CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

DOCTORAL SCHOOL

DOMAIN: MEDICINE

INTEGRATED AND PERSONALIZED RESEARCH ON MULTI-OMIC APPROACHES IN OBSTETRICS AND GYNECOLOGY

HABILITATION THESIS ABSTRACT

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Obstetrics and gynaecology are at a crossroads: since publication of the Human Genome Project, the various "-omic" layers—genome, epigenome, transcriptome, proteome, metabolome and microbiome—can be interrogated simultaneously, and their read-outs correlated instantly with clinical data through artificial intelligence. In the tertiary hospital where I practise every day, I witness the direct impact of this revolution: we can now anticipate respiratory distress in a pre-term infant, titrate the dose of misoprostol according to a mother's CYP genotype, and stratify the risk of ovarian-cancer relapse with a simple blood test. Building on that reality, this thesis distils two decades of applied research and shows how I have woven together disparate strands—clinical practice, molecular biology and algorithms—into a seamless continuum of precision medicine.

1. The questions that shaped the project

I started from four recurring challenges in daily practice:

- Pre-term birth due to pre-labour rupture of membranes (PPROM). How many hours of latency does a fetus under 34 weeks need for the outcome to improve?
- Maternal renal impairment. Can we find a simple biomarker that signals when a pregnant woman's renal function becomes dangerous for the fetus?
- Maternal obesity and metabolic risk. Can individual polymorphisms dictate personalised nutritional targets before conception?
- Gynaecological oncology. How can multi-omic signatures be translated into tools that help the tumour board decide on fertility-sparing management?

2. Methodology—where the laboratory meets the delivery ward

Answers were pursued within a consortium of four university hospitals and a laboratory core that I built stepwise. More than 6,000 patients were enrolled, their samples moving through a standardised pipeline: targeted NGS, DNA-methylation profiling, LC-MS metabolomics and 16S rRNA sequencing for microbiome analysis. A bespoke bioinformatic workflow in Snakemake and R/Python integrated the data layers into feature sets for deep neural networks, using internal k-fold validation and external testing in the CALG cohort (France). Wet-lab findings were linked to a digitised clinical registry, allowing real-time extraction of demographic, ultrasound and therapeutic variables for the algorithms.

3. Major findings

A retrospective analysis of 562 pregnancies with PPROM showed that every additional 24–48 hours of latency, under a strict protocol (antibiotics, corticosteroids, ultrasound surveillance), reduced neonatal respiratory distress by ~25 % and lowered mortality in extreme pre-terms from 41 % to 14 %. Gestational-age stratification yielded nuanced recommendations: below 28 weeks every extra day is worth fighting for; between 28 and 34 weeks latency is crucial; beyond 35 weeks planned delivery is reasonable. These data have already been embedded in the hospital protocol, cutting unnecessary admissions to neonatal intensive care.

In a mixed cohort of acute kidney injury and chronic kidney disease, a maternal creatinine > 1.2 mg/dL at admission doubled the risk of severe prematurity and increased the need for postpartum dialysis five-fold. Creatinine, urea and proteinuria were merged into the MOTHER-KID score—the first obstetric renal tool calibrated for a south-eastern European population; the hospital now uses it to decide whether intensified monitoring is required.

Profiling of LEP-2548 G>A, LEPR Q223R and HTR2A-1438 G>A confirmed that the LEP AG genotype raises the likelihood of a pre-pregnancy BMI > 30 kg/m². Although statistics varied, the finding supports a pre-conception nutrigenomic consult with weight targets tailored to genetic background.

Integrating transcriptomic, proteomic and epigenetic data yielded a BRCA/HRD + microRNA algorithm that stratifies ovarian cancer for PARP-inhibitor therapy (94 % sensitivity, 82 % specificity). The panel includes miR-21, the miR-200 family and lncRNA H19, and has already been adopted by the UMFCD tumour board. In parallel, a liquid-biopsy prototype based on circulating tumour DNA showed potential for monitoring residual disease.

4. Originality and impact

The thesis is original at the nexus of three worlds: a real-time clinical database, "-omic" layers, and AI algorithms. MOTHER-KID is the first renal–obstetric instrument validated locally; the multi-omic ovarian algorithm adds decisive value to therapeutic decisions; and the PPROM-Counsel mobile app (MVP in place) offers neonatologists individualised prognoses. Altogether, the work has generated 18 first-author and 34 co-author ISI papers (cumulative IF > 90, h-index 12), three grants as principal investigator and participation in five others as partner.

5. Academic relevance and capacity-building

Beyond metrics, the project has been a training ground for the next generation: 42 undergraduate theses, three doctoral candidates under supervision, the elective course "Reproductive Genetics & Omics Medicine", and the creation of the ObGyn Multiomics Lab—the first local university space where a resident can, in a single day, extract placental RNA and run a machine-learning model on ultrasound images from her own patient.

6. Future directions

Over the next five years I will transform the current laboratory into an interdisciplinary IBP-Lab hub, implement long-read sequencing for rare fetal anomalies and launch a phase-III trial with NAD^+-enhancing probiotics to prevent membrane rupture. An ambitious goal is to build a live AI platform that blends clinical, omic and imaging data, providing bedside personalised recommendations in real time.

7. Conclusion

The thesis demonstrates that precision materno-fetal medicine has moved beyond the exploratory stage: multiple validated biomarkers and algorithms can already reduce morbidity and guide personalised therapy. Their integration within a university hospital is feasible when research, practice and education do not remain sealed compartments. The experience presented here confirms my ability to generate original knowledge, to lead interdisciplinary teams and to translate results swiftly into guidelines and delivery suites—fully meeting UMF "Carol Davila" criteria for the habilitation certificate.