12-2024

Evaluation of the Etiology of Recurrent Pregnancy Loss (RPL): An Explanatory Mixed Methods Study Exploring Obstetrician Gynecologist Clinical Provider Behaviors and Factors Contributing to Incomplete Evaluations

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Determining the Etiology of Recurrent Pregnancy Loss (RPL): An Explanatory Mixed Methods Study Exploring Obstetrician Gynecologist Clinical Provider (OBCP) Practice Behaviors and Factors Contributing to Inappropriate Laboratory Test Utilization

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A Dissertation submitted to:

The Faculty of
The School of Medicine and Health Sciences
of The George Washington University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Translational Health Sciences

September 5, 2024

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Evaluation of the Etiology of Recurrent Pregnancy Loss (RPL): An explanatory mixed methods study exploring Obstetrician Gynecologist Clinical Provider behaviors and factors contributing to incomplete evaluations

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Conflict of Interest: No disclosures were reported.

Acknowledgments

This dissertation is dedicated to my two sons, James and Harrison, without whom I would not have had the inspiration to begin, persevere, and complete this journey.

This project would not have been completed without the incredible support and guidance of many individuals, to whom I owe my deepest gratitude. First and foremost, I want to express my heartfelt thanks to my parents, Drs. Ruth and Michael Grant. Thank you for instilling in me the values of perseverance and hard work. Your unwavering love, sacrifices, and encouragement have been the foundation upon which all my achievements are built. To my mother, my hero since childhood, without your encouragement and belief in me, I would not be where I am today. This accomplishment is as much yours as it is mine.

To my husband, Pablo, for your continual support and always keeping everything running smoothly. Your constant patience, love, and belief in me have been my anchor through this long and challenging journey. Your constant support has given me the strength to keep going, and I am forever grateful for your understanding during the late nights and long weekends I spent working on this project.

I would also like to extend my sincere thanks to my dissertation committee: Dr. Lisa Schwartz, Dr. Marsha Regenstein, and Dr. Aya Haghamad. Your expertise, insightful feedback, and guidance have been invaluable to my development as a scholar. I am especially grateful to Dr. Schwartz for your mentorship and for always pushing me to think critically and aim higher. Your support (and eagle eyes) throughout this process

have been instrumental in the completion of this dissertation. To my readers, Dr. James Crawford and Dr. Timothy Rafael, thank you for your support and enthusiastic encouragement throughout this project and my professional career.

This work is also deeply inspired by and dedicated to the women who have experienced recurrent pregnancy loss. Your courage, resilience, and perseverance in the face of heartbreak have motivated my efforts in this field. I hope that this research contributes, even in a small way, to improving care, support, and outcomes for women navigating this difficult journey.

Last, but certainly not least, my team members who always persistently supported me and for your hard work and dedication to our department. To all my friends, colleagues, and extended family who have been there through the highs and lows of this journey—thank you. Your words of encouragement and acts of kindness have meant more than you could ever know.

To all of you, thank you from the bottom of my heart.

Abstract

Evaluation of the Etiology of Recurrent Pregnancy Loss (RPL): An explanatory mixed methods study exploring Obstetrician Gynecologist Clinical Provider behaviors and factors contributing to incomplete evaluations

Background: More than 50% of patients with recurrent pregnancy loss (RPL) are left without explanations for their losses. However, current research suggests that up to 90% of these individuals could receive explanations through evidence-based laboratory testing. Professional guidelines vary in their recommendations for laboratory testing and RPL evaluation, which can contribute to delayed or fragmented care and untreated maternal disease. Inequities in access to genetic testing further complicate the diagnostic landscape of RPL since payor policies often determine which tests are covered, leaving many patients without access due to financial constraints.

Objective: This study aimed to evaluate current practices of Obstetrician Gynecologist Clinical Providers (OBCPs) in assessing RPL patients, explore factors influencing their behavior regarding laboratory testing, and identify barriers and facilitators in RPL evaluation to inform future care improvements.

Methods: This study was conducted using an explanatory sequential mixed methods design, which included retrospective chart review and semi-structured interviews with OBCPs. The quantitative phase included a retrospective chart review of RPL patients, which were defined as patients with two or more tests for chromosomal analysis of a product of conception (POC), OBCPs were recruited through purposeful and snowball sampling to participate in interviews, which were recorded and transcribed via Microsoft Teams and thematically analyzed via Dedoose software. The Consolidated

Framework for Implementation Research (CFIR) and the Theoretical Domains Framework (TDF) served as the foundational conceptual frameworks guiding the interview protocol and thematic analysis.

Results: Charts of 224 RPL patients, were reviewed for the number of RPL-related laboratory tests ordered and categorized as low (one to two tests), medium (three to four tests), and high (five to six tests) evaluations. Most evaluations (113 [50.4%]) fell into the "low" category, 30 (13.4%) fell into the "medium", and 81 (36.1%) fell into the "high" category. Fifteen interviews with OBCPs provided rich descriptions of their experience in RPL evaluations and revealed that differences in provider specialty and training, guideline preferences, patient influence, and access to laboratory results contributed to the variation in RPL evaluations. The evaluations were subsequently assessed for appropriate utilization; inappropriate utilization accounted for 47.3% (106) of the 224 evaluations, with overutilization (70 [31.3%]) being more prevalent than underutilization (36 [16.1%]).

Discussion: Laboratory testing for RPL evaluation is complex and impacted by the specialization of the provider, practice setting factors, patient influence, laboratory test ordering, access to test results, and laboratory test interpretation. Interventions to improve this process should include implementing protocols for POC collection and RPL laboratory testing and improved coordination among a multidisciplinary team of specialists including clinical laboratory providers. Future research should include the patient experience of this process to understand the barriers and facilitators from their perspective.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

RPL: Recurrent Pregnancy Loss

APLS: Antiphospholipid Antibody Syndrome

LA: Lupus Anticoagulant

aCL: Anti-cardiolipin

B2GPI: Anti-B2 glycoprotein I

OBCP: Obstetrician-Gynecologist Clinical Provider

CFIR: Consolidated Framework for Implementation Research

TDF: Theoretical Domains Framework

Hgb A1C: Hemoglobin A1c

TSH: Thyroid Stimulating Hormone

POC: Products of Conception

Chapter 1: Introduction

Overview

The definition of recurrent pregnancy loss (RPL) is not universally accepted, though most often defined as two or more pregnancy losses and affects approximately 1-4% of all reproductive age individuals (Diejomaoh, 2014). It is plausible that RPL is more common than realized since roughly 15-20% of clinically recognized pregnancies and up to 30% of early pregnancies result in spontaneous loss or miscarriage (Bashiri et al., 2012). There are several established causes of RPL, such as increasing maternal age, coagulation disorders, endocrine disorders, uterine anatomy abnormalities, genetic factors (including parental cytogenetic abnormalities), and environmental factors (Shapira et al., 2012; Van den Berg et al., 2014). Due to the myriad potential etiologies, an evaluation of RPL should include appropriate laboratory testing to exclude the most common causes of RPL in addition to a detailed review of the patient's medical and pregnancy history.

Establishing the etiology of RPL is imperative because many of the underlying conditions associated with RPL contribute to maternal morbidity and mortality (Davidesko et al., 2020; Schwarzman et al., 2020). For example, 15-20% of RPL cases are attributed to antiphospholipid antibody syndrome (APLS), which is a coagulation disorder that increases the risk of thrombosis during pregnancy and has a 4% lifetime risk of stroke (Yelnik et al., 2016). Endocrine disorders such as diabetes mellitus (DM), hypothyroidism, and polycystic ovarian syndrome are also associated with short and long-term health sequelae (Bellver et al., 2008; Mils et al., 1988). Additionally, RPL is disproportionately associated with significant psychological impacts, with patients

reporting feelings of anxiety, depression, and suicidality (Kolte et al., 2015; Shah et al., 2018; Quenby et al., 2021).

If the cause of RPL is left undetermined, patients are left without a clinical explanation and may not be receiving appropriate treatment either for the underlying disease or to prevent further pregnancy loss. For example, many patients are referred to fertility services for RPL, but In vitro fertilization treatment (IVF) would not increase the chances of a successful pregnancy in a patient with APLS as the thrombotic issue remains untreated. Similarly, if the parents carry chromosomal rearrangements that increase the chance of chromosomal abnormalities, only specialty testing of the embryos created via IVF would detect these chromosomal conditions. The result is added financial and emotional burden from costly and potentially unnecessary procedures.

Despite the importance of identifying the cause of RPL for patients from both a physical and psychological health standpoint, an explanation or etiology for RPL is currently undetermined in more than half of cases (American College of Obstetrics and Gynecology [ACOG], 2018). Current literature suggests that conflicting professional society guidelines and the complexity of laboratory testing may be contributing factors to inappropriate and incomplete diagnostic evaluation of RPL, which involves substantial laboratory testing (Papas & Kutteh, 2020). Similarly, the underuse of laboratory testing (genetic testing, in particular) is a widely cited issue that contributes to delay in diagnosis (Ducatman et al., 2020; Finucane et al., 2021; Kurian et al., 2021; Shahangian & Snyder, 2009).

Preliminary Findings

Laboratory stewardship programs examine test utilization to assess patterns of under- and over- ordering of tests (Dickerson et al., 2019). Follow-up of these assessments often involves engaging with clinicians to determine the cause of the utilization errors and potential solutions. In a laboratory stewardship effort at Northwell Health Laboratories in New York conducted in 2022, the records of 230 RPL patients, as defined by chromosomal analysis ordered on two or more products of conception (POC), were examined in the laboratory database for the period of 2014 to 2021. Although professional society guidelines vary in their recommendations (ACOG, 2001; ASRM, 2012; ESHRE, 2018), the laboratory tests that are primarily agreed upon include Hemoglobin A1C (Hgb A1C), Thyroid stimulating hormone (TSH), and APLS testing (Lupus anticoagulant (LA), Anti Cardiolipin (CDLPN) antibodies, Beta 2 glycoprotein I (B2G) antibodies). The tests ordered for these patients were tabulated in Table 1. The most frequently ordered tests were Hgb A1C and TSH (158/230 and 179/230, respectively), which is to be expected since these are routinely ordered during prenatal care.

Table 1

Frequency and results of RPL guideline-based laboratory tests performed in 230 RPL patients from 01/2014-12/2021 at Northwell Health Laboratories

TEST	Hemoglobin A1C %(n)	Thyroid Stimulating Hormone %(n)	Lupus Anticoagulant %(n)	Anti-Cardiolipin Antibodies (IgG/IgM) %(n)	Anti-Beta 2 Glycoprotein 1 Antibodies (IgG/IgM) %(n)
Abnormal	12.0% (19)	10.6% (19)	16.9% (13)	11.2% (10)	14.4% (13)
Normal	88.0% (139)	89.4% (160)	83.1% (64)	88.8% (79)	85.6% (77)
Total Performed	68.7% (158)	77.8% (179)	33.5% (77)	38.7% (89)	39.1% (90)
Not Performed	31.3% (72)	22.2% (51)	66.5% (153)	61.3% (141)	60.9% (140)

Although professional guidelines vary in their recommendation of whether parental chromosome analysis is warranted following a second pregnancy loss, only 26.96% of the 230 RPL patients had a maternal karyotype (paternal karyotypes were excluded due to difficulty of linking partners in the database). More importantly, of the 6,941 patients with at least one pregnancy loss and POC testing in the database from January 2014 through December 2021, 135 were identified as abnormal and suggestive of a potentially inherited chromosomal abnormality. This type of abnormal result always prompts a recommendation from the laboratory to perform chromosome analysis on both parents due to a higher risk of subsequent pregnancy loss due to translocations, inversions, and marker chromosomes (Gardner & Amor, 2018), yet only 39 maternal chromosome analyses (29.9%) were performed. The factors contributing to the failure by clinicians to order or complete guideline-recommended laboratory testing for patients experiencing RPL, or even a single pregnancy loss when chromosome analysis of the POC is abnormal, are currently unknown. This study aimed to explore these factors.

Statement of the Problem

Delays or inability to determine an etiology for RPL subsequently contribute to psychological trauma, unsuccessful and costly fertility treatments, and potentially untreated underlying maternal disease (Catov & Margerison-Zilko, 2016; Glazener et al., 1995; Nikcevic, Tunkel, & Nicolaides, 1998). Current literature suggests that a causal determination could be made in 90% of RPL cases if a patient-specific algorithm for recommended laboratory testing is ordered and followed through by clinicians caring for these patients (Papas & Kutteh, 2020). However, there are multiple professional guidelines for evaluating patients with RPL including the American College of Obstetrics and Gynecology (2001), American Society of Reproductive Medicine (2012), Royal College of Obstetrics and Gynecology (2011), and the European Society for Human Reproduction (2017), and it is not clear which, if any, guidelines clinicians are following. The factors that may contribute to a delay in or incomplete etiology evaluation for RPL that obstetrician-gynecologist clinical providers (OBCPs) face at various points throughout the healthcare system are unknown. This study aimed to explore barriers and facilitators to the evaluation of RPL etiology experienced by clinicians, focusing primarily on the laboratory testing component.

Purpose Statement and Research Questions

The purpose of this study was to describe OBCPs practice behaviors regarding etiology evaluation of RPL and to identify potential interventions at the pre-analytical, analytical, and post-analytical stages of laboratory testing that may support RPL evaluation. The study's specific aims and accompanying research questions were:

SA1: Assess the current OBCP practice behaviors for laboratory testing on RPL patients. RQ1: What are the current practice behaviors and ordering patterns by OBCPs for RPL evaluation? (Quantitative inquiry)

SA2: Explore contributing factors that influence OBCP behavior on laboratory testing for the evaluation of RPL etiology. RQ2: How do OBCPs describe their experience of evaluating patients for RPL? (Qualitative inquiry)

SA3: Integrate the findings from the chart reviews and qualitative interview themes of the study to suggest potential future interventions that may improve consistency and completion in laboratory test ordering. RQ3: How do the current test ordering practice behaviors and OBCP interviews inform future interventions to promote completed laboratory test evaluations of RPL?

Statement of Potential Impact

This study is innovative in its exploration of factors that contribute to the inappropriate and incomplete evaluation of RPL. The long-term goal of this research project is to inform the development of an intervention(s) that will improve the timeliness and diagnostic yield of laboratory evaluations for RPL, increasing their management's effectiveness. Knowing the facilitators and barriers to RPL evaluation faced by clinicians will inform the design and implementation of an improved diagnostic laboratory testing process, and therefore, improve the care and treatment for RPL patients.

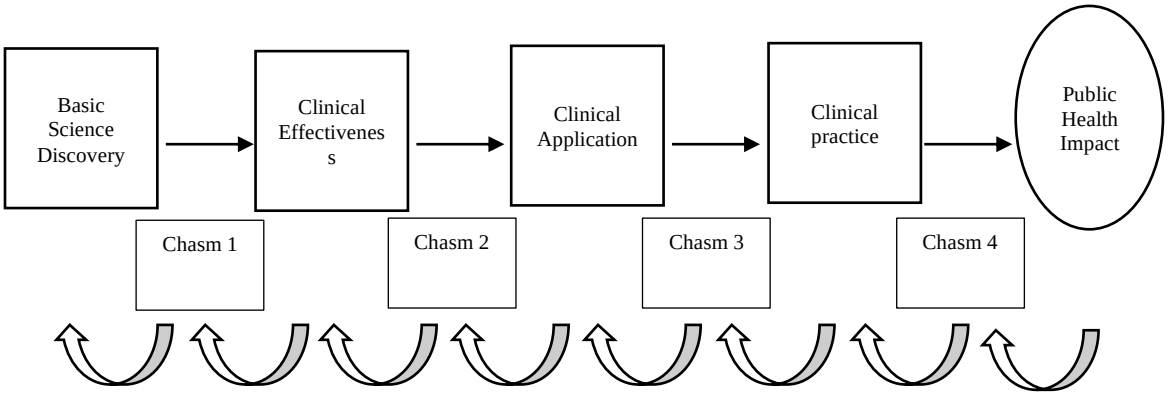
Translational Nature of the Study

The translational research process as described by Drolet and Lorenzi (2011) involves the movement and facilitation of basic science research into public health improvements along the "translational continuum" (Figure 1). This so-called "bench-to-

bedside" process is comprised of four phases including basic science research (T1), clinical application through human research (T2), widespread adoption into clinical practice (T3), and public health impact (i.e., improvement of disease prevalence or severity in a population [T4]; Drolet & Lorenzi, 2011). The continuum is considered "bi-directional" in that the public health sphere is intended to inform the basic science discovery process. Drolet and Lorenzi (2011) described "chasms" that exist between these distinctive stages and how translational researchers must utilize a variety of research methodologies and knowledge translation to progress to each stage. Similarly, the chasm or gap between stages may inform research in a prior stage.

Figure 1

Biomedical Science Translational Continuum



Note. Adapted from Drolet, B. C., & Lorenzi, N. M. (2011). Translational research: understanding the continuum from bench to bedside. Translational Research, 157(1), 1-5. https://doi.org/10.1016/j.trsl.2010.10.002

This study is translational by bridging the gap between T2 (clinical effectiveness) and T3 (widespread clinical application). A review of the current literature, further detailed in Chapter 2, suggests that there is a lack of understanding of current practices and perceived factors that may drive or inhibit the appropriate and complete evaluation of RPL etiology. By including key stakeholders, namely OBCPs, this study aimed to

understand the gap in translation between well-established laboratory testing for RPL etiology and how RPL evaluation is conducted in clinical practice. A potential outcome of this research is to inform possible strategies that may be implemented to improve the completion of laboratory evaluation of RPL.

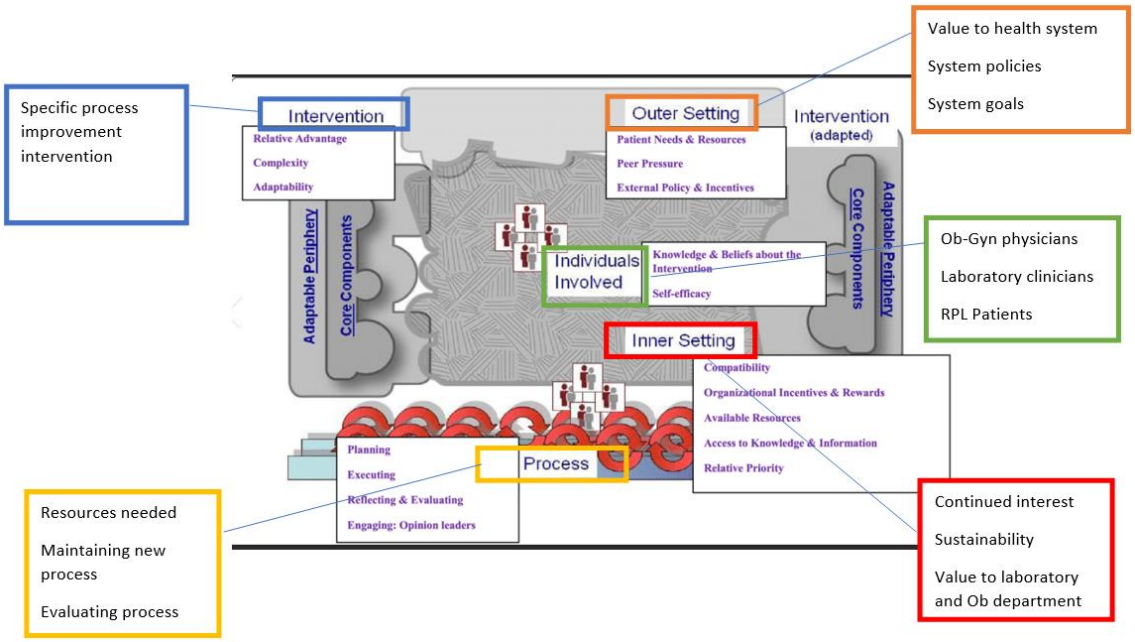
Conceptional Framework

Consolidated Framework for Implementation (CFIR)

The Consolidated Framework for Implementation (CFIR) is a widely cited implementation framework for researching interventions that involve multiple stakeholders on a multi-level organizational basis and served as the theoretical framework for the study (Damschroder et al. 2009). The CFIR framework has five key domains: individual, inner setting, outer setting, intervention, and process. In the context of complex disease diagnosis, CFIR allows researchers to take multiple layers of complexity related to the adoption, execution, and sustainability of interventions. The manner that the constructs of the CFIR (Figure 2) served as a framework for the research study are detailed below:

Figure 2

CFIR Diagram of Domains (Individuals, Outer setting, Inner setting, Intervention, and Process)



Note. Adapted from "Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science," Damschroder, L. J., Aron, D. C., Keith, R. E., Kirsh, S. R., Alexander, J. A., & Lowery, J. C. (2009).. BioMed Central. https://doi.org/10.1186/1748-5908-4-50

Individuals: The individuals involved include the clinicians that care for patients with RPL (OBCPs), RPL patients, and clinical laboratory professionals (CLPs), although the study focused on OBCPs.

Outer setting: The outer setting comprises the rest of the department and health system within which the OBCP practices. Additionally, insurance payor policies and medical guidelines exist within the outer setting. The qualitative arm of this study aimed to explore how these external factors contribute to test ordering behaviors.

Inner Setting: The inner setting refers to the context in which the primary stakeholders interact, communicate, and the shared infrastructure and culture of the

setting. In this study, OBCPs' perspectives and relationships within their current practice setting and department were explored.

Interventions: Existing and potential interventions as suggested by participants and inferred from the results were included.

Process: A new process for RPL evaluation would have to be sustainable with attention to the program's goals and incentives for the individuals and the health system. In this study, the stakeholders commented on ideas of process improvement and factors they believe contribute to inappropriate or incomplete laboratory test evaluations for RPL.

The Theoretical Domains Framework

In the setting of a mixed methods research study focused on the perceptions and experiences of individuals, a model of behavioral change theory can help contextualize individual responses. Determinant frameworks incorporate behavioral change theories and are frequently used to assess behavior change of healthcare professionals or adherence to clinical guideline changes. Additionally, the authors of CFIR highlight the benefit of using additional behavioral change frameworks within the individual domain in their guide to implementation (Damschroeder et al, 2009). Although laboratory testing for RPL is only one component of care for RPL patients, understanding the factors that surround individual behavior is useful to guide this research. Specifically, Birken et al. (2017) reviewed the use of the Theoretical Domains Framework (TDF) in conjunction with CFIR to highlight the value of using determinant frameworks in the implementation process.

The TDF incorporates both behavioral change theories and behavioral change approaches to implementation (Cane et al, 2012). The TDF originated as a systematic review of behavior change theories to integrate and simplify existing theories (Cane et al, 2012). For example, the Stages of Change model, transtheoretical model, and the Behavior Change Wheel (BCW) with behavior characterized by "Capability, Opportunity, and Motivation" (COM-B), are all incorporated within the TDF (Cane et al, 2012). A review article by Abraham et al. (2009) posited that behavior change is a critical component of improving healthcare, and thus the TDF can serve as an ideal lens through which to conduct a pre-implementation study (Abraham et al., 2009).

Methodology

Understanding the etiology of RPL is only one facet of RPL patient care. However, improving the diagnostic yield of laboratory testing is expected to help patients receive answers and pursue relevant treatment options. Therefore, the laboratory testing component and the surrounding OBCP behavior was the central focus of this study. The methodology was an explanatory, sequential mixed methods (quant→QUAL) design. The quantitative phase consisted of a retrospective chart review aimed at assessing current laboratory test ordering behaviors for the evaluation of RPL. The qualitative phase explored the described experiences of OBCPs in coordinating, interpreting, and utilizing laboratory testing for RPL evaluation. The practice behaviors of OBCPs and possible interventions were explored, and their responses were contextualized within the constructs and domains of CFIR and TDF.

Limitations and Delimitations

Limitations

As with any mixed methods study research, the experiences of the participants and research findings may not be generalizable to contexts outside of the system under investigation. However, purposeful sampling for diversity among participants and rich descriptions of findings allows readers to determine if the study's results may be applicable to their setting. Additionally, triangulation with multiple data sources and methods were conducted to establish trustworthiness as described by Lincoln and Guba (1986).

Delimitations

Obstetrician-gynecology clinical providers (including the titles MD, DO, NP, LPN, RN, and PA) from a single health system, Northwell Health, in which preliminary data regarding laboratory evaluation of RPL has been previously conducted, were included in this study. Northwell Health is a health system with 16 hospitals and numerous outpatient care facilities spanning urban and suburban New York state including Manhattan, Westchester, and Long Island primarily. The Core Laboratory of Northwell Health services Northwell hospitals as well as the Health and Hospitals Corporation of New York City (H&H NYC) which is New York City's public hospital system. Only clinicians who currently or recently (since 2020) care for patients with RPL were included in this study. Reproductive partners of patients with RPL were not included in the study. All participants were selected from the Northwell Health system.

Definition of Key Terms

Recurrent Pregnancy Loss (RPL): Two or more consecutive failed clinical pregnancies documented by ultrasound or histopathology

Antiphospholipid antibody syndrome: An autoimmune disorder that causes abnormal blood clots to form

Aneuploidy: The occurrence of one or more extra or missing chromosomes in a cell or organism

Microarray: Microarray technology is a general laboratory approach that involves binding an array of thousands to millions of known nucleic acid fragments to a solid surface, referred to as a "chip."

Translocation: A translocation, as related to genetics, occurs when a chromosome breaks and the (typically two) fragmented pieces re-attach to different chromosomes.

Chapter 2: Literature Review

Introduction

A review of literature was conducted to understand the factors surrounding the laboratory-based evaluation of recurrent pregnancy loss (RPL). The primary question grounding the review is "what is known about barriers and facilitators to the laboratory testing process for etiology for RPL"? An in-depth search for laboratory testing guidelines and recommendations for RPL etiology evaluation was also performed. The search was conducted utilizing databases including PubMed, MEDLINE, CINAHL, and Scopus. Search terms included "recurrent pregnancy loss," "recurrent miscarriage," "recurrent spontaneous abortion," and "multiple spontaneous abortion." Additional search terms used to examine research on the process of evaluating patients with RPL included "evaluation," "workflow," "coordination," "laboratory test process."

Definition and Etiology of RPL

The definition of recurrent pregnancy loss (RPL) differs across professional societal guidelines. The American College of Obstetrics and Gynecology (ACOG, 2002) defines RPL as two or more pregnancy losses, whereas the European Society for Human Reproduction (ESHRE, 2017) considers the diagnostic criteria for RPL as three or more (not necessarily consecutive) losses. The American Society of Reproductive Medicine (ASRM, 2012) defines RPL as two or more (not necessarily consecutive) failed clinical pregnancies as documented by ultrasonographic or histopathological exam, while the Royal College of Obstetricians and Gynaecologists (RCOG, 2011) defines RPL as the loss of three or more consecutive pregnancy losses. Therefore, whether to begin the evaluation for RPL after two or three pregnancy losses, and if they must have occurred

consecutively or not, depends on which guidelines (if any) are being followed (Saravelos & Regan, 2014).

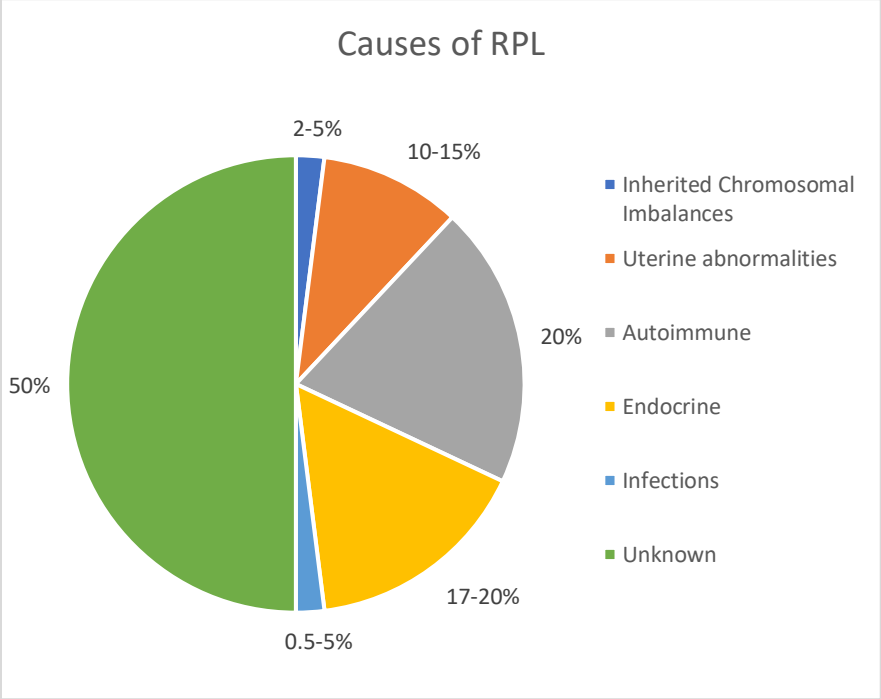
The most widely accepted causes of RPL include autoimmune, endocrine, and coagulation disorders, increasing maternal age, environmental factors, inherited cytogenetic abnormalities, and uterine anatomical/structural aberrations. Antiphospholipid antibody syndrome (APS) is an autoimmune coagulation disorder that accounts for 15 to 20% of RPL (Yelnik et al., 2016). Endocrine disorders, including diabetes mellitus (DM), hypothyroidism, and polycystic ovarian syndrome (PCOS) collectively explain up to 5% of RPL (Bellver et al., 2008; Mils et al., 1988). Hereditary thrombophilia disorders, including Factor V Leiden (Activated Protein C Resistance), prothrombin mutations, Protein S, Protein C, and antithrombin deficiency, are also risk factors for RPL (Kovalevsky et al., 2004), although most prospective studies have not identified a strong correlation except in patients with a history of thrombosis (Dizon-Townson et al., 2005).

It is well-known that socioeconomic factors such as minority race and ethnicity, under- or uninsured and lower education levels in patients are associated with increased risk of maternal morbidity and mortality (Creanga et al., 2014; Nicholls-Dempsey et al., 2023; Wang et al., 2020; Whitehead et al., 2009). The impact of these social determinants on RPL is less established. In 2010, Bryant et al., determined that these disparities persist in adverse obstetrical outcomes including increased risk for fetal demise, preterm birth, and fetal growth restriction. Specifically, Hispanic and black women were found to have double the risk for fetal demise after 24 weeks gestational age than their white counterparts (Bryant et al., 2010).

Cytogenetic abnormalities, including chromosomal rearrangements such as balanced translocations, Robertsonian translocations, and other chromosome abnormalities, account for another 3% of RPL causes. Parental age, increased body mass index (BMI), endocrine factors, environmental factors, such as tobacco smoking and alcohol intake, and uterine anatomical differences, such as adhesions and septations, are also associated with RPL (Jauniaux et al., 2006). Other possible associations, including endometrial lining and sperm-related factors, have conflicting evidence (ESHRE, 2017). There are additional potential causes of RPL, such as immunologic factors, still under scientific exploration (Stephenson et al., 2009). Despite these known causative and associated factors, the etiology for RPL is undetermined up to 50% of the time (Figure 3; ASRM, 2020). Evaluation for established causes of RPL relies heavily upon laboratory testing apart from uterine anatomical differences.

Figure 3

Distribution of RPL Causes



Note. A determined etiology for RPL is unknown greater than 50% of the time. Adapted from Ford, H. B., & Schust, D. J. (2009). Recurrent pregnancy loss: etiology, diagnosis, and therapy. Reviews in obstetrics and gynecology, 2(2), 76.

In addition to underlying maternal disease and environmental factors, up to 50% of all pregnancy losses (not limited to patients with RPL) are the result of a fetal chromosome abnormality (Rai & Regan, 2006). Therefore, chromosome analysis of fetal tissue, also known as products of conception (POC), can explain up to 50% of all pregnancy losses. However, there is a debate as to whether POC chromosome analysis is necessary after only the first pregnancy loss (Papas & Kutteh, 2020; van Dijk et al., 2020). The risk of non-inherited chromosomal abnormalities including aneuploidy (additional or missing chromosome) or polyploidy (extra sets of chromosomes) increases with increasing maternal age (Rai & Regan, 2006). However, 3-5% of couples with RPL

have inherited chromosomal rearrangements known as translocations, which can lead to miscarriage in 50-75% of each pregnancy (Gardner & Sutherland, 2006). Therefore, parental karyotype analysis may not be necessary if POC chromosomes are normal or abnormal due to aneuploidy or polyploidy but are necessary if chromosomal analysis of the POC identifies a translocation (Rai & Regan, 2006).

Just as POC cytogenetic results may not require follow up parental chromosomal analysis, patients often require different laboratory tests following a pregnancy loss dependent on their specific personal and pregnancy history. For example, hereditary thrombophilia testing is only recommended if a patient has a personal or family history of clotting issues (Pritchard et al., 2016). A sonohysterogram or other uterine radiology procedures would only be recommended if prior laboratory testing was otherwise normal or inconclusive (Turocy & Rackow, 2019). Coagulation testing, as a part of the APS evaluation, can only be performed minimally six weeks following a pregnancy loss (Devreese, 2020). Therefore, RPL evaluation is highly patient and situation dependent and heavily focused on complex laboratory testing.

Importance of Establishing RPL Etiology

Physical Health Impact

Having a prior pregnancy loss is associated with poor future obstetric outcomes including increased risk of preterm birth, poor fetal growth, and other obstetric complications (Quenby et al., 2021). Antiphospholipid antibody syndrome (APS) is a significant risk factor for thrombotic diseases including cerebral vascular thrombosis (stroke), deep vein thrombosis (DVT), and myocardial infarction (heart attack) both during pregnancy and throughout an individual's life and often requires lifelong

treatment with blood thinners (Schwarzman et al., 2020). Yet APS would not be routinely screened in individuals without symptoms of a coagulation condition. On the other hand, thyroid-stimulating hormone (TSH) is frequently screened in pregnant and reproductive age women, but TSH can be falsely elevated or decreased during pregnancy and hypo- and hyperthyroidism can be missed (Joosen et al., 2016). Additionally, diagnosing autoimmune hypothyroidism, also known as Hashimoto's disease, involves additional lab testing not routinely performed before or during pregnancy (Stagnaro-Green et al., 2011). Untreated hypothyroidism causes obesity, joint pain, cardiovascular disease, and pregnancy complications (Ozimek et al., 2016; Stagnaro-Green et al., 2011).

In contrast, balanced chromosome rearrangements or translocations may not directly cause health concerns in the carrier parent but will lead to miscarriage in up to 50% of pregnancies if not detected—perhaps leading to the highest risk of pregnancy loss of all known causes (Alibakhshi et al., 2020). Additionally, unbalanced chromosomal translocations in the fetus that do not result in pregnancy loss can lead to intellectual and developmental delays in children who inherit them from a carrier parent (Alibakhshi et al., 2020). Patients with a history of RPL are also at risk to have subsequent pregnancies with poor prognoses, including an increased likelihood of pre-term delivery and extended stays in the neonatal intensive care unit (NICU), although the underlying mechanisms for these complications are unknown (Saravelos & Regan, 2014).

Psychological Impact

Patients with RPL experience similar, if not more severe, psychological consequences due to the repeated trauma of multiple losses (Chen et al., 2020; He et al., 2019; Kolte et al., 2015). Women with RPL report wanting medical providers to

approach RPL differently with increased awareness than an isolated pregnancy loss (Koert, 2019). Specifically, patients express their need for additional specialty provider referral and support services (Bellhouse et al., 2019; He et al., 2019). Patients and their partners also describe an overall lack of understanding on behalf of healthcare providers and staff—specifically regarding the ability to address their questions and concerns about recurrence (Bellhouse et al., 2019; He et al., 2019). The inability to determine a known cause for RPL, as well as the experience of miscarriage itself, leads to numerous mental health concerns for both partners (Chojenta et al., 2014; Kolte et al., 2015; Lee & Rowlands, 2015).

In addition to potentially severe impacts on physical health, patients who experience pregnancy loss (PL) report significant psychological trauma including both short- and long-term behavioral health issues such as anxiety, depression, and post-traumatic stress disorder (Lasker & Toedter, 1994). Similarly, male partners indicate feeling negative psychological effects from PL but often do not seek or have access to behavioral health services to the same extent as their female partners (Miller et al., 2019). Additionally, men report feeling pressure to remain supportive and positive despite having to cope with their own feelings of loss (Miller et al., 2019).

A systematic review by van den Berg et al. (2018) reviewed qualitative and mixed methods studies on the perspective of patients and their partners during RPL. They found that patients desire timely communication, follow-up, and emotional support. A qualitative study by Koert et al. (2019) described how the individual emotional response of women can vary depending on their personalities, history of psychological disorders, and experience with past pregnancies. However, at a minimum, short-term trauma is

experienced by both patients and often their partners (Chen et al., 2020; Koert et al., 2019). Therefore, psychological support is recommended through social workers, trained mental and behavioral health professionals, and/or support groups.

Challenges of RPL Etiology Determination

Conflicting Guidelines

Clinicians face a lack of consensus among professional society guidelines regarding RPL evaluation (Table 2). Whether the losses were consecutive, or whether patients have any living children, furthers the uncertainty of when an evaluation for RPL is necessary (Rai & Regan, 2006). Professional guidelines also differ on whether biochemical pregnancies (where pregnancy hormones are present in blood or urine tests, but no evidence of pregnancy is identified by sonogram) should be included (van Dijk et al., 2020). Advanced maternal age, defined as 35 years or greater, and other environmental or lifestyle factors such as smoking, alcohol consumption, and obesity are associated with an increased risk of pregnancy loss, and formal RPL laboratory evaluation may be deemed unnecessary for a patient with one or more of these risk factors (Quenby et al., 2021). Up to 50% of patients with RPL will have a successful pregnancy without intervention in the future (Rai & Regan, 2006), so OBCPs may be less inclined to perform an evaluation of pregnancy loss if a patient has had two or fewer losses (Kutteh, 2019).

The Royal College of Obstetricians and Gynecologists (RCOG, 2011) suggests that RPL patients should be evaluated for APS, thyroid hormone, and diabetes but not parental cytogenetic analysis unless products of conception (POC) analysis indicate a translocation. In 2012, the ASRM published guidelines for RPL evaluation that includes

similar recommendations to RCOG except for cytogenetic analysis. ASRM recommends parental karyotype but not POC karyotype (ASRM, 2012). In 2017, the European Society of Human Reproduction and Embryology (ESHRE) put forth clinical guidelines for the evaluation and management of RPL patients which contained an exhaustive list of RPL risk factors, the level and quality of supporting evidence, and treatment considerations. Of interest is that ESHRE recommends individual and couple-based evaluation depending on factors such as age, number of losses, and relevant medical history (ESHRE, 2020). Interestingly, the American College of Obstetrics and Gynecology (ACOG) last published a practice bulletin for evaluation of RPL over two decades ago. Like ASRM, ACOG recommends parental cytogenetic analysis but does not mention POC cytogenetic analysis in the bulletin (ACOG, 2002). One of the few consistent recommendations across all guidelines is sonographic evaluation of the uterus after all laboratory testing has not yielded an explanation.

Table 2

Professional clinical society guidelines regarding RPL evaluation using laboratory testing.

TEST	ACOG (2002)	Royal College (2011)	ASRM (2012)	ESHRE (2017)
Parental Karyotype	✓	X	✓	+/-
POC Cytogenetic analysis	N/A	+/-	X	+/-
Antiphospholipid antibodies	✓	✓	✓	✓
Thyroid function	+/-	✓	✓	✓
Prolactin	N/A	N/A	✓	✓
Hemoglobin A1c	+/-	✓	✓	X
Hereditary thrombophilia	N/A	X	+/-	+/-
Sperm DNA fragmentation	N/A	N/A	X	+/-
PCOS and insulin resistance	N/A	N/A	X	X
Luteal insufficiency	X	N/A	X	X
Ovarian reserve testing	N/A	N/A	X	X
Vitamin D deficiency	N/A	N/A	N/A	+/-

Note. X: Not recommended; ✓: Recommended; +/-: conditional (situationally dependent); N/A: Not mentioned in guidelines

Of the conflicting recommendations, genetic testing is controversial. For example, ESHRE (2020) and RCOG (2011) do not recommend parental cytogenetic evaluation unless indicated by cytogenetic testing performed on the POC. However, ASRM (2012) recommends parental cytogenetic analysis for patients with two or more losses. Recent literature from Papas and Kutteh (2020) summarized and compared these recommendations across major societies while also advocating for additional genetic

testing. Specifically, the authors did not recommend traditional cytogenetic analysis on POC at all, instead, they suggested that chromosomal microarray analysis (CMA) on POC will have a higher yield for detection of cytogenetic abnormalities while being less time-consuming and less prone to failure than traditional chromosome analysis on pregnancy losses (Papas & Kutteh, 2020). The authors examined their database of patients and concluded that the etiology of RPL could be determined for 90% of their patients if they included endocrine and coagulation disorders in the patient in addition to performing microarray analysis on the POC (as opposed to traditional chromosome analysis). Follow-up cytogenetic testing of both parents can then be performed if the microarray results suggest an inherited rearrangement or translocation (Papas & Kutteh, 2020).

Complexity of Laboratory Testing for RPL

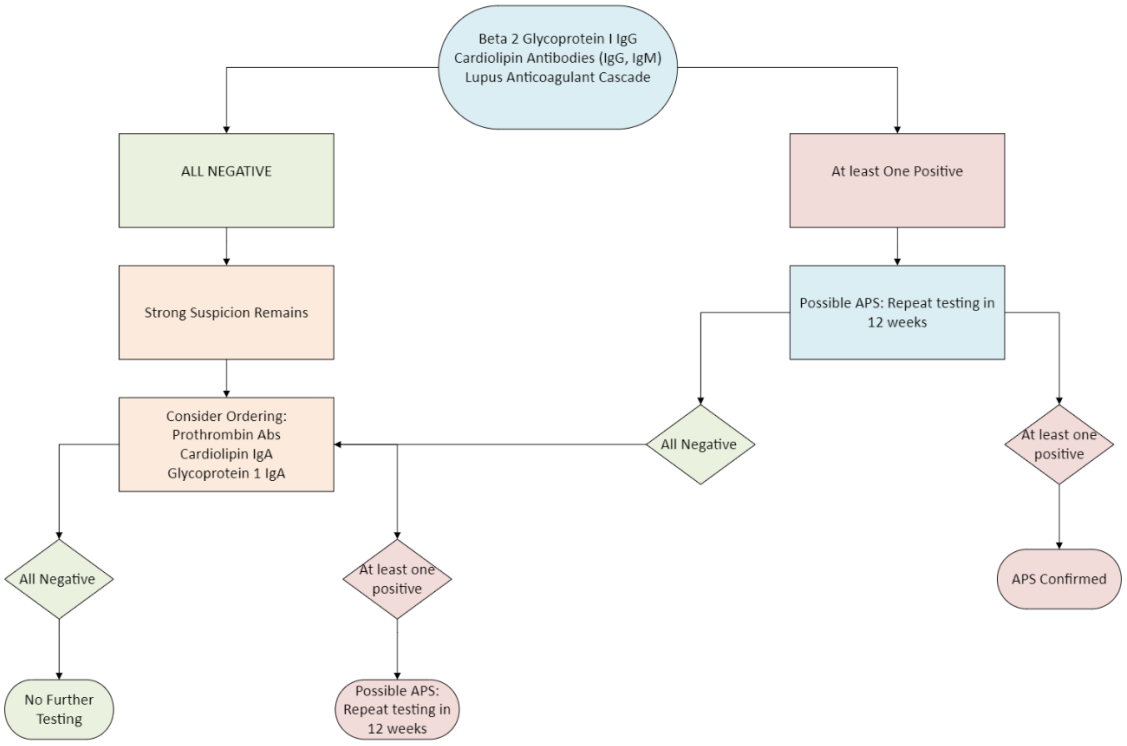
In addition to conflicting recommendations, it is unclear what type of provider should be ordering these tests. For example, certain routine tests such as thyroid stimulating hormone (TSH) and Hemoglobin A1c may be familiar to and frequently ordered by an obstetrician-gynecologist clinical provider (OBCP); other tests such as parental cytogenetics and hereditary thrombophilia testing may be outside of the typical scope of an OBCP (Quenby et al.,2021).

The conflicting practice guidelines, wide range of potential causes, and the subsequent expansive array of testing make the laboratory evaluation for RPL particularly challenging and is a barrier to determining the etiology of the diagnosis (Hickner et al., 2014; Laposata et al., 2004). As is evidenced in Table 2, each individual and couple may require every lab test for RPL at the same time or sequentially.

Additionally, the reflex nature of algorithmic testing often contributes to incomplete evaluations due to patients being lost to follow-up (Diejomaoh, 2014). For example, because of how pregnancy affects coagulation, collecting samples for APS testing is recommended no earlier than 6 weeks following a pregnancy and never during pregnancy (Yelnik et al., 2016). If a component of the APS testing is positive, then it is to be repeated in another 6 to 12 weeks (Levy et al., 2015; Yelnik et al., 2016) (Figure 4). Thyroid testing also involves reflexive testing to rule out an autoimmune cause of thyroid dysfunction (Stagnaro-Green et al., 2011).

Figure 4

Recommended APS Testing Algorithm

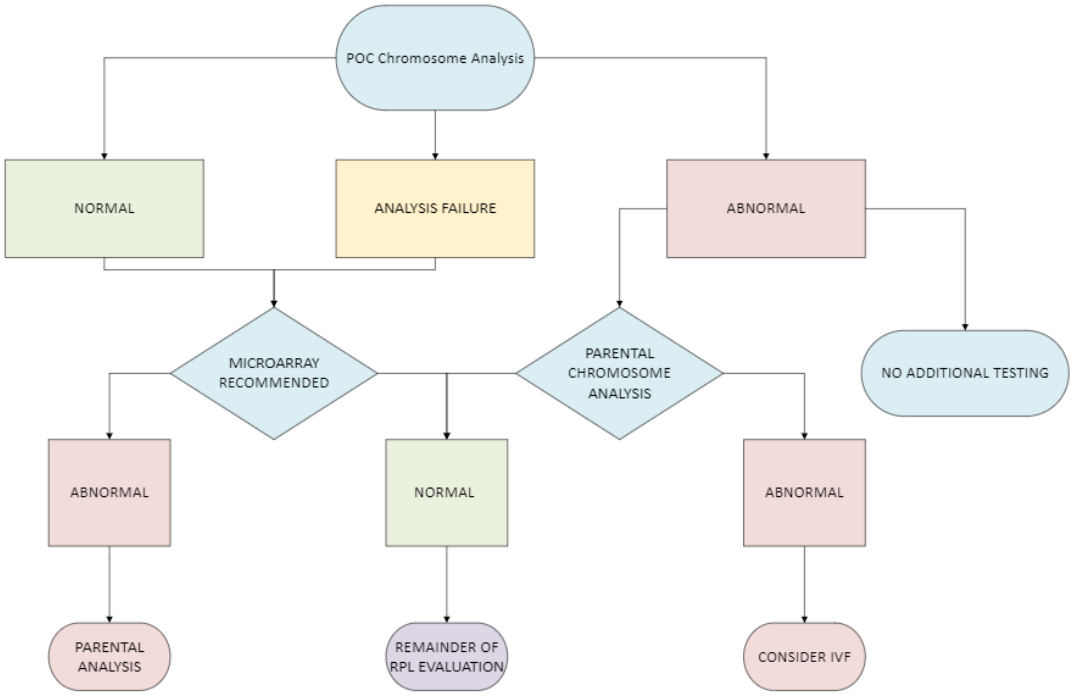


Note. Adapted from Devreese, K. M. (2020). Testing for antiphospholipid antibodies: advances and best practices. International Journal of Laboratory Hematology, 42, 49-58.

Similarly, cytogenetic testing is conducted in a reflex algorithm where chromosome analysis is performed first to rule out the most common cytogenetic abnormalities found in POC (Laurino et al., 2005). If chromosomes appear normal, current literature recommends more sensitive chromosomal testing, microarray analysis, to assess for smaller chromosomal abnormalities that cannot be visualized through routine chromosome studies (Papas & Kutteh, 2020). Chromosomal analysis on the POC can take several weeks or may fail depending on the quality of the sample, which may further delay results (Kutteh, 2015). POC analysis can also be contaminated by maternal cells. Therefore, if microarray analysis reveals a normal female chromosome complement, a further study to rule-out maternal cell contamination is recommended to delineate whether the results are truly reflective of the genetics of the fetus as opposed to those of the mother (Yelnik et al., 2016). If an abnormality is identified in the POC, parental chromosome analysis may be necessary to determine if it was inherited to advise parents on future pregnancy risks and prenatal testing options (Kutteh, 2015). Figure 5 summarizes the complex nature of reflex chromosome analysis for pregnancy loss.

Figure 5

The Cytogenetic Algorithm for POC and Parental Blood Samples



Note. Adapted from Gardner, R. J. M., & Amor, D. J. (2018). Gardner and Sutherland's chromosome abnormalities and genetic counseling. Oxford University Press.

It is important to note that parental karyotype is only recommended if cytogenetic testing or microarray testing on POC is abnormal and specifically indicates the possibility of an inherited unbalanced translocation (Papas & Kutteh, 2020). An unbalanced translocation refers to a rearrangement of chromosomal material that is missing or has additional chromosomal material (Gardner & Amor, 2018). An unbalanced translocation in offspring occurs when a parent has a *balanced* chromosomal rearrangement that does not affect them but can result in unequal division of chromosomal material during gamete production (meiosis) (Gardner & Amor, 2018).

Thyroid testing also involves a reflex testing cascade to rule out autoimmune hypothyroidism. Thyroid stimulating hormone (TSH) testing can be impacted by pregnancy and should be repeated six weeks after pregnancy if necessary. If TSH is high or low, a measurement of T4 is required. If T4 is abnormal, thyroid peroxidase (TPO) antibody testing is required to diagnose autoimmune thyroiditis.

Challenges to Laboratory Testing Follow-up

RPL evaluation typically occurs in the outpatient clinical setting following a pregnancy loss. However, the physician caring for the patient in the outpatient setting is rarely the same physician that treated the patient in the emergency or surgical department during the miscarriage. While many women suffering from a miscarriage will do so spontaneously at home without the need for further medical care, those who do need additional medical care will generally present either in the Emergency Department (ED) or be scheduled for outpatient surgery. Following up on laboratory testing results from an acute care setting to an outpatient setting presents an additional hurdle for clinicians who care for RPL patients. Laboratory testing (such as cytogenetic analysis on POC) will be ordered by the obstetrical surgeon covering the ED or performing the outpatient surgery. The surgeon is rarely the primary obstetrician caring for the patient during the pregnancy, except in rural or remote settings where specialty providers are not in abundance.

Patients experiencing pregnancy loss are typically counseled about their options for genetic testing on the POC during the emergency department, thus the subsequent outpatient obstetrical clinician evaluating for RPL often has little influence on what type of testing was performed on the POC (Bacidore et al., 2009). Test results are returned to the surgeon, who presumably has an obligation to forward to the patient's OBCP,

however, this may not consistently occur (Callen et al., 2015). Also, if a patient experienced pregnancy loss at home, then no specimen from the POC would be available for laboratory testing.

Research on the lack of follow-up specifically for RPL laboratory test results and subsequent recommendations is largely absent from the literature. However, the detrimental impact of failure to follow-up on laboratory test results and reflex testing recommendations in other disease states is a well-described problem (World Health Organization, 2008). A systematic review by Callen et al. (2011) discussed the detrimental effect of missed test results for hospitalized patients. The lack of outpatient follow-up on results of laboratory testing performed on inpatients once they are discharged ranged from 20.04%-61.6% and was 1.0% to 75% among patients treated in the ED (Callen et al., 2011). The deficiency to follow up was defined as a lack of acknowledgement or failure to communicate results as documented in the EHR (Callen et al., 2011). The authors concluded that information technology (IT) solutions can facilitate better test result management processes (Callen et al., 2011). However, they acknowledged that patients, clinical care providers, and administrators all need to engage to establish the most effective solutions (Callen et al., 2011).

Laboratory Testing Challenges Faced by Clinicians

Given the extensive, time-sensitive, and reflex nature of testing often required, as well as the lack of clear guidelines, for the determination of RPL etiology, it is not surprising that providers report feeling ill-equipped to manage RPL care and evaluation (Diejemoah, 2014). In a review article discussing RPL treatments, Diejemoah (2014) cited that clinicians face challenges regarding diagnosis and treatment of RPL due to the

myriad etiologies that span several specialties. However, the author did not formally interview OBCPs to understand the factors that contribute to difficulty in evaluating RPL patients. Papas and Kutteh (2015), who lead an RPL and fertility clinic at the University of Tennessee Medical Center, highlighted the challenges in diagnosis faced by clinicians by anecdotally noting the types of questions they routinely received from obstetricians or non-specialists. Among the most frequent questions was one regarding the appropriate laboratory testing needed to evaluate RPL patients (Papas & Kutteh, 2015). In 2015, Kutteh reviewed the current trends in RPL evaluation from a clinical perspective, and he noted that questions that clinicians have include:

1. What is the number of losses that constitute RPL?
2. What is considered a pregnancy loss?
3. What does an RPL evaluation consist of?
4. When are parental karyotypes indicated?
5. When is genetic analysis on the POC needed?
6. What is the prognosis for live birth?

Laboratory Involvement in Clinical Testing

To better understand the potential of improved processes between clinicians and the clinical laboratory for patients with RPL, literature about other complex health conditions that require multiple laboratory tests to establish a diagnosis was examined. Laboratory Stewardship programs are responsible for ensuring appropriate test ordering, accuracy of results, and appropriate allocation of finances and resources (Graden et al., 2020). Excessive numbers of tests that are time-consuming or involve manual processes can be costly from a resource perspective and add to the turnaround time for time-

sensitive tests (Murphy et al., 2020). Therefore, these programs may involve collaboration among clinicians and clinical laboratory providers, such as pathologists, infectious disease experts, and genetic counselors to review inappropriate utilization patterns and advise on appropriate test ordering to mitigate unnecessary testing.

Although not specific to laboratory evaluation for RPL, Zhi et al. (2013) conducted a 15-year meta-analysis of laboratory test utilization from 1997 to 2012 in chemistry, hematology, microbiology, and molecular tests and concluded that the overall inappropriate test ordering is estimated at 30% with the mean rate of underutilization being 44.8% (CI 33.8-55.8%). The authors noted that the phenomenon of underutilization is understudied but advised that the key to improving care is to focus on solutions that lead to appropriate test ordering upfront (Zhi et al., 2013). The utilization patterns of laboratory testing for RPL evaluation are unknown; however, the departments assessed by Zhi et al. (2013) perform testing for RPL. Additionally, there are studies that specifically assessed test utilization of coagulation (Lee & Zierler, 2011; Pilsczek et al., 2005), endocrine (Gill et al., 2017), and genetic testing (Carter et al., 2022; Finucane et al., 2021), which are also all components of RPL laboratory testing. Studies that review potential interventions for laboratory test utilization encourage collaboration between clinical providers and clinical laboratorians since the exact mechanisms for inappropriate utilization are often specific to the system, organization, and individuals involved (Baird et al., 2018).

Although coordination of care frameworks or models do not exist explicitly for RPL in the literature, oncology care closely represents the complex nature of RPL evaluation because both conditions require multiple and reflex laboratory testing and

communication of results among a diverse group of clinical specialists. For example, multidisciplinary tumor boards involve a review of laboratory and pathology testing to make diagnoses and guide treatment plans for oncology patients. In that setting, the laboratory consults directly with clinicians about the patient's diagnosis but does not contribute to the next steps in care or treatment.

Tomasone et al. (2016) published a systematic review of models of care coordination for oncology patients used by primary care clinicians. Based on the complexity of oncology patient populations and highly individualized care settings, the authors concluded that the research on this topic lacks uniformity and generalizability (Tomasone et al., 2016). Therefore, there is no gold standard model for coordination of care for cancer that could be applied to evaluation of RPL. However, a multidisciplinary RPL clinic was found to improve the rate of pregnancy and determination of RPL etiology for patients (Young, 2018).

Coordination of Care as a Strategy

There is limited discussion within the literature about the best approaches to coordinate testing and clinical care services specifically for RPL. Papas and Kutteh (2015) proposed an algorithm for RPL evaluation including the recommendations regarding laboratory testing, such as the inclusion of chromosomal microarray, which increases the likelihood of identifying RPL etiology. However, the authors did not address the coordination of collecting and sending samples to the laboratory or communicating results to patients and clinicians.

Graetz et al. (2009) and Meigs and Solomon (2016) discussed the limitations of electronic health records (EHR) and the ability of clinicians to access, notify and

communicate results to patients or specialists. They cite the overwhelming amount of data in an EHR, increased daily patient volumes making notification and follow up significant barriers. Therefore, the mere existence of laboratory results within a shared EHR system does not necessarily translate into effective communication and follow-up of test results (Meigs & Solomon, 2016) and is further complicated if a patient seeks care from multiple health systems. At a minimum, improved communication of laboratory results between clinicians and laboratory professionals within the same health system is needed. However, an understanding of the OBCP perspective on barriers and facilitators to evaluating RPL patients and the role of laboratory testing is crucial to inform potential interventions aimed at improving the process.

ESHRE (2017) recommends that patients with RPL be followed in an outpatient clinic with specialists that can deliver support, etiology evaluation, and management. The guidelines also recommend "close coordination with the laboratory to facilitate communication and interpretation of [RPL evaluation] laboratory results" (ESHRE, 2017, p.21). However, they did not offer a framework for accomplishing this communication. Bacidore et al. (2009) described a framework for coordinating services for patients presenting to the ED at the time of pregnancy loss. The authors discussed the need for coordination between ED and OBCPs as well as social workers (Bacidore et al., 2009). However, they did not describe how the laboratory testing results should be communicated to the patients and/or additional clinicians following discharge (Bacidore et al., 2009). Furthermore, the authors did not distinguish between an initial pregnancy loss versus RPL, and therefore, they did not describe a way to incorporate an RPL-specific laboratory testing evaluation (Bacidore et al., 2009).

Literature on RPL multidisciplinary clinics often cites the importance and necessity of laboratory testing, but the extent of collaboration, consultation, and role of the laboratory is not discussed (Young, 2018). Similarly, in a retrospective cross-sectional study, Kuroda et al. (2021) proposed a treatment strategy for RPL patients termed "OPTIMUM" (Optimization of Thyroid function, Immunity, and Uterine Milieu). However, their strategy did not address the coordination of RPL etiology evaluation between the laboratory and clinicians.

Theoretical Frameworks

To study the complex nature of laboratory test utilization for RPL evaluations and the relevant stakeholders, a framework is needed to provide a foundation and serve as a guide. The Consolidated Framework for Implementation (CFIR) is a commonly cited implementation framework that incorporates the perspectives of the stakeholders, the organization, the system, and the process involved in implementation. CFIR is used as a guide in both qualitative interviewing, quantitative survey, and mixed methods designed studies (Damschroder et al., 2009). The Theoretical Domains Framework (TDF) is a behavioral change framework utilized in studies that aim to understand the behavior and motivation of individuals surrounding process improvement and implementation (Cane et al., 2012). The combined use of the TDF as an accompanying framework to CFIR has been cited in a systematic review, which concluded that studies that combined CFIR and TDF did so when provider or individual behavior was a central focus of implementation (Birken et al., 2017).

Consolidated Framework for Implementation (CFIR)

CFIR is a frequently cited guide to intervention implementations which consider the context including the external and local environment and individuals involved (Kirk et al., 2016). Originally published in 2009 by Damschroeder et al., CFIR serves as a culmination of implementation theories and frameworks and consists of five primary domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation. Each domain is then broken down into constructs (Table 3).

Table 3

CFIR Domains and Constructs

Domains	**Constructs**
Intervention characteristics	Intervention source
	Evidence strength and quality
	Relative advantage
	Adaptability
	Trialability
	Complexity
	Design quality
	Cost
Inner Setting	Structural Characteristics
	Networks and communications
	Culture implementation
	Climate
Outer Setting	Patient needs and resources
	Cosmopolitanism
	Peer pressure
	External policies and incentives
Individuals Involved	Knowledge and beliefs about the intervention
	Self-efficacy
	Individual stage of change
	Individual identification with organization
	Other personal attributes
Implementation Process	Planning
	Engaging
	Executing
	Reflecting and evaluating

Since the original publication, CFIR has been cited by over 463 articles according to a 2022 Scopus search and is often used with the goal of improving patient care and with particular concern for contextual determinants (barriers and facilitators). Kirk et al. (2016) systematically reviewed the use of CFIR in publications and noted that 26 articles cited using the framework in a "meaningful way" including during the process of data collection, measurement, coding, analysis, and/or reporting in primarily qualitative or mixed-methods research studies. Kirk et al. (2016) concluded that the most frequently

cited domains were related to the complexity of the intervention, resources and communication within the inner setting, and knowledge and beliefs about the intervention within the individual domain. The authors concluded that CFIR is most beneficial to implementation if used as a guide throughout the research process (Kirk et al., 2016).

CFIR has been used to guide implementing improvements in maternal health services (Aruldas & Kant, 2022; DeSisto et al., 2019). For example, Aruldas and Kant (2022) conducted a qualitative study investigating how to improve post-partum maternal morbidity and mortality in India. The authors conducted qualitative interviews of health care workers and patients and used CFIR in their interview guide and thematic coding of interview transcripts. The study explored how patients and their families make decisions about what level and type of care to access emergency obstetric services and concluded that more information is needed (Aruldas & Kant, 2022). However, no articles on the use of CFIR in the coordination of care for patients with RPL were identified.

Most applications of CFIR within the laboratory context focused on interventions related to antimicrobial stewardship, which is an initiative aimed at reducing the inappropriate use of antibiotics while still testing and treating infectious diseases appropriately (Pevnick et al., 2021). The authors proposed a multicenter, randomized control trial focused on post-hospitalization medication management in an effort to reduce re-hospitalization (Pevnick et al., 2021). Specifically, they generated a pathway that would allow pharmacists to lead the chart review, optimization, and laboratory tests necessary to communicate with patients, reduce polypharmacy, encourage adherence, and reduce readmission (Pevnick et al., 2021). The authors used CFIR to determine barriers and facilitators in implementation of the intervention and in the thematic coding analysis

of participants' responses (Pevnick et al., 2021). Additionally, a National Institutes of Health (NIH)-funded study referred to as "IGNITE (Implementing Genomics in Practice)" also used CFIR to guide the development and implementation of a model for using genomic testing in clinical practice (Weitzel et al., 2016). The authors highlighted how critical the use of a framework was when bridging the many unique settings involved in IGNITE (Weitzel et al., 2016). Given that the current study examined transitions of care, review of clinical information to coordinate care, and appropriate test utilization amongst stakeholders, the CFIR framework served as a valuable guide during the data collection and analysis components of this project.

Theoretical Domains Framework (TDF)

The TDF has been well-established as a framework used in assessing barriers and facilitators to implementation (Atkins et al., 2017; Lipworth et al., 2013; Maharaj et al., 2021). Originally, the TDF was published in 2005 and contained 12 domains, which included: knowledge; skills; social/professional role and identity; beliefs about capabilities; beliefs about consequences; motivation and goals; memory, attention, and decision processes; environmental context and resources; social influences; emotion; behavioral regulation; and nature of the behaviors (Michie, 2005). The TDF was validated in a systematic review by Cane et al. (2012) and subsequently, the framework was refined into 14 domains: knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and resources; social influences; emotions; and behavioral regulation (Cane et al., 2012); see Table 4.

Table 4

Theoretical Domains Framework Domains

Domain	Constructs
Knowledge	Procedural knowledge
Skills	Competence, Ability
Social/professional role/identity	Professional identity Social identity, Professional confidence
Beliefs about Capabilities	Self-confidence, Perceived confidence
Optimism	Optimism, Pessimism
Beliefs about Consequences	Outcome Expectancies, Anticipated regret, Consequents
Reinforcement	Rewards, Incentives, Punishment, Contingencies
Intentions	Stability of intentions, Stages of change
Goals	Goal priority, Target setting, Action planning
Memory, Attention, and Decision Processes	Memory, Attention, Decision making, Cognitive overload
Environmental Context and Resources	Environmental stressors, Resources, Organizational culture
Social Influences	Social pressure, Social norms, Group conformity
Emotion	Fear, Anxiety, Stress, Depression, Positive/negative affect
Behavioral Regulation	Self-monitoring, Breaking habit, Action planning

Note. Adapted from Cane, J., O'Connor, D., & Michie, S. (2012a). Validation of the theoretical domains framework for use in behaviour change and implementation research. Implementation Science : IS, 7, 37-37. https://doi.org/10.1186/1748-5908-7-37

Schexnayder et al. (2021) used the TDF to evaluate improved access to cardiovascular disease evaluation for patients with HIV, and Miller et al. (2019) conducted a mixed-methods study on improving transitions of care between the ED and primary care in the Veterans Administration Health System. The TDF also was used in a qualitative study to determine the factors that contribute to improvement in the coordination of oncology treatment (Ellis et al., 2022). The authors used the TDF to thematically analyze clinician interview transcripts and concluded that some barriers, such as time and resources, could be overcome by rotating provider responsibility within

the team (Ellis et al., 2022). The use of the TDF by Ellis et al. (2022) illustrates its application to physician interviews, however, the study did not include non-clinical team members or patients.

Like CFIR, the TDF was used in a 2020 systematic review that assessed barriers and facilitators to implementation of antimicrobial stewardship programs (Rzewuska et al., 2020). The "environmental context and resources" domain, which includes data and information systems, lack of personnel, and inadequate financial resources, was most cited among barriers, along with having other higher priorities which mapped to the "goals" domain (Rzewuska et al., 2020).

In another study evaluating laboratory stewardship efforts, White et al. (2021) described their experience with an initiative focused on thyroid testing utilization quality improvement. The initiative was created to curb the number of inappropriately ordered thyroid tests in asymptomatic patients. Their team included endocrinologists from outside the laboratory and directors and technologists from within the laboratory. The team identified the providers that were more commonly ordering excessive testing by electronic data review and had the endocrinologists consult directly with the providers to discuss their test ordering practices. Following a collaboration between clinicians and the laboratory, a significant decrease in inappropriate test ordering was observed. Although White et al. (2021) did not explicitly cite the TDF, their proposed framework included five elements that closely align with the TDF, including appropriate incentives, goals, and motivation as crucial components to achieving the goals of the program (Table 5).

Table 5

Crosswalk between White et al (2021) framework and aligning TDF Domains

White et al Framework	Aligning TDF Domain
1. Clear vision and organizational alignment	Social/Professional Role and Identity
2. Appropriate skills for program execution and management	Skills Knowledge
3. Resources to support the program	Environmental context and resources
4. Incentives to motivate participation	Reinforcement
5. A plan of action that articulates program objectives and metrics	Goals Beliefs and Consequences

VanSpronsen (2021) interviewed medical laboratory technologists (MLTs) regarding their perceived barriers to participating in laboratory stewardship activities related to examining test utilization. Their responses were thematically analyzed and mapped to the TDF. The authors concluded that the themes most strongly mapped to the TDF were the "environmental context and resources" domain, which illustrates the impact of workplace culture on the roles of MLTs. The study was limited as they did not explore physicians' or patients' perspectives on the role that MLT's could play in test utilization management.

CFIR and TDF have also been used in tandem when exploring factors surrounding appropriate utilization of testing and adherence (Flemons et al., 2022). In an explanatory mixed-methods study, Flemons et al. (2022) applied CFIR and the TDF to their interview guide as well as in the coding and thematic analysis of their study on the barriers and facilitators of following perioperative surgical recommendations. The authors performed a chart review and noted that only 55.7% of recommendations were followed (Flemons et al., 2022). They then conducted qualitative interviews with

surgeons who were identified as adhering to or missing the most recommendations (Flemons et al., 2022).

Conclusion

While RPL is relatively common, there is no consensus or internationally accepted guidelines on either the definition or evaluation for this condition, leading to gaps in completed testing and care. A potential improvement in the follow-up and evaluation of patients with RPL may rely upon coordination of laboratory testing by clinical laboratorians and OBCPs. While there are some examples of the care coordination for certain conditions, there is not a specific process to coordinate appropriate RPL etiology evaluations. Before such processes can be implemented, it is critical to first identify the factors that may serve as facilitators and barriers to the RPL etiology evaluation, particularly the complex laboratory testing component. This study aimed to understand these factors from the perspective of OBCPs.

Chapter 3: Methodology

Introduction

This chapter is an overview of the methodology for this research study and discusses the data collection and analysis methods, including the philosophical paradigm, conceptual framework, interview participant selection, interview questionnaire, and study alignment.

Background

The objective of this study was to understand the factors contributing to incomplete evaluation, particularly in terms of laboratory testing, for patients with recurrent pregnancy loss (RPL) from the perspective of the obstetrician-gynecologist clinical provider (OBCP). An article written by the director of the pregnancy loss center at Vanderbilt University described the challenges of ordering laboratory testing including how many losses warrant an evaluation, as well as guidance as to what tests should be ordered and when (Kutteh, 2015). However, there has not been a research study that explores the gaps in testing for RPL patients and the OBCP perspective on these gaps.

Although previous literature suggests that a multidisciplinary collaborative approach to laboratory testing can reduce medical errors in test selection and interpretation, these articles are written from the perspective of laboratory professionals (Astion & Dickerson, 2018; Cadamuro et al., 2018; Callen et al., 2015; Ducatman et al., 2020; Mirham et al., 2021; White et al., 2021). This research study aimed to understand the OBCP perspective on how the laboratory testing component of an RPL evaluation can be improved. Therefore, the central research question driving this research was "What is the experience of OBCPs of the laboratory testing evaluation for RPL?" The long-term

goal of this study is to use this data to inform future interventions to facilitate completed laboratory testing and improve the identification of the etiology of RPL for individual patients.

Table 6

Specific Aims

Specific Aim	***Research Question***	***Method***
Aim 1: Assess the current OBCP practice behaviors for laboratory testing for RPL patients.	RQ1: What are the current practice behaviors and ordering patterns by OBCPs for RPL evaluation?	***Quantitative Analysis: Retrospective chart review of lab tests in patients with RPL***
Aim 2: Explore contributing factors that influence provider behavior on laboratory testing for RPL patients.	RQ2: How do OBCPs describe their experience of evaluating patients with RPL?	***Qualitative Analysis: Semi-structured interviews with OBCPs that ordered laboratory testing on the patients from the quantitative chart review***
Aim 3: Integrate the findings from the chart reviews and qualitative interview themes of the study to suggest potential future interventions that may improve consistency and completion in laboratory test ordering.	RQ3: How do the test ordering practice behaviors and OBCP interviews inform future interventions to promote completed laboratory test evaluations of RPL?	***Mixed Methods Analysis: Integrate findings from quantitative and qualitative phases***

Philosophical Underpinnings

This study adopted a pragmatic ontology, which is the philosophical viewpoint that there are multiple realities that may change depending on the research question and context (Creswell & Poth, 2018). The pragmatic philosophical paradigm can utilize several research methods since the primary objective is to use the method that results in data that can then be most practically applied to the given context (Morgan, 2007). Mixed methods research (MMR) is considered a hallmark of pragmatic research since

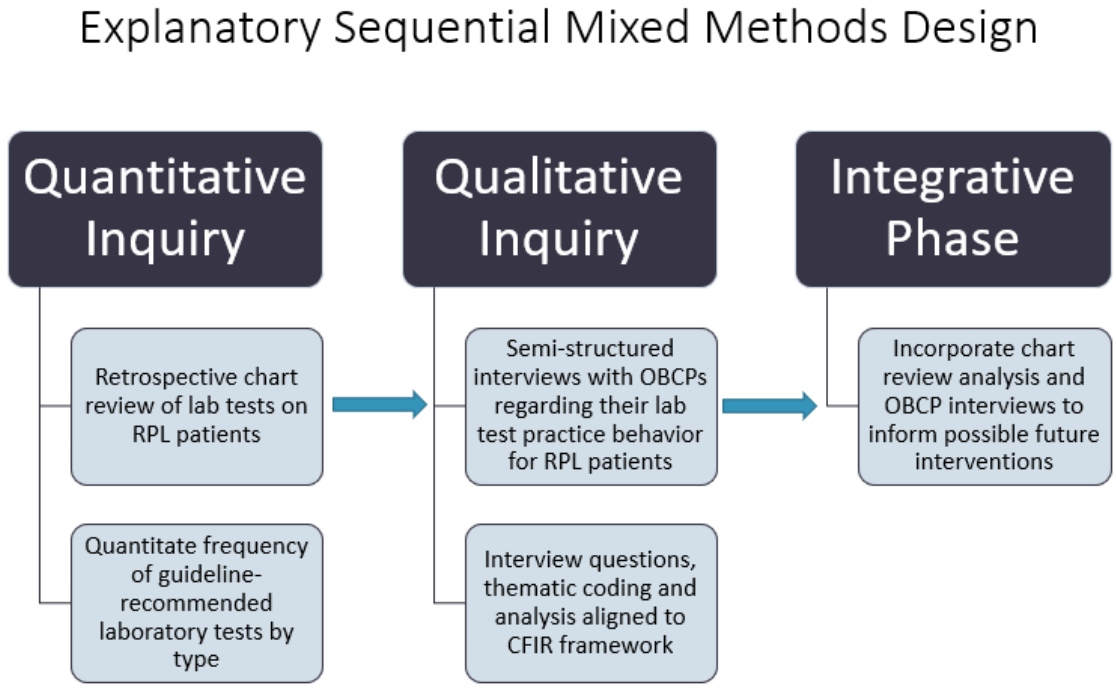
quantitative and qualitative research methods are combined in one study to bridge the gap in literature and understanding (Creswell & Poth, 2018). Additionally, MMR is frequently utilized in pre-implementation studies that assess barriers and facilitators to adherence of a program, guideline, or intervention (Borglin, 2015; Conlon, 2021; Flemons et al., 2022). While Kutteh (2015) discussed the frequently asked questions of clinicians evaluating the etiology of RPL, no previous systematic research could be identified that specifically explores the perspectives of OBCPs on factors that may be impacting the laboratory testing component of RPL evaluation. In a recent unpublished preliminary analysis of RPL patients conducted at Northwell Health identified existing gaps in laboratory testing for RPL. An exploration of the potential causes for these gaps with OBCPs, the key stakeholders, may inform next steps toward process improvement.

Study Design

This study used a sequential, explanatory mixed methods design focused on the factors surrounding the laboratory testing evaluation of RPL. The quantitative phase consisted of a retrospective chart review of patients with RPL to assess the frequency with which guideline-recommended testing was ordered. The results from the retrospective chart review, as detailed in Chapter 4, informed purposeful sampling followed by convenience sampling of OBCPs to interview during the qualitative phase. Focusing on test ordering behaviors across the low, medium, and high categories allowed for diversity of perspectives on how to best implement a model for RPL laboratory testing evaluation based on individual experiences of OBCPs.

Figure 6

Study Design



Methods

Quantitative Phase

Data Collection. A retrospective chart review from the Northwell Quality Assurance Database (QADB) was conducted on established patients who had cytogenetic testing (chromosome analysis) ordered on ≥2 products of conception (POC) from January 1, 2014, through June 30, 2021 (Figure 6). This time frame was selected because the database being utilized dates back to 2014 and although the analysis was being conducted in 2023, capping the time frame to 2021 allowed patients a two-year time frame to receive an RPL evaluation. For the quantitative phase, the participant inclusion criteria were all patients who had two or more pregnancy losses as documented by having at least two separate cytogenetic analysis tests on products of conception (POC). Exclusion criteria were patients who had two POC cytogenetics tests at the same time from a twin

pregnancy and patients who had no documentation of seeing a Northwell Health Physician for the care of their pregnancy. Unestablished patients were excluded since there would be no way of determining whether their provider sent laboratory testing to another laboratory. Although uterine radiological exams are also a recommended for RPL patients, evidence of these procedures was not collected as a part of this study as the focus was on laboratory testing. The chart review included any laboratory results following the second loss up to the current time (July 2023). Participants that had no return visits within that time frame were counted as having zero tests. Initial data from the QADB was filtered and downloaded into Excel for data analysis.

Data Analytic Plan. Using the Touchworks® electronic medical record system, records of those patients that met inclusion criteria were analyzed for incidence of laboratory testing results including chromosome and microarray analysis on POC, maternal karyotype, Hgb A1C, TSH, anticardiolipin antibodies (aCL), lupus anticoagulant (LA), and anti-beta2 glycoprotein I antibodies (B_2GPI). The tests were categorized as performed or not performed, and the performed tests were further delineated into normal and abnormal categories. Based on the number of tests performed, each patient's evaluation was ranked as "low," "medium," and "high": "Low" if one to two tests were performed, "medium" if three to four tests were performed, and "high" if five to six were performed. Each score was assigned a number value. For example, high=three, medium=two, and low=one. The reasoning for this grouping is because TSH and Hgb A1c are typically collected together at a first prenatal visit. All OBCPs that ordered tests for the patients within the quantitative section were selected for inclusion in the qualitative phase. Attention was paid to include the ordering OBCPs from evaluation

categories low, medium, and high to better understand what led to these test ordering patterns. Since the OBCPs ordered tests on multiple patients, an average evaluation score was tabulated for each participating OBCP from the quantitative data set.

Qualitative Phase

Participants. The study population for the qualitative phase of the research study included providers within the Division of Obstetrics and Gynecology (OBCPs) at Northwell Health in Long Island, New York, which was chosen due to the researcher's existing role within this health system. The credentials eligible for inclusion were Obstetrician Gynecologists physicians [Doctor of Medicine (MD) or Doctor of Osteopathic Medicine (DO)], Physician Assistants (PA), Certified Nurse Midwives (CNM), Registered Nurses (RN) and Nurse Practitioners (NP). The inclusion criteria for participation were providers caring for and evaluating RPL patients in current or recent (since 2020) practice, authority to order laboratory testing for RPL (current licensure), and utilization of the Northwell Health Laboratory for RPL laboratory testing.

Sampling and Recruitment. OBCPs identified through the quantitative phase of the study were purposefully selected and invited to participate in semi-structured qualitative interviews. All OBCPs from the quantitative phase with active Northwell Health email addresses were sent an email invitation to participate (Appendix A) along with a consent form (Appendix B). Although the original intention was to interview providers included in the original quantitative data set, only five participants were obtained. Therefore, convenience sampling for additional eligible colleagues contributed to the remaining 10 participants.

Data Collection. Since the aim of the qualitative phase was to understand factors contributing to the provider's laboratory test ordering for RPL patients, which includes an understanding of their individual behavior, their practice setting and external factors such as insurance coverage, the CFIR model was applied to develop a semi-structured interview protocol (see Appendix C). Although CFIR is often viewed as a tool for guiding implementation of an existing intervention, CFIR has also been used to guide pre-implementation research centering around factors that may drive or impede implementation (Damschroder et al., 2009; Flemons et al., 2022). Importantly, CFIR provides a qualitative interview guide to address each domain (Intervention, Outer Setting, Inner Setting, Individual Characteristics, and Process) to provide context for participant responses. The interview questions focused on the individuals' experiences of laboratory testing for RPL evaluation aligned with each domain (see Appendix C). The Theoretical Domains Framework (TDF) was used to refine themes and codes corresponding to the individual domain.

Data Analytic Plan. Interviews were conducted with individual participants online via Zoom. Transcripts and recordings were created by Zoom and manually reviewed and cleaned. The transcripts were coded and thematically analyzed utilizing CFIR constructs and domains as the underlying framework. The theoretical domains framework (TDF) was used to provide subcategories under the "individual" CFIR domain since the nature of qualitative interviewing relies heavily upon the individual experience including their beliefs, motivations, and insights (Cane et al, 2012). Analytical coding was descriptive, and thematic analysis was performed with Dedoose software.

Human Participants and Ethics Precautions

Quantitative Phase

Institutional Review Board (IRB) approval was obtained from Northwell Health and George Washington University (GWU) IRB committees for all research activities. The quantitative portion of the study obtained laboratory results from Touchworks® electronic medical record system and collected information was stored in the secure REDCap® database through Northwell Health. All quantitative data was de-identified. No information linking patients to laboratory test results was retained. Patient electronic medical record access was password protected and laboratory test results were de-identified.

Qualitative Phase

Confidentiality for this study was maintained by using code names for participants and keeping a file linking participants to code names on a separate, secure data platform at Northwell Health known as RedCap. The consent form to participate in the qualitative phase was emailed to participants for reviewing and signing before scheduling. Verbal consent was also obtained at the commencement of the interview, and participants were reminded that their participation is voluntary. Interview participants were compensated in appreciation for their time (Appendix B). The Zoom video conferences required a unique meeting link and were only accessible via username and password and were restricted to the individual "invited" to the meeting. Transcripts were auto generated using the feature embedded in Zoom, stored on a password protected computer, did not contain any interviewee identifiers, and were destroyed after analysis and research was complete.

Statement of Subjectivity

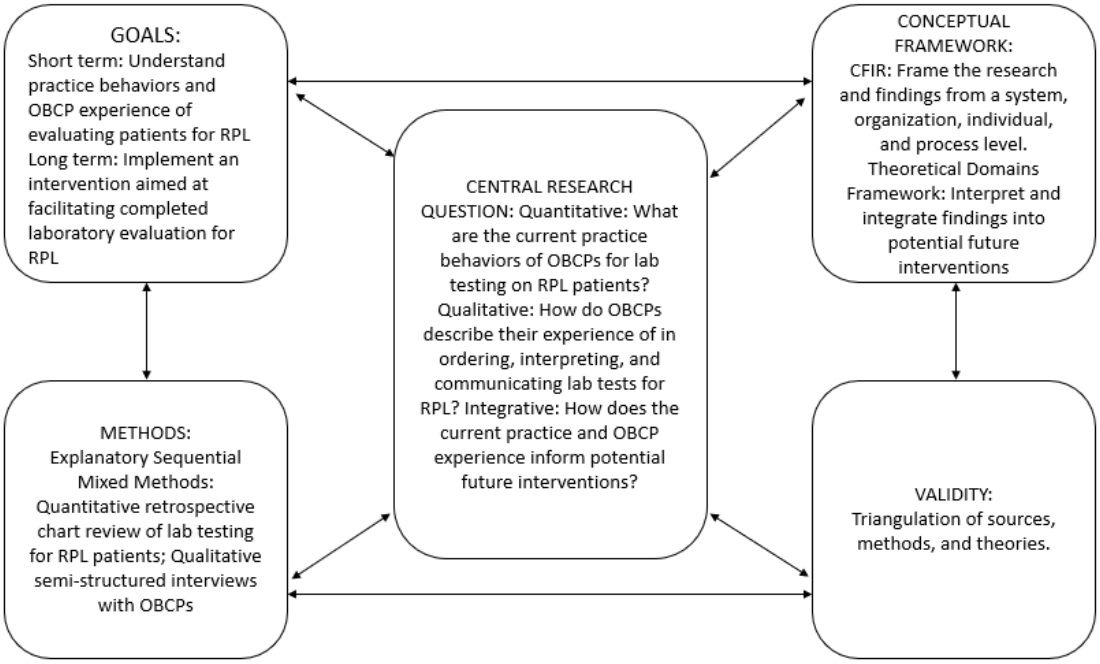
The researcher for this study has a background in human genetics and provides genetic counseling for patients with RPL. Additionally, the researcher's current professional role is within the Northwell Health Laboratory. Being intimately familiar with the laboratory test ordering and resulting system, it was crucial to maintain objectivity throughout the interviews. The use of CFIR as a guiding framework for the interview questions offered a degree of neutrality in forming the interview protocol. Bias was mitigated by utilizing a technique referred to as "bracketing," which employs a memo writing technique to recognize personal biases and to keep the researcher from interjecting or imposing the personal biases during interviews (Tufford & Newman, 2012). Additionally, reflexive journaling allowed the researcher to note assumptions, research motivations, and the position that the researcher had within the context of the interview participants (Tufford & Newman, 2012).

Summary

Maxwell (2013) describes the importance and balance of a research study's components including the goals, methods, validity, conceptual framework, and the central research question that must align with one another. Figure 7 demonstrates the alignment of this study.

Figure 7

Study Alignment



Note. Adapted from Maxwell, J. A. (2013). Qualitative research design: an interactive approach (3rd ed.). SAGE Publications.

This explanatory, mixed methods study began with a quantitative retrospective chart review of laboratory testing conducted on RPL patients who received care from Northwell Health from 2015-2021. Based upon the chart review outcomes, including completeness of ordering and follow up of abnormal results, OBCPs who ordered the laboratory testing were invited to participate in semi-structured qualitative interviews to understand what factors contribute to their current practice behaviors surrounding RPL evaluation. CFIR was used as the guiding framework to understand barriers and facilitators to ordering on varying levels of practice including individual, intervention, process, and inner and outer settings. The Theoretical Domains Framework (TDF) was

used to inform the analysis of the qualitative interview data and the role of behavior change as it may apply to future interventions to improve RPL laboratory testing.

Chapter 4: Results

The purpose of this study was to describe OBCPs practice behaviors regarding the evaluation of the etiology of RPL and to identify potential barriers and facilitators at the pre-analytical, analytical, and post-analytical stages of laboratory testing that may inform interventions aimed at improved RPL evaluation. The specific aims and research questions addressed by this study include the following:

> Specific Aim 1: Assess the current OBCP practice behaviors for laboratory testing on RPL patients. RQ1: What are the current practice behaviors and ordering patterns by OBCPs for RPL evaluation?
>
> Specific Aim 2: Explore contributing factors that influence OBCP behavior on laboratory testing for the evaluation of RPL etiology. RQ2: How do OBCPs describe their experience of evaluating patients for RPL?
>
> Specific Aim 3: Integrate the findings from the chart reviews and qualitative interview themes of the study to suggest potential future interventions that may improve consistency and completion in laboratory test ordering. RQ3: How do the current test ordering practice behaviors and OBCP interviews inform future interventions to promote completed laboratory test evaluations of RPL?

To assess practice behavior, a retroactive chart review of patients with RPL was conducted, followed by qualitative interviews with a purposeful sample of OBCPs. The themes from the interviews were then integrated with the results from the chart review.

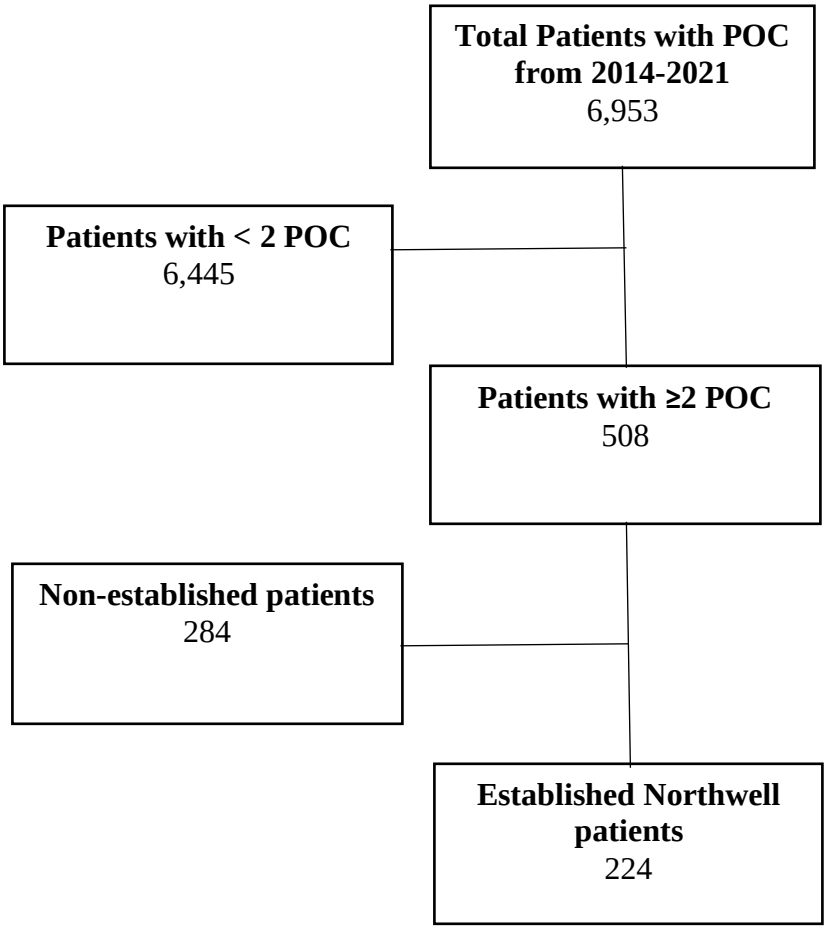
Quantitative Results

Patient Characteristics

6,953 patients were identified with documented cytogenetic analysis of POCs from 2014-2021. Of these, 508 (7.3%) had two or more cytogenetic analyses, and of these, 224 (44.1%) patients had documentation from a Northwell provider consult for the care of the pregnancy. Thus, 224 patients were included in the Phase I quantitative analysis of the study (Figure 8).

Figure 8

Quantitative Study Population



Patient demographics, including age at time of qualifying loss (second of two losses with fetal tissue sent for cytogenetic studies), race, and insurance type (Medicaid versus Private), are presented in Table 7. Patients with no documented insurance, were defined as "N/A" or "Not Available." The median age at the time of second loss (M=35, Range=18-48 years) was calculated from the difference between the order date of the second of two chromosome analyses on POC and the patient's date of birth. White was the most common race listed for patients (n=157; 70.1%), and 63.8% of patients (n=143) had private insurance.

Table 7

RPL Patient Demographics (N=224)

Median age at time of 2nd loss	35.0	
Race		
	n	**%**
White	157	70.1%
Black	19	8.5%
Asian	27	12.1%
Other-Hispanic	8	5.8%
Other	13	3.6%
Insurance		
Medicaid	60	26.8%
Private	143	63.8%
Not Available*	21	9.4%

*Chart lacked insurance information

Provider Characteristics

The ordering provider for the blood laboratory tests was documented for each patient. Cytogenetics testing on the POC is usually ordered by the obstetrical surgeon who does not evaluate patients for RPL, and therefore, the obstetrical surgeons were not considered the patients' OBCP. The total number of unique providers was 131 based within 60 unique practices within the Northwell Health System. Most providers were from the two major hospitals within the Northwell Health System, North Shore University Hospital in Manhasset, New York, and Long Island Jewish Hospital, in Great Neck, New York.

Products of conception (POC) cytogenetic analysis results

There were 488 total POCs analyzed from 224 patients; most patients had two total pregnancy losses (191; 85.3%), while 26 (11.6%) patients had three losses, and 7 (3.1%) patients had four losses (Table 7). None of the patients had more than four documented POC cytogenetic analyses. Of the 488 total POCs, 200 (41%) POCs had normal cytogenetic analysis, 233 (47.7%) were abnormal, and 55 (11.3%) POCs failed cytogenetic analysis. Cytogenetic analysis requires living and dividing cells, and some POC samples can fail to grow sufficiently for analysis. Many POCs that fail to grow also have abnormal chromosomes (Gardner & Amor, 2018). Without microarray analysis to follow up after a normal or failed chromosome analysis, it is possible that these samples had maternal cell contamination and/or abnormal chromosomes.

Table 8

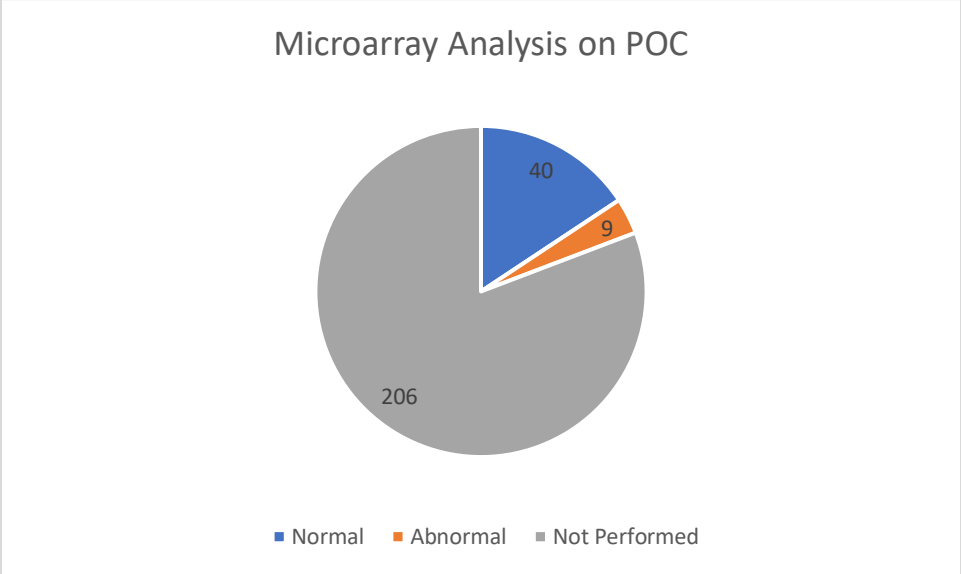
POC Chromosome Analysis Results

		Normal		Abnormal		Failure	
		n	**%**	**n**	**%**	**n**	**%**
First POC Results	**224**	90	40.2%	110	49.1%	24	10.7%
Second POC Results	**224**	92	41.1%	105	46.9%	27	12.1%
Third POC Results	**33**	13	39.4%	17	51.5%	3	9.1%
Fourth POC Results	**7**	5	71.4%	1	14.3%	1	14.3%
TOTAL	**488**	200	41.0%	233	47.7%	55	11.3%

Patients with normal and failed POCs (255 total) represent the group that could have benefitted from microarray analysis, however only 49 (19.2%) were performed. Of these microarray results, 40 (81.6%) were normal. Concerningly, 9 of 49 (18.4%) microarray analyses were abnormal (Figure 9), which could impact future reproduction for the patient (Papas & Kutteh, 2020).

Figure 9

POCs Eligible for Microarray



RPL Laboratory Tests Results and Performance

The 224 charts of patients who met all inclusion criteria were reviewed for documentation of completion of the following laboratory tests: Hgb A1C, TSH, maternal karyotype, anticardiolipin antibodies, lupus anticoagulant, and anti-Beta2 glycoprotein 1 antibodies. The findings are summarized in Table 9 and visualized in Figure 10 below. Reproductive partner karyotype was not included in analysis due to the difficulty of linking partners with RPL patients.

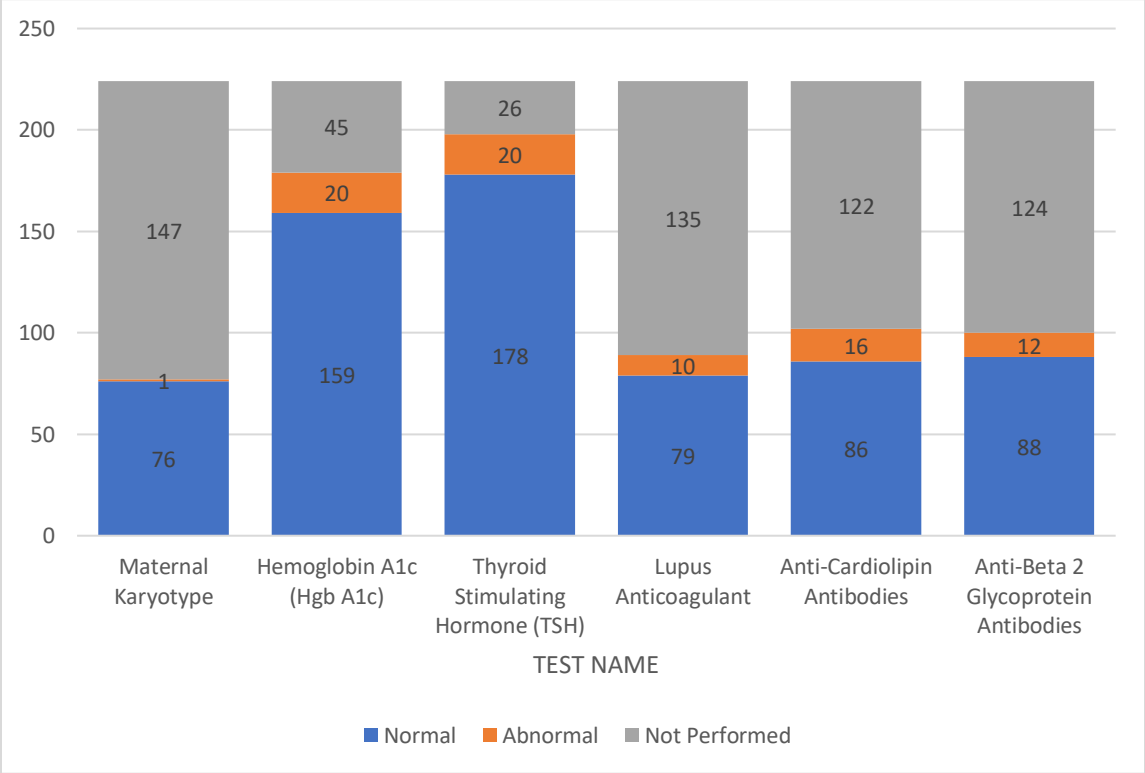
Table 9

RPL Laboratory Tests Performed and Results (N=224)

	Tests Performed						Total Not Performed	
	Normal		Abnormal		TOTAL			
Test Name	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Maternal Karyotype	76	98.7%	1	1.3%	77	34.4%	147	65.6%
Hemoglobin A1c (Hgb A1c)	159	88.8%	20	11.2%	179	79.9%	45	20.1%
Thyroid Stimulating Hormone (TSH)	178	89.9%	20	10.1%	198	88.4%	26	11.6%
Lupus Anticoagulant	79	88.8%	10	11.2%	89	39.7%	135	60.3%
Anti-Cardiolipin Antibodies	86	84.3%	16	15.7%	102	45.5%	122	54.5%
Anti-Beta 2 Glycoprotein Antibodies	88	88.0%	12	12.0%	100	44.6%	124	44.6%

Figure 10

Tests Performed (Normal or Abnormal) or Not Performed by Test Name



As observed in the preliminary study reported in Chapter 1, high levels of adherence were observed in ordering TSH and HbA1c. However, these may have been collected as part of routine obstetrical, gynecological, or annual medical care, and not specifically as part of an evaluation for RPL. Testing to assess antiphospholipid antibody syndrome (APLS) remained low and incomplete. Despite completion of all three tests being required to establish a diagnosis of APLS, they were performed in only the minority of cases: lupus anticoagulant (LA) testing (39.7%), anti-cardiolipin (aCl) (45.5%), and anti-beta2 glycoprotein I antibodies (B2GP1) (44.6%). Additionally, inconsistency was noted amongst the three APLS tests as the LA component was ordered less frequently than aCl and B2GP1.

Quantitation of RPL Laboratory Tests

For each patient, the evaluation was rated as "Low," "Medium," or "High" based on the number of tests considered part of a full RPL evaluation that were ordered. The low category was defined as ordering one to two tests. Medium category was defined as ordering three or four tests, and the high category was considered as ordering five to six tests. Most evaluations (113 [50.4%]) fell into the “low” category, 30 (13.4%) fell into the “medium”, and 81 (36.1%) fell into the “high” category. This distribution suggests that patients with more than two pregnancy losses are either receiving nearly all or almost none of the complete laboratory test panel for RPL evaluation, indicating potential overutilization or underutilization of laboratory tests.

Most providers illustrated variability in their test ordering behavior for different patients. Some OBCPs ordered a complete laboratory testing panel on one patient but may have ordered only one or two tests on a subsequent patient. Very few providers consistently ordered all six tests on every patient in their care. Many of the OBCPs with evaluations in the high category were highly specialized such as reproductive endocrinologists. In general, low category providers were more often generalists or hospitalists. Fourteen (20.9%) providers in the high category ordered a completed work up despite abnormal chromosomes being identified in the POC and thus being the explanation for the pregnancy loss, which would indicate overutilization of testing.

Patient Characteristics

Patient characteristics within each testing category (low, medium, or high) are presented in Table 10. Most patients in each category were white with two pregnancy losses. Interestingly, having three or four pregnancy losses did not correspond to an

evaluation with high adherence to guidelines nor did type of insurance. The highest percentage of patients in each adherence category (low, medium, and high) had private insurance (64.6%, 50%, and 70.9%, respectively). White patients were also the most represented race in each adherence category (69.0%, 73.3%, and 70.9%, respectively).

Table 10

Characteristics of RPL Patients Based on Evaluation Score Category

CATEGORY	**LOW (1-2)**		**MEDIUM (3-4)**		**HIGH (5-6)**	
	n=113		n=30		n=81	
Median Patient Age	35.2		34.8		34.7	
Number Of Losses	**n**	**%**	**n**	**%**	**n**	**%**
2 (N=191)	100	52.4%	24	12.6%	67	35.1%
3 (N=26)	11	42.3%	4	15.4%	11	42.3%
4 (N=7)	2	28.6%	2	28.6%	3	42.8%
Race	**n**	**%**	**n**	**%**	**n**	**%**
White (N=156)	77	49.4%	22	14.1%	57	36.5%
Black (N=20)	12	60%	2	10%	6	30%
Asian (N=27)	12	44.4%	4	14.8%	11	40.8%
Other-Hispanic (N=8)	3	37.5%	0	0%	5	62.5%
Other (N=13)	9	69.2%	2	15.4%	2	15.4%
Insurance Type						
Private (N=152)	80	52.6%	15	10.3%	57	37.5%
Medicaid (N=61)	28	40.7%	11	18.0%	22	36.7%
N/A (N=11)	5	45.5%	4	36.4%	2	18.2%

Quantitative Phase Summary

The quantitative phase of this research assessed OBCP laboratory testing practice behaviors for evaluation of RPL through a retrospective chart review. Out of 508 patients with RPL from 2014 to 2021, 224 patients met all inclusion criteria. Most of the 224 patients were white with two pregnancy losses with a median age of 35 at the time of the second loss. Of the 488 total POCs among 224 patients, there were 255 (52.3%) POCs that had normal or failed cytogenetic analysis and could have benefited from subsequent microarray analysis. Thus, microarray analysis was performed on only 49 out of the 255 (19.2%) POCs despite being indicated due to normal or failed chromosomal analyses.

Tabulation of the laboratory testing performed on 224 patients revealed that maternal karyotype was the least performed test, followed by lupus anticoagulant, anti-cardiolipin antibodies, and anti-Beta 2 glycoprotein I antibodies. The blood tests performed the most frequently were Hgb A1c and thyroid stimulating hormone. The blood test with the highest percentage of abnormal results was anti-cardiolipin antibody testing. In terms of adherence to laboratory testing guidelines for evaluation of RPL, 113 of 224 (50.4%) evaluations fell into the "low" category, 30 (36.1%) in the 'middle' category, and 81 (36.1%) in the "high" category. To better understand these patterns of utilization, semi-structured interviews with OBCPs were conducted.

Qualitative Phase Results

Participants

Among 113 unique providers identified as having ordered tests for RPL evaluation through the retrospective chart review, 67 providers were still employed at Northwell with valid Northwell email addresses, and all were contacted. Of this group,

five providers agreed to participate and were interviewed. An additional 38 providers listed in a departmental registry were identified and contacted via convenience sampling, with 10 agreeing to be interviewed, resulting in 15 interview participants. Of the 15 participants, all had the credential of Medical Doctor. Four of the participants specialized in maternal fetal medicine (MFM), two were reproductive endocrinologists, one was a hospitalist, two were complex family planning specialists, and six were generalists (Table 11).

Table 11

Northwell ObGyn Provider Participants' Characteristics

OBCP Participant Characteristics		
Professional Degree/License	n	%
MD	15	100
Specialty		
Maternal Fetal Medicine	4	26.7%
Generalist	6	40.0%
Hospitalist	1	6.7%
Reproductive Endocrinologist	2	13.3%
Complex Family Planning	2	13.3%
Years as Physician (including residency)		
1-5	1	6.7%
6-10	2	13.3%
11-19	6	40.0%
>20	6	40.0%
Years at Northwell		
1-5	4	26.7%
6-10	4	26.7%
11-20	4	26.7%
>20	3	20.0%

Resultant Themes

Qualitative data collection consisted of individual semi-structured interviews (mean length = 30.64 minutes), which were recorded and transcribed via Microsoft Teams. Each participant was assigned a unique study ID number and given a pseudonym

in the transcripts to protect their confidentiality. All transcripts (mean length = 22.86 pages) were de-identified and kept in a password-protected computer and file.

The qualitative analysis was conducted using both inductive and deductive coding. Thirty-two total number of codes were identified giving rise to four overarching themes related to factors contributing to provider practice behavior in RPL evaluation. Appendix D contains the complete coding book and corresponding themes.

Theme 1: Variations in Clinical Practice

Provider Specialty. OBCPs have varied training and specialty areas of clinical practice. Although all interview participants were medical doctors, their specialty varied, impacting their approach to RPL evaluation. There are multiple specialties within the ObGyn department, which address the multiple aspects of women's health. However, the participants expressed that having access to many specialists creates variation with their and their colleagues' approach to RPL evaluation. The variable ObGyn approaches to evaluation contributes to inconsistent continuity of care.

The different types of OBCPs include generalists, who see patients for any obstetrical or gynecological condition; specialists including Maternal Fetal Medicine (MFM) physicians, Reproductive Endocrinologists (REI) (sometimes referred to as fertility), and Complex Family Planning (CFPs) physicians, who specialize in treatment for miscarriage and abortion; and Hospitalists, physicians who see patients for ObGyn related concerns among hospitalized patients.

Generalists. Generalists who care for women at a variety of times during their reproductive age often experience a sustained relationship with patients since they come in for care on a more regular and frequent basis. This type of relationship allows for

generalists to follow the often-lengthy timing of results for RPL evaluation if indicated. However, they may refer to specialists to facilitate the evaluation.

> [Generalists] may approach it differently, but I would say most of us do approach it this way: Most of us are comfortable doing somewhat of an extensive work up. We don't go too deep with genetics, like karyotyping, but we'll be comfortable with doing most of a workup. There are some people in the department who will send straight to fertility. They may send straight to MFM because maybe they're not that comfortable... So, it definitely gets a little tricky at times -Participant 9 (Generalist)

Generalists develop a relationship with patients throughout their reproductive lives often beginning at puberty and are also often the first point of care to which patients return following a loss of pregnancy. For example, Participant 4 (Generalist) stated "I am a generalist, so oftentimes I see patients for confirmation of pregnancy at the very beginning. I do obstetrics, so I've had patients who had recurrent pregnancy loss establish care, or I've seen them after a miscarriage as well."

> Participate 7, also a generalist, also spoke to the long-term patient relationship: It's the first stop for most women, too. Even women that have low socioeconomic status or patients that don't go to the doctor [will go to the ObGyn]. Most women go to the gyn when they're young. They don't go everywhere else. So, it's kind of like an opportunity to assess them as a whole and send them where they need to be. - Participant 7 (Generalist)

Hospitalists. Although hospitalists are OBCPs who are also not highly specialized, they are specifically based within the hospital and are unlikely to begin a full laboratory RPL evaluation on a patient because their primary role is to care for patients who are actively experiencing a miscarriage but not to provide follow-up care.

> Hospitalists are attending physicians that are in the hospital 24/7, so we don't do outpatient. We solely take care of patients, supervise residents, do all the things that we do, our whole clinical basis is in the hospital...the ER would call us if they diagnose the miscarriage... or if they were in the process of passing tissue or anything like that, that's when we would see them, and then we would get their history and see that this may be their second or third first trimester miscarriage...but we would counsel them and let them know that this is something

> they do need to probably follow up on especially if this is a short term interval miscarriage from the prior one. So again, there's not that continuity with patients as you have when you're in the outpatient practices and the ambulatory setting..."- Participant 10 (Hospitalist)

Specialists. MFM, Complex Family Planning, and REI providers have additional training and board certification to address complex ObGyn issues compared to Generalists or Hospitalists. These specialists take care of patients considered high risk due to preexisting or newly emerging conditions in the patient and/or fetus and are required to recertify annually, which provides educational opportunities in the most current care for RPL.

> All [REIs] are double board certified. So, we do our required CME's [continuing medical education credits] every year. And then we also have a fellowship, so we review all the updated practice bulletins from ACOG and ASRM every year. - Participant 8 (REI)

CFPs are involved at times with the medical management of patients experiencing a "missed miscarriage," which is when an ultrasound may reveal that the fetus is no longer developing and has no heartbeat. These specialists guide patients with options for managing pregnancy loss with procedures like a D&C (dilation and curettage) or medical management of pregnancy termination via a prescription medication. CFPs may begin an RPL evaluation if one has not yet been started but may defer back to the patient's primary OBCP for follow up.

> If you've come to me and they've already had a loss and this is their second, then I'll say, "Have you spoken to your doctor about any blood work?" And if the answer is no, then we'll talk about doing a workup. - Participant 6 (CFP)

Definitions and Guidelines. The different guidelines and definitions for RPL contributed to variation in the evaluation process, particularly as it pertained to which tests are still considered evidence-based and when to begin an evaluation. Regardless of

specialty, participants varied as to when they considered a patient to have RPL warranting an evaluation. Most reported using two or more losses as a starting point for evaluation, even while acknowledging that guidelines may specify three losses:

> So, officially, it's three miscarriages, but I've been doing it for 40 years already, so I have a different view. My view is, after two pregnancy losses, I do the work up. And the reason it's after two is, if I find something, maybe I could do something, but really from the emotional point of view it's hard to say to women, "Well, you haven't had three miscarriages, which is the official terminology for habitual abortion, so we're going to wait until you one more, and *then* we'll do an evaluation." - Participant 3 (Generalist)

Similarly, Participant 2 (MFM) shared that "If people have had two miscarriages, I will start offering testing generally for them." Participant 8 (REI) agreed "RPL is two or more consecutive pregnancy losses. We also include biochemicals [pregnancies with positive hormone pregnancy tests but fail to grow into visible pregnancies on ultrasound]."

One participant shared that, to her surprise, a colleague may even perform the work up after only one pregnancy loss:

> In my colleague's practice, if you have an unexplained loss, then he'll do the work up. Just one unexplained loss. And, I understand the utility, right? It's pretty harmless to do that, and then you may find something that could help the next pregnancy and then you don't have to wait for two consecutive losses. - Participant 6 (CFP)

However, the decision to evaluate can be more nuanced depending on the patient's pregnancy history. Several participants raised the point that patients with miscarriages may also have living children, which can make having only one standard definition murky:

> I consider [RPL evaluation] if they've had three losses. I know some societies say it could be two losses, but I use the more typical three consecutive losses, not just one loss and a [successful] pregnancy, then [another] loss and a pregnancy. - Participant 15 (Generalist)

In addition to differences in the definition of how many losses warrant an evaluation, participants described how the various guidelines shaped their decision about which tests to order. Participants cited utilizing ACOG most commonly, and REI specialists cited the ASRM guidelines. However, some acknowledged that the guidelines are not current or are limited in scope:

> I think that because overall the guidelines are limited and we generally do continue to look at SMFM, ACOG, and the reproductive endocrinology guidelines to make sure that we sort of stay up to date. And in addition to that, reviewing the new studies that are coming out to see if there is any additional intervention that we can potentially utilize. So, I would say those three societies would be the biggest that we kind of refer to. - Participant 1 (MFM)

MFM and REI participants shared their collaborative practice approach that led to the creation of an internal practice protocol regarding appropriate tests to order for RPL evaluation. Participant 1 (MFM) described, "There are no specific guidelines actually...So we have our internal sort of algorithm, and we came up with that based on evidence from different societies and different studies that are available."

One participant noted not utilizing professional guidelines and instead relying on other resources, including professional conferences:

> I don't think there's specific ACOG guidelines, but...at this point I don't really have to refer back to guidelines, but I read the chapter in Creasey and Resnick, our MFM text. I will check Up to Date to make sure there's nothing new that I have missed . . . If I go to conferences, it's kind of a hot topic at conferences. - Participant 11 (MFM)

Participant 9, a Generalist, explained that their practice has a relatively standardized protocol, but the evaluation is patient-centered depending on how extensive of a workup the patient desires.

> We tend to have one way, primarily, with maybe some modifications here and there because we do have some patients that don't really want to be too aggressive. They're just trying to get through the loss, so we may approach it differently. - Participant 9 (Generalist)

Due to the different and relatively outdated guidelines, some testing may no longer be recommended, but this may be unclear to some OBCPs. For example, Participant 12 (REI) acknowledged that testing for inherited thrombophilias may not be indicated, yet most, if not all participants mentioned it being a part of their protocol, "I mean you can find a study to say that you should be treating those patients, but the overall evidence base is pretty low for some of those more non-acquired type of thrombophilias."

OBCPs may be unaware of best practices if guidelines are not kept up to date. Participant 5 (Generalist) raised a specific example about a procedure called endometrial biopsy that he acknowledged that some clinicians may no longer perform. He described how there are conflicting opinions on the relevancy of the procedure:

> A lot of endocrinologists don't do this anymore, but it was standard practice when I was coming up wherein we would assess luteal phase abnormalities, and that is something that I still continue to do. We do have annual recertification through the American Board of Obstetrics and Gynecology, and I haven't seen any new literature that says that we that we should be doing these things now versus what we used to do twenty or thirty years ago. - Participant 5 (Generalist)

Referrals to Interdepartmental and External Specialists. Given the varying definitions and guidelines on when to begin an evaluation and what tests to order, OBCPs may refer to a different ObGyn specialist to complete the evaluation process. However, the referral process varied and lacked standardization. Although generalists see patients more often during and after pregnancy than their specialist colleagues, they may refer to a specialist evaluation or management of a more complex or high-risk condition.

Additionally, some participants, like Participant 4 (Generalist), were aware of departmental resources, such as a dedicated RPL clinic: Years ago, I did order them, but there's such an extensive panel and we're not used to ordering the tests in the office, so I just defer to MFM unless I think the patient really won't go for the referral. At times, I might send them, but for the most part, I think the counseling is very helpful, and I want to make sure the right labs are sent. So, I encourage them to go. - Participant 4 (Generalist)

Similarly, some participants discussed what they believed may influence their colleagues' practice behaviors when faced with a patient with RPL:

> I think, most of the time, my generalist partners wouldn't want to make those decisions or give people these labels. Generally, I would find they would refer them to myself or maybe [other MFM clinicians in the department] to make that diagnosis or send them to a hematologist to make that diagnosis. - Participant 2 (MFM)

Participant 4 (Generalist) added:

> Every time I tried to order, we wouldn't necessarily order the right one for the lab [tests], and then we would reach out to MFM to get the panel, and they gave us a list. It was just very cumbersome. - Participant 4 (Generalist)

A patient with RPL may see each type of provider within the ObGyn department from their generalist, followed by CFPs or hospitalists if they experience a loss, back to their generalist, and then possibly to a specialist such as MFM or REI. Multiple visits to providers following the pain of a pregnancy loss may add to the emotional turmoil the patient experiences.

While participants shared their experiences of referring patients to other colleagues within the department, most reported that they did not have a process in place to follow up, resulting in a lack of continuity of care:

> "Patients kind of feel shuffled around and they haven't gotten any answers, and you know there's all this emotional trauma from what they have gone through, and they need someone that's willing to sit down with them and listen. A lot of times there are reasons that it doesn't happen, but a lot of times it doesn't happen." - Participant 12 (REI)

In some instances, a specialist may not know if a patient experiences a loss, thereby becoming a patient with RPL.

> We're generally consultative only. We don't have private patients, and we usually just see them for a consult or ultrasound. So, we may not find out [if a patient has a miscarriage]. I may see a patient, do an ultrasound, and she may ultimately lose that pregnancy. I may not know about it because I'm a consultant. I have had one or two cases where I saw the patient for an RPL and then there was a loss, and then the obstetrician did reach out to me. But it was, I would say, a minority of the cases. - Participant 1 (MFM)

Additionally**,** if patients do not have follow up appointments, they may not return after having a miscarriage, therefore delaying the evaluation:

> We have patients who go elsewhere when they have a miscarriage. They may go outside of the system. I would say most of my patients who would see me in the office at any point if that happened, and I'm not directly involved in their second miscarriage, most of them, if not all, will call and let us know. Patients…get more concerned earlier and faster, and if there's work up that could be done, they ask for it maybe earlier. - Participant 9 (Generalist)

The patients and some providers may also not be aware that MFM specialists see patients preconceptionally. For example, Participant 9 (Generalist) shared "Sometimes we don't see patients coming in between for preconception counseling. They're already pregnant in the first trimester and then if they are recurrent pregnancy loss patients, they will have a consultation with Genetics." Participant 9 (Generalist) went on to say, "Some people don't know about MFM preconceptually or for RPL. They may [know that they can see] REI [preconceptionally], but they might think that that automatically means that they're committing to IVF."

Some participants noted the challenge of making a referral due to differences in appointment scheduling processes:

> I would say reproductive endocrinology, at least within our system is a little more challenging than maternal fetal medicine or urogynecology because in Allscripts, the urogynecologists have what they call a concierge referral, so once you click the box, they automatically call the patient at home to set up the appointment. [Whereas MFM], they're not on our electronic record, so it's hard to access them. And then, because infertility takes up most of their business, recurrent pregnancy loss is secondary to what they do. So, they're dealing with so many patients, not even able to get pregnant that referring to them for recurrent pregnancy loss is a little more challenging, I'll say. - Participant 5 (Generalist)

Specialists from other departments outside of ObGyn were frequently used to facilitate the evaluation process. For example, to address potential thrombophilic conditions, some OBCPs may refer to other specialists such as a hematologist, as noted by Participant 9 (Generalist):

> Some people are not that comfortable. The tests take a while to come back. They come back at different times. Then there's the counseling part. Some people send straight to hematology, but I would say most people in my group would feel comfortable doing it. -Participant 9 (Generalist).

Participant 12 (REI) had previous clinical experience as a Generalist, and therefore, he commented on his previous referral practice.

> I usually would consult with maternal fetal medicine to get recommendations, or if the patient had a hematologist, I would talk to the hematologist to get the recommendations about those the non-acquired thrombophilias. That was what I did as a generalist. - Participant 12 (REI)

Supporting Staff and Clinical Provider Resources. Specialist OBCPs are more likely to have access to additional resources such as supporting providers like genetic counselors, nurse practitioners, and registered nurses who may facilitate the patient's evaluation process compared to their generalist colleagues. These resources were noted to influence the RPL evaluation process.

Genetic Counselors. MFM specialists often work closely alongside genetic counselors who counsel patients about genetic testing during pregnancy. This relationship facilitates the genetic testing portion of the evaluation.

> I see patients with the genetic counselors...when I speak to patients, I have my counselor [explain the genetic testing to patients] if we think it is more recurrent pregnancy loss, and we always do the karyotype on the parents.... The genetic counselors also call [patients] themselves, they get the front desk staff, help them to get the paperwork. They are the intermediate staff to get the results before they come for [an MFM] consult. -Participant 13 (MFM)

Genetic testing, most commonly chromosome analysis, from the reproductive partner requires a blood sample from that individual. Several participants shared that coordinating that collection can be challenging, and genetic counselors are used to facilitate partner testing:

> I know sometimes when it's the partner's testing, I may refer them to genetic counseling just so that they can explore, not just karyotype testing, but if they want their expanded carrier testing. But if they decline that, then sometimes it is a little challenging because the order for the partner is not the patient, so sometimes coordinating that can be that difficult. - Participant 15 (Generalist)

Nurse Navigators. One OBCP MFM described her working relationship with a nurse who serves as a navigator and facilitates evaluations by following up on laboratory test results, creating referrals, and providing multiple levels of support and guidance for patients:

> I would say if we had a lack of resources [the evaluation process would be more challenging]. For example, if we did not have a nurse in place who was a navigator and who I could ask to order specific labs and follow up on them, that would make it extremely challenging. And then I would have to defer to the obstetrician or the PCP [primary care physician]. But because we do have [the Nurse Navigator], it makes it more fluid. -Participant 1 (MFM)

Additionally, Participant 12 (REI) added, “We did have in my other practice when I was a generalist. We had a nurse that managed, or she was in charge of, helping to coordinate everything for our early pregnancy loss patients.”

Theme 2: Patient Characteristics and their Influence on Evaluation

Participants discussed how patients often influenced the evaluation process. At times, the physical and/or emotional health concerns of patients led to the OBCP’s offering testing that they acknowledged had a low likelihood of explaining the underlying cause of RPL. Other providers described how they attempted to reassure patients that an extensive evaluation may not be indicated. Some referred to performing the lab testing as harmless but that it could help assuage some fears for patients:

> I try to stick to more strict criteria, but I feel like with my patient population, sometimes I'll even do it earlier than I would otherwise want to because patients can be very demanding to start some kind of work up. - Participant 2 (MFM)

Maternal Co-Morbidities. Given the commonality of underlying maternal health conditions in RPL patients, providers are motivated to evaluate patients quickly. However, evaluation or management of these conditions is often optimal during the preconception period (i.e., when the patient is not pregnant). And yet, participants acknowledged that preconception visits do not occur as frequently as post-conception visits, thereby limiting evaluation for conditions that are impacted by pregnancy:

> At least sometimes, people with recurrent pregnancy loss will have some underlying health thing that we will recognize and can treat. And, for example, I found a patient who herself had Turner's syndrome through her evaluation. She never knew it. That's important for her because she could get an echocardiogram and proper treatment. - Participant 11 (MFM)

Additionally, recognizing these conditions before pregnancy can improve their chances of a subsequent successful pregnancy outcome:

> For RPL, if you have a patient that you see before as part of your preconception visit, you are able to discuss the history and talk about the appropriate testing. You know, if you see the poorly controlled diabetic before she gets pregnant, you can really improve the chances of her having a healthy pregnancy. - Participant 12 (REI)

Patient Psychological Health. Patients desire an explanation of what is causing the RPL but also need emotional and behavioral health support. One participant shared their process for referring to a specialist for that aspect of care:

> There's two parts to it, and I always tell the patients from the neck up and the neck down. From the neck down, I'm the scientific approach to try to find out what caused the pregnancy loss. You know, the majority of the time we're not going to find a reason [through the blood tests], but we're going to go for it. "We're going to give it a shot," I say. For the neck up, I use a social worker who specializes in pregnancy loss, and I say, "It's important you see her if you want to see her. If you don't want to see her, it's fine, but suffering in silence is not necessary." - Participant 3 (Generalist)

Similarly Participant 7, also a generalist, noted that patients may push to have an evaluation prior to meeting the two or more unexplained pregnancy loss definition:

> I know that sometimes they get nervous when they just have one and I try to calm them down to tell them that, you know, it's most likely that they're going to get pregnant again and that everything will be fine, and that it is not uncommon. I would say that would be where I find more of the resistance and patients trying to get a workup sooner [than is necessary]. - Participant 7 (Generalist)

And Participant 6, a CFP recalled:

> I have the perfect example; I just had a patient who had her second miscarriage with me. But the first miscarriage was an explained loss. It was a genetic issue. But she was so beside herself and wants everything that she's actually going to a reproductive endocrinologist. So, I did all the blood work. I did the inherited thrombophilias and antiphospholipid antibody testing and everything was normal, but I'm aware this is not warranted, right? - Participant 6 (CFP)

Few providers mentioned having an established system for behavioral health service referrals, though several mentioned the psychosocial impact on patients. Participant 2 (MFM) shared how pregnancy loss can impact patients and what is the most challenging aspect of providing care:

> I think just trying to help the patient deal with the loss. I feel like the biggest thing for most patients is the psychosocial impacts of this and how they're handling pregnancy losses. I think there's not a lot of focus on how common it is to have miscarriages. So, I feel like I have patients that have one miscarriage and they're really upset and frustrated by it without realizing how normal it is for most women to have a miscarriage.

In some instances, managing the psychosocial aspects of RPL may be challenging in the limited time allotted for appointments.

> My experience was that a lot of the RPL patient visits take a lot of time. Like the patients are, I mean not to overly generalize, but there are usually a lot of emotional problems that are going on too. Maybe not clinical depression, but patients are usually devastated. And not just in the acute setting, but there's a lot of anxiety when there's a new pregnancy. And I've had patients talk to me about feeling defeated and like, "What's wrong with me?" And so, I don't see a way that you can do justice for one of these patients in a 10-minute patient visit. - Participant 12 (REI)

Social workers that can provide psychosocial support were leveraged by some OBCPs. However, Participant 3 (Generalist), described his referral process for mental health support.

> She's a private social worker, but she takes our insurance. I got her on a plan and if you want to talk to her, you can. She does a lot of my work because there are many emotional parts to this. - Participant 3 (Generalist)

Socioeconomic Factors. Socioeconomic factors shape a patient's access and experience of healthcare. These may contribute to prolonged or untreated behavioral and physical health conditions. One participant commented that it is challenging for patients to navigate through the evaluation process for RPL:

> There's also a lot of trauma in the healthcare system, particularly for historically marginalized communities too, right? So, accessing the traditional healthcare system is not always a safe and feasible possibility for many people. And for these patients, additional fail safes may be necessary to ensure the highest level of care since seeing a fertility specialist may be stigmatizing for some patients. Realistically though, we always have to actively work to center our marginalized patients, whether that be from patients who are publicly insured. But, going to fertility is not a reasonable option for many of those patients because REI is a service that's available to some, but not all, right? If they have recurrent miscarriages but they're Medicaid or managed Medicaid insured, that's not even a realistic option for them. Maybe that's not the label that they would like to attribute to what they're going through because it in some ways stigmatizes what they're experiencing. -Participant 14 (CFP)

Theme 3: Laboratory Testing-Related Challenges

Laboratory testing presented challenges to participants due to uncertainty about appropriate or evidence-based tests, needing to coordinate different sample types from both reproductive partners, and challenges with insurance coverage.

Lack of Standardized Processes for POC testing. The most challenges with laboratory testing stemmed from POC testing. Lack of standardized protocols for POC collection, testing, and result follow-up was a significant barrier within the RPL evaluation process. Participant 8 (REI) described how POC testing may not be performed on the first miscarriage, which leaves patients without an opportunity to know the cause of the loss. Additionally, POC genetic testing may require follow up testing like microarray, which is not always done:

> There are issues with a lot of times the generalists don't do the genetic testing on the POC because they're like it's just the first miscarriage, and then when they miscarry again...either they didn't think to do it, or they miscarried on their own. So now they have no idea what's going on. The other component where there's a sort of a gap is that a lot of times they don't reflex [to microarray], so we get female normal karyotypes and don't know if it is maternal cell contamination. -Participant 8 (REI)

Also, genetic testing on POC is not the priority for a patient experiencing an active loss in an emergency:

> I think a lot of times things like [the Genetics Department] get, I don't know if deprioritized is the right word, but potentially put farther down on the priority list just because, if someone comes in and is hemorrhaging or has a septic abortion, in those clinical scenarios, the patient's stability has to be prioritized first. - Participant 14 (CFP)

Furthermore, when a patient experiences a pregnancy loss at home, genetic testing on the POC may not occur:

> Because pregnancy losses happen at home and tissue is often not saved. And even if tissue is saved, it's not saved in the proper media that allows for tissue growth. So, your patient will lose the pregnancy or they're bringing in tissue, and you'll send it off to the lab, but the tissue is already devitalized. -Participant 5 (Generalist)

Approximately 50% of POCs have abnormal or unbalanced chromosomes, rendering a complete bloodwork evaluation unnecessary. Participant 5 (Generalist) explained how not having the POC tissue to test affects the evaluation process:

> And oftentimes you don't have the tissue to send out to check for chromosome abnormalities, but most of them, when you can identify pregnancy losses, 50% of them are a result of nondisjunction where you just get abnormal cell division early on. -Participant 5 (Generalist)

Lack of Access to Test Results and Subsequent Follow Up Challenges. The most significant issue with laboratory testing may be lack of access to previous and recent test results, creating fragmentation in the evaluation and diagnostic process. When the POC genetic test results are not available to OBCPs, they may order additional tests that may be unnecessary. Participant 2 (MFM) shared an experience with a patient that was under treatment but did not fit the criteria for RPL. She consulted with a patient who had an extensive evaluation that was potentially unwarranted, "I saw one patient that was being treated by [an external specialist] who had one loss due to Turner and then one

chemical pregnancy and then was on this regiment of Lovenox and metformin and steroids." Therefore, the ability to access other previous laboratory test results, particularly genetic testing, is critical for optimal evaluation of RPL patients:

> Having the [POC] labs go into the [hospital EMR] is not great. Even sometimes my [OBCP colleagues] will send me their recurrent miscarriage patients, and then they come to see me, and I realize that nobody ever went over [the results]. They sent the genetics, but they never called the patient to review it or if they did, the patient doesn't remember it. And then I'm the first one to tell them, "Oh, this isn't recurrent pregnancy loss. This is a chromosome issue." So, I would say because it goes into that spot, it doesn't get seen or followed up on. -Participant 2 (MFM)

Participant 9 (Generalist) noted that genetic tests do not need to be repeated, so not having access to all results can lead to over testing and over expenditure of healthcare dollars:

> I always tell them, for inherited thrombophilia, you don't ever have to check that again. I hate the waste of resources. I hate the waste of the healthcare dollars, so I'm like "You sure you didn't do it? You're sure?" But we should hand these to the patients and say, "These are now your results." -Participant 9 (Generalist)

Difficulty Following Up on Lab Testing. POC results and other genetic testing, like blood chromosome analysis, can also take a long time to come back and may appear in a different EMR, making it difficult for OBCPs to follow up with patients. Participant 9 (Generalist) explained how the lengthy time for genetic testing results on POC and on patients can lead to patients potentially not receiving their results:

> Both [types of genetic testing] are difficult because they take a lot longer to come back compared to when you get a patient for follow up from an ER or post-op visit. I have gotten into habit when I see the patient, I always look it up just in case it's back. But I'll always tell her, "Please call me back," and I give her a 4-to-5-week time frame from the procedure in question. And I say, "Listen, this is on my mind, but I need you to call me because it doesn't come in their outpatient chart most times—or ever, really." -Participant 9 (Generalist)

Hospitalists that spend all or most of their time within the hospitals or interact with patients that are actively experiencing a miscarriage described that patients are

contacted by resident physicians with abnormal results but shared that there may not have sufficient resources to follow up on normal results.

> The results are slated to go to the inbox of the attending or the practice. If they are an unregistered patient, meaning they do not have an affiliated outpatient practice provider, then the follow up goes to the resident. It is required to review whether it's normal or not, but I think if there's any abnormal findings, they would get a red flag for them to contact that patient to make sure they're coming back. But I would assume that again it would be more for the abnormal, but a patient can get the results if they follow up, if they come to the clinic in two weeks. - Participant 10 (Hospitalist)

Generalists may not have access to POC test results since the results go back to a different EMR, thereby making following up on results challenging. However, different practice settings may have more standardized protocols to follow up than others:

> [When I was a Generalist] oftentimes when [POC testing] was done, I think that we did a good job following up, because I know that in different settings, I've heard [following up] has been an issue where the test kit was ordered but then nobody ever follows up on it. -Participant 12 (REI)

Following up on APS testing is also challenging due to the lengthy time needed for following up of abnormal results:

> For example, APS testing, you're typically supposed to do at least 12 weeks apart to confirm any findings that could have been found on initial testing and ultrasound may have to be coordinated with their period. So, I think that's, for a lot of patients, the biggest hurdle is they feel this process takes a lot of time on their part to get information, and they still may not get a clear answer. - Participant 15 (Generalist)

Difficulty Interpreting Test Results. Another concern with laboratory testing is the interpretation of the results. An antiphospholipid antibody test panel contains more than half of a dozen individual lab tests. Different permutations of positive results included on the panel could infer an increased risk of having APS:

> The mildly elevated anticardiolipin antibodies...you know, those intermediate results? I think sometimes it causes a lot of confusion. You're always thinking, “Is this really something?” If I wait 12 weeks is this still going to be positive or

> negative. But then they get pregnant before you have time to repeat them. So, I find sometimes that's something that can be difficult when you get those intermediate results that you don't necessarily want to act on; something that's not clearly abnormal and give someone the label of APS, but also not wanting to miss something if there is really something abnormal. -Participant 2 (MFM)

Some providers used a genetic counselor's support to help explain the POC genetic testing results since they felt that it was challenging and/or time consuming to explain:

> `I think that's something I usually defer to genetic counseling. Usually I'm not doing that, so I think having a [genetic counselor] referral [is important] because that's a lot to explain. In some cases, genetic testing may not be offered to patients with one or fewer pregnancy losses, even though the results could be useful. - Participant 6 (CFP)

Insurance Coverage Concerns. Insurance coverage for genetic tests has become increasingly complex, often requiring prior authorization and potentially resulting in expensive patient bills based on coverage policy.

> I'm not sure that these tests are necessarily covered, and that I think they're expensive testing or they're not sent that often, but I think a lot of genetic testing also isn't covered by insurances. I haven't recently sent it, but I could see my patients being upset if these very expensive tests are sent and not covered, and I don't know enough about the insurance coverage and every insurance is different. - Participant 4 (Generalist)

Lack of insurance coverage for expenses related to reproductive endocrinology testing or procedures can prevent some patients from being able to obtain these services, as noted by Participant 5, a generalist. “A lot of insurances are very reticent to cover reproductive endocrinology expenses. It may be infertility or recurrent pregnancy loss, but a good portion of that can potentially be out of pocket expense for a patient which might be cost prohibitive.” The concern for potentially high out of pocket costs and a lengthy time to determine coverage for genetic testing affects patients’ decision making. For example, Participant 14 (CFP) shared, “I have had one patient who had a miscarriage

who decided not to do cytogenetics because I think the whole process of obtaining the cost information was too overwhelming for her. Participant 6, a CFP, also noted this:

> I used to sign chromosomes with reflex to microarray. I no longer do that. I send chromosomes and then I hold the cells. I was so fed up with insurance. If they want microarray, they can talk to a genetic counselor. Then there are some people with anomalies that I'll have my office do the BI [insurance benefits investigation], but it was way too much for my office to do the BI for everybody. - Participant 6 (CFP)

Theme 4: OBCP Recommendations to Improve the Evaluation Process

Coordination and Protocol Development. Participants were asked to describe potential solutions to some of the challenges in evaluating patients with RPL. Many described the benefits that departmental collaboration would provide, for example, by maintaining an up-to-date list of evidence-based laboratory tests. Additionally, this type of collaboration could simplify the referral process both within and outside the department. Educational opportunities for providers and community outreach could improve patient care and foster healthcare literacy respectively. Standardizing the referral process between specialists will help ensure optimal evaluation:

> We collaborate a lot with MFM, hematology and oncology. I think it would be nice to have a collaboration or a work group where we streamline the processes because a lot of times you know some of these patients have had clotting disorders that need a good handoff from us to MFM with the consultation of the hematologist either or both during and after conception. - Participant 8 (REI)

Participant 12 (REI) shared that generalists may need additional resources and the assistance of specialists to perform the RPL evaluation:

> I think that if it's going to be up to the generalist to do, I think you would need to make sure that there was some support in place from MFM. I think MFM would be more appropriate than REI because I found in my experience a lot of the patients that had recurrent pregnancy loss, and if I was consulting somebody, it was because they had complicated medical conditions.

Participant 14 (CFP) felt that departmental guidance from the Northwell ObGyn leadership on standardizing the referral process would facilitate better patient care:

> I think leadership from the top would be very helpful in this endeavor because I think you can obviously directly equate how we better standardize these processes to better patient outcomes and better patient satisfaction and less fragmentation of care and all of the same things we've been discussing.

Similarly, Participant 7 (Generalist) explained how she believes a clinical program specializing in RPL would be helpful for patients, particularly as a starting point for the lengthy process:

> Maybe a program designed specifically for recurrent pregnancy loss that I can look to for the patients that would help them with their mental state, and that would have them begin the process. - Participant 7 (Generalist)

One participant shared her experience within a multi-specialty work group in which providers from different departments collaborated with specialists in and outside of their department, including the laboratory:

> I think that because of our program [MFM-based RPL clinic], we sort of have, you know the genetics portion, we have the placental pathology portion, and we have all those kinds of specialists in our program, it significantly helps to streamline any challenges that we may face with tests and test ordering and interpreting. So again, because we have this program, it makes it less challenging. I think to a significant extent we've had a couple of cases that were somewhat complicated and not straightforward, and we had a group discussion about what potential interventions we could offer her with the next pregnancy. So, there's great teamwork. Participant 1 (MFM)

Similarly, this provider suggested a dedicated RPL program would be a centralized place for referrals. "Maybe a program designed specifically for recurrent pregnancy loss that I can look for the patients to kind of like that would help them with their mental state and have them start the work up."- Participant 7 (Generalist)

Laboratory Coordination. Since not all providers share the same EMR access, some OBCPs rely on their relationship with the laboratory, which provides a centralized place to both obtain and add testing orders on existing samples if necessary.

Improved Access to Laboratory Test Results. Having access to a patient's laboratory results is challenging for OBCPs due to different EMR systems including separate systems for the hospital and outpatient services. Even when OBCPs have access to both EMR systems synthesizing relevant results remains difficult since time to prepare for visits is limited. Participant 8 (REI) suggested "Even just sharing the EMR systems with the providers will help a lot to get that information back and forth."

> I'm very grateful for the [laboratory genetic testing coordination team's] email, and that I can be in touch with you guys. If I can't find things, or if it's because another patient that's coming in that I'm just trying to figure out if I should do her counseling. -Participant 2 (MFM)

One participant shared that insurance coverage for tests should be communicated from the lab to providers.

> And I think more communication between providers and the lab personnel if there is any information that can be disseminated about [insurance coverage] would be very helpful to us because...we live in the world where financial considerations significantly impact people's care, but that really shouldn't be a reason that someone chooses not to have a test that they otherwise would have wanted.-Participant 6 (CFP)

Development of Standard Laboratory Testing Protocols. In addition to departmental guidance on the RPL evaluation process, developing internal laboratory test protocols can ensure consistency. Participant 8 (REI) described how the practice collaborated to decide on the laboratory test panel for their patients: "We have panels in our EMR that we created, and we all agreed upon what to draw. So, we just hit the recurrent pregnancy loss panel."

POC collection protocol. Improving the coordination of genetic testing on the POC, including times when a pregnancy loss occurs at home, could provide explanations for the cause of losses and prevent unnecessary testing. Some participants discussed the importance of genetic testing on the POC to potentially avoid over-testing for other conditions unnecessarily. For example, Participant 3 (Generalist) stated "Every pregnancy loss, every D&C has chromosomes. I've instituted that so if you have a 45X [abnormal chromosomes], one of the most common, then I'm not going crazy with the $1,000,000 work up."

Therefore, an OBCP's evaluation may vary depending on the availability of these test results. If the patient's POC results are abnormal, an evaluation may not need a further evaluation:

> A lot of patients have miscarriages, and they never come back to find out about the chromosome issues, and since you have patients where there was a trisomy 16 or a Turner's and they're coming in for recurrent pregnancy loss, there's actually not recurrent pregnancy loss. - Participant 2 (MFM)

In instances where a patient is at high risk of having a miscarriage, such as first trimester bleeding, clear instructions and supplies to collect the pregnancy tissue at home would improve the availability of genetic testing for those patients.

> I have people bring in their miscarriages from home and put it in the refrigerator and bring it to my office. I just don't think people are educated [about the options for collecting POC]. So, if somebody wants to pass at home (she wants expectant management), but she wants genetic testing, I'll say to the patient" That's fine. Just bring it to me." I give them a urine specimen cup, and they put the POC's in the cup and bring it to the office. So, it doesn't have to be a procedure to send for genetics. - Participant 6 (CFP)

Alternate Sample Collection Protocol. One OBCP described how he collects a cell-free DNA test (also known as NIPS (Non-invasive Prenatal Screening)) on a blood sample from a patient if the loss, such as an absent heartbeat, is discovered during an office visit. The cell-free DNA tests predict the chances that a pregnancy may have a common chromosomal abnormality and is typically performed at 10 weeks of an ongoing pregnancy. He shared that he had cases where the POC genetic test failed, but he was able to get results from the NIPS test, "I had two positive NIPS in which the D&C was no growth."- Participant 3 (Generalist)

Implementation of Patient Navigators. Dedicated nurse navigators compile previous laboratory test results and coordinate follow up visits, which facilitates a patient-centered approach to RPL evaluation. Participant 9 suggested that an existing navigator could coordinate RPL evaluations and referrals in addition to their current role for MFM patients.

> Patient navigator has been quite a successful concept for a lot of our practices in areas such as high-risk OB and cardiology and for our cancer patients. I understand [the navigation] would be maybe less intense and less time sensitive then you know navigating a current pregnancy with an abnormal fetal finding, an abnormality or sick mom... "You need genetic counseling, and why don't you see the MFM?" It's really hard to navigate. - Participant 9 (Generalist)

Participant 5, also a Generalist, agreed:

> MFM does a good thing, and they have patient navigators. So, they have nurses who deal with patients who have fetal abnormalities...a nurse is navigating all of your visits with the neonatologist or pediatric surgeons. So, if there are patient navigators for recurrent pregnancy loss, where once you lose two pregnancies in their first trimester, second trimester, now they take over and they get you in with the radiologist, they get you into genetic counseling and so forth. - Participant 5 (Generalist)

Even participants whose practice had a nurse navigator felt they could benefit from additional support.

> Maybe having another navigator would be helpful because as our program is growing, I think it's overwhelming for one person who also has other responsibilities. This is not her primary responsibility. Or just getting a navigator for maybe our program and maybe one other program, so they kind of have a more limited scope. - Participant 1 (MFM)

Participant 9 described a way that patient navigators could facilitate patient referrals due to fragmentation of healthcare:

> There's a lot more that can be done from a reproductive endocrinology point of view that doesn't have to be that this patient is committing to REI or IUI [intrauterine insemination]. It could be just to assist with the management, the hematology workup. I think even social work even...There's so many different things that could be navigated, but I think that would be a great way [to help patients navigate healthcare]. Many times, patients—I won't say they get lost to follow up—but they end up kind of self-referring. The doctors aren't really connected. -Participant 9 (Generalist)

Appointment Availability and Extended Consult Time. The availability of additional time slots dedicated to patients with RPL was suggested as a means of accommodating more patients. Participant 1 (MFM) stated, “I think having more slots available in our schedule I think that would be great too because we are not only seeing RPL patients.” Participant 12 (REI) described how he arranged for longer appointment times for RPL patients:

> When I was a generalist, I would try to book them in a longer patient appointment slot, or I would put them at the end of the day so that I [had more time]. I don’t think I ever was able to have an RPL patient encounter in 10 minutes.

Educational Opportunities. Annual departmental reviews of current recommendations in RPL evaluation and management could promote consistency and continued engagement where scientific discoveries and recommendations are evolving

frequently. For example, Participant 8 (REI) suggested “Even maybe like a biannual review or part of the OB GYN Summit that's in May, would also be helpful.”

> I think if there’s faculty development it would be helpful or training in that since I don’t review them regularly and I do rely on MFM to interpret them. If I got the results, I still would reach out to MFM regarding management. Maybe it would be helpful if there were some standardized guidelines within the department regarding pregnancy loss. - Participant 4 (Generalist)

Education for the patient community was also suggested by this provider who recognized that not all patients may know how to navigate the health care system:

> If you think of the services that need to be culturally sensitive [and] have language interpretation. Health care literacy is a problem...and you'll have the patients who English is not their first language and culturally they're not sure what [the services] are. Like many people think something might be wrong with them, but there's nothing that could be done. And so, there's that sensitivity, especially being in Queens, of how diverse we are, and I think this opportunity is there and probably to reach out to the different communities to different religious communities and give talks out there in the community. -Participant 9 (Generalist)

Qualitative Phase Summary

The qualitative phase of this study aimed to explore the research question: How do OBCPs describe their experience of evaluating patients for RPL? In-depth interviews were conducted with 15 OBCPs, all of whom were physicians but from diverse specialties with different training.

The OBCP interviews about their practice behaviors on RPL evaluations revealed four themes. Theme 1, Variations in Clinical Practice, stemmed from the different specialty types of OBCPs involved in the care of RPL patients and their respective practice setting, variations in interpretation of professional guidelines, and availability of other healthcare provider to support RPL evaluation. Theme 2, Patient Impact on Evaluation, discussed how the physical and mental health of patients and socioeconomic factors influence the evaluation process. Completing the multiple tests and procedures

involved in assessing RPL etiology can take months to complete. Although the OBCP participants shared that most patients are highly motivated to uncover answers explaining their losses, socioeconomic barriers to healthcare prevent patients from accessing and navigating healthcare. Theme 3, Laboratory Testing-Related Challenges, described factors related to accessing, interpreting, and following up on laboratory test results. POC testing was especially challenging to both coordinate and uncover results due to EMR access issues and the lengthy time to complete certain tests. Theme 4, OBCP Recommendations to Improve the Process, included suggestions for potential interventions that may promote optimal care including standardized protocols for testing and referrals, better coordination with the laboratory, and education for both practitioners and patients. Overall, the analysis from the OBCP interviews contributes to a richer understanding of the physician experience of the RPL evaluation process. OBCPs have varied training and practice settings that make coordination challenging. There are also multiple contributory factors that support and inhibit the RPL evaluation process, so a solution to improve it must be multifaceted.

Data Integration

The integration of the quantitative and qualitative results sections addresses the research question, "How do the test ordering practice behaviors and OBCP interviews inform future interventions to promote completed laboratory test evaluations of RPL?" The possible reasons for variation in RPL test ordering, including inconsistent anti-phospholipid antibody syndrome analysis and the limited number of POC microarray results, were reflected in the interviews with OBCPs. Some OBCP participants were not initiating a workup and deferring to specialists or specialized clinics whereas other

participants were referring only for certain aspects of the evaluation such as genetics and hematology. Some of the specialist participants ordered all tests as prescribed by internal protocols, whereas the generalists were less likely to have the same degree of uniformity.

The interviews raised some potential explanations for evaluations categorized as "low" including limited access to previous medical records, lack of supporting staff such as nurse navigators, and limited length of appointment time. Some generalists deferred to their specialist colleagues to ensure best practices. These participants mentioned that the guidelines are outdated, or not specific, and departmental guidance or educational opportunities would be useful.

Other low category evaluations were initiated by hospitalists practicing within the hospital or specifically caring for patients during acute care for pregnancy loss. These OBCPs may not evaluate patients for RPL because it is outside the scope of their care during these—often emergent—episodes. Hospitalists do not see patients in the outpatient setting, and therefore, lack a mechanism to follow up on multiple laboratory tests. However, they did offer genetic testing on POCs and follow up on abnormal results. In some cases, evaluations categorized as "low" may have been clinically appropriate.

Evaluations categorized as "medium" included those with complete RPL testing based on abnormal POC chromosomes, as well as incomplete RPL testing based on normal POC chromosomes. Evaluations in this category aligned with OBCPs who described taking on a patient-specific approach to laboratory testing. They did not tend to have a strictly uniform approach to evaluating patients including a specific testing algorithm. Some OBCPs focused more on obtaining previous medical records before

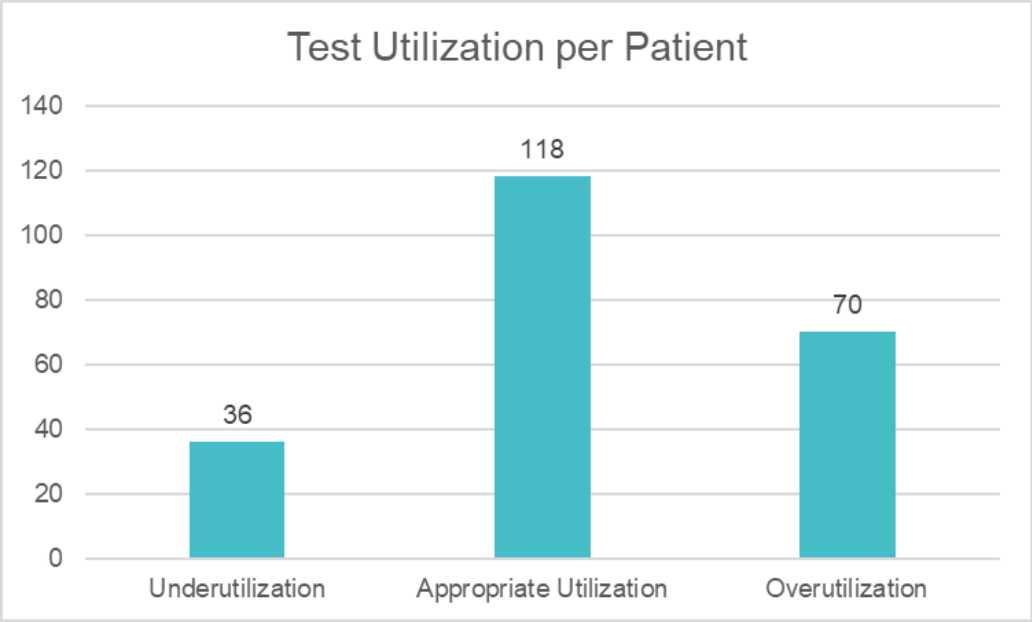
initiating additional testing. This practice was—in certain instances—facilitated by having a nurse navigator to compile previous test results from past pregnancies.

Evaluations in the "high" category aligned with the practice described by certain participants who had a more standardized approach with predetermined laboratory test lists thereby ensuring a more uniform evaluation. These providers were more likely to have a RPL evaluation policy developed through practice collaboration. Some of these OBCPs, such as REI providers, were also affected by being on separate EMR systems, which contributed to not having complete patient medical records. This lack of access could explain why a complete evaluation was unnecessarily ordered for 14 (17.3%) patients that had abnormal chromosomes on POC.

Based on the interviews with participants, the influence of patients and the availability of previous test results clearly impacted how the participants proceeded with RPL evaluations. Several participants shared that there may be no need to perform further testing based on the POC results when abnormal and thus the cause of the pregnancy loss. In these cases, the appropriate utilization of testing was illustrated (Figure 11). Therefore, appropriate test utilization is largely determined from the POC chromosome testing results. For example, if a patient with a "low" number of tests had two or more abnormal POC chromosome results, the low evaluation was appropriate. Whereas a "high" or "medium" evaluation for a patient with two abnormal POC chromosomes would be considered overutilization. A "low" evaluation for a patient with POCs with normal chromosomes would be considered underutilization since that patient has unexplained RPL.

Figure 11

Laboratory Test Utilization by POC Chromosome Results



Out of the 224 patients, 36 (16.1%) evaluations represented testing underutilization where patients with normal POC chromosome results did not receive any further evaluation. Included in the appropriate category (118 [52.7%]), are 86 (72.9%) patients that had one or more abnormal POC results and therefore, additional evaluation was not warranted. The other 32 (27.1%) of patients in the appropriate category were patients that had normal POC chromosome analysis that did warrant a complete evaluation. The remaining 70 (31.3%) patient evaluations illustrated an overutilization of testing because they also had abnormal POC chromosome results and thus testing was not warranted. Collectively, the inappropriate utilization of RPL testing (both over and under) represented almost half of all patient evaluations 106 (47.3%).

Table 12 illustrates utilization patterns across patient characteristics including number of losses and demographics.

Table 12

Laboratory Test Utilization by Patient Characteristics and Demographics

Category	**UNDERUTILIZATION**		**APPROPRIATE**		**OVERUTILIZATION**	
	n=36		n=118		n=70	
Median patient age	35.2		35.2		34.9	
Number of losses	**n**	**%**	**n**	**%**	**n**	**%**
2 (n=191)	29	15.2%	106	55.5%	56	29.3%
3 (n=26)	5	19.2%	9	34.6%	12	46.2%
4 (n=7)	2	28.6%	3	42.9%	2	28.6%
Race	**n**	**%**	**n**	**%**	**n**	**%**
White (n=156)	23	14.7%	82	52.6%	51	32.7%
Black (n=20)	6	30.0%	13	65.0%	1	5.0%
Asian (n=27)	3	11.1%	13	48.1%	11	40.7%
Other-Hispanic (n=7)	1	14.3%	3	42.9%	3	42.9%
Other (n=13)	3	23.1%	7	53.8%	3	23.1%
Insurance type	**n**	**%**	**n**	**%**	**n**	**%**
Private (n=152)	21	13.8%	82	53.9%	49	32.2%
Medicaid (n=61)	14	23.0%	31	50.8%	16	26.2%
N/a (n=11)	1	9.1%	5	45.5%	5	45.5%

Patients with two or four losses had appropriate evaluations (106 [55.5%]), (3 [42.9%]) more often than under- or over-utilization. However, individuals with three losses (n=26) had the highest percentage in the overutilization category (12 [46.2%]).

Patients had most evaluations in the appropriate category regardless of race. However, only one (5%) Black patient fell into the overutilization category, which was the lowest percentage across all races. Additionally, more Medicaid patients fell into the underutilization category (14 [23.0%]) than their privately insured counterparts (21 [13.8%]).

Chapter Summary

This chapter reviewed the results from the quantitative, qualitative, and integrated phases of this explanatory, sequential mixed methods research study. The quantitative component consisted of an in-depth, retrospective chart review of 224 RPL patients' records assessing laboratory tests performed on blood and POC from 2014 to 2021. The results from the quantitative phase revealed a low percentage of the three tests for antiphospholid antibody syndrome being ordered as compared to TSH and HgbA1c. Microarray testing following normal or failed chromosomal analysis on POC was particularly underutilized. Most evaluations were categorized as low (only 1-2 tests conducted) than medium (3-4 tests) or high (5-6 tests). Even after excluding abnormal chromosomal analysis on POC as a reason to not perform extensive RPL evaluation, roughly one-third (76 [33.9%]) of the total 224 patients did not receive any RPL evaluation beyond cytogenetic testing on the POC.

The qualitative phase consisted of semi-structured interviews with 15 OBCPs, all of whom were medical doctors but from a variety of specialties. The qualitative results suggested that the variation in evaluation adherence (high, medium, and low) was related largely to the provider's specialty. Challenges of coordinating between specialists contribute to fragmented care for patients. The participants described patients tending to

be the drivers of the evaluation process. However, without a standardized process for patients to follow, it is likely that navigating the system would be challenging, especially for those with limited health literacy.

The integration of the quantitative and qualitative results indicated that provider specialty, available resources, and degree of coordination greatly impacts the OBCP's ability to order and follow up on RPL test results. These findings align with the existing literature on RPL that discusses how outdated guidelines, conflicting definitions, and lack of inter- and intra-departmental coordination contributes to delays in determining the cause of RPL for patients (Pappas & Kutteh, 2020). The results further suggest that addressing these challenges could lead to more effective and comprehensive evaluations for patients with RPL moving forward.

Chapter 5: Discussion

Introduction

More than 50% of patients with RPL do not receive an explanation for the cause of their condition (Saravelos & Regan, 2014). Patients with RPL suffer from significant trauma, depression, anxiety, and often underlying physical health problems (Chojenta et al., 2014; Kolte et al., 2015; Lee & Rowlands, 2015). A completed laboratory evaluation may provide RPL patients with a cause for their condition up to 90% of the time (Papas & Kutteh, 2020). This chapter aims to situate the major findings described in Chapter 4 within the context of the conceptual framework and existing literature. The translational nature of the findings, including proposed interventions, the study's limitations, and future research directions are also discussed.

Major Findings

The research presented in this dissertation examined OBCP practice behaviors as they relate to the laboratory testing evaluation process for patients with RPL. In this explanatory mixed-methods study, the quantitative phase of this study revealed that patients with RPL undergo variable degrees of testing recommended by professional guidelines. Initially patient evaluations were identified as low (1-2 tests), medium (3-4 tests), and high (5-6) based upon the number of guideline-recommended tests performed. Out of the 224 patients in the dataset, more evaluations were categorized as "low" (113 [50.4%]) or "high" (81 [36.6%]) than medium (30 [13.4%]). Thus, most patients are either getting a full work up with all six tests, or an incomplete work up (most often the Hgb A1c and TSH only). Testing for APLS and microarray analysis on POC occurred less frequently than testing for endocrine conditions like diabetes and thyroid disorders.

Since Hgb A1c and TSH tests are part of routine 1st trimester care during pregnancy, these patients may never have had a consultation or further evaluation for RPL. These findings were supported in the qualitative phase regarding OBCPs decision-making process for ordering testing for RPL evaluation.

The qualitative phase of the study involved thematic analysis of recorded interviews with 15 MDs from the ObGyn department at Northwell Health in New York. The OBCPs were generalists, hospitalists, maternal fetal medicine (MFM), reproductive endocrinologists (REI), or complex family planning (CFP) specialists. Variability within the provider's specialty, along with practice setting and resources, impacted the level and extent of evaluation provided for RPL.

The multiple specialties within the ObGyn department led to inconsistency in referrals and the evaluation process. Some OBCPs described feeling comfortable completing an RPL evaluation while others referred to specialists within the ObGyn department or specialists outside the department. Generalists expressed their desire to have departmental guidance, education, and collaboration to ensure that RPL evaluations continue to be evidence-based. Interestingly patients were seen as the primary drivers of the evaluation process, and their return to care following a loss was often dependent on self-referral. Several OBCPs commented on the extent to which patients may push for evaluation even when their losses were explained (i.e., POC had abnormal chromosomes) or if they did not meet the definition of RPL (i.e., had fewer than two unexplained losses).

In the integrative phase of the study, it was clear that simply counting the total number of tests (low, medium, or high) recommended by professional guidelines for RPL

evaluation did not correlate with the appropriateness of the testing. Therefore, further analysis based on whether the POC results were normal (further RPL evaluation was necessary) or abnormal (further RPL evaluation was unnecessary) was conducted, and the designation of high, medium, and low for the number of tests performed was replaced by whether the testing was appropriate (underutilization, appropriate utilization, overutilization). For example, a "low" evaluation for patients with abnormal POC chromosomes in one or more POCs was deemed appropriate whereas a "high" evaluation was deemed overutilization when the POC results were abnormal. Collectively, inappropriate utilization accounted for 106 (47.3%) of evaluations and overutilization was more frequent (70 [31.3%]) than underutilization (36 [16.1%]). Based on descriptive analysis, Medicaid patients fell into the underutilization category (14 [23.0%]) more often than their privately insured counterparts (21 [13.8%]). However, the small number of evaluations in these categories limited further inferential statistical analyses. Collectively, these findings indicate several opportunities to implement interventions that would improve appropriate and comprehensive RPL evaluations.

Interpretation and Discussion of Findings

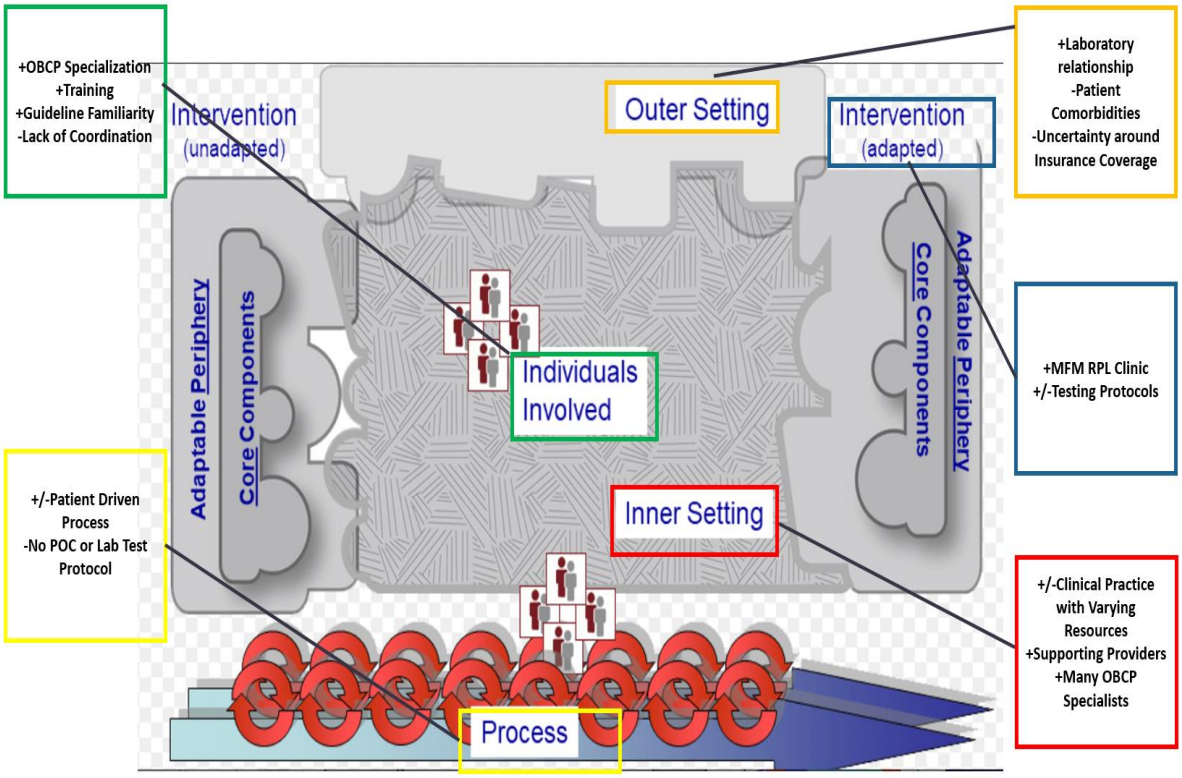
The primary goal of this research project was to understand OBCP practice behavior surrounding RPL evaluations, with the long-term goal of identifying potential interventions to facilitate this process. The Theoretical Domains Framework (TDF) guided the qualitative analysis of OBCP behavior as it pertains to RPL evaluations. The framework provided a comprehensive structure to capture the complexity of behavior and uncover specific barriers and facilitators. The factors influencing decision making within the evaluation process included how OBCPs identified within their professional role and

specialty, their beliefs about their capabilities to conduct the evaluation, and their beliefs about how their peers are conducting evaluations. The use of TDF in this research emphasizes the multifaceted nature of behavioral motivation and change in the clinical setting. The insights derived from this analysis utilizing the TDF could inform the development of targeted interventions including the solidification of laboratory and process protocols to alleviate uncertainty for OBCPs.

The Consolidated Framework for Implementation Research (CFIR) was chosen to guide this research to better understand the OBCP perspective on the RPL evaluation process within the context of their environment including their clinical practice, department, the health system, existing interventions, and external factors such as the influence of patients and policies. CFIR was also used to frame discussion of future interventions to better facilitate RPL evaluation. There are many factors that affect RPL evaluation, including the specialization of the provider, their practice setting, the influence of patients, laboratory test ordering, access to test results, and laboratory test interpretation. How the identified barriers and facilitators to RPL evaluation align within the CFIR framework is illustrated in Figure 12 and further described below.

Figure 12

Alignment of Major Findings to CFIR Framework Domains



Note. Adapted from Damschroder, L. J., Aron, D. C., Keith, R. E., Kirsh, S. R., Alexander, J. A., & Lowery, J. C. (2009). Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. BioMed Central. https://doi.org/10.1186/1748-5908-4-50

Individual Domain

The specialization, training, and familiarity with professional guidelines and definitions were identified to fit within the individual domain of CFIR. OBCP specialty training impacted the degree to which the participants ordered RPL evaluations. OBCP participants that conducted RPL evaluations expressed familiarity with laboratory testing involved with RPL evaluations but conceded that the evaluations can be challenging for several reasons. The factors that impacted the extent of RPL evaluations stem from

coordination issues among OBCPs and other specialists, including uncertainty as to which OBCPs (specialty and non-specialty) handle which parts of the evaluation, varying confidence levels with several aspects of laboratory testing, and the availability of additional resources, such as nurse navigators or genetic counselors.

OBCP participants described using differing combinations of guidelines, definitions, and other academic resources to guide their decision making on RPL evaluation. Specialist OBCPs are required to undergo annual education and training to maintain their specialty board certifications, which provides additional exposure to current research on RPL. REI OBCPs were the only participants using the ASRM guidelines, which have been cited in recent RPL evaluation literature as being beneficial in determining up to 90% of explanations for RPL (Papas & Kutteh, 2020).

Inner Setting

The ObGyn department and individual practice clinic setting align with the inner setting of the CFIR framework. The Northwell Health ObGyn department is large, consisting of many distinct practices. While there is some well-coordinated collaboration within individual practices, the OBCP participants described a lack of coordination of care within the department itself. Different OBCPs may refer patients to various specialties within and outside of the ObGyn department. Specialist practices tended to have better collaboration, whereas generalist practices were not always aware how colleagues in their same practice were handling RPL evaluation. Specialist practices also benefited from supporting providers, such as nurse navigators and genetic counselors, who obtain patient medical and family history, communicate detailed clinical testing information, and coordinate referral appointments.

Outer Setting

The influence of patients, insurance coverage concerns, and coordination with specialty departments external to ObGyn, such as the laboratory and hematology department were identified to fit within the outer setting domain of CFIR. Patient factors, such as maternal health conditions and psychosocial concerns, were influential on the evaluation process. Overall, the initiation and completion of the evaluation for RPL is often patient driven. Patients return to their OBCP when they are in pursuit of additional answers as to what caused the miscarriage and if there is treatment available to improve the probability of having a successful subsequent pregnancy. Patients that do not return to care are also at risk of untreated maternal health conditions, including complex psychosocial and behavioral health needs, which complicates the RPL evaluation process. Patients coping with a lack of explanation for multiple losses may push providers to perform potentially unnecessary tests, whereas cultural and socioeconomic barriers may inhibit patients from returning to care. Multiple appointments with different providers for various evaluations may prolong the process for patients that already have barriers to accessing medical care. Additionally, as one participant highlighted, patients may fear that fertility services will not be covered by their health insurance or may be culturally stigmatizing.

Though many OBCPs discussed referrals to specialists outside the department, few OBCPs interviewed for this study had a psychological and behavioral health care referral protocol. The participants commented on the psychological impact and trauma experienced by RPL patients, but it was not clear if referrals to behavioral health specialists were routinely integrated.

Process Domain

The specialty referral process and laboratory testing process were aligned to the process domain. The RPL evaluation process often relies on patients to self-navigate, however, there is not a standardized process for patients to follow. OBCPs within the same department may proceed with RPL evaluation differently according to their internal clinic standards or their specialty and training, which may contribute to incomplete or delayed evaluations. Specialist OBCPs may only see patients long after a miscarriage when it is often too late to request genetic testing. Without these results, patients may not receive an explanation for their most recent loss and may undergo unnecessary tests and procedures.

Complex family planning (CFP) and highly experienced providers have mechanisms and processes in place to ensure that this information is captured. CFP providers may care for women during a miscarriage particularly if it requires a procedure like a D&C or D&E. As a result, these specialists have systems in place to ensure the collection of POC for genetic testing analysis. Therefore, they are optimal providers to lead the development of a protocol for collecting POC at home. However, some CFPs expressed that they and their patients have concerns about insurance coverage for these sometimes-costly genetic tests, such as microarray.

Since hospitalist OBCP lack the resources to follow up on normal results, a patient with normal POC chromosome analysis may never receive their POC genetic testing results if the patient does not return to care. Although normal results are often considered to not require urgent follow up, in the context of RPL, normal POC results could indicate that a patient's RPL is unexplained, and they are at a higher risk of further

loss (Gardner & Amor, 2018). Additionally, normal POC chromosome results could miss subtle chromosomal changes only detected by microarray analysis, and normal female chromosome results should be further evaluated for maternal cell contamination.

If patients return to care, it is typically to review the results from the POC chromosome analysis with their generalist OBCP and to determine the cause of the recent pregnancy loss. However, this study identified several barriers to obtaining genetic testing on POC, including separate EMR systems that did not communicate with each other, the length of time for test results to be available, and their location within the EMR. Several OBCP participants remarked on the difficulty in retrieving laboratory results, most often POC chromosomal analysis, from the EMR system. The POC results can take up to four weeks to return, and patients may return to care prior to these results being complete, leaving the possibility for an incomplete evaluation given the importance of the POC analysis.

In terms of other laboratory testing, some providers may be over-utilizing or repeating laboratory tests due to a lack of access to results from outside providers or EMR systems. Other providers may not order additional testing based on previous results, medical history, or because it does not fall within their practice domain like hospitalists. However, 67.3% (76) of patients with POCs with normal chromosomes only had one to two further tests and could have benefited from additional RPL testing.

Intervention Domain

The intervention domain aligns with the factors currently used to improve RPL evaluation and proposed interventions. Existing interventions include the standard laboratory protocols used by some individual OBCPs and the REI specialists. The REI

specialists could share with the other OBCPs what resources were used to develop the protocol, how they maintain or periodically evaluate the list, and what, if any, components they would prefer Generalist OBCPs order prior to an REI consultation. For example, one REI participant said she would prefer the parental genetic testing be collected prior to the REI consult because of the lengthy time to result. However, most Generalists were not comfortable ordering that test.

Supporting providers, such as nurse navigators and genetic counselors, aid in the communication of genetic and other testing results, including their purpose and limitations. Therefore, with the appropriate referral protocol in place, genetic counselors could facilitate the genetic testing component of the evaluation on behalf of OBCPs who are not as familiar with this testing. The nurse navigators also facilitate appointments and communication with patients. Aside from expanding the number of these supporting providers, the existing supporting providers may benefit from a standardized referral and laboratory testing protocol.

Although some specialist OBCPs had implemented a standardized testing protocol into their clinical practice, such as a preset test list in their EMR, most participants agreed that there was no departmental—or professional organization — consensus on what tests to order or when to begin a RPL evaluation. Even those OBCPs who referred some or all aspects of the evaluation to specialists agreed that they still would welcome a departmental consensus, guidance, and education on the recommended laboratory tests.

Another important existing intervention is the MFM RPL clinic. This clinic provides consultations for RPL evaluation accommodates both during pregnancy and

preconception. The MFM OBCPs in this clinic collaborate with external specialists from the laboratory, pathology, and hematology departments. However, some participants were unaware or were uncertain about what patients should be referred to this program. Future directions for the clinic should include continuing to increase awareness of the clinic, additional appointment slots, and continued multidisciplinary case review and collaboration.

Translation of Study Findings to Proposed Interventions

This research study aimed to understand OBCP practice behavior in evaluating patients with RPL to improve the appropriate utilization of these evaluations and leverage existing factors that facilitate the evaluation process. Additionally, it sought to lay the groundwork for future research on the patient experience of RPL care, thereby bridging the translational gap between T2 and T3 on the translational spectrum. The laboratory component of an RPL evaluation was the central focus of this research study including how clinicians order, interpret, and synthesize results. Despite existing guidelines, RPL evaluations are not being conducted appropriately, resulting in both the under- and overutilization of testing. This can potentially lead to poor health outcomes, including undiagnosed morbidities, mental health concerns, further pregnancy losses, or, in the worst case, the birth of a child with a chromosomal disorder. More importantly, patients with RPL may not receive treatment for underlying health problems, including psychological distress.

To develop a comprehensive and coordinated RPL evaluation protocol, participants suggested educational opportunities including annual presentations to the department in the form of grand rounds or the yearly ObGyn summit with reviews of the

most current evidence-based literature on RPL evaluation were suggested. Additional opportunities to obtain continuing education credits specific to RPL should also be offered to OBCPs, especially those who may not have other additional training or education opportunities available through their professional organizations. The development of referral and laboratory protocols could stem from working groups and educational sessions.

Identifying patients at the time of a second pregnancy loss and facilitating the transition back to outpatient care would improve timely treatment of maternal physical and behavioral health conditions. However, laboratory results can often be siloed among the ordering providers in differing EMR systems. Most commonly, the POC genetic testing results are in an EMR not available to all providers. Some guidelines do not recommend POC chromosome analysis on the first loss, but it is impossible to determine a pattern or explanation by the time the patient has a second loss. Without the POC results, no necessary follow up or reflex testing will be performed, such as microarray analysis and maternal cell contamination studies after a normal female chromosome result on a POC. Thus, this testing is a critical step in RPL evaluation and yet represents one of the largest gaps in the process. Given the laboratory's central nature, a multidisciplinary RPL team including the laboratory could facilitate POC testing, patient result communication, and follow up care coordination.

Coordination of Care in Partnership with the Clinical Laboratory

Laboratory testing factors represent multiple sources of evaluation delays, and providers often do not have access to both in- and outpatient results. One solution to the challenges faced by OBCPs could be a greater role for the laboratory in coordination of

RPL evaluation. In recognition of the challenges of having separate EMR systems for the hospitals and outpatient clinics, Northwell Health is in the process of implementing a universal EMR system to improve the availability of previous test results to providers. This change will improve the availability of the POC testing results to providers and reduce overutilization of duplicate tests. However, this updated EMR system will not proactively identify laboratory tests that were not collected nor identify patients with RPL that may have recently experienced a loss and need reintegration to care. Participation from the laboratory could add to this process by facilitating the availability and communication of relevant information.

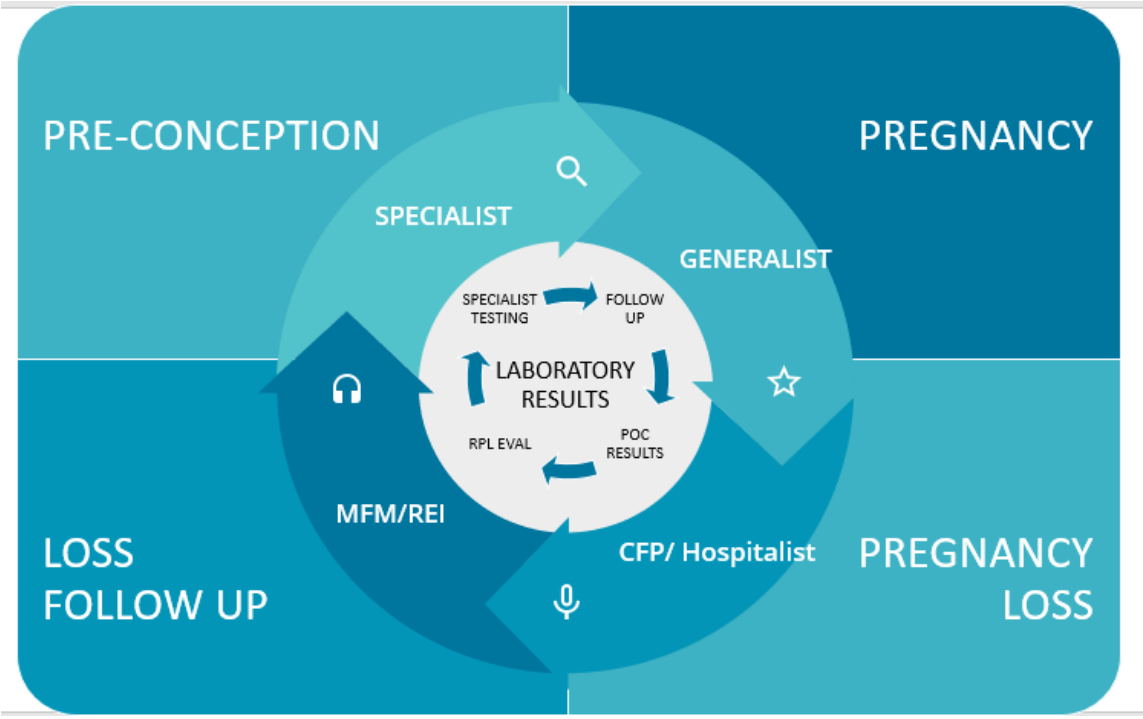
The laboratory maintains a central database of laboratory results from the most common EMR systems in the Northwell Health System. Thus, the laboratory could serve as a centralized department to ensure availability of all test results and to serve as a conduit between providers within the cycle of referrals (Figure 13). Specifically, if RPL-related laboratory test results were consolidated into a single test result document with a comprehensive interpretation for all tests as used in techniques from Lab 2.0 and Diagnostic Management Teams (DMTs) discussed below, hospital results could seamlessly coexist with outpatient results in both their respective EMR systems.

Additionally, the laboratory can assist in this effort by identifying patients at the time of their second loss via electronic reporting systems already in place. These electronic reports are currently utilized to identify duplicate laboratory tests on the same patient to reduce overutilization. However, the reports could also be used to identify patients with their second or more order for chromosome analysis on POC. The

Generalist ObGyn could subsequently be notified of these patients thereby driving an improved transition back to care.

Figure 13

Potential Laboratory Role in Care Coordination in RPL Cycle



Laboratory-centered coordination would help avoid unnecessarily repeating testing, allow for follow-up on abnormal test results that need repeating (APS), and flag normal test results that require subsequent tests (chromosome analysis). Clinical laboratory specialists are routinely available to comment on the purpose and limitations of laboratory tests and aid in interpretation of results. However, literature suggests that providers may not be aware of this service or are less inclined to reach out to the laboratory directly (Dickerson et al., 2019). Leveraging existing systems within the laboratory can enhance clinical care coordination, bridging the gap between laboratory and clinical practices. One such system is the Diagnostic Management Team (DMT).

Diagnostic management teams. Diagnostic management teams (DMTs) are integrative and multidisciplinary teams that traditionally include physicians and clinical and technical laboratory experts that review individual laboratory results from a disease-specific perspective and compile a synthesized lab report with a diagnostic interpretation (Sarkar, Botz, & Laposata, 2018). DMTs utilize patient's laboratory results to facilitate diagnosis and recommend next steps in care for patients. Sarkar, Botz, and Laposata (2018) originally developed the concept of the DMT and described the role of the clinical laboratory in the facilitation of the diagnosis of coagulation disorders. Coagulation testing is also a significant part of the evaluation of RPL, so there is an overlap with the nature and scope of collaboration of care for both conditions. Thus, DMTs may serve as a good model for improving the efficiency of locating and synthesizing results from RPL evaluations. However, the DMT relies on laboratory tests collected at one time and does not offer a strategy to monitor or track patients throughout their ongoing and follow-up care in the healthcare system. Another critique of DMTs is the challenge of scalability, as creating a single laboratory interpretation can be time-consuming, especially when serving multiple hospitals within a health system. Although having a dedicated team of experts for each recurrent pregnancy loss patient may not be practical, generalists can still stay informed about the multidisciplinary RPL team and consult with its members within the health system to leverage specialized expertise as needed.

Although there is little information regarding the specific nature of how the clinical laboratory can best collaborate with clinical providers directly, pathologists and pharmacists have experience in bridging the silos in the healthcare system by serving as

conduits between laboratory and clinical providers. Therefore, a collaboration between ObGyn providers and laboratory professionals could be implemented for RPL if there were sufficient resources to obtain all laboratory results related to RPL and a clinical expert to provide an overarching interpretation. In line with this approach, Clinical Lab 2.0 (CL 2.0) offers a value-based model that leverages laboratory data to address gaps and improve health care services for prevalent and high-risk conditions (Shotorbani, 2016).

Clinical Lab 2.0. Clinical Lab 2.0 (CL 2.0) is an initiative that promotes a value-based model that utilizes laboratory data to identify, close gaps, and promote health care services for highly prevalent, costly, and high-risk disease states (Shotorbani, 2016). The CL 2.0 model provides a framework for determining which disease states would benefit from laboratory-led interventions from a financial and population health perspective (Crawford et al., 2017). Within the CL 2.0 literature, a 2018 quantitative study on pregnancy outcomes involving ED visits, NICU admissions, and length of stay is most closely related to the topic of reproductive health (REF). The authors identified patients at elevated risk for pregnancy complications (missing prenatal visits, HIV positive, etc), created a summary report of missing laboratory tests and appointments in the patient's chart, and provided this information to managed care organization (MCO) care coordinators (Swanson et al, 2018). The coordinators then contacted patients directly to remind them of appointments and necessary next steps in prenatal care. Interestingly, 80% of the gaps in completing necessary laboratory testing were closed following the intervention (Swanson et al, 2018). Therefore, the concept of relaying laboratory information to a coordination team could apply to evaluation of patients with RPL.

Summary of Proposed Interventions

Based on the findings of this study, enhancing and expanding the multidisciplinary team of specialists, including clinical laboratory providers, could help improve the diagnostic understanding of the etiology of RPL. The team's focus should center around developing departmental and practice-based protocols including specialty referral criteria, patient results follow up, POC collection and genetic testing, and determining insurance coverage is critical for patients who experience RPL. While developing a comprehensive test panel for assessing RPL may risk overutilization, current technology enables providers to review prior results when ordering and deselect unnecessary or redundant tests. Creating patient-facing brochures with instructions on what to do if they are experiencing a potential miscarriage along with a kit for home collection may provide high risk patients with necessary support. Finally, leveraging the expansive presence of the Northwell Health system within the community with women's health fairs may improve access and breakdown existing barriers to receiving healthcare. Below, Table 13 illustrates the proposed elements of an intervention strategy that incorporates existing interventions and those recommended by the participants.

Table 13

Summary of Proposed Interventions within the CFIR Domains

CFIR DOMAIN	INDIVIDUAL	INNER SETTING	OUTER SETTING	PROCESS	INTERVENTION
PROPOSED INTERVEN-TIONS	•OBCP Education • Participation in annual review of EB RPL laboratory testing	•Implementation of standardized laboratory testing protocols •Additional supporting providers (NP, GCs) where possible •Annual grand rounds and educational sessions	•Laboratory involvement in multidisciplinary work group • Consolidated lab report • Patient-oriented education • Community Outreach	•Development of referral process protocol •Laboratory testing protocol • POC collection protocol	• Promotion of existing interventions in practice •Additional RPL clinic appointments •Standardized testing protocol development

Limitations

Despite the important findings that provided a framework for proposed interventions to better facilitate RPL evaluation, this study had several limitations. This study was limited to only one health system. Although these findings are likely not unique to other similar large, complex health systems, the findings from this study may not be generalizable to other health systems. Among patients identified through the retrospective chart review with ≥2 POCs (n=508), only patients with at least one outpatient visit to a Northwell Health ObGyn were included in subsequent analyses. Thus, some patients with RPL may have undergone further evaluation outside of the Northwell Health system. Additionally, some patients may have been offered further evaluation but declined.

Interview participants included 15 OBCPs, all of whom were physicians with MD credentials despite attempts to recruit OBCPs with other credentials. Therefore, the viewpoints and experiences of other OBCPs were not included in this study. Yet the OBCPs included in the study represented decades of experience and specialization in maternal conditions including RPL, and it is hoped that through the rich descriptions of the findings in this study that readers will be able to apply findings to their own setting. Additionally, this study exclusively focused on the OBCP perspective, but to better understand factors contributing to delayed or incomplete RPL evaluation, future studies should include patient perspectives surrounding this process.

Finally, another limitation of this study is that the researcher is a genetic counselor embedded in the Northwell Laboratory and works alongside the OBCPs, which may have introduced bias in interpretation of the results. However, extensive efforts were made to reduce bias by journaling and creating memos to reflect where internal bias may have arisen.

Recommendations for Future Research

Given the influence of patients on the evaluation process, as well as the nature of their entry into a variety of different care points the evaluation cycle (i.e., the hospital, a specialist clinic, etc.), future research into the experience of patients with RPL in the evaluation process would be valuable in informing best practices in RPL evaluation. Patients can speak to their individual experience of referrals and test completion and how (or if) they were informed of test results. Additionally, patient motivation was noted by participants to facilitate the evaluation process, and therefore, future research should focus on ways to capitalize on patient involvement and ensure engagement among

patients who may be disenfranchised. Research examining test utilization patterns from other health systems could identify similarities and differences of OBCP practice behavior in the evaluation of RPL. Finally, post-implementation of interventions informed by this research project could be measured by random sampling and ongoing chart review of RPL patients or utilizing the informatics team to create electronic chart monitoring solutions.

Additional quantitative studies, such as surveys, could capture more insight into a larger number of OBCP's and their practice behavior. For example, a survey that gauged knowledge within the latest guidelines and testing recommendations for RPL may identify areas where OBCPs lack knowledge of specific evidence-based criteria for testing. However, OBCPs in this study noted that it was more often their specialty or lack of resources rather than their knowledge, that resulted in their not ordering testing.

Summary

In sum, this study explored the factors surrounding the OBCP perspective on the RPL laboratory testing evaluation process. The study's findings, aligned with current literature, suggest that close coordination with the laboratory would facilitate completed evaluations, assist in interpretation, and connect specialist providers that lack access to certain laboratory results. In this study, OBCPs that had a close connection to laboratory personnel reported that they were more easily able to obtain laboratory test results, and that the clinical laboratory was an asset to their multidisciplinary team.

Laboratory testing utilization research rarely incorporates the provider perspective. There are a number of specialties within the ObGyn department that promote comprehensive care but can contribute to a fragmented evaluation experience for patients

with RPL. A lack of protocols for POC collection and the referral process can inhibit the evaluation process. More importantly, patients may not be informed of results from POC testing unless they self-present back to their primary ObGyn or are contacted with abnormal results from the hospital.

Generalist OBCPs reported a lack of departmental guidance and resources to sufficiently complete the laboratory evaluation. Specialists are well-suited to evaluate patients with RPL because they have additional training in this area; however, they may struggle to obtain all laboratory results or lack appointment availability, and patients may have cultural or socioeconomic barriers to obtaining care from these providers. The results of this study indicate that providers could benefit from closer coordination within the ObGyn department and with specialists within the laboratory, as well as more education regarding RPL evaluation. A coordinated approach to managing RPL evaluation would clarify provider roles and facilitate better patient care. Furthermore, interdepartmental collaboration with the laboratory, hematology, and behavioral health departments, among others, can support appropriate and comprehensive care for RPL patients.

List of Appendices

Appendix A. IRB Approval Letters

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

Date: February 01, 2024
To: Schwartz, Lisa S, EdD
From: The George Washington University Committee on Human Research, Institutional Review Board (IRB), FWA00005945
Subject: **IRB# NCR235361** , "*Evaluation of the Etiology of Recurrent Pregnancy Loss (RPL): An Explanatory Mixed Methods Study Exploring Obstetrician Gynecologist Provider Practice Behaviors and Factors Contributing to Incomplete Laboratory Testing Evaluations*"

Exempt Determination Date: 02/01/2024

The request for an exemption determination for the above-referenced study has been completed. The study was determined to be research that is **exempt** from IRB review under DHHS regulatory **category 2**. The project as described in the application may proceed without further oversight by the OHR.

The exemption determination applies only to the project described in your IRB Application. Any changes that may alter in any way the risks to participants, type of information to be accessed, addition of new populations, or change in PI may not be instituted without submission of a Modification within the iRIS system and further review by the OHR prior to implementation of the changes. Please note, it is the responsibility of the GW research team to ensure all approved research personnel have up-to-date CITI training at all times in order to conduct human subjects/participants research.

For Exempt studies involving collaboration with external institutions/sites: Research studies that are registered as exempt are not eligible for institutional reliance agreements. Please reach out to any collaborating site(s) that will be engaged in human subjects research activities on this study to discuss next steps according to their reviewing Institutional Review Board's policies and procedures. If you have questions, please contact the GW Office of Human Research.

Questions or concerns regarding the exemption determination made for the study should be directed to the GW Office of Human Research at ohrirb@gwu.edu or (202) 994-2715.

Feinstein Institutes for Medical Research
Northwell Health

Institutional Review Board
FWA #00002505
Office of the Human Research Protection Program
125 Community Drive
Great Neck, NY 11021
Phone: 516-465-1910

The study cannot begin enrollment until you receive Northwell Institutional Approval (IA). Institutional Approval is separate from IRB approval, and will be issued in a separate letter. For IA guidance click here, or visit the HRPP website.

To: Emelia Grant

From: Human Research Protection Program

Date: November 03, 2022

RE:**IRB #:**22-0838
Protocol Title: Assessing gaps in laboratory testing for patients with recurrent pregnancy loss (RPL)

Dear Emelia Grant:

The above referenced project meets the criteria:45 CFR 46.104 (d) (4)(ii) Secondary research uses of identifiable private information or identifiable biospecimens, if information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

The following investigator is approved to participate in this study: Emelia Grant.

HIPAA Authorization
A full waiver of HIPAA authorization has been granted because, based on the justifications provided in the protocol, the below criteria are met: 1. The PHI use or disclosure involves no more than minimal risk to the privacy of individuals based on at least the presence of (1) an adequate plan presented to the IRB to protect PHI identifiers from improper use and disclosure; (2) an adequate plan to destroy those identifiers at the earliest opportunity, consistent with the research, absent a health or research justification for retaining the identifiers or if retention is otherwise required by law; and (3) adequate written assurances that the PHI will not be reused or

disclosed to any other person or entity except (a) as required by law, (b) for authorized oversight of the research study, or (c) for other research for which the use or disclosure of the PHI is permitted by the Privacy Rule. 2. The research could not practicably be conducted without the requested waiver or alteration. 3. The research could not practicably be conducted without access to and use of the PHI.

It is your responsibility to notify the IRB in writing of any changes or modifications made in the research study design, procedures, etc. which do not fall within one of the exempt categories. Such changes necessitate a new, complete IRB submission. If the IRB receives no correspondence on this study for three years, the file will be closed.

The Institutional Review Board will be notified of this action at a meeting.

Investigators are reminded that research must be conducted in accordance with all applicable Department of Health and Human Services regulations 45 CFR 46, Food and Drug Administration regulations 21CFR 50, 21CFR 56,21 CFR 312, 21 CFR 812, and the Health Insurance Portability and Accountability Act (HIPAA).

All studies are subject to audits by the Office of Research Compliance and/or Institutional Review Board to confirm adherence to institutional, state, and federal regulations governing research.

NOTE: This approval is subject to recall if at any time the conditions and requirements as specified in the IRB Policies and Procedures are not followed (see next page and web site: https://feinstein.northwell.edu/sites/northwell.edu/files/2020-12/HRPP-Policies-and-Procedures.pdf)

NOTE: All IRB Policies and Procedures must be followed, including the following:

1. Using only IRB-approved consent forms, questionnaires, letters, advertisements, etc. in your research.
2. Submitting any modifications made to the study for IRB review prior to the initiation of changes except when necessary, to eliminate apparent, immediate hazards to the subject.
3. Reporting unanticipated problems involving risk to subjects or others.
4. Prior to implementation, any changes made to studies utilizing TAP must have COPP, as well as IRB approval.

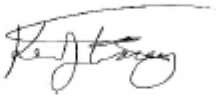
Feinstein Institutes for Medical Research
Northwell Health

FWA #00002505
Human Research Protection Program
125 Community Drive
Great Neck, NY 11021
Phone: 516-465-1910

****THE BELOW REFERENCED STUDY MAY NOW BEGIN ENROLLMENT****

To: Emelia Grant

From: Kevin J. Tracey, MD
Executive Vice President, Research



Date: November 03, 2022

Re: **IRB #:** 22-0838
Protocol Title: Assessing gaps in laboratory testing for patients with recurrent pregnancy loss (RPL)

Dear Emelia Grant:

The Feinstein Institute for Medical Research has confirmed that the above referenced study has obtained all appropriate approvals.

The above referenced study now has institutional approval for commencement at the Northwell Health Facilities listed in the initial submission application.

Please note: It is the study team's responsibility to contact with Research IT for all future modifications regarding the electronic data storage.

Appendix B. Dissemination Activities

Abstract from the 2024 American College of Medical Genetics (ACMG) Annual Clinical Genetics Meeting

Evaluation of the Etiology of Recurrent Pregnancy Loss: A Retrospective Chart Review Assessing OBGYN Provider Practice Behavior

Ninette Cohen, PhD; Aya Haghamad, PharmD; Erika Dadabo; Timothy Raphael, MD; Dzhamala Gilmandyar, MD; Dwayne Breining, MD; Emelia Grant, MS, CGC

Introduction

Recurrent pregnancy loss (RPL) is defined as two or more losses and affects roughly 2-3% of reproductive-aged couples. Current literature suggests that conflicting professional society guidelines and the complexity of laboratory testing may be contributing factors to inappropriate and incomplete diagnostic evaluation of RPL, which involves substantial laboratory testing (Papas & Kutteh, 2020). Diagnostic latency subsequently contributes to psychological trauma, unsuccessful and costly fertility treatments, and untreated underlying maternal disease. Delays in diagnosis can contribute to a high rate of recurrence and maternal/fetal morbidity and mortality.

Northwell Health is New York State's largest health care provider and private employer, with 21 hospitals, 850 outpatient facilities and more than 12,000 affiliated physicians. Our primary objective was to assess the current OBGYN practice behavior for laboratory testing on RPL patients using a multidisciplinary focus group, including both clinicians, laboratorians and genetic counselors.

Methods

A retrospective chart review was conducted by examining the records of patients with product of conception (POC) testing at Northwell Health. Records of all POC testing from 2014 to 2021 were assessed from the Northwell Health Quality Assurance Database. Patients were included if they had two or more POCs and had chromosome analysis completed. Patients were excluded if they only had one POC during the study period, or they had no additional laboratory testing. The charts were then searched for hemoglobin A1C, thyroid stimulating hormone (TSH), lupus anticoagulant (DRVVT, aPTT, PTT, SCT), cardiolipin antibody (IgG and IgM), beta-2-glycoprotein (IgG and IgM), and hereditary thrombophilia (Protein C, Protein S, Prothrombin, Antithrombin, Factor V Leiden) testing. If the patient had results for any of the above tests, it was recorded as being 'Normal' or 'Abnormal' based on the report findings. If the patient had the testing multiple times, we recorded it as abnormal if the sample was abnormal at least one time. If the testing was not performed, it was recorded as 'NP'.

Results

A total of 6,940 unique patients were assessed. Of those, a subset of 230 (3.3%) patients were randomly selected and met the inclusion criteria. Out of the 230 patient charts analyzed, 27% had maternal karyotypes performed, and among these, 96.8% were normal and 3.2% were abnormal. Hemoglobin A1c was performed on 69% of patients and 12% were abnormal. TSH was performed on 78.2% of patients and 10.6% were abnormal. Lupus anticoagulant was performed on 33.6% of patients and 16.9% were abnormal. Anti-cardiolipin antibody testing was performed on 38.9% of

patients and 11.2% were abnormal. Anti-Beta 2 glycoprotein antibody testing was performed on 39.3% of patients and 14.4% were abnormal. Out of the 248 POCs with normal chromosomes or no growth, only 19.4% had a reflex microarray. Among these, 83.3% were normal and 16.7% were abnormal.

Conclusions

Based on the gaps seen in the chart review we collaborated with OB/GYN clinicians and proposed a process to facilitate lab test completion prior to clinical consult, obtain lab test results from other sites, obtain genetic testing on prior losses, and review of placental pathology/autopsy by a pathologist. We established monthly meetings with our high-risk OB/GYNs, onboarded a patient care coordinator, and are working to develop an order-set to streamline laboratory testing. The exercise of examining how to best follow up laboratory testing for RPL patients led to the collaboration with OB/GYN clinicians in the system and paved the way for the ongoing teamwork in the opening of the RPL clinic. Future research will focus on evaluating outcomes for RPL enrolled in this enhanced service.

Appendix C. Email Invitation to Interview Participants

To Whom it May Concern,

You are invited to participate in a research study on **Recurrent Pregnancy Loss (RPL)** because you are a healthcare provider within the Department of Obstetrics and Gynecology. We would like to understand your experience and perspective as a provider that cares for patients with RPL, and we hope to use this feedback to improve clinical care for RPL patients within the Northwell Health System.

The interviews will last for approximately 30 minutes and will take place over Microsoft Teams. The consent form to participate in this interview is attached. I will also obtain your consent to participate at the beginning of the interview. Please review the attached consent form and reach out to me with any questions or concerns.

As a thank you for participating, you will receive a $25 Amazon gift card after the interview. If you are interested in participating in the interview, please let me know of a few days and times within the next few weeks that you are available.

Thank you for your time and consideration to participate in this study.

Kind Regards,

Emelia Grant

Appendix D. Interview guide by CFIR domain

Demographics	
Professional degree? Specialty?	
How long practicing?	
At Northwell?	
How many people in your practice?	
How many people in your practice see patients with RPL?	

CFIR Domain	Ob-Gyn Clinical Providers (OBCPs) questions
Individual Characteristics	1. How do you define RPL? 2. When do you decide that lab testing is warranted for RPL patients? 3. How do you decide what lab tests to order for RPL patients? o What guidelines, if any, do you follow? 4. What circumstances or factors make evaluating patients for RPL (laboratory work up) challenging for you? 5. **How confident do you feel in your knowledge and background of RPL testing recommendations** 6. **What is most important to you in evaluating RPL patients? What is a successful outcome in your view?**
Process	1. If a patient under your care has a miscarriage, how would you typically find out about it to follow up? a. If a procedure is necessary (e.g., D&C), are you typically performing the procedure and sending POC or referring out? b. Would you do anything differently if you found out that it was a patient's second or third loss? c. How do you follow up with laboratory test results 2. What challenges, if any, do you face in ordering, obtaining, or interpreting laboratory test results for RPL?

	a. If challenges, are there tools or interventions for other lab test results that may aid in ordering, interpreting, or obtaining RPL test results?
Intervention	1. To what extent do the clinical guidelines for RPL influence your clinical practice? 2. What factors promote adherence to following guidelines for laboratory testing? 3. What kind of tools might help facilitate completeness of test ordering including follow up?
Inner Setting	1. How do you feel about the level of agreement or concordance within your practice about how to approach RPL evaluation? (i.e. number of losses, microarray, etc) 2. How similar are your colleagues to you in how they decide to evaluate RPL patients? 3. How does the practice stay current on laboratory testing recommendations for RPL patients? 4. How often do you and your colleagues collaborate on evaluations for RPL patients?
Outer Setting	1. How does insurance coverage factor into laboratory testing ordered for RPL patients? 2. If you are a sub-specialist, how do patients with RPL get referred into your practice? 3. If you are not a sub-specialist, how do you refer patients with RPL out of your practice (to a specialist)? 4. To what extent do you collaborate with other departments (i.e. referrals to specialists or receive referrals)? 5. What external factors do you feel impede your ability to evaluate patients with RPL?

Note. Adapted from the CFIR Interview Guide (Damschroeder et al., 2013)

Appendix E. Pre-Determined Codes

CODE	*DEFINITION*
INDIVIDUAL	OBCPs
• *SKILLS*	The technical and clinical competencies required to provide optimal care (e.g., proficiency in performing procedures like ultrasounds or counseling patients on genetic testing). Communication skills for effectively engaging with patients, especially during sensitive consultations related to pregnancy loss or fertility issues.
• *SOCIAL/ PROFESSIONAL ROLE/ IDENTITY*	How ObGyn providers perceive their professional role, responsibilities, and identity (e.g., being a patient advocate, a guide through fertility challenges). Expectations about their behavior from colleagues, patients, or professional bodies.
• *BELIEFS ABOUT CAPABILITIES*	Confidence in their ability to perform specific tasks or provide certain types of care (e.g., managing high-risk pregnancies or supporting patients through recurrent miscarriages). Self-efficacy in handling difficult cases, such as when delivering unfavorable diagnoses.
• *BELIEFS ABOUT CONSEQUENCES*	Perceptions of the outcomes associated with different clinical behaviors (e.g., performing genetic testing vs. not offering it, or providing emotional support during pregnancy loss). Beliefs about the short-term and long-term consequences for patients and their own practice

	(e.g., potential benefits of interventions or risks of inaction).
REINFORCEMENT	External incentives or disincentives (e.g., financial bonuses for meeting certain clinical outcomes, penalties for missing targets). Feedback mechanisms that reward or reinforce specific behaviors, like positive patient outcomes reinforcing guideline-adherent behavior.
• *GOALS*	The personal and professional goals that drive their clinical practice (e.g., providing patient-centered care, reducing pregnancy complications). Alignment between individual and organizational goals (e.g., meeting institutional targets for patient outcomes).
• *MEMORY, ATTENTION, DECISION PROCESS*	Cognitive processes involved in making clinical decisions (e.g., how they recall and apply guidelines for high-risk pregnancies). The impact of workload or stress on decision-making (e.g., the ability to maintain attention in a busy clinic).
ENVIRONMENTAL CONTEXT AND RESOURCES	External factors influencing provider behavior, such as time constraints, availability of resources (e.g., access to specialized genetic tests), or institutional policies.

	The role of the healthcare setting (e.g., large hospital vs. smaller practice) in shaping their clinical actions.
• *SOCIAL INFLUENCES*	The effect of peer behavior, patient expectations, and professional networks on provider decisions (e.g., how team collaboration or patient pressure influences their care choices). Influence from supervisors, mentors, or professional bodies on their practice.
• *BEHAVIORAL REGULATION*	Strategies providers use to regulate and change their behavior (e.g., adopting new guidelines, tracking patient outcomes). Use of reminders, checklists, or decision aids to improve clinical practice consistency.
• *KNOWLEDGE*	Understanding of the clinical guidelines, procedures, and best practices in ObGyn care (e.g., management of recurrent pregnancy loss or early pregnancy interventions). Awareness of the latest research, technologies, and legal or policy changes impacting their practice.
• *EMOTION*	How emotions, like empathy, stress, or anxiety, affect their behavior (e.g., the emotional toll of managing patients with recurrent pregnancy loss). The role of emotional regulation in high-stakes or emotionally charged situations.
INNER SETTING	Clinical Practice, ObGyn Department
OUTER SETTING	Laboratory, Patients, Payors, Outside Health Systems

INTERVENTION	Existing interventions aimed at facilitating the process
	Suggested recommendations for future innovation
PROCESS	RPL evaluation process

Appendix F. Qualitative Codes and Themes

Theme	Category	Definition	Example
Variations in Clinical Practice	*Provider Specialty*	The field or specialization of the healthcare provider (e.g., obstetrics, gynecology, reproductive endocrinology, genetics) and its influence on decision-making.	**"...**there's **not that continuity with patients** as you have …in the outpatient practices and the ambulatory setting..."- Participant 10 **(Hospitalist)**
	Definitions and Guidelines	The use and adherence to clinical definitions and standardized practice guidelines for managing RPL.	"**There are no specific guidelines actually**...So we have our internal sort of algorithm…based on evidence from different societies and different studies."-Participant 1 (MFM)
	Referrals to Interdepartmental and External Specialists	The practice of referring patients to specialists within or outside the provider's organization for additional evaluation or management.	"There are some people in the department who will send straight to fertility…because maybe they're not that comfortable... So, **it definitely gets a little tricky at times**" -

			Participant 9 (Generalist)
	Supporting Staff and Clinical Provider Resources	Availability and role of ancillary staff (e.g., nurses, genetic counselors) and other clinical resources that support patient management.	"...**if we did not have a nurse in place who was a navigator and who I could ask to order specific labs and follow up on them, that would make it extremely challenging**…But because we do have [the Nurse Navigator], it makes it more fluid. - Participant 1 (MFM)
Patient Characteristics an their Influence on Evaluation	*Maternal Co-Morbidities*	The presence of maternal health conditions (e.g., diabetes, hypertension) that may affect pregnancy outcomes and management of RPL.	"...if you see the poorly controlled diabetic **before she gets pregnant, you can really improve the chances of her having a healthy pregnancy**." - Participant 12 (REI)
	Patient Psychological Health	The psychological and emotional well-being of the patient and its impact on care and provider decision-making.	"I know that sometimes they get nervous when they just have one and I try to calm them down…where **I find more of the resistance**

			with patients trying to get a workup sooner [than is necessary]." - Participant 7 (Generalist)
	Socioeconomic Factors	The influence of the patient's socioeconomic status (e.g., income, education, employment) on access to care and treatment decisions.	"A**ccessing the traditional healthcare system is not always a safe and feasible possibility for many people**...Going to fertility is not a reasonable option for many of those patients because REI is a service that's available to some, but not all."-Participant 14 (CFP)
Laboratory Testin Related Challenge	*Lack of Standardized Processes for POC testing*	Challenges due to the absence of standardized processes for testing products of conception (POC) after miscarriage.	**"A lot of times the generalists don't do the genetic testing on the POC** because they're like, 'it's just the first miscarriage,' and then when they miscarry again…they miscarried on their own. **So now they have no idea what's going on**.- Participant 8 (REI)

	Lack of Access to Test Results and Subsequent Follow Up Challenges	Difficulty in obtaining timely access to lab or diagnostic test results, complicating patient follow-up.	"Having the [POC] labs go into the [hospital EMR] is not great…my [OBCP colleagues] will send me their recurrent miscarriage patients, and then **they come to see me, and I realize that nobody ever went over [the results]...**And then I'm the first one to tell them" -Participant 2 (MFM)
	Difficulty Following Up on Lab Testing	Challenges providers face in tracking lab tests, ensuring results are received, and acting on those results.	"**Both [chromosomes and microarray] are difficult because they take a lot longer to come back**...I say, 'Listen, this is on my mind, but I need you to call me because it doesn't come in their outpatient chart most times—or ever, really.'" -Participant 9 (Generalist)
	Difficulty Interpreting Test Results	Challenges providers face in understanding or explaining complex lab or genetic test results to patients.	"The mildly elevated anticardiolipin antibodies...you know, **those intermediate results? I think sometimes it causes a**

			lot of confusion. " - Participant 2 (MFM)
	Insurance Coverage Concerns	Issues related to patients' insurance coverage for diagnostic tests, treatments, or specialist referrals.	**"I'm not sure that these tests are necessarily covered, and I think they're expensive testing**... I could see my patients being upset if these very expensive tests are sent and not covered" - Participant 4 (Generalist)
OBCP Recommendations to Improve the Evaluation Proces	*Coordination and Protocol Development*	The creation and use of protocols to improve coordination of care among healthcare providers, departments, and institutions.	"**I think it would be nice to have a collaboration or a work group where we streamline the processes** because some of these patients have had clotting disorders that need a good handoff from us to MFM with the consultation of the hematologist either or both during and after conception." - Participant 8 (REI)
	Laboratory Coordination	The relationship between clinical providers and	"**I'm very grateful for the [laboratory genetic testing coordination**

		laboratories, including communication about tests and results.	**team's] email**, and that I can be in touch with you guys." -Participant 2 (MFM)
	Improved Access to Laboratory Test Result Access	The ability to easily access lab results through improved processes, including digital platforms and shared systems.	
	Development of Standard Laboratory Testing Protocols	The creation of uniform laboratory testing protocols for managing RPL, ensuring consistency in testing and interpretation.	"We have panels in our EMR that we created, and we all agreed upon what to draw. So, **we just hit the recurrent pregnancy loss panel.**" - Participant 8 (REI)
	POC collection protocol	Guidelines for the collection and processing of products of conception (POC) following a miscarriage.	
	Alternate Sample Collection Protocol	Procedures for collecting alternative types of samples	

		(e.g., blood) when standard POC collection is not possible.	
	Implementation of Patient Navigators	The use of patient navigators to assist patients in understanding their care and coordinating between various providers.	"MFM does a good thing, and they have patient navigators...a nurse is navigating all of your visits…So, **if there are patient navigators for recurrent pregnancy loss, where once you lose two pregnancies in their first trimester, second trimester, now they take over** and…they get you into genetic counseling and so forth." - Participant 5 (Generalist)
	Appointment Availability and Extended Consult Time	The availability of provider appointments and the time allocated for consultations, particularly for complex cases like RPL.	"When I was a generalist, I would try to book them in a longer patient appointment slot, or I would put them at the end of the day so that I [had more time]. **I don't think I ever was able to have an RPL patient encounter in 10 minutes**."-Participant 12 (REI)

	Educational Opportunities	Opportunities for providers and staff to receive ongoing education related to RPL management, including the latest research and guidelines.	

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