# **INVITED COMMENTARY**



# Commentary on Infertility and Restorative Reproductive Medicine

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#### **ABSTRACT**

In 1972, a seminal article was published demonstrating that women, adequately trained, could detect the approach of ovulation in the fertile window of their menstrual cycle. It was demonstrated that the symptoms perceived by women at the vulva correlate closely with changes in steroid hormone levels associated with folliculogenesis and the luteal phase. The fertility charting performed by women trained to recognize vulvar symptoms associated with hormonal changes serves as an instrument for detecting potential pathologies and monitoring the effects of treatment These findings established the biological foundations of a tool of fertility awareness tracking that has facilitated the development of restorative reproductive medicine (RRM): an approach that can be applied to identify and treat the underlying causes of infertility/subfertility.

Several core characteristics—or foundational pillars—of the RRM approach to fertility can be identified. These include: a commitment to respecting healthy physiological processes, comprehensive health care for both the couple and the potential embryo, and the provision of education and continuous support throughout the therapeutic process.

This commentary aims to elucidate the interplay of these foundational pillars by drawing upon evidence from peer-reviewed biomedical literature. Finally, the challenges faced by RRM in strengthening its scientific foundations, engaging with the broader scientific community, and promoting the dissemination of this approach are described.

Keywords: infertility, natural family planning

# **Foundations**

In 1972, Drs. Evelyn and John Billings and colleagues published a seminal article demonstrating that 22 women, adequately trained, could detect the approach of ovulation in

the fertile window of their menstrual cycle. The fertile window is defined as the days within the menstrual cycle when sperm can survive in the female reproductive tract to make fertilization of the ovum possible, and therefore, the couple is potentially fertile. It was demonstrated that the symptoms perceived by women at the vulva correlate closely with changes in steroid hormone levels associated with folliculogenesis and the luteal phase. This directly accessible information provides a clinical window into ovarian function, which has significant implications for birth regulation and the study of patients with reproductive disorders.

Subsequently, Dr. Thomas Hilgers and colleagues introduced a standardized system for women to record these symptoms, which reflected the manifestations of various structural and endocrine pathologies affecting female internal anatomy and the gonadal endocrine axis.<sup>2</sup> This developed further the concept of fertility biomarkers, which provide information about normal ovarian cycle conditions or suggest the presence of pathological conditions.<sup>3</sup> The fertility charting associated with the symptoms experienced by women thus becomes a window through which physiological normalcy can be assessed, or underlying pathologies can be suspected. Many other clinicians and researchers have also expanded our knowledge of the medical applications of fertility biomarkers.<sup>4</sup>

These findings established the biological foundations of a tool of fertility awareness tracking that has facilitated the development of restorative reproductive medicine: an approach that can be applied to identify and treat the underlying causes of infertility/subfertility. The fertility charting performed by women trained to recognize vulvar symptoms associated with hormonal changes serves as an instrument for detecting potential pathologies and monitoring the effects of treatments.<sup>5</sup>

However, the emergence of in vitro fertilization (IVF) in 1978, with the first successful birth of a baby girl, introduced a solution that operates independently of the causes of infertility. As a result, the RRM approach, which focuses on uncovering the underlying biological causes of infertility, has lost priority in clinical practice.

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# **Pillars**

We recognize several essential characteristics or pillars of the restorative reproductive medicine (RRM) approach for fertility, which can be summarized as follows: respect for healthy physiology, health care for the couple and the potential embryo, and education and support throughout the therapeutic process.

RRM places particular emphasis on the preventive care and restoration of reproductive physiology when it is impaired. It prioritizes identifying the underlying causes of infertility or recurrent pregnancy loss to provide appropriate treatment. This aligns with the classical medical tradition of striving to understand the dysfunction of physiological processes and assisting in their recovery. The therapeutic process seeks to protect maternal and perinatal health by minimizing morbidities associated with treatments, both for the mother and the embryo. A concrete example of this concern is the low incidence of multiple pregnancies with RRM, described later in this commentary.

The RRM approach provides an essential alternative for couples who wish to avoid commercialization often associated with assisted reproductive techniques. In many fertility centers, the commercial transaction of germ cells (sperm and oocytes) is routine practice. RRM avoids exposing the embryo to complete vulnerability, including quality control assessments, selection processes, and cryopreservation for storage. This perspective promotes a humanization of medical procedures for women with infertility issues.

The third pillar of a restorative approach is education and support. Restorative management focuses on educating couples affected by infertility so that they can actively participate in restoring their altered biological functions. This includes lifestyle modifications and understanding the ovarian cycle. It also includes continuous support provided during the therapeutic process, which addresses the emotional impact on both partners. The frustration and stress stemming from infertility and its effects on their emotional well-being require healthcare professionals to remain attentive and willing to discuss challenges and provide guidance for appropriate management.

The fertility charting system, which reflects hormonal fluctuations and reproductive function, serves as an essential tool for monitoring therapeutic progress. It enables both couples and physicians to objectively assess reproductive health and progress in treatment.

For the female, RRM involves treating underlying metabolic, hormonal, and other health conditions, and addressing health and lifestyle habits that may impact reproductive function. It includes recommending vitamins and dietary supplements that are demonstrated to support healthy physiology, managing stress, supporting or stimulating healthy ovulation, and providing hormonal support during the luteal phase. When indicated, it may also involve corrective or reparative surgeries such as myomectomy, polypectomy, endometriosis surgery, or tubal repair surgery.

For the male, RRM likewise involves addressing health and lifestyle habits that may impact reproductive function, and treating underlying metabolic, hormonal, and other conditions. It may include recommending vitamins and dietary supplements that are demonstrated to support healthy physiology, managing stress if present, and supporting or stimulating healthy spermatogenesis. When indicated, it may also involve corrective surgery, such as varicocelectomy.

Finally, RRM includes therapeutic strategies to sustain pregnancies, with a particular focus on early pregnancy, including hormonal support beginning prior to conception. Maintaining healthy metabolic status during pregnancy is also a key component.<sup>6</sup>

# **Outcomes**

Over the past 20 years, multiple centers in different countries have used RRM in treating infertile or subfertile couples. It is particularly insightful to examine the first published study reporting the outcomes of this approach in Irish patients. Within the context of clinical practice by family physicians trained specifically in NaProTechnology (a specific system of restorative reproductive medicine based on Creighton Model FertilityCare charting), Dr. Boyle and his team analyzed live birth outcomes in 1,072 patients.<sup>7</sup>

In a cohort characterized by substantial risk factors, including an average age of 35.8 years, an average infertility duration of 5.6 years, 76% of patients with primary infertility, and 33% having undergone prior attempts using assisted reproductive technologies, RRM (specifically NaProTechnology) was applied. Pathological findings underlying infertility included decreased estrogenic cervical mucus production, intermenstrual bleeding, luteal phase defects, and suboptimal estrogen and progesterone levels. None of these diagnoses had been considered in patients previously assessed and treated under the traditional infertility approach within reproductive medicine.

The interventions implemented included fertility charting, ovarian stimulation, medications to enhance the fertile window (by increasing cervical mucus production), and bioidentical hormonal support of the cycle. Treatment responses were evaluated based on reproductive biomarkers from fertility charting and laboratory evaluation, with dosage adjustments made as required. Notably, the therapeutic approach in this study was predominantly medical, not surgical. Among the 1,072 patients treated, 364 achieved pregnancies. Life table analysis indicated a crude conception rate of 33.0% at 24 months (adjusted proportion of 64.8%) and a crude live birth rate of 25.5% at 24 months (adjusted to 52.8%). Additionally, there were 13 twin pregnancies (4.6%). The life table is a statistical tool that allows for the cumulative probability analysis of pregnancy over time. The difference between crude and adjusted proportions accounts for patient dropout rates; while the crude proportion tends to underestimate treatment efficacy, the adjusted proportion assumes that those who discontinued treatment had the same prognosis as those who continued. The authors note that the actual effectiveness likely falls between these two proportions.

#### Access

Several noteworthy aspects of the Irish study illustrate the practical application of a restorative approach. First, generalist physicians who are adequately trained in restorative reproductive medicine can provide this treatment with competitive outcomes. Additional studies with other family physicians and obstetrician-gynecologists in the United States, Canada, United Kingdom, and Poland, have reported similar findings. The ability of trained generalist physicians or clinicians to offer infertility evaluation and treatment is a significant advantage for patient access to evaluation and treatment. Infertility duration is a critical prognostic factor, and early access to medical care can improve treatment outcomes.

# **Diagnosis**

Another key feature of restorative reproductive medicine is the emphasis on identifying underlying causes, which often reveals multiple contributing factors to infertility. This requires a multifaceted management approach by the physician. In the multinational study, an average of 4.7 different diagnoses per couple was reported. In all outcome studies reported to date, this has resulted in a dramatic reduction in the diagnosis of "unexplained infertility". Providing a definitive diagnosis to patients is always beneficial.

### **Timeline**

Another distinctive aspect of restorative reproductive medicine is the timeline for observing results. The diagnostic process necessitates patient training in symptom perception and charting, which typically takes two months. This is followed by reproductive hormone profiling and other examinations, such as follicular ultrasound, as indicated by the fertility chart and clinical history. Subsequently, medications and lifestyle changes are used to correct identified deficiencies and optimize the menstrual cycle, a process that may require additional cycles for full normalization. Given these factors, treatment analysis is typically conducted at 12 or 24 months, presenting a significant challenge. Infertility patients are often inclined to seek multiple medical opinions and switch providers. Consequently, treatment discontinuation rates are high. In the Irish study, nearly half of the patients discontinued treatment (44.6 per 100 couples at 12 months and 62.7 per 100 couples at 24 months). Similarly, in another published study, the dropout rate reached 56% in two years. 9 A comparable phenomenon is observed in patients undergoing in vitro fertilization (IVF), with discontinuation rates varying by country: 26% in France, 34% in the United Kingdom, 43% in Japan, and 65% in the United States.10

# **Comparisons**

Comparing the outcomes of restorative reproductive medicine with those of in vitro fertilization is challenging, as these are fundamentally different approaches, and both the timelines and patient populations are not directly comparable. However, it is useful to examine published data from the Latin American Network of Assisted Reproduction (RedLARA), which represents over 90% of assisted reproduction centers in Latin America. In 2020, the organization reported a live birth rate of 14.9% per oocyte aspiration and 24% per embryo transfer. For women aged 34–40, the live birth rate per embryo transfer was 25.2%. These figures do not account for fertilized but non-transferred embryos. 11

The U.S. Centers for Disease Control and Prevention (CDC) provides live birth rates per planned oocyte retrieval, varying by age group: 53.4% for women under 35 years, 39.9% for ages 35–37, 25.4% for ages 38–40, and 8.5% for women over 40. This report corresponds to 2022 data.<sup>12</sup>

In the United Kingdom, the Human Fertilisation and Embryology Authority reported a global success rate of 31% in 2022.<sup>13</sup> The highest pregnancy rates per embryo transfer were observed in women under 34 years (42%), followed by 34% in those aged 35–37, 26% in the 38–39 age group, and 16% in women aged 40–42. These figures reflect the use of patients' own oocytes. Notably, these statistics do not account for fertilized but non-transferred oocytes, which would increase the success rate by including subsequent transfers.

# Reflections

Restorative reproductive medicine (RRM) and in vitro fertilization (IVF) represent very different approaches to infertility. In IVF, each cycle is considered a treatment, and it is not always clear from which stage of the procedure the pregnancy rate is calculated: from the start of the cycle, fertilization of the egg, or embryo transfer. The emphasis is placed on the technical skill at each step. In contrast, RRM focuses on optimizing the cycle, continuing over an extended period, where the couple attempts to conceive through intercourse, without surplus embryos and with minimal adverse effects. If we are to compare, we must not only evaluate the final birth rate but also consider the economic cost, emotional burden, health risks for the mother, embryos, and long-term outcomes for the children. A full discussion of each of these issues is beyond the scope of this commentary.

It is worth noting the high abandonment rate observed in fertility treatments. This can be explained by several factors such as stress, emotional burden, economic costs, and limited coverage for procedures or medications. Additionally, medical prognosis is another factor influencing abandonment and the subsequent "consultation tourism." However, it seems to also reflect a characteristic of modern society: the demand for rapid results. It is worth considering whether taking the necessary time to improve underlying physiology may lead to a healthier outcome.

Undoubtedly, it is good and desirable to gain a deeper understanding of the biological processes involved in reproduction. In fact, much progress has been made in this knowledge, and it has greatly helped couples in building their families. However, it is equally important to respect fully the human experience and relationships.

Classical medicine, with its Hippocratic tradition, cares for the integral well-being of the human person. It recognizes characteristics in humans that cannot be reduced solely to biological processes. We do not treat highly sophisticated machines but persons, with relational meaning, open to the other. Humanistic medicine allows us often to cure the patient, but always to accompany them and help them give meaning to their suffering when biological healing is beyond our reach. Restorative reproductive medicine seeks to provide a humanistic and humanizing response to patients with infertility.

#### **Future**

Restorative reproductive medicine ultimately offers a real possibility of addressing the underlying factors of infertility in an integrated, multidisciplinary, and participatory manner. Progress has been made along this path, as outlined above, but undoubtedly much remains to be done. It is essential to foster systematic research on how to improve our diagnostic capacity regarding the factors involved in infertility, incorporating a full range of scientific disciplines, including basic science-trained researchers, to inform our clinical work. Centers working with this approach should engage in initiatives that allow the collection of clinical data from patients and the treatments used, in order to identify the best clinical practices. This platform, the Journal of Restorative Reproductive Medicine, is an excellent venue for sharing experiences that can improve our practices. The meetings and resources of the International Institute for Restorative Reproductive Medicine (IIRRM) and its sister organizations offer opportunities to build connections that enable collaborative work. The IIRRM sponsors the Surveillance of Treatment Outcomes for Restorative Reproductive Medicine (STORRM), a registry for RRM treatments and outcomes.

Many medical specialists in gynecology or reproductive medicine have experience with treatments or procedures that can become part of RRM. In this regard, healthcare professionals who work offering RRM, face the challenge of how to encourage many colleagues to participate. I believe it is a mutually beneficial opportunity for professional growth. Opening up and showcasing the benefits of this approach for patients will enable a frank and honest dialogue in the search for truth. This attitude is necessary to fulfill another significant challenge ahead: introducing modules in the curricula of universities offering health-related degrees that expose undergraduate and postgraduate students to the foundational concepts of restorative reproductive medicine.

Sharing clinical information and experiences helps foster professional growth and improve our clinical practices. This ultimately leads to better care for our patients. With them, we must be very clear about what we offer in managing infertility, the characteristics of the RRM approach, and what they can expect as outcomes. The pioneers of this approach, who laid the scientific foundations, challenge us to continue opening therapeutic alternatives that offer an increasingly effective

restorative approach for human fertility.

# CONFLICTS OF INTEREST DISCLOSURE

The author declares that he has no conflicts of interest.

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