

CURRENT PRACTICE BEHAVIOR SURROUNDING RECURRENT PREGNANCY LOSS

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ABSTRACT

Recurrent pregnancy loss (RPL) is not clearly defined, and conflicting recommendations exist in terms of what testing or evaluations should be performed. Due to these discrepancies in the guidelines for RPL care, it is unclear what guidelines clinicians are following in practice. The current study aims to compare current practice behaviors of clinicians that evaluate patients with RPL to the guidelines, in order to understand what gaps in care may exist for these patients. A retrospective chart review was conducted by filtering the Northwell Health database for patients with two or more products of conception (POC) testing performed (n=429), and a total of 229 patient charts were examined for genetic testing, lab results, and provider notes. POC microarray was most often not performed but was warranted almost 50% of the time. Of the entire POC data available from Northwell Health's database, maternal karyotypes were only performed 29.1% of the time when the lab recommended parental karyotypes based on the POC sample results. Specific lab tests for RPL, including antiphospholipid antibody testing, which accounts for up to 20% of RPL cases (ASRM, 2012), were not performed the majority of the time (60-67%). Overall, only 20.1% of the sample was found to have a complete RPL evaluation. The other 79.9% of the sample did not have a complete evaluation. These results demonstrate that patients experiencing RPL are not receiving all the care they need, which leaves patients without an explanation and at increased risk for underlying diseases.

TABLE OF CONTENTS

	Page
ABSTRACT.....	1
Introduction.....	3-12
Methods.....	12-14
Results.....	15-18
Discussion.....	18-23
Works Cited.....	24-27
Appendix.....	28-30

INTRODUCTION

Recurrent pregnancy loss (RPL) affects 2-3% of couples every year and can be detrimental to parents and families. In roughly 50% of cases, no etiology of the RPL is identified, and the residual psychological trauma is often not addressed, regardless if a cause was identified (ESHRE, 2017, p. 15). RPL is one of the top 8 reasons patients are referred to prenatal genetic counselors (Norton & Chard, 2020). There are multiple society-published medical guidelines that suggest how clinicians should approach cases of RPL, but these guidelines conflict on their recommendations and how they define RPL. It is unclear what – if any – guidelines clinicians are following in practice (Papas and Kutteh, 2020). In this potentially fragmented care, patients could be missing significant information about the causes of their RPL, the risk to their future pregnancies, potential solutions, and care for the psychological effects of recurrent pregnancy loss.

Pregnancy Loss

Miscarriage, typically defined as the loss of a pregnancy before viability (Quenby et al., 2021), is unfortunately fairly common: 15-25% of pregnant women experience sporadic loss of a clinically recognized pregnancy (ASRM, 2012). Most miscarriages (80%) occur in the first trimester, whereas 1-5% occur in the second trimester (Dugas & Slane, 2022). Even though miscarriage is very common, evaluation into the etiology is often only recommended after multiple miscarriages—leaving the underlying cause unknown in many cases (ESHRE, 2017; ASRM, 2012; RCOG, 2011).

Further complicating matters, the number of miscarriages that constitute an evaluation is still up for debate. Some guidelines recommend an evaluation after two miscarriages (ESHRE, 2017; ASRM, 2012) whereas others recommend an evaluation after three or more (RCOG,

2011). Additionally, some guidelines restrict cases of RPL to be defined as miscarriages that are consecutive, while other guidelines say the miscarriages can be nonconsecutive (ESHRE, 2017; ASRM, 2012; ACOG, 2002). These inconsistencies in the definition of RPL prevent many patients from receiving a workup that could improve their care: around 5% of pregnant women experience two consecutive pregnancy losses whereas only 1% have three consecutive losses (ASRM, 2012). Additional data suggests that the risk of miscarriage in subsequent pregnancies is 30% after two previous pregnancy losses compared to 33% after three previous losses. The similarity in these numbers suggests that evaluations could be beneficial after two losses rather than three (Ford & Schust, 2009).

Known Causes/Risk Factors of RPL

Genetic Etiologies

2-4% of cases of RPL are associated with a parental balanced structural chromosome rearrangement, most commonly a balanced reciprocal translocation or a Robertsonian translocation. Other structural abnormalities associated with RPL are inversions, insertions, and mosaicism (Ford & Schust, 2009). Aneuploidy is another genetic cause of pregnancy loss, accounting for 80% of first trimester losses (Mitchell, 2021). When analyzing karyotypes performed on products of conception (POC), the karyotype of a second pregnancy loss was abnormal 70% of the time if the first loss also had an aneuploidy (ACOG, 2002). However, fetal aneuploidy is linked to advanced maternal age, and therefore these high rates of aneuploidy are most commonly attributed to nondisjunction rather than an inherited form of aneuploidy, such as cases of Robertsonian translocations or other chromosomal aberrations. Even so, further analysis showed that recurrent aneuploidy in pregnancy is possible despite normal parental karyotypes; prenatal genetic testing (PGT) studies for those with RPL found that more than 50% of embryos had an aneuploidy (ACOG, 2002).

Endocrine Etiologies

Endocrine factors account for another 17-20% of cases of RPL, such as uncontrolled thyroid disease, diabetes, PCOS, luteal phase defect, and hyperprolactinemia (Ford & Schust, 2009). Of these endocrine factors, thyroid disease is the most consistent factor recommended for follow-up, whereas the others have conflicting evidence or are not recommended to test for based on current guidelines (Papas & Kutteh, 2020). Therefore, these other endocrine factors are not included in this study. Thyroid abnormalities, such as hypothyroidism, are associated with an increased risk of miscarriage. However, the association between RPL and antithyroid antibodies is still under debate (Vega & Williams, 2019). Some suggest that those with antithyroid antibodies are more likely to develop hypothyroidism during pregnancy (Poppe, Velkeniers, & Glinooer, 2008). However, this association needs to be studied further.

Immunologic Etiologies

About 20% of identified causes are related to immunologic factors. Examples of these include acquired thrombophilias such as antiphospholipid antibody syndrome, inherited thrombophilias such as Factor V Leiden, prothrombin gene mutations, and *MTHFR* gene mutations, anticoagulant deficiencies, and blood group alloimmunization (ASRM, 2012). However, blood group alloimmunization is not mentioned in the current guidelines, and hereditary thrombophilia (Factor V Leiden, prothrombin, and *MTHFR*) testing is only recommended in specific cases (Papas & Kutteh, 2020). Therefore, these immunologic factors are not included in this study.

Thrombophilia, a condition that increases the risk for blood clots, is also associated with RPL. This association is based on the theory that thrombosis can impair placental development and therefore could lead to miscarriage. Some argue that thrombosis is more likely associated

with losses after 10 weeks' gestation since around that time is when maternal blood begins to flow within the intervillous spaces of the placenta. However, others argue that sufficient nutrition transfer between mother and fetus depends on uterine blood flow, therefore linking thrombosis with miscarriage regardless of gestational age at the time of loss (Ford & Schust, 2009). There are many different types of thrombophilia, some that are acquired and some that are inherited. Among cases of acquired thrombophilia, antiphospholipid syndrome (APLS) has been clearly linked to poor obstetric outcomes, including RPL (NHS, 2022; Ford & Schust, 2009). In APLS, the immune system produces abnormal antibodies called antiphospholipid antibodies that target proteins on fat molecules (phospholipids), which makes the blood more likely to clot (NHS, 2022). However, the mechanism behind how APLS leads to RPL is not completely understood (Ford & Schust, 2009).

Anticoagulant deficiencies may also be related to pregnancy loss. Examples include antithrombin deficiency, protein c deficiency, and protein s deficiency (Ford & Schust, 2009). These substances typically protect from excessive clotting; however, the body is not making enough of them in these cases, so affected individuals are at higher risk for blood clots and their associated complications (Sencen, 2018). Fortunately, most women with abnormal blood clotting disorders have normal pregnancies (Calderwood & Greer, 2005).

Other Etiologies

Additional etiologies that may be associated with RPL include uterine anatomy anomalies such as a septate uterus, intrauterine adhesions, uterine fibroids, and cervical insufficiency (Ford & Schust, 2009); infections such as mycoplasma, ureaplasma, chlamydia trachomatis, L monocytogenes, and HSV (ACOG, 2002; Ford & Schust, 2009); and certain environmental exposures such as chemicals, radiation, medication, and other toxins (Gardella &

Hill, 2000; Triche & Hossain, 2007). However, this study focused solely on laboratory testing and clinical consultation rather than radiologic examinations, so these etiologies were excluded from this study.

Patient Experience

Early pregnancy losses have negative emotional and mental health effects on the parent(s), including anxiety, depression, and self-blame (Nikcević, 2007). The feelings of grief, loss, self-blame, and failure that occur after a pregnancy loss can be compounded after multiple losses (ESHRE, 2017, pg 17). Discovering the cause of a miscarriage can relieve these negative emotional effects (Nikcević, 2007). Follow-up medical care for an early pregnancy loss can help relieve these emotional effects, even when no cause is identified (Nikcević, 2007).

In 2015, Bardos et al. conducted an online national survey to evaluate the public's attitude and understanding of miscarriage. Of the 1,084 study participants, 15% of them had personally experienced a miscarriage or had a partner who experienced a miscarriage. Of the participants who had personally experienced an early pregnancy loss, 88% wished to know the source of their miscarriage if there was something they could do to prevent another miscarriage. Of the same group, 78% would still want to know the source of their miscarriage, even if there was nothing that they could do to prevent another miscarriage (Bardos, 2015). Furthermore, women want to know the etiology of their miscarriages, and will pursue follow up care, if they are given the opportunity (Nikcević, 1998).

Guidelines

In 2001, the American College of Obstetricians and Gynecologists defined recurrent pregnancy loss as two or more consecutive pregnancy losses, recommending RPL care only after this requirement is met. ACOG's recommendations in 2001 included parental cytogenetic

analysis in every case and cytogenetic analysis of the product of conception (POC) at the provider's discretion. A screening for uterine anatomical abnormalities using hysterosalpingography, hysteroscopy, sonohysteroscopy, or 3D ultrasonography was recommended as well. These guidelines do suggest testing for antiphospholipid syndrome, but do not recommend screening for thrombophilias, endocrinologic abnormalities, metabolic disorders, glucose intolerance, thyroid dysfunction, infectious diseases, or a luteal phase defect in RPL cases (ACOG, 2001). These guidelines are the oldest recommendations discussed.

The American Society of Reproductive Medicine (ASRM) defines RPL as two or more clinically confirmed spontaneous pregnancy losses and recommends investigation into the losses. The ASRM did not specify if the losses needed to be consecutive or not (ASRM, 2020). The ASRM recommends parental karyotypes to detect balanced translocations. They do not recommend cytogenetic analysis of the POC in every case, but state that it can be helpful. They do recommend screening for lupus and antiphospholipid bodies. The ASRM also recommends screening for uterine anomalies and hormonal or metabolic conditions. They do not recommend screening for infectious causes or thrombophilias (ASRM, 2012).

The European Society of Human Reproduction and Embryology (ESHRE) defines RPL as two or more pregnancy losses. These do not have to be consecutive (ESHRE, pg. 7). Each recommendation is listed as a "Strong", "Conditional" or "Good Practice Point (GPP)". They also rank the amount of evidence they have to support the recommendation. ESHRE conditionally recommends genetic analysis of the POC utilizing array-based Comparative Genomic Hybridization. All women experiencing RPL should have a uterine anatomy evaluation. Parental karyotypes should not be routinely performed, but may be in individual cases. Hereditary thrombophilia screening is not routinely recommended unless the mother has

additional risk factors for hereditary thrombophilia. ESHRE does recommend screening for antiphospholipid bodies, lupus antibodies, and thyroid abnormalities (ESHRE, pg 7-10). These are the most recently published guidelines.

When compared, these guidelines contrast in their recommendations, including cytogenetic analysis, POC cytogenetic analysis, antiphospholipid antibodies, thyroid function, prolactin, hemoglobin A1c, and hereditary thrombophilia. The Royal College of Obstetricians and Gynaecologists (RCOG, 2011) recommends cytogenetic analysis should be done on the POC in cases of RPL. If a balanced translocation is discovered through cytogenetic analysis of the POC, the parents should have karyotypes done. ASRM (2020) and ACOG (2001) recommend that all parents should have karyotyping done, regardless of whether the POC karyotype is done. ESHRE does not recommend karyotyping routinely, but in specific cases (Li, 2018). While POC cytogenetic analysis is recommended after a third pregnancy loss by RCOG, it is recommended according to provider discretion by ASRM, ESHRE, and ACOG. Antiphospholipid antibody screening is recommended by each group, but the specific types of screenings differ, which are described in more detail in Table 1. Thyroid function testing is not recommended by ACOG, but is recommended by RCOG, ASRM, and ESHRE. However, these guidelines differ in what hormones they suggest testing. For example, prolactin testing is recommended by ASRM, conditionally recommended by ESHRE, and is not recommended by ACOG or RCOG. Hemoglobin A1c is recommended by RCOG and ASRM, but it is not recommended by ESHRE or ACOG (Papas & Kutteh, 2020). Overall, this displays that all the guidelines have different recommendations, which could be affecting the treatment of individuals with RPL.

Effectiveness of Current RPL Evaluation Guidelines

In a prospective study, Popescu et al. (2018) evaluated how the incorporation of chromosomal microarray in standard RPL care could affect the number of pregnancy losses that can have a cause identified. They included 100 patients who had all experienced two or more miscarriages in a private RPL clinic. Each patient had the full ASRM 2012 recommended RPL workup. In addition, a 24-chromosome microarray (CMA) analysis was performed on the product of conception (POC). Following ASRM standards, patients were evaluated by karyotyping for parental chromosomal abnormalities, pelvic sonohysterography, hysterosalpingogram, or hysteroscopy looking for uterine anomalies, immunological tests for lupus anticoagulant and anticardiolipin antibodies, and blood tests for thyroid stimulating hormone (TSH), prolactin and hemoglobinA1c (Popescu et al., 2018).

After these evaluations, 45 (45%) of the patients had a cause for the pregnancy loss determined. Of these patients, four were identified to have abnormal parental karyotypes, 19 had an abnormal anatomic evaluation, nine had an endocrinologic abnormality, and 17 had an autoimmune issue. 55 (55%) of the patients did not have an etiology identified after the ASRM recommended RPL workup and, if their evaluation had ended after the ASRM workup, they would not have had a cause of pregnancy loss identified. All 100 patients had a 24-chromosomal microarray investigation of the product of conception. Of all 100 patients, 67 (67%) had an abnormal POC CMA. The majority of the patients with an abnormal POC CMA result had a normal ASRM workup. Out of the 67 patients with an abnormal POC CMA, 50 (74.6%) had a normal ASRM workup. Of the 33 patients who had a normal POC CMA, the majority (84.8%) had an abnormality identified in the ASRM workup. Overall, when the ASRM workup and POC

CMA were both utilized, 95/100 (95%) of patients had a cause identified for their pregnancy loss (Popescu et al., 2018).

These findings illustrate that most individuals do not find the cause of their pregnancy losses with the current recommendations. Less than half would have identified a cause of their RPL strictly following ASRM guidelines (Popescu et al., 2018). In addition, it confirms that researchers are interested in the care of women experiencing RPL and how to make it more effective. However, this study consisted of women who were being evaluated at a RPL specialty clinic and may not be representative of all women experiencing RPL. As it is unclear if women not being treated at an RPL center are receiving all of the recommended care, there is potentially an even higher percentage of women with no cause identified to their RPL.

Goal of Study

While there have been a significant amount of studies done on RPL, no studies have established how actual clinical practice behavior compares to what the guidelines recommend. Therefore, this study aims to examine current clinical practice behaviors of clinicians evaluating patients experiencing RPL to determine how current practice compares to the medical guidelines in order to understand the gaps in care that persist for these patients.

Research questions: How does clinical practice compare to the guidelines for patients experiencing RPL? What discrepancies exist in laboratory testing?

Table 1: Guideline recommendations adapted from Papas & Kutteh 2020

Screening Test	ACOG 2001	RCOG 2011	ASRM 2012	ESHRE 2017
Parental karyotype	Recommended	Not recommended unless POC reveals unbalanced translocation	Recommended	Conditional: only after individual risk assessment
POC cytogenetic analysis	At provider's discretion	Recommended after third miscarriage	Not recommended	Conditional: explanatory purposes, but if performed recommend using CMA
Hemoglobin A1c	Not recommended	Recommended	Recommended	Not recommended
TSH	Not recommended	Recommended	Recommended	Recommended
Antiphospholipid antibodies	Recommended	Recommended for lupus anticoagulant and cardiolipin antibody	Recommended for lupus anticoagulant, cardiolipin antibody, and B2 glycoprotein	Recommended or lupus anticoagulant, cardiolipin antibody; B2 glycoprotein considered good clinical practice
Thrombophilia	Not mentioned	Not mentioned	Not mentioned	Not mentioned

Table 1 shows the differing recommendations for an RPL workup that exist by comparing the recommendations from ACOG 2001, RCOG 2011, ASRM 2012, and ESHRE 2017. We are specifically comparing their recommendations for parental karyotype, POC cytogenetic analysis, Hemoglobin A1c, TSH, Antiphospholipid antibodies, and thrombophilia. To note, the guidelines only mention hereditary thrombophilia, not acquired.

METHODS

This 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 obtained from the Northwell Health Quality Assurance Database which consisted of a total of 6,940 unique patients. Of this entire set, the data was filtered to only include data of patients who had two or more POCs undergo cytogenetic testing (n=429). The original data set was filtered a second time for POC results where the lab recommended parental karyotypes (n=135), in order to ascertain how many parental karyotypes were then performed. Testing from multiple gestation pregnancies was excluded. Of the patients in the set, 229 retrospective chart reviews were completed searching for genetic testing, lab results, and provider notes. An illustration of the workflow is included in Appendix A.

POC Testing

Completed orders of genetic testing of the POC samples, including karyotypes and microarrays, were analyzed. POC karyotype results were recorded as Abnormal, Normal, or a Failure. POC microarrays were recorded as being Abnormal, Normal, Not Performed - Y (NP-Y), Not Performed - N (NP-N). Not Performed - Y included samples that did not have microarray testing, but this testing could have been illusive. Not Performed - N included samples that did not have microarray testing, but this testing would not have provided more information than the POC karyotype.

Parental Karyotypes

The results of maternal and paternal karyotypes were recorded. They were classified as 'Normal', 'Abnormal', 'Not Performed (NP)' or 'Not Performed - Y(NP-Y)'. If a karyotype was not performed, but was considered necessary, the result was considered 'Not Performed - Y.' A karyotype was considered necessary for the mother or father if the POC testing recommended parental karyotypes, such as in the case of POC samples with chromosomal translocations. A karyotype was also considered necessary for the mother if the hemoglobin A1C, TSH, lupus

anticoagulant, cardiolipin antibody, and beta-2-glycoprotein testing were all within normal limits.

Maternal Labs

The patient's chart was searched for the presence of 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 testing was performed, it was recorded as being 'Normal' or 'Abnormal'. The testing laboratory's reference range was utilized to determine if the sample was within normal limits. 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' or Not Performed.

RPL Evaluations

Provider notes were analyzed for the presence of a formal RPL evaluation from a doctor and/or genetic counselor. An evaluation was considered to be present if the official reason for the appointment was for a history of RPL or if the consultation included the entry of ICD diagnostic code N96.0. Notes written by physicians of all specialties were checked for an RPL evaluation or workup.

Laboratory-Recommended Parental Karyotypes

The entire data set was filtered for POC results where parental karyotypes were recommended by the lab. This included POC results showing translocations, inversions, marker chromosomes, or ring chromosomes. Of the 134 cases this included, a maternal karyotype was recorded as Performed or Not Performed. Paternal karyotypes were not evaluated due to a lack of access to the paternal medical records.

RESULTS

The data was analyzed via Excel in order to determine what percentage of the sample size had genetic and lab testing performed for an RPL workup as well as what the results were. We are interested in this information in order to compare practice behaviors to the guidelines as well as to determine any gaps in care for PRL patients.

POC Testing

All samples must have had POC karyotype performed at minimum to be part of the study. Out of 501 POC karyotypes in the sample size, 193 (38.5%) were normal, 240 (47.9%) were abnormal, and 68 (13.6%) failed. Follow up testing via microarray is warranted when either the POC karyotype is normal, or the karyotype fails. Out of the 491 POC testings analyzed for microarray, 49 (9.8%) had a microarray performed, and among these, 42 (87.5%) were normal and 6 (12.5%) were abnormal. However, 437 POCs analyzed (89%) did not have a microarray performed. Of those without a microarray performed, it was warranted for 200 (45.8%).

Table 2: POC Testing

Karyotype (501)	Performed (501)	Normal (193)	38.5%
		Abnormal (240)	47.9%
		Failure (68)	13.6%
Microarray (491)	Performed (49)	Normal (42)	85.7%
		Abnormal (6)	12.3%
		VUS (1)	2%
	Not Performed (437)	NP-Y (200)	45.8%
		NP-N (237)	54.2%

Table 2 shows the total number of POC karyotypes, recorded as normal, abnormal, or failure. These must have been performed in order to be included in the study. This table also shows if microarray was done on POC tissue. If a microarray was performed, it was recorded as normal or abnormal. If it was not performed, it was recorded as NP-Y (not performed yes) or NP-N (not performed no). NP-Y includes samples that did not have microarray testing when it was warranted, whereas NP-N includes samples that did not have microarray testing, but it wasn't necessary. To note, the total number of microarray entries do not add up to 501 because POC microarray data was an add-on point to the study after data collection began.

Parental Karyotypes

Parental karyotypes are warranted when the POC karyotype indicates a translocation or another potentially inherited chromosomal abnormality. Additionally, a maternal karyotype would also be warranted if maternal lab results were normal. Out of the 229 patient charts analyzed, 62 (27%) had maternal karyotypes performed, and among these, 60 (96.8%) were normal and 2 (3.2%) were abnormal. Out of the 167 (73%) that did not have maternal karyotype performed, 19 (11.4%) were warranted, based on either POC testing or maternal lab results.

Paternal karyotypes were performed far less often in this sample, at only 12 (5.2%). Of these, 11 (91.7%) were normal and 1 (8.3%) was abnormal. Out of the 214 (93.4%) that did not have paternal karyotype performed, it was warranted for 3 (1.4%), based solely on POC testing.

Table 3: Parental Karyotypes

Maternal (229)	Performed (62)	Normal (60)	96.8%
		Abnormal (2)	3.2%
	Not Performed (167)	NP-Y (19)	11.4%
		NP-N (148)	88.6%
Paternal (229)	Performed (12)	Normal (11)	91.7%
		Abnormal (1)	8.3%
	Not Performed (214)	NP-Y (3)	1.4%
		NP-N (211)	98.6%

Table 3 shows parental karyotypes, maternal and paternal, denoted first as performed or not performed. If performed, they were recorded as normal or abnormal. If not performed, they were recorded as NP-Y (not performed yes) or NP-N (not performed no). NP-Y includes samples that did not have the specific parental karyotype when it was warranted, whereas NP-N includes samples that did not have the specific parental karyotype, but it wasn't necessary. A visual representation of this data is included in Appendix C.

This study was limited in the ability to view the number of paternal karyotypes performed, as the paternal identity information was not available. The paternal karyotype information was only visible when it was included in the mother's chart. Therefore, more paternal karyotypes may have been performed than what this study determined.

Maternal Labs

Out of the 229 patient charts analyzed, hemoglobin A1c was performed for 158 (69%) of the sample, and of those who had it performed, it was abnormal for 19 (12%). Thyroid stimulating hormone levels were performed for 179 (78.2%) of the sample, and of those who had it performed, it was abnormal for 19 (10.6%). These were the only two tests that were performed the majority of time. Lupus anticoagulant was performed for 77 (33.6%) of the sample, and of those who had it performed, it was abnormal for 13 (16.9%). Cardiolipin testing was performed for 89 (38.9%) of the sample, and of those who had it performed, it was abnormal for 10 (11.2%). Beta 2 glycoprotein testing was performed for 90 (39.3%) of the sample, and of those who had it performed, it was abnormal for 13 (14.4%). Hereditary thrombophilia testing was performed for 59 (25.8%) of the sample, and of those who had it performed, it was abnormal for 17 (28.8%).

Table 4: Maternal Lab Results

		HB A1C (229)	TSH (229)	Lupus Anticoagulan t (229)	Cardiolipi n (229)	B2G (229)	HT (229)
Performed	Normal	139	160	64	79	77	42
	Abnormal	19	19	13	10	13	17
Not Performed		71	50	152	140	139	170

Table 4 shows maternal labs, denoted first as performed or not performed. If performed, they were recorded as normal or abnormal. A visual representation of this data is included in Appendix B.

RPL Evaluations

Of our sample of 229, 38 (16.6%) had an MD evaluation, 16 (7%) had a GC evaluation. Of the 229 patients, 46 (20.1%) had a complete evaluation and 183 (79.9%) did not have a complete evaluation.

Table 5: RPL Evaluations

	MD Evaluation (229)	GC Evaluation (229)	Complete Evaluation (229)
Y	38	16	46
N	191	213	183

Table 5 shows different types of RPL evaluations, including an MD evaluation, genetic counselor evaluation, and a complete evaluation. Evaluations were considered complete if Hb A1c, TSH, LA, cardioplipin, and beta-2-glycoprotein labs were performed and if a maternal karyotype was warranted. Thrombophilia was excluded since the guidelines only recommend testing on an individual basis. They were denoted as Y if they were done, and N if they were not done.

Laboratory Recommended Parental Karyotypes

Of the 134 cases where the laboratory recommended parental karyotypes, 39 cases (29.1%) had a maternal karyotype performed. In 95 cases (70.9%), a maternal karyotype was not performed. Of these 39 cases where a maternal karyotype was performed, 19 karyotypes (48.7%) were ordered by a genetics professional.

Table 6: Laboratory Recommended Parental Karyotypes

Laboratory Recommended Parental Karyotype (134)	Performed (39)	29.1%
	Not Performed (95)	70.9%

Table 6 displays the number and percentages of cases where a maternal karyotype was performed when the laboratory recommended parental karyotype testing. A visual representation of this data is included in Appendix D.

DISCUSSION

In this study, we were interested in examining what RPL workups, if any, are done in practice, and how practice behaviors compare with the existing guidelines for RPL.

POC Testing Findings

As mentioned previously, it was a requirement for POC karyotype testing to be performed on at least two POCs to be included in this study. Of our sample of 501, 240 (47.9%)

of the POC testings reported were abnormal. This finding was expected, as about 50% of miscarriages occur due to aneuploidy (ACOG, 2002). If the POC karyotype was normal or was a failure, a microarray was warranted. However, a microarray was only performed for 49 (9.8%) warranted POCs. Of these, 6 (12.3%) were abnormal. This shows the importance of performing microarray as second tier testing, as these abnormalities would have been missed without microarray analysis. Of the 437 cases (89%) where a microarray was not performed, it was warranted for 200 (45.8%). This demonstrates that a large proportion of patients are not getting the recommended follow-up care they need, which could provide a cause for their RPL. This data also shows the importance of performing POC karyotypes, as almost 50% were found to be abnormal. However, POC testing for both karyotype and microarray does not have clear recommendations in the guidelines.

Paternal Karyotype Findings

Both maternal and paternal karyotypes were examined, and were considered warranted if POC karyotype testing revealed a translocation. Maternal karyotypes were also warranted if maternal hemoglobin A1C, TSH, lupus anticoagulant, cardiolipin antibody, and beta-2-glycoprotein testing were all within normal limits. Of note, only 62 out of 229 patients (27%) had maternal karyotype performed. However, 60 (96.8%) of those performed came back normal. This finding is expected, as only 2-4% of RPL is thought to be caused by a parental balanced structural chromosome rearrangement (Ford & Schust, 2009). Of the 167 (73%) that did not have a maternal karyotype performed, it was warranted for 19 (11.4%) based on POC testing or maternal labs. This again demonstrates that a proportion of patients are not getting the recommended follow-up care they need, which could provide a cause for their RPL.

Paternal karyotypes were only performed for 12 out of 229 (5.2%) cases. Of those performed, 11 (91.7%) came back normal. This finding is slightly less than expected when compared to maternal karyotype results. Of the 214 (93.4%) that did not have paternal karyotype performed, it was warranted for 3 (1.4%) based solely on POC testing. This finding is expected, as a most balanced chromosomal rearrangements are less likely to be inherited in an unbalanced manner if the father is the carrier (<1%) compared to if the mother is the carrier (can be up to 10-15% depending on the chromosomes involved as well as the type of rearrangement) (Amor & Gardner, 2018, p. 273).

Maternal Lab Findings

Of all the laboratory testing included in this study, hemoglobin Alc and TSH were the only labs that were performed the majority of the time, for 158 (69%) and 179 (78.2%) of the sample respectively. As these particular lab tests are often performed as part of routine prenatal care, we cannot be confident that all of these labs were ordered for the specific purpose of an RPL evaluation, which may explain our findings. Of all the tests performed, 10-30% of the time the results were abnormal, depending on the specific test. These abnormal results may require additional follow up, however this was out of the scope of our study. Many cases had only one or two labs performed, but the full workup was not completed, even if the labs that were performed were normal. In the cases where labs were not performed, a cause for RPL could have been missed.

RPL Evaluation Findings

An MD evaluation was considered to have been performed if the official reason for the visit was RPL. Of our sample, only 38 (16.6%) had an MD evaluation. Additionally, there was no consistency of specialty the MD had who performed these evaluations. Chart notes were

analyzed from fertility doctors, genetics professionals, and sometimes the patient's PCP.

Laboratory testing for RPL was also ordered by cardiologists and endocrinologists. In terms of a genetic counseling evaluation, only 16 (7%) of our sample met with a genetic counselor. These findings demonstrate how patients with RPL are experiencing gaps in their care because of this uncertainty surrounding who in the healthcare field is responsible for ordering RPL workups.

A workup for RPL was considered complete when all maternal labs were performed excluding thrombophilia, as well as a maternal karyotype if it was warranted. Of note, only 46 (20%) of our sample had a complete evaluation. Therefore, 80% of the sample could have potentially identified a cause for their RPL, but were not given the necessary care to do so.

Laboratory Recommended Parental Karyotypes

In cases where the POC was found to have a translocation, inversion, or another possibly-inherited chromosomal abnormality, the positive yield of parental karyotypes would be higher than in other cases. In other words, these are the cases where parental karyotype information would be the most important. However, maternal karyotypes were only ordered for 39 out of the 134 recommended cases (29.1%). In the other 95 (70.9%) cases, maternal karyotypes were not performed. These individuals could be carrying chromosomal aberrations that cause an increased risk of miscarriage or pregnancy with anomalies. In the cases where a maternal karyotype was performed, a genetics professional ordered the testing for 19 patients (48.7%). As genetics professionals are ordering the karyotypes about half of the time, they are an important part of the RPL team. However, this study found that patients are only seeing a genetic counselor 7% of the time. In a clinic or area where access to a genetics professional is limited, there could be an even larger proportion of cases where parental follow up is not performed.

Limitations

The methodology of this study was only able to include cases where the patient had at least two POC testings. Many women miscarry outside of the hospital and are unable to have POC testing. In addition, POC testing is not routinely performed at all hospitals. The findings of this study may not be representative of women who are not having POC testing. This group could potentially be missing important information and care regarding their miscarriages, especially in cases of spontaneous chromosomal aberrations.

The database utilized to access patient charts is limited to the labs and visits performed within the Northwell hospital system. It is possible patients had follow up care and testing at other institutions that could not be accounted for in this study. In addition, it is possible that patients denied or did not pursue follow-up.

This study was limited in sample size. A larger sample should be studied, in order to see if the findings of this one are representative. In addition, these findings were limited to one institution and may not be representative of all institutions. Therefore, future research could evaluate similar questions at separate institutions.

Areas of Future Study

Comparison of medical society guidelines in cases of RPL displayed notable discrepancies amongst their recommendations. Future research focusing on the reasons for these disagreements and how physicians account for these differences is warranted. In addition, no research exists looking at who is performing follow-up care and guidelines do not specify who this should be tasked to. This study was able to quantify the number of patients receiving individual parts of an RPL workup. However, it was unable to determine if the results of the workup were communicated to patients, which could be missing from follow-up care.

Insurance coverage is a major contributor to medical decision making. It is unclear how insurance coverage affects follow-up care in cases of RPL. Questions in this area have yet to be explored, such as what labs are routinely covered by insurance, if patients do not pursue RPL evaluations due to poor coverage, or if medical society guidelines affect insurance coverage.

Conclusion

The guidelines for RPL care are ambiguous and contradictory, which is reflected in patient care in this study. Overall, 79.9% of patients in this sample did not receive the testing or follow-up that would be considered a complete RPL work-up. This could be attributed to a lack of ownership of this type of care in one department, thereby creating a gap for patients. It could also be due to the inconsistent guidelines causing confusion in what these patients need. Patients experiencing RPL deserve quality care and this issue deserves more attention from the medical community in the future.

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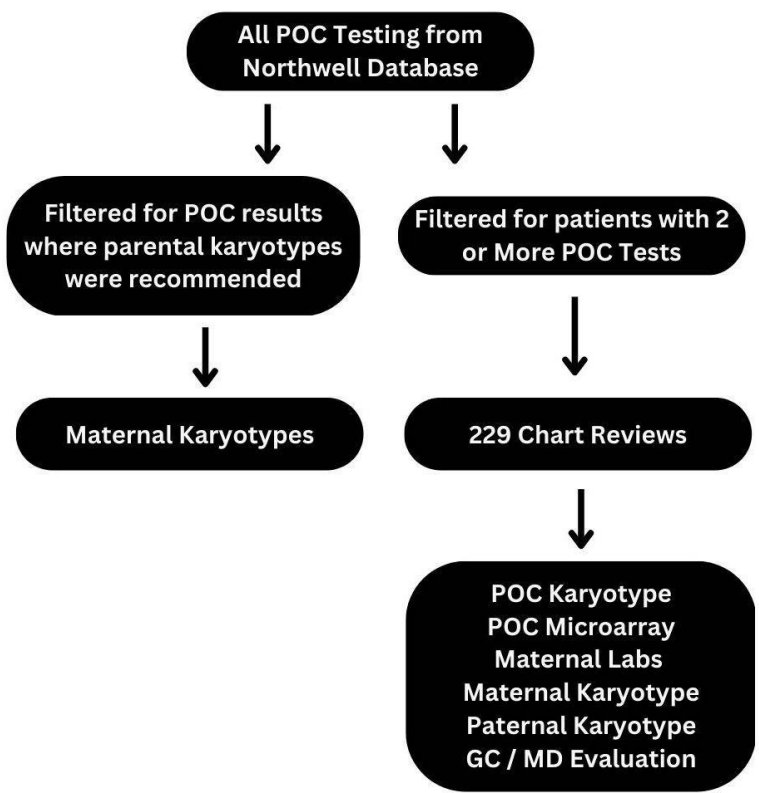
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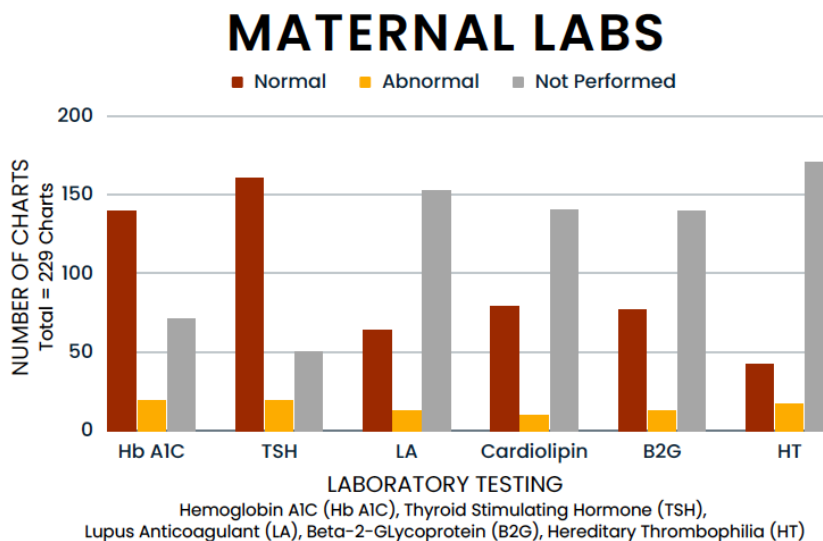
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Appendix A



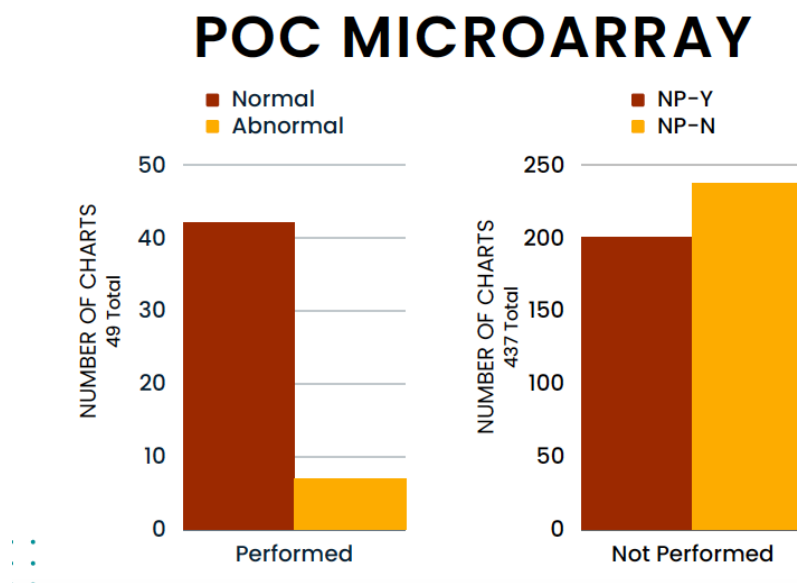
Appendix A. This is a visual representation of the data utilized in this study.

Appendix B



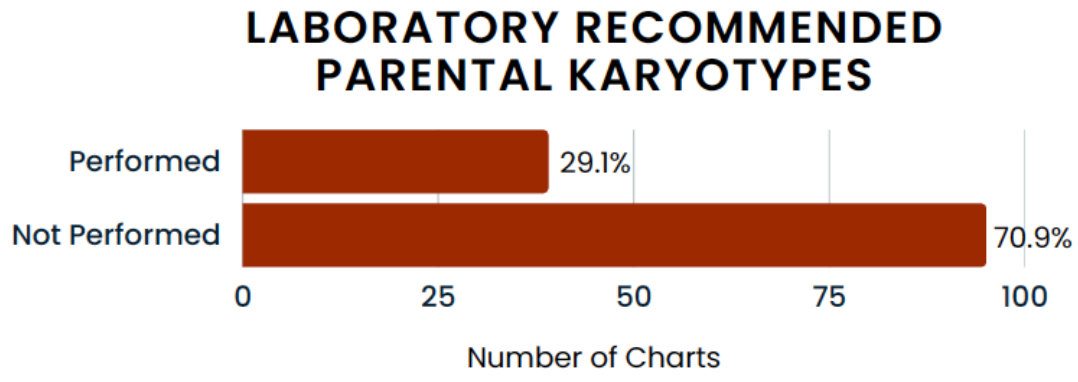
Appendix B. This is a visual representation of the maternal laboratory testing information. It shows the number of patients who had normal, abnormal, or no testing performed for hemoglobin A1c, thyroid stimulating hormone, lupus anticoagulant, beta-2-glycoprotein, and hereditary thrombophilia.

Appendix C



Appendix C. This is a visual representation of the POC microarray testing. On the left, 49 POC samples had microarray testing performed. On the right, 437 POC samples did not have microarray testing performed.

Appendix D



Appendix D. In cases where the laboratory recommended parental karyotype testing, this is a visual representation of the number of maternal karyotypes that were performed versus not performed.