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Multielemental analysis of 18 essential and toxic elements in amniotic fluid samples by ICP-MS: Full procedure validation and estimation of measurement uncertainty

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ABSTRACT

Amniotic fluid is the substantial factor in the development of an embryo and fetus due to the fact that water and solutes contained in it penetrate the fetal membranes in an hydrostatic and osmotic way as well as being swallowed by the fetus. Elemental composition of amniotic fluid influences the growth and health of the fetus, therefore, an analysis of amniotic fluid is important because the results would indicate abnormal levels of minerals or toxic elements. Inductively coupled plasma mass spectroscopy (ICP-MS) is often used for determination of trace and ultra-trace level elements in a wide range of matrices including biological samples because of its unique analytical capabilities. In the case of trace and ultra-trace level analysis detailed characteristics of analytical procedure as well as properties of the analytical result are particularly important. The purpose of this study was to develop a new analytical procedure for multielemental analysis of 18 elements (Al, As, Ba, Ca, Cd, Co, Cr, Cu, Mg, Mn, Ni, Pb, Sb, Se, Sr, U, V and Zn) in amniotic fluid samples using ICP-MS. Dynamic reaction cell (DRC) with two reaction gases, ammonia and oxygen, was involved in the experiment to eliminate spectral interferences. Detailed validation was conducted using 3 certified reference mterials (CRMs) and real amniotic fluid samples collected from patients. Repeatability for all analyzed analytes was found to range from 0.70% to 8.0% and for intermediate precision results varied from 1.3% to 15%. Trueness expressed as recovery ranged from 80% to 125%. Traceability was assured through the analyses of CRMs. Uncertainty of the results was also evaluated using single-laboratory validation approach. The obtained expanded uncertainty (U) results for CRMs, expressed as a percentage of the concentration of an analyte, were found to be between 8.3% for V and 45% for Cd. Standard uncertainty of the precision was found to have a greater influence on the combined standard uncertainty than on trueness factor.

1. Introduction

Amniotic fluid is essential for the proper development of the embryo and fetus. Water contained in the amniotic fluid comes originally from maternal plasma and penetrates the fetal membranes in a hydrostatic and osmotic way. As the placenta and fetal blood vessels grow, water and solutes of the maternal plasma penetrate through the placenta to the fetus and to the amniotic fluid [1]. Current knowledge of the concentration of elements in amniotic fluid and their role in fetal growth is limited. However, considering that the fetus swallows amniotic fluid, it is possible that it may be an essential source of dietary components. Mineral content in amniotic fluid could be a potentially valuable marker of prenatal mineral status and exposure to toxic metals. Essential and toxic elements concentration in amniotic fluid may be a predictor of complications and disorders in pregnancy. It is well known that low Mg levels in amniotic fluid are associated with complications of pregnancy such as preeclampsia and diabetes [2]. There are several factors that may influence on mineral concentrations

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in amniotic fluid such as week of gestation, mother's age, maternal smoking and the analytical methods used [3,4]. In previous studies it was found that Zn and Cu in human amniotic fluid increase and Mg decreases during pregnancy [4,5]. Moreover, it was observed that the concentration of metals such as Ni, Cd and Ba increased in amniotic fluid with maternal age. Positive correlation was shown between Ni, Sr, Cd, U and Mn in amniotic fluid and blood pressure and between Mg in amniotic fluid and umbilical artery pulsatility index (UAPI) [4]. Obtained results suggest that knowing of minerals concentration in amniotic fluid and their relations with other markers of maternal and fetus health status is important to improve clinical diagnosis of fetal development. Evaluation of minerals level in amniotic fluid will allow to assess mineral status as well as placental and fetal development during gestation. However, reference ranges for the concentration of elements in amniotic fluid are not established yet which unable to interpret the results extensively.

Recently in two large metanalyses invasive prenatal techniques including amniocentesis have been found to be safe causing no extra risk of miscarriage [6,7]. Thus, one can expect significant increase in applying of this method into routine obstetric practice not only as a diagnostic test especially for primary infections in pregnancy but also as an access for intrauterine treatment [8].

Based on a literature review, there are only a few available studies related to the mineral concentration of amniotic fluid [2–5,9,10]. Papers published in this field mostly concern determination of elements by different analytical techniques such as colorimetric, atomic absorption spectrometry (AAS), electrothermal atomic absorption spectrometry (ETAAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), ICP-MS and neutron activation analysis (NAA). Only two reports deal with the use of ICP-MS for multi-elemental determination in one analytical run [4,10]. Additionally, no fully validated analytical procedures have yet been established; this also applies to the demonstration of the traceability of measurement result and building the uncertainty budget. This objective can be achieved by using an advanced analytical technique that allows multi-elemental analysis (at low concentration levels) and application of reliable analytical procedure. ICP-MS is widely used for determining trace and ultra-trace elements in environmental and biological samples owing to its unique analytical capabilities. It offers several advantages that include elemental specificity, multi-isotope detection, and more importantly, high sensitivity along with a wide linear dynamic range and extremely low detection limits. However, the ICP-MS analysis is subject to spectral and non-spectral interferences, which are mostly associated with the quadruple ICP-MS instrument [11,12]. Spectral interferences occur mainly due to polyatomic and isobaric ions, which have the same as analyte *m/z* ratio. Most relevant sources of interfering ions are sample matrix, reagents and constituents of gaseous plasma (Ar). Non-spectral interferences named matrix-effects are caused by sample matrix, where organic as well as inorganic compounds are contained. It is well known that the amniotic fluid mainly contains water with electrolytes along with additions of carbohydrates, proteins, lipids, phospholipids and urea. As a result, it can be expected the high concentration of elements such as: H, C, O, N, Na, Cl, P which can, along with Ar, be a source of numerous spectral and non-spectral interferences that have an influence on the analytes quantification quality. Besides a sensitive analytical technique, the quality assurance of the obtained results is crucial in quantitative analysis. The introduction of three basic metrological rules (validation of measurement procedure, establishing traceability and estimation of uncertainty of measurement result) into chemical measurements will accomplish this task. In multielemental procedure, all of these parameters should be determined for each of the analyzed elements to ensure reliable analytical results [13,14].

Detailed characteristic of analytical procedure as well as properties of the analytical result is particularly important in the case of analysis of human body fluids, such as amniotic fluid or serum. The results of analysis may lead to actions and decisions involving a patient and prescribing a medical treatment or finding out the mechanism and state of a disease [15]. Two of the most important parameters that need to be determined in the procedure described herein are: detection limit and uncertainty of measurement result. The former parameters provide information about the detection capabilities of an analytical method and the latter help in deciding whether the measured value should be designated to one or another medical actions. The uncertainty of result may be the key factor in cases when an outcome is on the borderline of a decision limit. Unfortunately, diagnostic laboratories very often do not provide the uncertainty of the analytical result, usually due to having only a single replicate of analysis of the sample resulting in a shortening of measurement.

The aim of this study was to develop a new analytical procedure for multielemental analysis of 18 elements (Al, As, Ba, Ca, Cd, Co, Cr, Cu, Mg, Mn, Ni, Pb, Sb, Se, Sr, U, V and Zn) in amniotic fluid samples using the ICP-MS technique. Particular attention was focused on detailed validation of the proposed procedure and evaluation of two properties of the measurement result - traceability and uncertainty. The measurement uncertainty of the result for selected essential and toxic elements was estimated by a single-laboratory validation approach. In the final step, the application of the presented procedure was performed for amniotic fluid analyses.

2. Material and methods

The study protocol was approved by the Bioethics Commission of the Research Ethical Committee, Polish Mother's Memorial Hospital Research Institute in Poland (approval no. 50/2016). Informed consent was obtained from all patients. The study was conducted in accordance with Helsinki Declaration.

2.1. Instrumentation

An ICP-MS Elan DRC II (PerkinElmer SCIEX, Canada), equipped with a cyclonic spray chamber, a concentric glass nebulizer and a quartz torch with an injector were used in the experiment. A quadrupole mass analyzer with gold coated rods was employed. The incorporation of a DRC into this type of instrument can effectively eliminate polyatomic spectral interferences caused by its limited resolving power. Ammonia and oxygen were used as the DRC reaction gases. In order to determine the above mentioned elements, three separate analytical runs have to be performed: (i) with ammonia (Al, Ca, Cr, Mn, V) and (ii) oxygen (As, Sb, Se) as reaction gases in the DRC mode and (iii) in standard mode (Ba, Cd, Co, Cu, Mg, Ni, Pb, Sr, U, Zn). Operating conditions for ICP-MS instrument are given in Table 1.

For sample pretreatment (digestion procedure) a microwave assisted digestion system Ethos One (Milestone Srl, Italy) was used. The heating program proceeded in the following steps: (i) ramp time – 20 min to reach 180 °C, (ii) hold time – 40 min at 180 °C and (iii) cooling – 30 min. The maximal power during the digestion process was set at 1500 W.

2.2. Chemical and reagents

2.2.1. Standard solutions

Calibration standards of analyzed elements were prepared by appropriate dilution of a 1000 mg L^{-1} stock solution of Sb in 2% HNO_3 (Pure Single-Element Standard, Atomic Spectroscopy Standard, PerkinElmer Pure) and a 10 mg L^{-1} multielement stock solution in 5% HNO_3 (Multielement Calibration Standard 3, Atomic Spectroscopy Standard, PerkinElmer Pure). The calibration curves for the determined elements were constructed in the concentration ranges: 0.05–20 μg L^{-1} for As, Ba, Cd, Co, Cr, Cu, Mn, Ni, Pb, Sb, Se, Sr, U, V, 0.5–200 μg L^{-1} for Al, Zn, 5–1500 μg L^{-1} for Ca and Mg. Analyses were performed using internal standards in order to eliminate drift of the