Austin Journal of Obstetrics and Gynecology

Open Access

Austin Publishing Group

Review Article

Recurrent Pregnancy Loss and Infertility: A Time for Change

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Received: January 05, 2018; **Accepted:** January 24, 2018; **Published:** January 31, 2018

Abstract

Infertility and Recurrent Pregnancy Loss (RPL) is considered two independent entities. Infertility is defined as the inability to conceive after 12 months or more of unprotected intercourse, while RPL is characterized by a history of 2 or more clinically documented pregnancy losses. There is a fine line, however, that links the two entities in the form of biochemical pregnancies. In these cases, a woman with a positive hCG test is not considered infertile since the outcome of the test confirms that fertilization has occurred. At the same time, because implantation is incomplete and therefore not sonographically observed, these cases are not considered pregnancy losses. This medical condition places these patients in a gray area, demonstrating the need for a change.

Thus, this review aims to challenge the artificial separation between infertility and RPL. Not only do these women share the same unfulfilled desire to deliver a baby, in many cases, they also share common etiologies, diagnoses, and treatments. In this study, we will discuss some of the main etiologic factors germane to cases of both RPL and infertility. We propose to reevaluate the definition of infertility so that couples who are unable to conceive will not be considered fertile. Finally, we will advocate implementing a multidisciplinary approach for both the consistently infertile and RPL populations that will involve the collaboration of experts from various specialties in the same evaluation and treatment facility.

Keywords: Infertility; Recurrent pregnancy loss; Infertility common etiology; RPL etiology; Infertility evaluation; RPL evaluation

Introduction

Although recurrent pregnancy loss, RPL, and infertility are generally treated as distinct and separate entities, there is a fine line that links those two entities--the bio-chemical pregnancy, which accounts for 13 to 26% of all pregnancies [1,2]. In this kind of non-visualized pregnancy, a positive pregnancy test detects the presence of Human Chorionic Gonadotropin (HCG) secreted by the embryo, confirming that fertilization has occurred. Nevertheless, a decline in HCG levels is discovered prior to visualization of either a normal pregnancy or an ectopic pregnancy, indicating that the pregnancy has ceased early [3]. The specific window of time, during which these early pregnancy losses occur, is peri-implantation or immediately post-implantation, whereby the growth of the early embryo is disrupted and thus results in a non-viable pregnancy. In these circumstances, if fertilization transpires, patients are not considered infertile. At the same time, if complete implantation does not occur, preventing clinical pregnancy, patients do not satisfy RPL criteria either. These cases of early pregnancy loss become significant as they can implicate similar outcomes for future pregnancies.

In addition, evaluating and handling cases involving biochemical pregnancies is complicated because of the artificial division between RPL and infertility. Thus, non-visualized pregnancies demand a change of perception by challenging the commonly accepted separation between RPL and persistent infertility. This review aims to challenge and address this disparity by appraising several aspects. First, a considerable portion of these populations share common etiologies (Figure 1). Second, a typical protocol for diagnosis and treatment is shared in many cases involving both RPL and infertile couples (Table 1). Finally, as a consequence of varying standards of care and inconsistent definitions for RPL and infertility, cases of biochemical pregnancies are difficult to manage. Further inquiry into this topic will provide the necessary insight to establish a practice, in which cases of RPL and infertility are managed under a common multi-disciplinary clinic.

Definitions

Infertility is defined as 'failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination' [4].

Originally, RPL was defined by the European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynecologists (RCOG) as three consecutive pregnancy losses at less than 20 weeks of gestation [5,6]. Regardless of these definitive criteria, many physicians commenced clinical examinations after just the second pregnancy loss, because they realized that little clinical insight was gained from investigation after a third loss [7]. Thus, in 2008, the American Society of Reproductive Medicine (ASRM) published an amended definition of RPL [8]. The ASRM still insists that cases of two consecutive losses should be judged individually for need of further clinical evaluation and recommends a thorough investigation only after three losses [4].

Etiologic Link between RPL and Infertility

Uterine factors

Many uterine factors are both congenital and/or acquired and can

Citation: Kumar D and Harlev A. Recurrent Pregnancy Loss and Infertility: A Time for Change. Austin J Obstet Gynecol. 2018; 5(1): 1090.

Table 1: Basic evaluation tests for RPL and infertility.

Performed	Aim	Test	
RPL + Infertility	myometrium, endometrium, ovaries, pelvis	2D Ultrasound	Uterine assessment
RPL + Infertility	Uterine cavity (congenital anomalies), myometrium, endometrium	3D Ultrasound	
RPL + Infertility	Uterine cavity, myomas, endometrium (Asherman syndrome)	Hysteroscopy	
Infertility	Uterine cavity	Hysterosalpyngography	
Infertility	Endometriosis, tubal potency	Laparoscopy	
Infertility	fallopian tubes potency	Hysterosalpyngography	Fallopian tubes assessment
RPL + Infertility	Hydrosalpinges	3D Ultrasound	
RPL + Infertility	Ovulation dysfunction, implantation failure	Thyroid function, Prolactin	Endocrine assessment
RPL + Infertility	Glucose intolerance, hyperandrogenemia	Diabetes mellitus screening	
Infertility	Sperm count and basic function	Basic semen analysis	Male evaluation
RPL + Infertility	DNA fragmentation, Sperm Immunoglobulin, Reactive oxygen species and antioxidants capacity	Advanced Semen analysis	
Infertility	Ovarian reserve assessment	FSH, Antral follicular count or AMH	Ovaries
RPL	Translocations, deletions	Karyotype of the couple	Genetic
Infertility	Assessment of azoospermia	Karyotype and micro-deletions of the male	
RPL	Autoimmune disorders	Anti-cardiolipin antibody and lupus anticoagulant	Autoantibodies and immune function
Performed	**Aim**	**Test**	
RPL + Infertility	myometrium, endometrium, ovaries, pelvis	2D Ultrasound	Uterine assessment
RPL + Infertility	Uterine cavity (congenital anomalies), myometrium, endometrium	3D Ultrasound	
RPL + Infertility	Uterine cavity, myomas, endometrium (Asherman syndrome)	Hysteroscopy	
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Infertility	Ovarian reserve assessment	FSH, Antral follicular count or AMH	Ovaries
RPL	Translocations, deletions	Karyotype of the couple	Genetic
Infertility	Assessment of azoospermia	Karyotype and micro-deletions of the male	
RPL	Autoimmune disorders	Anti-cardiolipin antibody and lupus anticoagulant	Autoantibodies and immune function

RPL: Recurrent Pregnancy Loss; AMH: Anti Mullerian Hormone.

cause anatomical and pathophysiological disturbances to the female reproductive tract, resulting in RPL and infertility (Table 1).

Leiomyomas/myomas/fibroids: Approximately 20-40% of women develop uterine fibroids during their reproductive years [9]. Uterine fibroids, also known as leiomyomas or simply myomas, are benign solid growths that arise in the uterus [10]. There are three main types of fibroids classified according to their anatomic location inside or around the uterus: submucosal, subserosal, and intramural [9]. Leiomyomas can cause pain and may also affect fertility and pregnancy depending on their size and location.

Fibroids can detrimentally impact reproductive functions by impairing gamete/embryo transport, altering uterine contractility, and/or distorting endometrial glands, all of which can lead to improper implantation and/or conception [9,11,12]. Intramural fibroids within the uterine wall can distort the uterine cavity while submucosal fibroids in the uterine cavity can obstruct the tubal ostia, thus preventing sperm-egg fusion and transport [11]. It is hypothesized that the hyper estrogenic environment associated with fibroids results in subfertility [11]. Another theory suggests that myomas can disrupt endometrial blood supply or alter the biochemical composition of the endometrial fluids, creating a sperm-toxic environment [11].

One study reported that large fibroids can increase the risk of threatened abortions [13]. As fibroid size increased from small, 3-5 cm, to large, >10cm, there was an increase in risk of abortion from

19.74% to 34.38%. Other studies, however, show no such association with size but report pregnancy loss rates in women with fibroids almost double or triple that of women with normal uteri [14]. In studies involving women who undergo *In Vitro* Fertilization (IVF) treatment, submucosal fibroids cause the most adverse effects followed by intramural fibroids [9,10].

A systematic review was conducted to assess the effect of fibroids on fertility and pregnancy rates. The relative risks for fibroids at all locations in the uterus were significant for decreased implantation rates (RR = 0.821, p =.002) and live birth rates (RR = 0.697, p < .001) and increased risk of spontaneous abortion (RR = 1.678, p < .001). The study also explored the effect of fibroid location on fertility. They found similar results using data from prospective studies and all studies in women with intramural fibroids, suggesting that myomas of other locations, and not just submucosal, can significantly lower pregnancy outcomes both biochemically and clinically [15]. This is evidenced by decreased implantation rates (RR = 0.684, p < .001) and increased spontaneous abortions (RR = 1.747, p = .002) in patients with intramural fibroids.

When patients experience pain, bleeding, and infertility due to fibroids, myomectomy can be performed [10]. Although much of the research involving myomectomy lacks proper control groups, one study reported a significant reduction in miscarriage rates from 41% to 19% after resection and another study reported that about half of the women who underwent treatment were able to properly conceive again [16,17]. After myomectomy, women who were either infertile or for idiopathic reasons could not conceive improved their chances of conception particularly by generating a window of opportunity in which the recurrence of fibroids is delayed [18].

Leiomyomas can greatly impact fertility and reproductive outcomes and are considered an important factor in cases involving RPL and infertility.

Congenital uterine anomalies: Congenital uterine anomalies, or Mullerian anomalies, are a result of complications that arise during fetal development of the two symmetrical genital ducts, primarily the paramesonephric (Mullerian) ducts, and in part, the mesonephric (Wolffian) ducts [19,20]. These anomalies are classified according to shape and include structures such as septate uterus, unicornuate and bicornuate uterus, and uterus didelphys. These anomalies can result in infertility, pregnancy loss, and other reproductive complications [21].

There are two primary mechanisms through which congenital uterine anomalies can cause infertility and RPL. First, they can engender inadequate blood supply to the embryo, as in the case of subseptate uterus, which is hypothesized to be relatively avascular. This can compromise decidual and placental blood supply [20]. Second, they can mechanically distort the uterine cavity, which can impair fetal growth and result in second-trimester loss [20,22].

Infertile women (6.3%) have significantly more Mullerian anomalies than fertile women (3.8%, p < 0.05) [23]. The septate uterus, in particular, can interfere with normal implantation and placentation, leading to infertility [19]. It is also thought to lower sensitivity to pre-ovulatory hormone changes and interrupt early embryo development, leading to first-trimester miscarriage [20,24]. The unicornuate uterus can reduce intraluminal volume and also compromise vascular blood supply to both the placenta and developing fetus. The other anomalies such as bicornuate uterus and arcuate uterus, especially, have debatable effects on reproductive outcomes [23,25].

In one study, both the RPL population alone (13.3%) and the combined infertile and RPL populations (24.5%) contained a greater number of congenital uterine anomalies than the unselected population (5.5%) [26]. An extensive review appraised data from 1950 to 2007 on congenital uterine anomalies. Results showed that the appearance of anomalies in the general and infertile populations were 6.7% and 7.3%, respectively. However, in the RPL population, it was much higher 16.7%. In particular, the septate uterus in the infertile group (41%) and the arcuate uterus in the fertile and RPL groups (68% and 65.2%) were the most predominant. Thus, it was recommended to increase the use of diagnostic measures in RPL patients such as hysterosalpingogram and 2D ultrasound followed by more definitive procedures including hysteroscopy and laparoscopy [19].

Hysteroscopic septum resection as a surgical treatment seems beneficial and is effective in women with RPL, improving reproductive prognosis [27,28]. In fact, one study divided patients with uterine septum and otherwise unexplained infertility into two groups [29,30]. One group volunteered for operation and the other opted for no treatment. In the group that underwent septectomy, 43.1% achieved pregnancy versus 20.0% in the control group (p = .03). In another study, the miscarriage rate was 20.2% before resection and less than 5.0% after successful resection [31,32]. This helps validate hysteroscopic metroplasty as a safe and effective method to improve fecundity and reproductive outcomes in RPL and infertile patients.

Congenital uterine anomalies, although not as common as other factors, can lead to infertility and RPL because they result in mechanical distortions of the female reproductive tract and thereby, create an unsuitable environment for proper implantation and embryonic growth and development.

Intrauterine adhesions or Asherman's syndrome: Intrauterine Adhesions (IUA), also known as Asherman's syndrome, cause partial or complete dysfunction of the endometrium and are usually caused by trauma/insult to the region following any uterine surgery or curettage [33,34]. The highest incidences of IUA occur after miscarriage curettage [33]. Furthermore, IUA has been linked to infertility, RPL, poor implantation, and abnormal placentation.

In many patients with dense IUA, vascularity in the endometrium and myometrium is compromised [33]. These patients may also experience infertility and RPL due to complete damage of tubal ostia or stenosis of ostia/uterine-cavity caused by partial blockage by fibrotic adhesions and expansion of scarring endometrial tissue [35,36].

IUA can also impede proper blood flow of spiral arteries, diminishing endometrial growth and receptivity for implantation [37]. IUA can affect fertility and menstrual function, resulting in amenorrhea or hypomenorrhea [38]. It can also stunt endometrial development due to traces of residual endometrial tissue and scarring [39]. Infection and inflammation may additionally hinder endometrial

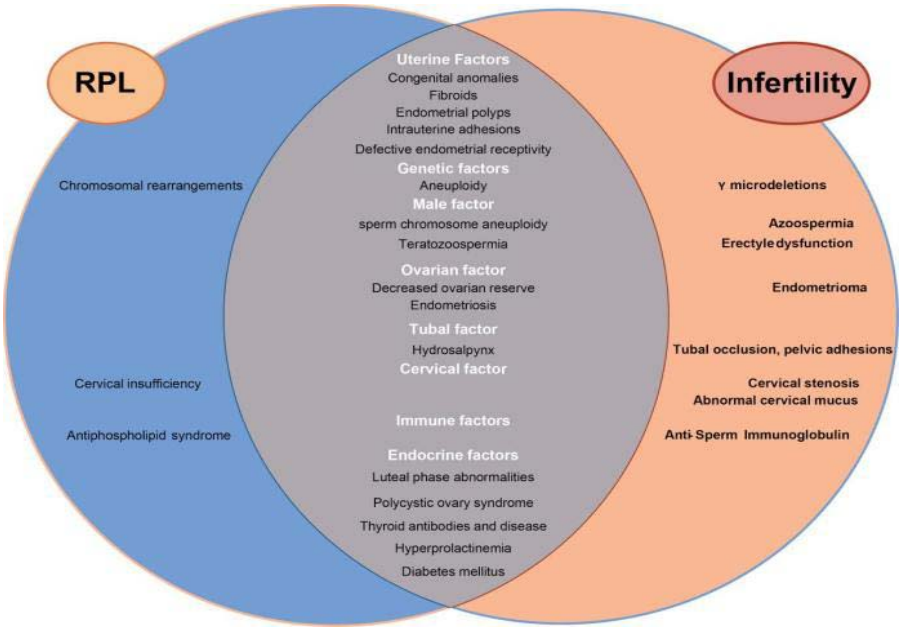

Figure 1: Common and mutually exclusive etiologies between RPL and infertility.

regeneration. Similarly, low postpartum estrogen levels may fail to help repair scarring and damaged endometrium [35]. In severe cases, there is only a 20-40% chance of successful pregnancy following treatment [36]. A study of 187 women who underwent hysteroscopic adhesiolysis reported a high percent of term pregnancies after the procedure (79.7%) [40].

By causing excessive scarring and diminished endometrial receptivity, IUA plays a definite role in both RPL and infertility cases, and hysteroscopic adhesiolysis may be a beneficial treatment option.

Defective endometrial receptivity: Defective endometrial receptivity is characterized by the failure of the endometrium to support implantation. This failure can be attributed to gynecological disorders such as PCOS, luteal phase defects, hydrosalpinx, and endometriosis, and can lead to infertility and RPL [41].

About 6-10 days after ovulation, the endometrium expresses cell adhesion proteins [42]. These proteins such as integrins and cadherins allow for adequate uterine receptivity by creating a hospitable environment for blastocyst implantation [41,43].

Women with certain gynecological disorders have a reduced expression of cell adhesion proteins and can exhibit decreased uterine receptivity [41]. Overall, this diminished receptivity affects both women with RPL and infertility.

Immunological factors

Antiphospholipid syndrome: Antiphospholipid Syndrome (APS) is an autoimmune disorder characterized by antiphospholipid antibodies that cause thrombosis and poor obstetric outcomes [44,45]. The main Antiphospholipid Antibodies (APA) are anticardiolipin (aCL), anti-β2-glycoprotein I, and Lupus Anticoagulant (LA) [45]. These antibodies bind to negatively charged phospholipids, activating monocytes, platelets, and endothelial cells [45,46]. APS is strongly associated with RPL [47]. Although the relationship between APS and infertility is tenuous, evidence suggests there is an association [48].

One study reported that the APA level in women with RPL is approximately 15% in the first trimester, much higher than the 1-5% seen in healthy women [45]. Women with APS usually present with a higher rate of pregnancy loss, especially after more than 10 weeks of gestation, and loss in the second trimester is directly correlated with the presence of LA and aCL [45].

APA activate endothelial cells, which in turn upregulate production of tissue factor, causing inflammation and thrombosis [45,49]. Subsequently, tissue factor, a procoagulant, initiates neutrophil activity resulting in trophoblast damage via activation of an inflammatory response pathway and placental dysfunction; eventually it may lead to pre-eclampsia. Similarly, APA can further reduce trophoblast growth by disrupting phospholipid adhesion forces [48]. These antibodies can disrupt the activity of annexin A5, a natural anticoagulant, leading to increased coagulative activity and pregnancy loss [46]. They can also decrease the secretion of hCG, which is important for maintaining pregnancy [50]. Furthermore, APA can interact with prothrombin, protein C, and plasmin clotting factors and hinder inactivation of pro-coagulants [46].

In a study involving mice with APA, the antibodies were associated with thrombosis, impaired hormone production, implantation failure due to aCL, and decreased blood flow to the fetus [51].

APS is clearly associated with RPL. Research suggests that APS causes thrombosis, hormone imbalances, reduced hCG levels, and implantation failures, all of which can lead to infertility. Therefore, APS becomes a common factor in both women with RPL and infertility.

Other immunological factors

Other immunological factors that contribute to RPL and infertility are antisperm and antinuclear antibodies. Antisperm

Antibodies (ASAs) can originate within the male due to iatrogenic or testicular/prostrate damage and dysfunction [52]. Rarely, ASAs can also be present in females who have an allergic immune response to their partner's sperm cells. ASAs can block sperm movement, capacitation, fertilization, and embryo implantation [52]. ASAs that target the sperm head can affect sperm penetration of the uterine cervical mucus and consequently, reduce sperm quality [53]. One study showed that sperm containing antibodies were much more susceptible to phagocytosis by macrophages in the female genital tract [54].

Elevated levels of immunoglobulins such as IgA and IgG antibodies were reported in women who had miscarried, primarily in the first-trimester [55]. IgG antisperm antibodies that targeted sperm tails were significantly related to higher rates of recurrent spontaneous abortions [56].

Antinuclear Antibodies (ANAs) also play an important antagonistic immunological role. ANAs are a subclass of autoantibodies that target and destroy structures within the cell nucleus, which can be especially devastating to a woman's reproductive function [57]. It can specifically affect essential structures such as DNA and/or other nuclear components, resulting in poor oocyte and embryo development [58]. In addition, low-titer ANAs present in the sera have been reported in patients with both explained and unexplained pregnancy loss [59]. This finding is hard to interpret, however, because of limited supporting research.

Overall, autoantibodies can damage the sperm or egg, affecting gestation and resulting in possible recurrent miscarriage and infertility.

Male factors

An estimated 30-40% of reproductive-age males experience a reduction in sperm quality and quantity [60]. Because the male genome constitutes half the genetic content of the embryo, male factors are important in fertility and pregnancy [60,61]. Male factors include sperm function and semen parameters as well as erectile dysfunction and anatomic anomalies such as micropenis and hydrospadias [62]. Male factors are an obvious and well-established cause of infertility and surprisingly, growing evidence supports their association with RPL.

Higher incidences of abnormal sperm parameters can prognosticate reproductive capability. Chromosomal aberrations in sperm can lead to implantation failure, cessation of embryonic development, and eventually early pregnancy loss [63]. In two different studies, researchers divided males into two groups: men with proven fertility (control group) and male partners of couples with RPL (study group) [64,65]. Both groups were evaluated with tests for sperm viability by hypo-osmotic swelling test, acrosome status, and nuclear chromatin decondensation. The study group had subnormal scores for all three criteria, indicating poor sperm quality and the subsequent inability to sustain the embryo, leading to early pregnancy loss.

Abnormal sperm morphology, chromosomal aberrations, and single gene mutations are also associated with fertilization failure, poor embryo development, and infertility [66,67]. Despite normal semen parameters, male partners can have underlying genetic abnormalities in sperm DNA. This can include incomplete protamine packaging resulting in greater susceptibility to damage [68]. In addition, using FISH analysis, a study revealed that men with RPL had more sperm aneuploidy than controls in the sex chromosomes (53 % *vs.* 3%, p <.001) [69].

Research shows that antioxidants could be beneficial because they alleviate oxidative stress, which most likely contributes to sperm DNA fragmentation and lipid peroxidation [70,71]. Because reproductive capacity pertains to not just the woman but the couple as a whole, the importance of male factors should not be overlooked in cases of both RPL and infertility.

Endocrine factors

Polycystic Ovary Syndrome (PCOS), diabetes mellitus, hyperprolactinemia, luteal insufficiency, and thyroid autoimmunity disorders are seen frequently in clinical practice. They establish a hormonal link between RPL and infertility.

Diabetes mellitus: Diabetes mellitus is a chronic disorder characterized by hyperglycemia due to issues with insulin production or insulin sensitivity, and presents itself in two main forms: type 1 diabetes (T1D) and Type 2 diabetes (T2D). T1D is characterized by the inability to produce adequate insulin. T2D, which is more prevalent, is characterized by insulin resistance primarily due to fatty diets and sedentary lifestyles [72,73]. Sufficient insulin production and/or supplementation is vital to maintaining a healthy pregnancy [74].

Women with uncontrolled T1D generally experience late menarche [74]. Hyperglycemia, in these women, can weaken the embryo by causing glucose deficiency. Insulin resistance in patients with T2D can result in ovulatory dysfunction, hyperandrogenism, hyperinsulinemia, and infertility [74]. Hyperinsulinemia disrupts the hypothalamus-pituitary-gonadal axis by reducing sex hormone-binding globulin (SHBG), which leads to a subsequent increase in blood testosterone levels and can result in anovulation [75]. Patients with T2D display elevated glucose production in the liver, which causes widespread insulin resistance. Inadequate glucose consumption due to hyperinsulinemia and hyperglycemia causes apoptosis of the embryonic cells, leading to miscarriage [73].

Just like in the case of PCOS, many diabetic women are obese, and research indicates that obese women produce blastocysts of poor quality and exhibit delayed conception [75]. Diabetic patients who concurrently have low BMI display high HbA1c levels and have irregularities in their menstruation [75]. Studies report that elevated HbA1c levels are associated with poor pregnancy prognosis and an increased risk of miscarriage [76].

Uncontrolled diabetes mellitus, primarily in concomitance with hyperinsulinemia, hyperglycemia, and obesity, is considered a risk factor for both RPL and infertility.

Polycystic ovary syndrome: Polycystic Ovary Syndrome (PCOS) is the most common endocrine abnormality in females. It affects 6-15% of reproductive age women and its prevalence in women with RPL is 56% [77-79]. The Rotterdam Criteria are most commonly used to diagnose PCOS [80-82]. At least two of the following three criteria must be present before a diagnosis can be made: oligo/anovulation, hyperandrogenism, and the presence of polycystic ovaries.

PCOS patients are generally characterized as having high LH levels and elevated production of androgens by theca cells. Hyperandrogenism can, in turn, suppress FSH production, leading to endometrial dysfunction, oligo-ovulation, and infertility [79]. One study reported an increased expression of the androgen receptor gene in women with PCOS compared with fertile women. This increased activity coupled with elevated androgen levels, suppressed alpha-beta3 integrins, which are cell-adhesion proteins and biomarkers of uterine receptivity [83]. Another study showed that compared to fertile women, women with PCOS had significantly increased activity of plasminogen activator inhibitor-1 (PAI-1). This hyperactivity promotes hypo-fibrinolysis and can consequently lead to increased thrombosis and placental insufficiency [84]. The impact of this mechanism was further validated by two studies which looked at metformin treatment for PCOS patients. Women who received metformin treatment and also had a reduction in PAI-1 activity had lower miscarriage rates compared with women who received metformin but did not experience a simultaneous decrease in PAI-1 activity [84, 85]. Also many women with PCOS exhibit lower serum levels of glycodelin and insulin-like growth factor-binding protein 1 (IGFBP-1), which are considered important molecules for proper decidualization and implantation [84,86]. Studies suggest that PCOS is associated with insulin resistance, obesity, and hyperhomocysteinemia, all of which can affect implantation by suppressing activity of cell-adhesion proteins. Hyperhomocysteinemia can also result in miscarriage because of its pro-coagulative nature, similar to cases of thrombophilia [87,88].

These factors link PCOS with both women experiencing infertility and RPL [89].

Thyroid antibodies and disease: Thyroid disorders are very common in women of reproductive age and are mainly caused by autoimmune disorders of the thyroid gland. Hyperthyroidism has little to no association with recurrent miscarriage or infertility [90,91]. Hypothyroidism, on the other hand, affects 3-5% of reproductive age women and is associated with miscarriage, pre-eclampsia, and preterm birth [92].

Adequate thyroid activity is necessary to maintain estradiol and progesterone production, and hypothyroidism results in poor thyroid activity [93]. Subclinical hypothyroidism can directly cause anovulation and increase prolactin levels [94]. Women with hypothyroidism usually display elevated levels of thyroid-regulating hormone (TRH). Physiologically, TRH stimulates Thyroid-Stimulating Hormone (TSH), which then activates the thyroid hormones, triiodothyronine (T3) and thyroxine (T4). However, TRH also stimulates prolactin, which suppresses GnRH and engenders ovulatory dysfunction [95]. Increased prolactin can disrupt the positive-feedback mechanism between estrogen and the gonadotropins, resulting in suppressed LH and FSH secretion.

Th1 cytokines promote production of interferon- ϒ, which causes inflammation and is associated with spontaneous abortions and implantation failures [96]. In one study, women with reduced fertility and with anti-thyroid antibodies displayed high levels of interferon-ϒ compared to women with no anti-thyroid antibodies ($p = 0.005$). The more favorable, pregnancy-promoting Th2 cytokines inhibits Th1 cytokines by the release of IL-4, 5, and 10 [97]. In a group positive for autoimmunity, reduction in IL-4 and IL-10 were observed ($p = 0.005$ and $p = 0.01$, respectively) [97].

Another plausible explanation for thyroid autoimmunity and poor reproductive performance is diminished vitamin D levels. In a study of patients with AITD compared to healthy individuals, vitamin D levels were significantly lower in the AITD group (72% *vs.* 30.6%, $p < .001$). Vitamin D is responsible for regulating the HOXA10 gene, which is vital for proper implantation and has anti-inflammatory properties. Vitamin D, in addition, promotes Th2 cytokines over Th1 cytokines [98].

High TSH levels associated with hypothyroidism can stimulate peripheral NK cell activity, outside of normal NK cell activity originating in the uterus. These excess peripheral NK cells, found in leukocytes in the blood, can migrate towards the uterus and alter the immune and humoral response, possibly endangering the microenvironment of the uterus for embryonic development. However, these studies suggest further research is needed to validate this underlying mechanism [99,100].

Overall, thyroid autoimmunity, especially in the form of hypothyroidism and the presence of thyroid antibodies, can be an important cause of RPL and infertility in reproductive age women.

Hyperprolactinemia: Hyperprolactinemia is characterized by elevated levels of the hormone prolactin in the blood. Hyperprolactinemia can be caused by a variety of factors including prolactinomas, anti-psychotic medications, antidepressants, chronic renal failure, and other idiopathic etiologies [101]. Studies have shown that high circulating prolactin levels can lead to chronic anovulation and other reproductive defects [102,103].

High prolactin levels were reported to impede progesterone production, resulting in luteal defect and infertility. Hyperprolactinemia can dysregulate hypothalamic function, resulting in defective ovulation and follicle activity [102].

High prolactin levels can suppress dopamine secretion, which in turn reduces GnRH activity, resulting in hypogonadotropic hypogonadism and disruption of the hypothalamus-pituitary-gonadal axis [104,105]. Similarly, another study utilized a murine model to demonstrate how hyperprolactinemia reduced the activity and expression of kisspeptin, a peptide that normally promotes production of GnRH [106].

A treatment study of 352 women who experienced recurrent spontaneous pregnancy loss demonstrated the association between high prolactin levels and miscarriage. These women were divided into two groups: those that received bromocriptine, a drug that reduced prolactin levels, and those that did not receive treatment. The treatment group had greater percentage of successful pregnancies compared to the control group (85.7% *vs.* 52.4%, $p < .05$). In addition, patients who miscarried displayed elevated levels of serum prolactin compared to those who had successful pregnancies (31.8-55.3 ng/mL *vs.* 4.6-15.5 ng/mL, $p < .05$) [107].

These studies and mechanisms demonstrate that hyperprolactinemia can lead to early pregnancy loss and infertility.

Luteal phase defect: Luteal Phase Defect (LPD) or insufficiency is attributed to poor progesterone production and/or progesterone

receptivity [108]. Luteal insufficiency can be caused by PCOS, thyroid and prolactin disorders, and iatrogenic interventions during assisted reproduction [109]. The corpus luteum normally produces progesterone at a level adequate for endometrial receptivity, whereby Th2 cytokines are favored, and prostaglandin activity is inhibited, to create a suitable microenvironment for implantation [110]. In LPD, however, all of this is compromised.

In many cases of luteal insufficiency, women also display poor luteal blood flow and reduction in FSH and LH circulation, which are essential for blastocyst maturation, implantation, and embryonic development [111,109]. LPD can cause implantation failure and anovulation in the first trimester, making it an important factor to consider in cases of infertility and RPL.

Decreased ovarian reserve: Decreased Ovarian Reserve (DOR) is a condition where the ovary's ability to produce viable oocytes declines because of age-related, iatrogenic, congenital, or idiopathic causes [112]. Women with diminished ovarian reserve usually have increased serum FSH levels and/or poor response to gonadotropic stimulation [113]. Advanced maternal age is the most prevalent cause of DOR but it can affect young women as well due to premature ovarian failure. DOR is caused by congenital chromosomal anomalies, non-chromosomal iatrogenic causes, and infections [112]. About half of women with premature ovarian failure and primary amenorrhea experience chromosomal anomalies [114]. Premature reduction of ovarian reserve in women is also associated with pseudohypoparathyroidism type 1a--a genetic disorder characterized by lack of response to parathyroid hormone [115], which may cause semi-resistance of surrounding thecal and granulosa cells to gonadotropins [116].

Supporting data show that the rate of oocyte chromosomal aneuploidy in women of reproductive age is 8% versus 10% to 30% in older women (ages 35-44) [117]. DHEA supplementation in women with DOR actually was associated with an odds ratio significantly lower than the odds of miscarriage in an IVF control population (OR = 0.49, p = .04) [118]. This suggests that DHEA can be profoundly beneficial to women with DOR and exemplifies the implicit direct relationship between DOR and pregnancy loss. DOR results in a smaller number of oocytes, fewer embryos for transfer, and an overall decreased chance of pregnancy. In addition to a reduction in quantity, many of the released oocytes are of poorer quality, making them less viable for proper implantation and thus more likely to result in miscarriage or infertility [112,117].

In summary, DOR is related to infertility and RPL because it results in fewer competent oocytes that can carry and sustain a pregnancy.

Conclusion and Future Considerations

This review advocates for a change by challenging the traditional notion that treats RPL and infertility as mutually exclusive entities. The disparity between both entities arose as a result of varied treatments and completely separate investigations of these populations by caregivers of different specializations.

Clearly, the definitions for fertility and chemical pregnancies should be better defined to create a cohesive overlap between RPL and infertility. A study showed that biochemical pregnancies constitute about 37% of reported pregnancies and each additional non-visualized loss decreases the chances of a live birth by at least 10% [119]. These results demonstrate the immediate necessity to include biochemical pregnancies in the definition of recurrent miscarriage as a non-exclusive entity. Thereby, couples with 2 or 3 chemical pregnancies will be defined within the criteria of RPL and undergo RPL workup. This calls for change in the workup for both RPL and infertility groups.

Both from our clinical experience and as a product of common associations and characteristics present in RPL and infertility, we put forth two promising clinical initiatives. The first is to consider non-visualized pregnancies in the same way we consider clinical pregnancies in terms of abortions. The second is to evaluate and treat RPL and persistently infertile patients and patients who share both pathologies under the same clinic in a multi-disciplinary fashion involving experts such as reproductive endocrinologists, obstetricians, and mental health counselors. This collaborative effort can help to dissolve the disparity by evaluating couples experiencing biochemical pregnancy loss under the same clinic. The implementation of these changes, we believe, will translate to better diagnosis and treatment of patients involved in cases of RPL and infertility.

Compliance with Ethical Standards

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author's contributions

DK was responsible for acquisition of the data, analysis and interpretation of data and drafting of the manuscript

AH conceived the idea concept and design and revision of the manuscript draft.

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Austin J Obstet Gynecol - Volume 5 Issue 1 - 2018
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Citation: Kumar D and Harlev A. Recurrent Pregnancy Loss and Infertility: A Time for Change. Austin J Obstet Gynecol. 2018; 5(1): 1090.