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The Influence of Preanalytical Factors on the Algorithm of Multiplex Spectroscopy of Placental Samples

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ABSTRACT

Aim. To evaluate the effect of preanalytical processing of placental samples on the results of Raman spectroscopy.

Materials and methods. Thirty placental samples were prospectively studied. The samples were examined using the InSpectr M spectrometer at three stages of preanalytical processing of the material: native tissue, after fixation in formalin, after deparaffinization of the section. Statistical analysis included descriptive statistics, the Shapiro – Wilk test, the Friedman test with the post-hoc analysis, and the Spearman's rank correlation.

Results. The analysis of the samples revealed 33 Raman peaks (415–2,915 cm^{-1}), most of which were distributed abnormally (Shapiro – Wilk test, $p < 0.05$). The Friedman test with the Durbin – Conover post-hoc analysis revealed a group of stable analytes: 19 analytes retained intensity after fixation, 6 – after deparaffinization, and 10 – at all processing stages. The Spearman's rank correlation revealed selective relationships between processing stages for individual analytes (890; 1,117; 1,204; 753, 830, and 2,225 cm^{-1}).

Conclusion. The study revealed a significant effect of preanalytical sample processing on the spectral characteristics of placental tissue, the prospects for the clinical use of Raman spectroscopy, and the need to develop standardized protocols.

Keywords: Raman spectroscopy, placenta, limiting factors, preanalytical material processing, spectral profile

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Влияние преаналитических факторов на алгоритм мультиплексного спектроскопического анализа образцов плаценты

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РЕЗЮМЕ

Цель. Оценка влияния преаналитической подготовки плаценты на результаты рамановской спектроскопии.

Материалы и методы. Проспективно исследованы 30 образцов плаценты. Образцы исследовались при помощи спектрометра «ИнСпектр М» (ООО «РамМикс», Россия) на трех этапах преаналитической обработки материала: нативная ткань, после фиксации в формалине, после депарафинирования среза. Статистический анализ включал описательную статистику, тест Шапиро – Уилка, тест Фридмана с пост-хок тестом и корреляцию Спирмена.

Результаты. Исследование образцов выявило 33 рамановских пика (415–2915 $см^{-1}$), большинство из которых распределялись ненормально (критерий Шапиро – Уилка, $p < 0,05$). Тест Фридмана с пост-хок тестом Дурбина – Коновера выявил группу стабильных аналитов: 19 аналитов сохранили интенсивность после фиксации, 6 – после депарафинирования, а 10 – на всех этапах обработки. Тест Спирмена выявил избирательные взаимосвязи между этапами обработки для отдельных аналитов (890, 1117, 1204, 753, 830 и 2225 $см^{-1}$).

Заключение. Исследование выявило значительное влияние преаналитической подготовки образцов на спектральные характеристики плацентарной ткани, перспективность клинического использования рамановской спектроскопии и необходимость разработки стандартизированных протоколов.

Ключевые слова: рамановская спектроскопия, плацента, ограничивающие факторы, преаналитическая обработка материала, спектральный профиль

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

Источники финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Исследование одобрено комитетом по этике при ММКЦ «Коммунарка» ДЗМ (протокол № 6 от 08.08.2023).

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INTRODUCTION

The placenta is a unique, temporary, multifunctional organ that plays a critical role in ensuring normal fetal development. In recent years, researchers have increasingly focused on the potential of using data from physicochemical metabolic processes occurring in the placenta, which constitute the essence of its metabolome, as informative biomarkers and predictors of pathological conditions during pregnancy and its consequences [1, 2]. However, traditional histopathological examination methods have several limitations, including the subjectivity of visual assessment, the lack of data on metabolic pathologies, and significant time requirements.

Raman spectroscopy (RS) represents a promising alternative to classical morphological methods, providing detailed information on the conformation of macro- and micromolecules, making it a suitable tool for identifying analytes of pathological conditions in real time. Despite the widespread use of RS in oncology and other areas of medicine, its use in placental medicine [3–6] is limited to only a few pathological conditions [7–9]. Of particular interest is the potential use of RS for diagnosing inflammatory processes in placental tissue.

A key issue limiting the widespread adoption of this method in clinical practice, despite the obtained approval of the device for clinical use, is the presence of factors that can influence the outcome. These include the purity of the sample material, the presence of non-biological contaminants in the samples, background fluorescence, Gaussian noise, and preanalytical processing, which creates significant difficulties in interpreting results, especially when working with archival histological samples [10-12]. A particular methodological challenge is the need for prospective collection and analysis of a large number of samples followed by histological verification, which is associated with significant time and material costs. The influence of these limiting factors makes it impossible to extrapolate the results of a retrospective study to the data obtained in real time.

The aim of this study was to evaluate the effect of the stages of preanalytical processing of placental tissue on the RS results.

MATERIALS AND METHODS

The protocol for the study was reviewed and approved by the Ethics Committee at Moscow Multidisciplinary Clinical Center "Kommunarka" (Minutes No. 6 dated August 8, 2023).

Thirty placental tissue samples were prospectively randomized for the study. The mothers ranged in age from 19 to 43 years (median (*Me*) – 30.5 years); gestational age was 36 to 41 weeks (*Me* 39 weeks); birth order was 1 to 5 (*Me* 2); the fetal health status according to the Apgar scale at the first and fifth minutes of life, respectively, ranged from 1/3 to 9/10 (*Me* 8/9), the newborns' weight was 2,580 to 4,400 g (*Me* 3,510 g), and the placenta weight was 269 to 650 g (*Me* 437.5 g). Eighteen mothers delivered spontaneously through the birth canal, three had medically induced vaginal deliveries, and nine had cesarean deliveries.

The spectroscopic examination of each placental tissue sample was performed at three preanalytical stages: without fixation in media (native material) (stage 1); after fixation in 10% neutral buffered formalin for 24 hours (stage 2); and after deparaffinization of a 20-μm-thick section (standard histological processing) (stage 3). We used the InSpektr M spectrometer, version M-532 (RU No. RZN 2015/2419 dated June 18, 2021, manufacturer: RamMix LLC, Russia), consisting of an Olympus CX41 optical microscope and a spectrometer unit with the excitation wavelength of 532 nm. The laser spot diameter at the focal point was 10 μm, and the laser power was 10 mW. Instrument control, spectral recording, and data acquisition were performed using the specialized InSpektr software (RamMix LLC, Russia).

Data processing was performed using the Jamovi software (version 2.6.26, The jamovi project (2024)) – a freely distributed, open-source program for statistical analysis. Statistical analysis methods included descriptive statistics, testing for normality using the Shapiro – Wilk test, the nonparametric Friedman test (presumably rejecting the hypothesis of normal data distribution for most analytes) for comparing related samples followed by the post-hoc analysis (Durbin – Conover pairwise comparisons), and Spearman's rank correlation to assess the monotonic relationship between pairs of processing steps for each analyte. Data visualization was also performed using the Jamovi software.

RESULTS

The spectroscopic studies revealed that the spectra of placental samples were characterized by the presence of Raman peaks in the spectral range of 415–2,915 cm^{-1} and contained fluorescence intensity

values for 33 vibrational modes (components/analytes) (Table 1).

Table 1

Grouping of Placental Raman Peaks by Functional Classes with Shifts Indicated (cm^{-1})

Raman shift (cm^{-1})	Components/analytes*
1. Lipids and lipid components	
415; 533; 628; 1,300; 1,304; 1,445; 1,463; 2,915	Phosphatidylinositol, cholesterol ester, glycerol, (CH_2)-lipids, fatty acids, CH_2 deformation (lipids), phospholipids, collagen, CH_3, CH stretching of lipids
2. Proteins and amino acids	
641; 753; 830; 890; 933; 1,002; 1,174; 1,204; 1,365; 1,445; 1,554; 1,627; 2,554	Tyrosine, tryptophan, proline, hydroxyproline, tumor structural proteins, collagen, phenylalanine, amide III, glycine, amide II, amide I (β-form), methionine (S–H)
3. Nucleic acids (DNA/RNA)	
720; 810; 830; 1,230; 1,287; 1,304; 1,361; 1,609	DNA, phosphodiester (Z-marker), PO_2^- (nucleic acids), antisymmetric phosphate stretch, cytosine, adenine, guanine (N7, B/Z-marker)
4. Carbohydrates and glycans	
1,048; 1,117; 1,370	Glycogen, glucose, saccharides
5. Pigments and specialized metabolites	
957; 1,157; 1,528	Carotenoid, cholesterol, β-carotene (C=C)
6. Mineral components	
957	Hydroxyapatite
7. Combined/Overlapping Modes	
1,445–1,463; 2,225	CH_2/CH_3 deformations, C≡N

* the complete list of 33 components/analytes is provided in [13].

Analysis of the fluorescence intensity distribution for 33 analytes revealed that some shifts did not follow a normal distribution (Shapiro – Wilk test, $p < 0.05$). The greatest number of deviations from a normal distribution was observed for the native material (30 Raman shifts). After fixation in formalin, the number of anomalously distributed shifts decreased to 13. A limited number of deviations (19 Raman shifts) were also observed for the deparaffinized samples.

Due to the rejection of the hypothesis on a normal data distribution for a larger number of analytes, nonparametric methods were used for further statistical analysis.

Given the exploratory nature of the analysis of 33 analytes to identify potentially stable markers, rather than to confirm strict hypotheses, and the high risk of false-negative results when adjusting for 99 comparisons (33 analytes, 3 stages of preanalytical material processing), the Bonferroni correction was not applied. Unadjusted *p*-values are provided below, with an explicit indication that further validation is needed.

The analysis of differences in fluorescence intensity between the stages (Friedman test with the Durbin – Conover post-hoc analysis) showed that the group of analytes (Raman shifts at 753; 830; 890; 957; 1,002; 1,117; 1,174; 1,204; 1.230; 1,300; 1,304; 1,361; 1,365; 1,370; 1,445; 1,463; 1,528; 1,609; 1,627 cm^{-1}) did not show statistically significant differences in fluorescence intensity between stages 1 and 2. Analytes corresponding to Raman shifts of 1,048; 1,361; 1,370; 1,528; 2,225; 2,554 cm^{-1} did not have differences in fluorescence intensity between stages 2 and 3. A group of analytes (Raman shifts of 933; 1,157; 1,230; 1,304; 1,365; 1,370; 1,528; 1,554; 1,609; 1,627 cm^{-1}) maintained the stability of fluorescence intensity between stages 1 and 3. The most stable were analytes with Raman shifts of 1,230; 1,361; 1,365; 1,370; 1,528; 1,609; 1,627 cm^{-1}, which did not exhibit significant changes between at least two pairs of stages ($p > 0.05$), among which 2 analytes (1,370 and 1,528 cm^{-1}) did not have significant changes at all three stages (Tables 2, 3).

Table 2

Repeated Measures ANOVA for the 1,370 cm^{-1} Analyte

Pairwise comparisons (Durbin – Conover post-hoc analysis)	Statistics	*p*
1,370 (stage 1) – 1,370 (stage 2)	1.913	0.061
1,370 (stage 1) – 1,370 (stage 3)	0.137	0.892
1,370 (stage 2) – 1,370 (stage 3)	1.776	0.081

Note. $\chi^2 = 4.36$; df = 2; $p = 0.113$ (Friedman test).

Table 3

Repeated Measures ANOVA for the 1,528 cm^{-1} Analyte

Pairwise comparisons (Durbin – Conover post-hoc analysis)	Statistics	*p*
1,528 (stage 1) – 1,528 (stage 2)	0.136	0.892
1,528 (stage 1) – 1,528 (stage 3)	1.701	0.095
1,528 (stage 2) – 1,528 (stage 3)	1.565	0.123

Note. $\chi^2 = 3.48$; df = 2; $p = 0.176$ (Friedman test).

The Spearman's correlation demonstrated that correlation between the stages was observed only for a limited number of analytes. The 890- (Table 4) and 1,117 cm^{-1} analytes demonstrated significant correlation between stages 1 and 2, the 1,204 cm^{-1} analyte – between stages 2 and 3, and the 753, 830, 1,204 (Table 5), and 2,225 cm^{-1} analytes – between stages 1 and 3.

Table 4

Spearman's Rank Correlation Matrix for the 890 cm^{-1} Analyte

Parameter	890 (stage 1)	890 (stage 2)	890 (stage 3)
890 (stage 1) Spearman's ρ (rho)	–	–	–
df (degrees of freedom)	–	–	–

End of table 4

Parameter	890 (stage 1)	890 (stage 2)	890 (stage 3)
p	–	–	–
890 (stage 2) Spearman's ρ (rho)	0.570**	–	–
df (degrees of freedom)	26	–	–
p	0.002	–	–
890 (stage 3) Spearman's ρ (rho)	0.007	0.072	–
df (degrees of freedom)	26	26	–
p	0.972	0.717	–

Table 5

Spearman's Rank Correlation Matrix for the 1,204 cm^{-1} Analyte

Parameter	1,204 (stage 1)	1,204 (stage 2)	1,204 (stage 3)
1,204 (stage 1) Spearman's ρ (rho)	–	–	–
df (degrees of freedom)	–	–	–
p	–	–	–
1,204 (stage 2) Spearman's ρ (rho)	–0.051	–	–
df (degrees of freedom)	26	–	–
p	0.797	–	–
1,204 (stage 3) Spearman's ρ (rho)	–0.386*	0.430*	–
df (degrees of freedom)	26	26	–
p	0.042	0.023	–

DISCUSSION

RS of 30 placental samples (native material, samples fixed in 10% neutral buffered formalin for 24 hours, and deparaffinized sections from paraffin blocks) revealed significant changes in spectral characteristics reflecting changes in the biochemical composition of the placental tissue. The data obtained demonstrated that each sample preparation method had a significant effect on the placental spectral profile.

The greatest variability in spectral characteristics was observed in native samples, where 30 of 33 analytes did not follow a normal distribution. This could be due to either the natural heterogeneity of placental tissue or the initial degradation of biomolecules (lipids, proteins) after cessation of blood supply [13]. Moreover, the high coefficient of variation in labile analytes, including lipid and protein components, confirmed their sensitivity to post-extraction changes.

Fixation in formalin resulted in significant stabilization of the spectral profile, manifested by a decrease in the number of anomalously distributed shifts to 13. This is apparently due to formalin ability to form cross-links between proteins, which reduces macromolecular degradation. At the same time, a significant decrease in the correlation between native and fixed samples indicated profound biochemical changes caused by protein denaturation and modification of lipid structures [14].

The deparaffinization process caused a repeated increase in the number of deviations from the normal distribution (19 anomalously distributed shifts) and, as a result, a discrepancy between these spectral profiles and those of the fixed samples. The correlation between fixed and deparaffinized samples was maintained for only one analyte (1,204 cm^{-1}) and indicated both a change in formalin-induced shifts and a pronounced effect of paraffin on the lipid and alcohol content and on hydrophobic components [15].

The Friedman test with post-hoc analysis allowed us to divide all analytes into three groups: labile, partially stable (showing stability of fluorescence intensity between one or two pairs of stages), and absolutely stable (analytes at 1.370 and 1,528 cm^{-1}), whose fluorescence intensity was stable across all three stages. Based on this, these vibrational modes can be further considered as potential reference markers for the analysis of materials with different preanalytical histories.

A limitation of the study was a relatively small sample size (n = 30) and the exploratory nature of the multiple comparison analysis without strict adjustments. However, the identified patterns provide a basis for targeted research with pre-formulated hypotheses.

CONCLUSION

This study demonstrates that preanalytical processing of placental tissue significantly affects its biochemical composition and spectral characteristics. Native tissue differs radically from processed tissue; its spectra cannot be directly compared with fixed/deparaffinized samples without adjustments. Machine learning methods are necessary to compare spectral data from native and processed tissue due to the nonlinear nature of changes. Thus, Raman spectroscopy can be used to monitor changes in placental tissue, but it requires consideration of the influence of preanalytical factors on data interpretation and the development of standardized protocols, with the potential for retrospective studies and implementation of the method in clinical practice.

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Author Contribution

Rodionov V.E. – conception and design, analysis and interpretation of the data, substantiation of the manuscript or critical revision of the manuscript for important intellectual content. Avdalyan A.M – conception and design. Nichiporov A.I., Kukushkin V.I., Chernov I.A. – analysis and interpretation of the data. Avraamova S.T. – substantiation of the manuscript or critical revision of the manuscript for important intellectual content. Kirillov Yu.A. – conception and design, substantiation of the manuscript or critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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