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Epidemiology

Serum levels of copper, iron, and manganese in women with pregnancy, miscarriage, and primary infertility

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ABSTRACT

Background: Iron (Fe), copper (Cu), and manganese (Mn) play a significant role in female reproduction and fetal development. At the same time, high levels of metals may exert toxic effects. Correspondingly, both excess and deficiency of essential trace elements were shown to be associated with female infertility and adverse pregnancy outcome, although the existing data are rather contradictory. Therefore, the objective of the present study was to reveal the potential role of altered iron, copper, and manganese status in female reproductive health problems through assessment of serum metal levels in healthy non-pregnant and pregnant women, as well as patients with miscarriage and primary infertility.
Methods: A total of 150 healthy controls, 169 pregnant women (II trimester of pregnancy), 75 women with miscarriage, and 91 patients with primary infertility were enrolled. Serum metal levels were assessed using ICP-MS.
Results: Pregnant women are characterized by a significant increase in serum Cu an Mn levels by 40% ($p < 0.001$) and 16% ($p = 0.043$) as compared to the controls, respectively. Serum Cu levels in women with miscarriage and infertility were 30% and 35% lower than those in pregnant women ($p < 0.001$). No significant difference in serum iron levels were observed between the control and pregnant women. Women who had miscarriage were characterized by 13% ($p = 0.042$) higher serum Fe levels as compared to the pregnant ones. Multiple regression analysis demonstrated that serum copper levels was significantly associated both with pregnancy ($\beta = 0.436$; $p < 0.001$) and reproductive health problems in women ($\beta = -0.272$; $p < 0.001$). The latter was improved significant after adjustment for serum Fe and Mn levels, age, and BMI ($\beta = -0.431$; $p < 0.001$). The model incorporating serum Cu, Fe, Mn, and anthropometric parameters accounted for 23% of variability in reproductive status ($p < 0.001$).
Conclusions: It is proposed that the lack of pregnancy-associated increase in metal levels in miscarriage and infertility may be indicative of at least partial role of metal insufficiency in impaired pregnancy and reproductive function in general. However, detailed clinical studies as well as experimental investigations are required for assessment of the potential causes and mechanisms of the observed associations.

1. Introduction

Essential metals play a significant role in a myriad of physiological processes including female reproductive function [1]. Correspondingly, deficiency of essential trace elements is associated with impaired fertility and/or adverse pregnancy outcomes [2], whereas trace element and mineral supplementation may improve female fertility [3]. Our earlier studies demonstrated that women requiring assisted reproductive technologies are characterized by lower levels of essential trace elements [4]. Moreover, maternal micronutrient deficiency may

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significantly increase the risk for various metabolic disorders (diabetes, cardiovascular diseases, *etc*.) in offspring [2].

Copper is essential for fetal growth and development playing a significant role in energy supply, myelination, neurotransmitter metabolism, and connective tissue development [5]. Correspondingly, the existing studies indicate a significant elevation of serum Cu levels in pregnancy, whereas low copper status may be associated with pathological pregnancy [6] and miscarriage [7]. Pregnancy-associated increase in blood copper may be indicative of increased metal requirements due to its role in embryogenesis and fetal development [5]. Moreover, increased follicular fluid Cu levels is associated with better oocyte growth, fertilization, and embryo differentiation [8]. However, the results of other studies demonstrated that increased serum and urine Cu levels are associated with preeclampsia [9] and abortions [10].

Adequate iron supply is also critical for fetal development, being tightly related to brain development through neuronal and glial energy metabolism, neurotransmitter metabolism, myelination, and oxygen transport [11]. Therefore, iron-deficiency anemia results in intrauterine growth retardation as well as adverse pregnancy outcome [12]. The results of meta-analysis demonstrated a direct relationship between prenatal iron intake and improved birth weight [13]. Correspondingly, iron metabolism is tightly regulated in pregnancy resulting in increased iron absorption and mobilization to meet the organism's requirements [14]. In turn, impaired iron metabolism may result in adverse pregnancy outcome. Particularly, iron deficiency is associated with higher rate of preterm birth [15] and spontaneous abortions [16]. The significant role of iron in female reproduction [17] is also supported by the observation of reduced iron status in ovulatory infertility [18]. At the same time, elevated iron body burden under inadequate dosage of iron supplements [19] or impaired iron metabolism [14] may also have adverse effects in pregnancy. Particularly, preeclampsia was shown to be associated with increased serum iron, ferritin and transferrin saturation [20].

Manganese was shown to play a significant role in pregnancy and fetal development [21] being in agreement with the findings of elevated blood Mn levels in pregnancy [22]. Particularly, within a physiological range maternal Mn levels are directly associated with birth weight [23]. However, at overexposure manganese exerts a variety of toxic effects resulting in impaired neurodevelopment [24]. Correspondingly, increased manganese exposure was shown to have significant negative impact on fetal development [25]. Taken together, these findings corroborate the results obtained by Chung et al. who demonstrated that both high and low maternal blood Mn levels are associated with adverse fetal neurodevelopment [26]. In turn, data on manganese balance and its disturbances in healthy and pathological pregnancy are conflicting. Particularly, increased Mn intake in undernourished women was found to be associated with lower rate of spontaneous abortions [27]. As in the case of copper and iron, women with preeclampsia were characterized by reduced serum Mn levels [28]. At the same time, several reports of higher blood Mn levels in cases of miscarriage exist [29].

Generally, the existing data on the association between iron, copper, and especially manganese levels with pregnancy or female reproductive health problems are rather contradictory. Therefore, the objective of the present study was to reveal the potential role of altered iron, copper, and manganese status in female reproductive health problems through assessment of serum metal levels in healthy non-pregnant and pregnant women, as well as patients with miscarriage and primary infertility.

2. Materials and methods

All procedures performed within the project were in agreement with the ethical principles of the Declaration of Helsinki (1964) and later amendments (2013). All women were enrolled in the present investigation on a voluntary basis and were informed about the experimental procedures. The informed consent was signed by all examinees before the investigation. The protocol of the present study (#12-2/2018) was approved by the Local Ethics Committee of the Yaroslavl State University (Yaroslavl, Russia).

Table 1
Age and body mass index (BMI) of the examined women.

	Control	Pregnancy	Miscarriage	Primary infertility
n	150	169	75	91
Age, years old	33.1 ± 5.0	33.4 ± 4.4	34.8 ± 6.3	35.5 ± 5.1
BMI, kg/m^2	21.6 ± 2.2	22.3 ± 1.9	21.2 ± 2.0	21.0 ± 2.3
Marital status:				
Married, % (n)	83% (125)	90% (152)	89% (67)	91% (83)
Cohabiting, % (n)	12% (18)	7% (12)	7% (5)	3% (3)
Single, % (n)	5% (7)	3% (5)	4% (3)	6% (5)
Years married	4.2 ± 2.9	5.3 ± 3.6	4.7 ± 3.1	5.2 ± 4.6
First pregnancy, % (n)	–	39% (66)	47% (35)	–
Planned pregnancy, % (n)	–	78% (132)	82% (62)	–
Primary infertility causes (ICD-10 codes):				
Endocrine (Anovulatory) (N97.0)	–	–	–	18% (16)
Tubal origin (N97.1)	–	–	–	41% (37)
Uterine origin (N97.2)	–	–	–	32% (29)
Unspecified (N97.9)	–	–	–	9% (9)
Education (highest):				
Secondary school	3% (4)	4% (7)	2% (2)	1% (1)
College	17% (26)	19% (32)	15% (11)	12% (11)
University	79% (118)	77% (130)	82% (61)	84% (76)
PhD	1% (2)	–	1% (1)	3% (3)

Data expressed as Mean ± SD or % (n); n.a. – information not available (for non-pregnant groups).

2.1. Studied cohort

A total of 485 examinees including 150 healthy controls, 169 pregnant women (II trimester of pregnancy), 75 women with miscarriage, and 91 patients with primary infertility were enrolled in the present study. All examined women lived in Moscow (Russia) for the last 5 years or more and were recruited at Center for Biotic Medicine (Moscow) in 2017–2018. Sampling was performed in the second trimester of pregnancy in all groups of pregnant women (including those with subsequent miscarriage). 6.3% of all invited subjects (31 of 516) refused to participate in the study and provide information about their pregnancy outcome.

The examinees have provided personal information on marital status (and years married) and education, as well as specified whether the present pregnancy is the first one and planned (Table 1). All examined women (100%) were Caucasian.

Only women with healthy pregnancy were included in the present study (no gestational diabetes, eclampsia, *etc*.). The following exclusion criteria were also used: i) diabetes mellitus (including gestational) and other metabolic disorders; ii) secondary infertility; iii) acute inflammatory and surgical diseases; iv) in vitro fertilization (IVF) induced pregnancy; vi) smoking (both current and former); vii) excessive alcohol consumption; viii) the presence of metal implants (including dental amalgam fillings); ix) vegetarianism and other specific eating habits; x) occupational exposure to metals in the past.

Pre-pregnancy body mass index (BMI) was recorded. BMI was calculated using the values of body height (m) and weight (kg) using the standard formula (BMI = Body weight / Height^2). No significant group difference in age and body mass index were revealed (Table 1).

2.2. Sampling

Blood samples for analysis were collected in the morning (8.00 a.m.) after overnight fasting from the cubital vein using "Vacuette" tubes (Greiner Bio-One International AG, Austria) and centrifuged at 1600 g for 10 min to obtain serum. The obtained serum samples were diluted with an acidified (pH = 2.0) diluent (1:15; v/v) containing 1% 1-butanol (Merck KGaA, Darmstadt, Germany), 0.1% Triton X-100 (Sigma-Aldrich, Co., St. Louis, MO, USA), and 0.07% HNO_3 (Sigma-Aldrich, Co., St. Louis, MO, USA) in distilled deionized water (18 MΩ cm) ((Labconco Corp., Kansas City, MO, USA)).

2.3. ICP-MS analysis

The obtained samples were subjected for analysis of copper (Cu), manganese (Mn), and iron (Fe) levels using inductively-coupled plasma mass spectrometry (ICP-MS) at NexION 300D (PerkinElmer Inc., Shelton, CT, USA) equipped with 7-port FAST valve and ESI SC-2 DX4 autosampler (Elemental Scientific Inc., Omaha, NE, USA). The system was calibrated using standard 0.5, 5, 10 and 50 μg/L solutions of copper, manganese, and iron prepared from commercially available Universal Data Acquisition Standards Kit (PerkinElmer Inc., Shelton, CT, USA). In addition, internal online standardization was performed using Yttrium (Y) and Rhodium (Rh) solutions (10 μg/L) (Pure Single-Element Standard, PerkinElmer Inc., Shelton, CT, USA).

2.4. Laboratory quality control

Procedures on laboratory quality control were performed daily before and after each set of analyses using the certified reference material ClinCheck Plasma Controls (levels I and II, RECIPE Chemicals + Instruments GmbH, Munich, Germany). The calculated recovery rates (%) for copper, manganese, and iron were found to be within the range of 92–112% and the allowable limits (Table 2). The laboratory of Center for Biotic Medicine (Moscow) is also a participant of the system of External Quality Assessment Schemes in the field of Occupational and Environmental Medicine (EQAS OELM).

2.5. Statistical analysis

Statistica 10.0 (Statsoft, OK, USA) was used for data processing. Data normality assessment was performed using Shapiro-Wilk test. The mean ± standard deviation (SD) values were used as descriptive statistics. Paired-group comparisons were performed using Mann-Whitney *U* test False Discovery Rate (FDR) adjustment for p-value was applied due to multiple comparisons. Multiple regression analysis was performed in order to specify the association between serum metal levels (independent predictors) and healthy pregnancy as dependent variable (0 – non-pregnant controls; 1 – healthy pregnancy). In addition, regression models were constructed to reveal the relationship between serum Cu, Fe, and Mn levels and reproductive health problems (dependent variable). The latter were graded as "0″ (pregnancy – reproductive health), "1″ (miscarriage), and "2″ (primary infertility). The models were adjusted for variability in body mass index (BMI) and age of the examinees. All tests were considered significant at $p < 0.05$

Table 2
Laboratory quality control using ClinChek® PlasmaControl.

Metal	Certified value, mg/l	Certified range, mg/l	Obtained value, mg/l	Recovery rate, %
Level I				
Cu	0.733	0.623–0.843	0.782 ± 0.106	107
Fe	0.885	0.752–1.02	0.933 ± 0.117	105
Mn *	4.58	3.67–5.50	5.15 ± 0.70	112
Level II				
Cu	1.26	1.08–1.45	1.17 ± 0.16	93
Fe	1.24	1.05–1.42	1.30 ± 0.09	105
Mn *	15.3	12.2–18.3	13.8 ± 2.5	92

The obtained data are expressed as Mean ± SD; * The levels of Manganese (Mn) in ClinChek® PlasmaControl are provided as μg/l.

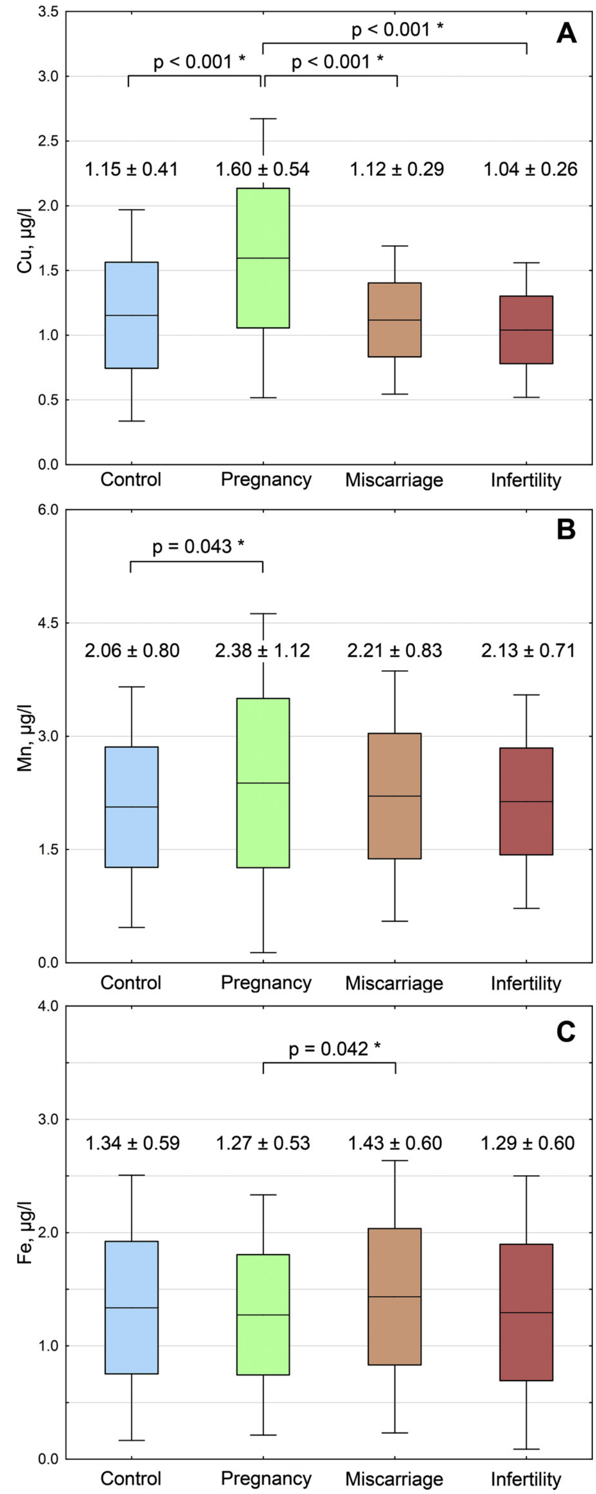

Fig. 1. Serum copper (A), manganese (B), and iron (C) levels (μg/ml) in women with different reproductive status.
Data are expressed as Mean (line) ± 1SD (box) and 2SD (whiskers); * - significant group difference at $p < 0.05$.

Table 3
Multiple linear regression analysis of the association between healthy pregnancy (0 – non-pregnant controls; 1 – pregnant women) and serum copper, iron, and manganese.

Parameter	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Cu, μg/ml	0.436	< 0.001 *	0.428	< 0.001 *	0.435	0.001 *
Fe, μg/ml	–	–	−0.076	0.135	−0.045	0.402
Mn, μg/ml	–	–	0.081	0.111	−0.005	0.920
Age, y.o.	–	–	–	–	0.101	0.089
BMI, kg/m^2	–	–	–	–	0.113	0.039 *
Multiple R	0.436		0.449		0.493	
Multiple R^2	0.190		0.202		0.243	
Adjusted R^2	0.187		0.194		0.229	
P for a model	< 0.001		< 0.001		< 0.001	

Data expressed as regression coefficients (β) and the respective p values; Model 1 – serum Cu (crude); Model 2 – serum Cu, Mn, Fe (crude); Model 3 – adjusted for age and BMI; * - significant at $p < 0.05$.

3. Results

The obtained data demonstrate that pregnant women are characterized by a significant increase in serum Cu and Mn levels by 40% and 16% as compared to the control group, respectively (Fig. 1). At the same time, serum Cu levels in women with miscarriage and infertility were 30% and 35% lower than those in pregnant women. At the same time, no significant group difference in serum Mn levels between pregnant women and those with reproductive health problems were revealed. No significant difference in serum iron levels were observed between the control and pregnant women. At the same time, women who had miscarriage were characterized by 13% higher serum Fe levels as compared to the pregnant ones.

Regression analysis was performed in order to reveal the relationship between healthy pregnancy and serum metal levels (Table 3). The obtained data demonstrate that higher serum copper is characterized by a direct relationship with pregnancy in all models. Moreover, the model including only copper (Model 1), serum Cu, Fe, and Mn levels (Model 2), as well as metal levels adjusted for age and BMI (Model 3) accounted for 19%, 19%, and 23% of pregnancy status variability at $p < 0.001$.

Further multiple regression analysis (Table 4) demonstrated that copper was independently negatively associated with reproductive health problems in women both in crude and adjusted for age and BMI models. Although iron and manganese levels were not significantly interrelated with reproductive status of women, inclusion of these metals into the model significantly improved the relationship between serum copper and reproductive status in adult women. The general model incorporating serum Cu, Fe, Zn, and anthropometric parameters as independent predictors accounted for 23% of variability in reproductive status.

Table 5
Correlation between serum copper, manganese, and iron in women with different reproductive status.

Group	Cu vs Fe		Cu vs Mn		Fe vs Mn	
	r	p	r	p	r	p
Total	−0.152	0.001 *	0.151	0.001 *	0.011	0.816
Controls	−0.136	0.099	−0.104	0.211	0.090	0.276
Pregnancy	−0.200	0.011 *	0.263	0.001 *	−0.094	0.238
Miscarriage	−0.075	0.524	−0.095	0.418	0.083	0.481
Infertility	−0.041	0.700	0.026	0.805	0.095	0.371

Data expressed as correlation coefficients (r) and the respective p values; * - correlation is significant at $p < 0.05$.

Correlation analysis (Table 5) also demonstrated that the relationship between the studied metals significantly varies between the groups. It is notable that correlation of serum copper with serum manganese and iron was found to be significant only in pregnant women, but not in healthy controls or subjects with reproductive health problems.

4. Discussion

The obtained data demonstrate that pregnancy is associated with increased serum copper and manganese levels but not iron. Although serum Cu and Mn levels in women with miscarriage and infertility did not differ significantly from the controls, these levels were significantly lower than those in pregnancy. Oppositely, serum iron levels were elevated in women with miscarriage, whereas no significant difference was detected in pregnant women in comparison to the controls. Moreover, multiple regression analysis demonstrated that copper was characterized by a significant inverse association with reproductive dysfunction.

The observed increase in serum Cu levels in pregnancy corroborates the results of the earlier study by Alvarez et al. (2007) [30], being also in agreement with essential role of Cu in pregnancy [2]. A systematic review also demonstrated a significant increase in serum Cu levels in from the first to the third trimesters of pregnancy [31]. The obtained data partially corresponds to the observation of reduced Cu status in infertile women [32]. Serum Cu levels were found to be reduced in women who had miscarriage [6]. An Iranian study also revealed a significant decline in serum Cu levels in women with second-trimester induced abortion [33].

However, the existing data on copper and adverse pregnancy outcome are contradictory. Certain studies demonstrated a tendency to increased copper levels in pathological pregnancies [34], abortions [10], as well as association between high serum Cu and implantation

Table 4
Regression analysis of the association of serum copper, iron, and manganese with female reproductive health problems (0 – pregnancy (control), 1 – miscarriage, 2 – primary infertility).

Element	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Cu, μg/ml	−0.272	< 0.001 *	−0.498	< 0.001 *	−0.431	< 0.001 *
Fe, μg/ml	–	–	0.002	0.997	−0.008	0.878
Mn, μg/ml	–	–	−0.031	0.534	−0.037	0.471
Age, y.o.	–	–	–	–	0.225	< 0.001 *
BMI, kg/m^2	–	–	–	–	−0.023	0.659
Multiple R	0.272		0.495		0.490	
Adjusted R^2	0.073		0.238		0.227	
p for a model	< 0.001 *		< 0.001 *		< 0.001 *	

Data expressed as regression coefficients (β) and the respective p values; Model 1 – serum Cu (crude); Model 2 – serum Cu, Mn, Fe (crude); Model 3 – adjusted for age and BMI; * - significant at $p < 0.05$.

failure [35].

One of the mechanisms underlying the association between healthy pregnancy and copper status is the interplay between sex hormones and copper metabolism. Particularly, it has been demonstrated that estradiol playing a significant role in female reproduction significantly increases copper handling through up-regulation of Cu transporter expression (Ctr1, DMT1). Moreover, estradiol was shown to impact the effect of Cu supplementation [36]. Moreover, blood Cu levels fluctuate siggnificantly during the estrous cycle, being negatively associated with E2 [37]. Copper may also directly interact with gonadotropin-releasing hormone (GnRH) with formation of Cu-GnRH complex, being a more potent inducer of luteinizing hormone (LH) release through interaction with GnRH receptors [38]. In turn, excessive estrogen production results in elevation of blood Cu levels in association with altered hepatic copper distribution [39]. Cu,Zn-SOD deficiency was also shown to be associated with impaired progesterone secretion and infertility in mice [40].

Although the association between copper deficiency and female infertility are not widely studied in humans, the earlier studies in ruminants demonstrated a significant effect of Cu deficiency on impaired reproduction. Particularly, Cu deficiency in buffalo-cows was associated with reduced progesterone levels especially in the luteal phase [41]. Moreover, hypocupremic cattle were anestrous and had higher incidence of miscarriage, whereas copper supplementation improved reproductive function in 91.7% of cases [42]. Moreover, copper supplementation significantly reduced DNA damage in maturating bovine oocytes as well as increased cell number per blastocyst [43].

Copper is also essential for fetal development, being characterized by more than 10-fold higher levels in the fetal organism as compared to adults [44]. Particularly, it has been demonstrated that increased Ctr1 expression in embryonic tissues is required for adequate copper supply and growth and development [45]. Moreover, low serum Cu levels were observed in low birth weight newborns [46] thus supporting the role of adequate Cu supply in embryogenesis.

A significant increase in serum Mn levels was observed in pregnant women. The obtained data are in agreement with the results from NHANES 2011–2012 demonstrating elevation of blood Mn levels in pregnancy [22] thus supporting a hypothesis of essentiality of manganese during growth and development [47]. However, it is underlined that pregnancy-associated elevation of Mn levels is beneficial only within the reference physiological range, whereas excessive Mn exposure may cause adverse outcomes [48]. Particularly, both low and high levels of Mn in blood [49] and urine [50] were shown to be associated with low birth weight. It is also notable that hair Mn levels were directly related to fetal growth parameters including chest circumference [51].

A relationship between manganese status and adverse pregnancy outcome was also demonstrated. Particularly, lower maternal whole blood Mn levels were associated with intrauterine growth restriction in offspring, whereas umbilical cord blood Mn concentration was shown to be increased in these children [52]. The relationship between Mn exposure and certain developmental outcomes may be also mediated through direct relationship between cord blood Mn and prolactin levels [53]. These findings are generally in agreement with the observation of higher rate of DNA damage and apoptosis in oocytes during maturation under Mn-deficiency conditions [54]. Moreover, increased Mn intake with drinking water was shown to be protective for the fetus [55]. The association between manganese metabolism and pregnancy is supposed to be mediated by endocrine signals. Particularly, progesterone [56] and prolactin [57] was shown to increased Mn-SOD expression.

In contrast to the results of the present study, multiple studies have demonstrated the association between low iron intake and infertility [18], poor pregnancy or developmental outcome [58], as well as beneficial role of iron supplementation.

The observed increase in serum iron levels in women with miscarriage is in agreement with the earlier indications of higher risk of fetal growth restriction and preterm delivery in women with elevated hemoglobin, hematocrit, and ferritin levels [59]. High ferritin or hemoglobin level was also associated with gestational diabetes mellitus [60]. Spontaneous abortion, as well as preterm delivery are characteristic for stage 3 toxicity [61]. Excessive iron intake was shown to be associated with oxidative stress that may underlie adverse pregnancy outcome, being also associated with reduced copper status [62]. Generally, the observed relationship between increased iron levels and adverse pregnancy outcome raises the well-known question of personalized improvement of iron status based on laboratory markers of iron deficiency [19].

Although in multiple regression models only serum copper was significantly associated with reproductive status of women, inclusion of Mn and Fe into the model improved this association. This observation may occur due to a modifying effect of metal interaction [63–65] on copper handling and involvement into physiological pathways.

Hypothetically, the observed increase in serum Cu and Mn levels in pregnancy is indicative of increased requirements in metals for adequate development of the fetus. It is proposed that inability of the maternal organism to maintain high levels of these metals may at least partially contribute to reproductive health problems. Oppositely, the absence of significant decrease in serum iron in pregnancy may occur due iron supplementation, whereas excessive iron intake may at least partially contribute to miscarriage through oxidative stress or other mechanisms of iron toxicity.

5. Conclusion

The obtained data demonstrate increased serum copper and manganese levels in pregnancy, whereas women with reproductive health problems did not differ significantly from the controls. The lack of such increase in miscarriage and infertility without significant group difference with healthy controls may be indicative of impaired metal handling, rather than of true copper and manganese deficiency. Hypothetically, altered metal handling may result in decreased copper and manganese mobilization from depots in pregnancy for providing fetus and placenta with adequate copper and manganese supply for proper growth and development. Therefore, personalized assessment and improvement of trace element status may be considered as a potential tool for improvement of female reproductive system. However, detailed clinical studies as well as experimental investigations are required for assessment of the potential causes and mechanisms of the observed associations.

Declaration of Competing Interest

The authors declare no conflict of interest

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