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Development of an ICP-MS/MS-based methodology for the analysis of (ultra) trace elements in follicular fluid samples of patients undergoing IVF treatment

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INTRODUCTION & AIM

An increasing rate of infertility in the population worldwide has been documented in recent years. The exposure to environmental contaminants may contribute to this issue, including the exposition to heavy metals (HM) and metalloids acting as endocrine disruptors, and promoting the generation of oxidative stress. In this context, some trace elements are essential for our organism, while others have unknown biological functions. However, other elements as HM are considered non-essential and potentially toxic. Due to this, the effects of HM on the reproductive function have become a topic of special interest. Currently, information on the impact of specific (ultra) trace elements on female fertility remains limited.

Previous studies have relied on biological matrices such as blood and urine as biomarkers of exposure, but very few have looked at ovarian follicular fluid (FF), which can provide much more relevant information due to its properties and importance in the process of follicular development. In addition, protocols and analytical techniques to determine the compounds of interest at very low concentrations and in very small volumes are highly variable, as they are in constant development.

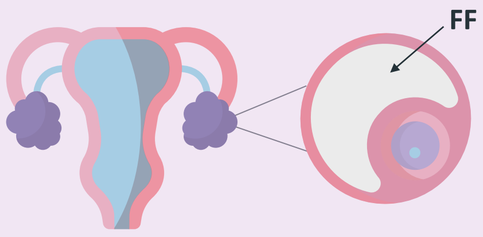

Figure 1. Schematic illustration showing location of FF.

Due to the current concern about environmental exposure to HM and metalloids and their impact on female fertility, this study aims to develop a new analytical procedure without sample digestion based on ICP-MS/MS for the characterization of 22 analytes in FF to determine the presence of HM in patients with fertility problems and therefore, be able to implement this technique in future studies.

METHOD

Four FF samples (*n*=4) were randomized selected and collected between March and April 2023, from female patients recruited from the assisted reproduction center IVF-Life Alicante, Spain, during an *in vitro* fertilization (IVF) treatment. After processing them, they were analyzed by ICP-MS/MS (Agilent Technologies, Santa Clara, CA, USA), in He and no-gas mode. Finally, data of interest were compiled in a database. Samples were obtained and treated following the steps shown in Figure 2.

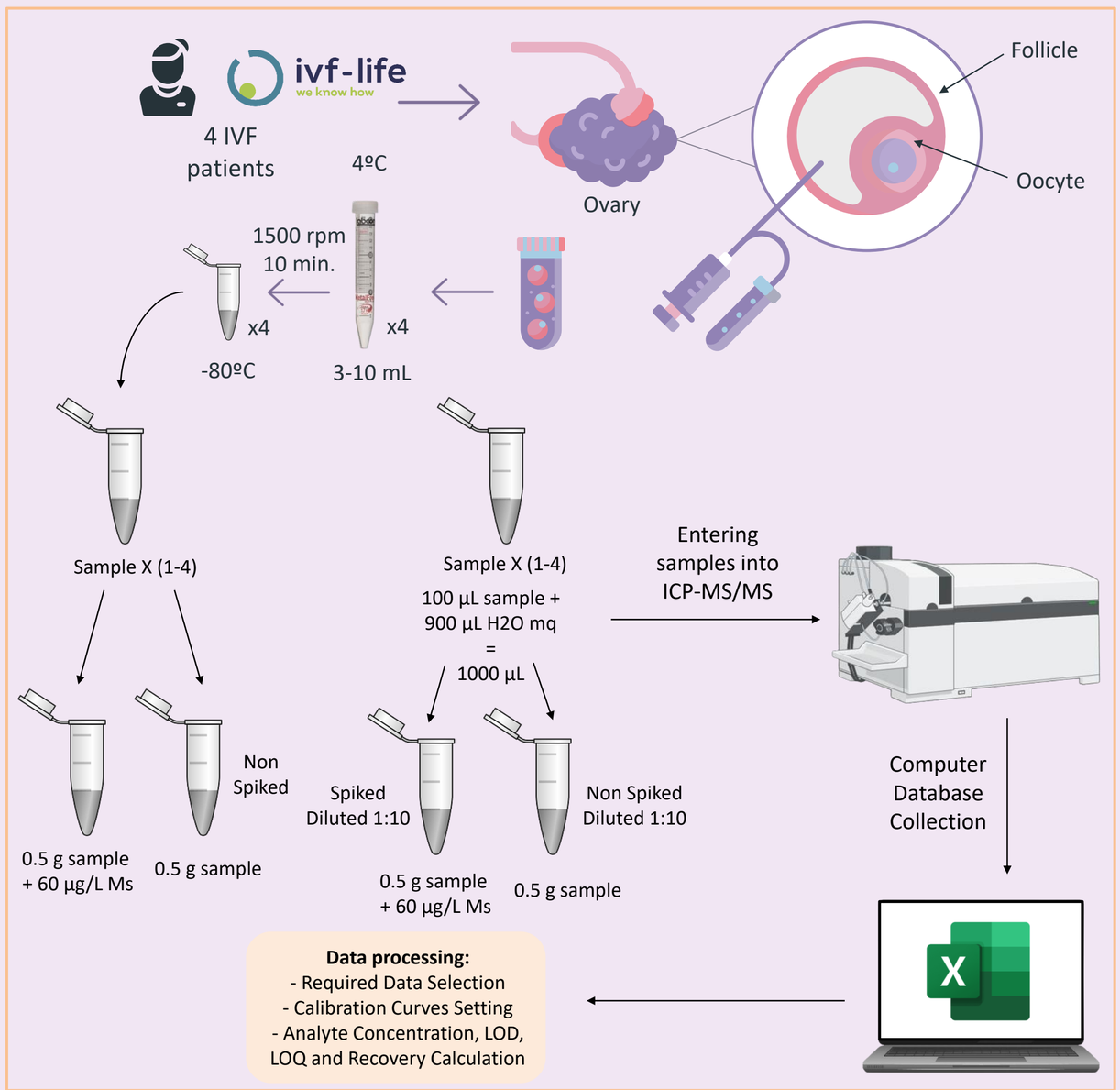

Figure 2. Graphical diagram of the main steps followed in sample collection and processing. Ms refers to the multielemental standard solution and Sample to the follicular fluid samples of each patient.

RESULTS & DISCUSSION

Analyte recovery ranged from 70% to 130%, with better results observed in no-gas mode (Figure 3) compared to He mode, in which they were not so homogeneous and optimal.

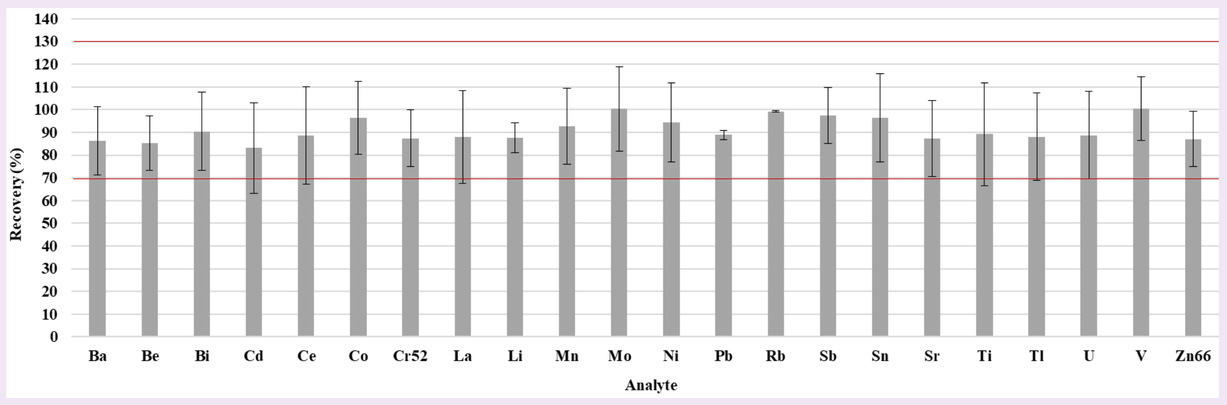

Figure 3. Recovery values for four spiked follicular fluid samples (at 60 µg/L), calculated from 5 replicate measurements. No collision gas was added. The mean (bars) and the standard error of the mean (error bars) are shown.

Limits of detection (LOD) and quantification (LOQ) in He and no-gas modes (µg/L), were obtained on the same day, for each isotope. Both LOD and LOQ were low in both mode, but it is worth noting that the values have been mostly lower in no-gas mode than in He mode.

Only determinations for analytes in no-gas mode were valid due to recovery data. Finally, among the 22 elements analyzed, only 6 were not detected. Minor concentrations were observed for ^{137}Ba, ^{209}Bi, ^{59}Co, ^{55}Mn, ^{95}Mo, ^{60}Ni, ^{121}Sb, ^{118}Sn, ^{205}Tl and ^{51}V, while intermediate concentrations were found for ^{7}Li and ^{88}Sr. Major concentrations were identified for ^{52}Cr, ^{85}Rb, ^{47}Ti and ^{66}Zn (Table 1).

Table 1. Analyte concentrations, measured in no-gas mode, divided into 4 ranges.

Concentration	Analyte
Not Detected	^{9}Be, ^{140}Ce, ^{111}Cd, ^{139}La, ^{208}Pb, ^{238}U
Up to 8,47 µg/L	^{137}Ba, ^{209}Bi, ^{59}Co, ^{55}Mn, ^{95}Mo, ^{60}Ni, ^{121}Sb, ^{118}Sn, ^{205}Tl, and ^{51}V
Up to 41,49 µg/L	^{7}Li and ^{88}Sr
Up to 393,50 µg/L	^{52}Cr, ^{85}Rb, ^{47}Ti, ^{66}Zn

CONCLUSION

A new procedure was developed in this study, with several advantages. One of them is the good results in terms of the recovery for a wide variety of elements using ICP-MS/MS in the poorly studied biological matrix that is FF.

Another advantage is the low amount of sample required to perform the analysis and the development of a green method where the sample is not digested and highly diluted, which allowed us to avoid the excessive dilution of the concentration of analytes. Moreover, the developed method provides a novel approach to diagnose and predict health risks in women with reproductive pathologies and to assess their reproductive health.

FUTURE WORK

As future work, our target is to apply this method to a greater number of FF samples to analyze the concentrations of various elements. This method offers valuable insights into patients' reproductive health status and the potential implications in their reproductive outcomes.
Further research in this field is essential to deepen our understanding of these elements and their impact on women's health.