	0.927	0.004	0.968	−0.015	0.893	−0.130	0.236	−0.135	0.203	−0.022	0.814
t4.15 Days of Fe supplementation	0.109	0.297	0.041	0.711	−0.026	0.822	0.107	0.341	0.033	0.761	−0.080	0.473
t4.16 Multiple R	0.448		0.372		0.258		0.340		0.430		0.324	
t4.17 R^2	0.201		0.138		0.066		0.116		0.185		0.105	
t4.18 Adjusted R^2	0.119		0.050		0.029		0.025		0.102		0.013	
t4.19 p for the model	0.007		0.112		0.756		0.242		0.015		0.334	

Data presented as regression coefficient (β), partial correlation coefficient (PC), and individual p value for every association

*Partial correlation is significant at $p < 0.05$

The observed low hair Cu and Zn content in women with IVF-induced pregnancy only partially corresponds to the earlier studies. In particular, pregnant women with a history of recurrent spontaneous abortions were found to have significantly lower blood zinc and copper levels in comparison to pregnant women without complicated anamnesis. Blood selenium, lead, and cadmium were increased in comparison to the control values [38]. At the same time, women with unexplained infertility had significantly decreased serum Zn levels, whereas Cu levels, as well as Cu/Zn ratio were increased in comparison to the healthy controls [39]. Another study showed distinct patterns of blood trace elements changes in pregnant women who underwent intrauterine insemination or IVF. In particular, these women had a significant increase in transferrin saturation, reduced total iron-binding capacity, and serum Se, without any significant difference in serum copper levels in comparison to the group of women with natural pregnancy [40]. Despite the presence of certain indications of the role of Se in female fertility [41], we failed to detect any group difference in hair Se content.

Magnesium has been shown to play a significant role in a variety of physiological functions, including female reproductive health [40]. Decreased hair Mg content in IVF-pregnant women may be indicative of poor Mg status due to low Mg intake in pregnancy [42]. In addition, women undergoing ovarian hyperstimulation in IVF demonstrated a significant decrease in ionized magnesium due to the influence of estrogens [43].

Moreover, the previous studies indicated that higher blood Zn and Mg concentrations were associated with the increased probability of pregnancy [11]. It is notable that hair Zn content in women undergoing ovarian hyperstimulation was positively associated with the number of oocytes collected, whereas correlation between hair Se and the number of follicles and oocytes collected after stimulation was not linear [44]. At the same time, no significant difference between blood and follicular fluid zinc content was revealed in infertile women undergoing IVF between conception and non-conception cycles [45].

Decreased hair Zn content in women with IVF pregnancy may be indicative of poor zinc status due to both increased requirements and low dietary intake [46]. Taking into account the association between maternal zinc deficiency and poor fetal outcome including neural tube defects [47], zinc status in pregnant and especially IVF-pregnant women should be monitored. Moreover, it has been demonstrated that Zn deficiency may contribute to adverse health effects of certain toxic substances including alcohol exposure in fetal alcohol spectrum disorders development [48].

Multiple regression model revealed the absence of a significant association between IVF-induced pregnancy and hair Zn content; anthropometric parameters, including body weight and BMI, were significant predictors. The inverse association between hair Zn and body weight may be related to the biological function of Zn in insulin production [49] and signaling [50]. Correspondingly, earlier studies have demonstrated lower indices of zinc status in obesity [51, 52].

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The observation of lower hair levels of Ca in women with IVF-induced pregnancy is in agreement with the findings that women undergoing IVF treatment were characterized by lower dietary Ca intake [53]. Multiple studies have demonstrated the involvement of calcium signaling in the process of in vitro fertilization [54]. At the same time, studies aimed at assessment of Ca status in women undergoing IVF are lacking. Hypothetically, low Ca stores in the examinees may be associated with the high prevalence of vitamin D deficiency in women using assisted reproductive technologies [6].

Multiple studies have demonstrated the association between toxic trace element exposure and infertility. In particular, exposure to Hg, Pb, and Cd in women undergoing ovarian stimulation for IVF was associated with altered DNA methylation in whole blood [55]. However, it has been demonstrated that Cd, Pb, and Hg in the follicle fluid may be not only negatively associated with the outcome of in vitro fertilization. In particular, although follicular fluid Cd levels were associated with higher risk of embryo cleavage and fragmentation, the metal concentration is directly related to oocyte fertilization and pregnancy [56]. Similarly, no association between hair Hg content and IVF outcome was found [57]. We also failed to detect any significant group difference in hair Hg, Pb, and Cd content with respect to the type of pregnancy. Only hair As levels were significantly higher in women with IVF pregnancy. The observed increase in hair As content in IVF-pregnant women is in agreement with the earlier observation of elevated urinary As levels in female participants of the US-based Study of Metals and Assisted Reproductive Technologies [58]. It has been proposed that the increase in urinary As in women undergoing IVF may be associated with the frequency of sea foods consumption [59]. A previous study demonstrated that the level of hair As in women undergoing in vitro fertilization directly correlates with follicular fluid arsenic, lead, and mercury concentrations [60]. Therefore, elevated hair As levels may be indicative of the increased risk of reproductive [61, 62] and developmental [63, 64] toxicity. Human studies demonstrated that increased As exposure during pregnancy may be associated with the risk of fetal loss and infant death [65]. It is also notable that the Se/As ratio in women who underwent IVF was significantly higher as compared to the control group, being indicative of the antagonism between these metalloids. In turn, it has been demonstrated that hair Se/As ratio is characterized by a tighter association with population health and demography as compared to hair Se and As content separately [66].

Interesting data on hair Ba content were obtained, being indicative of decreased hair Ba content in women with IVF pregnancy. The role of barium in reproductive health is contradictory. Certain experimental studies demonstrated possible toxic effect of Ba on the reproductive system, whereas clinical observations of Ba toxicity are inconsistent [67].

Taking into account antagonistic interactions between certain essential and toxic trace elements in the organism [68], the observed decrease of essential elements in hair may predispose the organism to the potentially deleterious effects of toxic elements. In addition, the obtained data should be also taken into account when planning infant nutrition in order to correct deficiencies and prevent possible metal overload [69].

Conclusion

The obtained data demonstrate an elevated risk of copper, iron, zinc, calcium, and magnesium deficiency and arsenic overload in women undergoing IVF. These findings allow to propose that essential trace element deficiency and toxic trace element overload may at least partially contribute to impaired fertility in women, resulting in increased requirements for advanced reproduction technologies including IVF. Taken together, these findings underline the necessity of regular monitoring of micronutrient status in IVF-pregnant women in order to prevent potential deleterious effects of altered mineral homeostasis.

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Compliance with Ethical Standards The research protocol of the current study was approved by the Ethics Committee for Interdisciplinary Investigations (Tomsk State University/Psychological Institute of the Russian Academy of Education). The study was carried out in agreement with the principles of the Declaration of Helsinki and its later amendments. All women took part in the present investigation on a voluntary basis and were informed about the experimental procedures. The informed consent was signed by all participants before the investigation.

Conflict of Interest The authors declare that they have no conflict of interest.

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