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Case Report

Rapid Ovarian Reserve Decline in a Woman with Pericentric Inv(9) Variant

Leeann M. Bui [†], Laura G. Cooney [*,‡] and Aleksandar K. Stanic [‡]

Department of Obstetrics and Gynecology, University of Wisconsin, Madison, WI 53792, USA; leeann.bui@wisc.edu (L.M.B.); stanickostic@wisc.edu (A.K.S.)

* Correspondence: lcooney2@wisc.edu

† Present address: Department of Obstetrics and Gynecology, Santa Clara Valley Medical Center, Santa Clara, CA 95128, USA.

‡ L.G.C. and A.K.S. are equal senior authors.

Abstract: Inv(9) is one of the most common chromosomal variants and is generally considered to be a variant of no clinical significance. We describe a case of a 35-year-old woman with a normal baseline fertility workup who presented to a university-affiliated fertility clinic after eight months of attempting conception. She underwent a rapid decline in anti-Mullerian hormone (AMH) from 10.0 ng/mL to 0.5 mg/mL and cycle day 3 (CD3) antral follicle count (AFC) from 58 to 4 total follicles during 18 months of follow-up. Her karyotype demonstrated a reportedly benign 46XX, Inv(9)(p11q13) variant. During follow-up and fertility treatment, she achieved pregnancy three times, but they all ended in chemical pregnancies. A systematic review of the literature identified 24 publications evaluating the association between infertility or recurrent pregnancy loss (RPL) and Inv(9). We report the prevalence of Inv(9) in women with infertility and the prevalence of infertility or RPL in women with Inv(9) mutation. Although Inv(9) has previously been considered to be a normal variant, several publications support the possible correlation between Inv(9) with reproductive failure. There has been limited literature regarding this association, and future studies should consider higher-resolution genomic detection methods to identify Inv(9)-related chromosomal rearrangements in couples presenting with infertility.

Keywords: case report; AMH; inversion 9; chromothripsis; infertility

Citation: Bui, L.M.; Cooney, L.G.; Stanic, A.K. Rapid Ovarian Reserve Decline in a Woman with Pericentric Inv(9) Variant. *Women* **2023**, *3*, 421–431. https://doi.org/10.3390/women3030032

Academic Editors: Tomer Avidor-Reiss, Samantha Beth Schon, Angela K. Lawson and Deborah Ikhena-Abel

Received: 3 July 2023
Revised: 30 July 2023
Accepted: 14 August 2023
Published: 6 September 2023

1. Introduction

Infertility is defined as the inability to conceive after 12 months of unprotected intercourse and is estimated to affect approximately 8–12% of reproductive-aged couples worldwide [1]. Although an underlying etiology for infertility such as ovulatory dysfunction, tubal factor, or male factor can be identified at least 85% of the time, for the remainder of couples, their infertility is classified as "unexplained" [1]. Initial infertility testing often includes markers of ovarian reserve, such as anti-Mullerian hormone (AMH), a laboratory value correlated with a woman's age, antral follicle count (AFC), and outcomes of ovarian stimulation [2].

Diminished ovarian reserve (DOR) is a term used to characterize a woman's potential for poor fertility outcomes with assisted reproductive technologies due to decreased oocyte quantity and quality [2]. Although there is not an international consensus on its definition, DOR is largely defined by the Bologna criteria as at least two of the following three criteria: (1) advanced maternal age (≥40 years) or any other risk factor for poor ovarian response (POR), a previous POR (≤3 oocytes with a conventional stimulation protocol or canceled cycle), and an abnormal ovarian reserve test (AFC < 5–7 follicles or AMH < 0.5–1.1 ng/mL) [3]. Clinically, patients may fall anywhere on the ovarian reserve spectrum, ranging from normal ovarian reserve to DOR to primary ovarian insufficiency (POI). Workup of POI, defined based on a period of amenorrhea or oligomenorrhea and

FSH in the menopausal range, includes karyotype, testing for adrenal and thyroid antibodies, FMR1 premutation testing, and pelvic ultrasonography [4]. Although there is not a clinically standardized workup for DOR, recent studies have identified mutations or single-nucleotide polymorphisms (SNPs) in genes involved in the FSH or LH receptors, formation of primordial and pre-antral follicles, DNA repair, and changes in epigenetic programming, among others, that may be associated with DOR [5].

Here, the authors describe the case of a 35-year-old woman with a rapid decline of ovarian reserve over the course of 18 months whose testing revealed a reportedly benign 46XX, Inv(9)(p11q13) karyotype. Chromosomal inversions are common structural alterations that occur when a piece of a chromosome breaks at two points, inverts 180 degrees, and reinserts within the same chromosome. When the chromosome inversion involves the short (p) and long (q) arms of the chromosome and includes the centromere, this is referred to as a chromosomal pericentric inversion. We present a case report and literature review evaluating the reproductive outcomes in Inv(9).

2. Case Report

A 35-year-old woman with no significant past medical history first presented in February 2019 to discuss her inability to conceive for eight months. The patient reported menarche at age 13 with regular menstrual cycles every 28 days. She started combined oral contraceptives (COCs) at age 16 due to a history of acne before switching to the NuvaRing in 2011. The patient stopped using the NuvaRing in May 2018 to attempt conception with her husband. Her menses returned two months after stopping NuvaRing. At the time of initial evaluation, the patient reported her menstrual cycles were five to six weeks apart with luteal spotting 10–14 days before her menses. She reported a history of deep cystic acne treated with COCs and Accutane but denied hirsutism (Ferriman Gallway score 0) and hair loss. She denied a history of eating disorders, significant weight changes, galactorrhea, hot flashes, or symptoms consistent with hypo or hyperthyroidism. Her BMI was 21.7 kg/m^2. Baseline laboratory workup drawn on cycle day (CD) 3 showed an estradiol (E2) of 111 pg/mL and a follicle-stimulating hormone (FSH) of 3.5 mIU/mL. Transvaginal sonography on CD 10 of the same cycle reviewed a thin endometrial lining of 2 mm and an AFC of 58 with no dominant follicles or cysts (right ovary AFC: 32; left ovary AFC: 26) (Figure 1a,b). Labs were repeated 6 weeks later on CD 3 of the subsequent menstrual cycle and showed an E2 of 66 pg/mL and FSH of 2.6 mIU/mL. Additional testing including thyroid stimulating hormone, prolactin, free and total testosterone, DHEA sulfate, and 17 hydroxyprogesterone were normal.

She was diagnosed with polycystic ovary syndrome (PCOS) based on Rotterdam criteria for oligomenorrhea, clinical hyperandrogenism, and polycystic ovarian morphology on ultrasound [6]. Further infertility evaluation revealed normal uterine cavity and bilateral tubal patency on saline infusion sonogram, normal partner semen analysis, and an AMH of 10.0 ng/mL.

Two months after the initial presentation, the patient started fertility treatment. The patient completed four cycles of letrozole (LET)-stimulated controlled ovarian stimulation (COS) with timed intercourse, one cycle of LET-stimulated COS with intrauterine insemination (IUI), and three cycles of clomiphene citrate (CC)-stimulated COS with IUI. She went up to maximum doses of letrozole 7.5 mg and clomid 150 mg and ultrasound monitoring showed 1–2 dominant follicles each cycle. She achieved a pregnancy after her second IUI, but it ended in a chemical pregnancy. A decision was then made to proceed with in vitro fertilization (IVF).

In preparation for her IVF cycle, approximately 18 months after the initial presentation, her ovarian reserve testing was repeated demonstrating a surprisingly low AMH at 0.7 ng/mL and CD3 AFC of 4 (Figure 1c,d) (Figure 2). To rule out lab error, AMH was drawn a week later and was 0.5 ng/mL. The patient's incredibly rapid decrease in ovarian reserve prompted a POI investigation although she did not meet the criteria yet. Additional POI workup was negative including screening for Fragile-X Syndrome (CGG repeats 30 and 30), anti-adrenal antibodies

(anti-21-hydroxylase), anti-thyroid antibodies (anti-thyroid peroxidase), and hemoglobin A1c. The patient denied any history of interval pelvic surgery or exposure to gonadotoxins. Karyotype testing revealed 46XX, Inv(9)(p11q13) and the interpretation of the report was that this was a "prevalent" and "well-known chromosomal variant with no clinical significance".

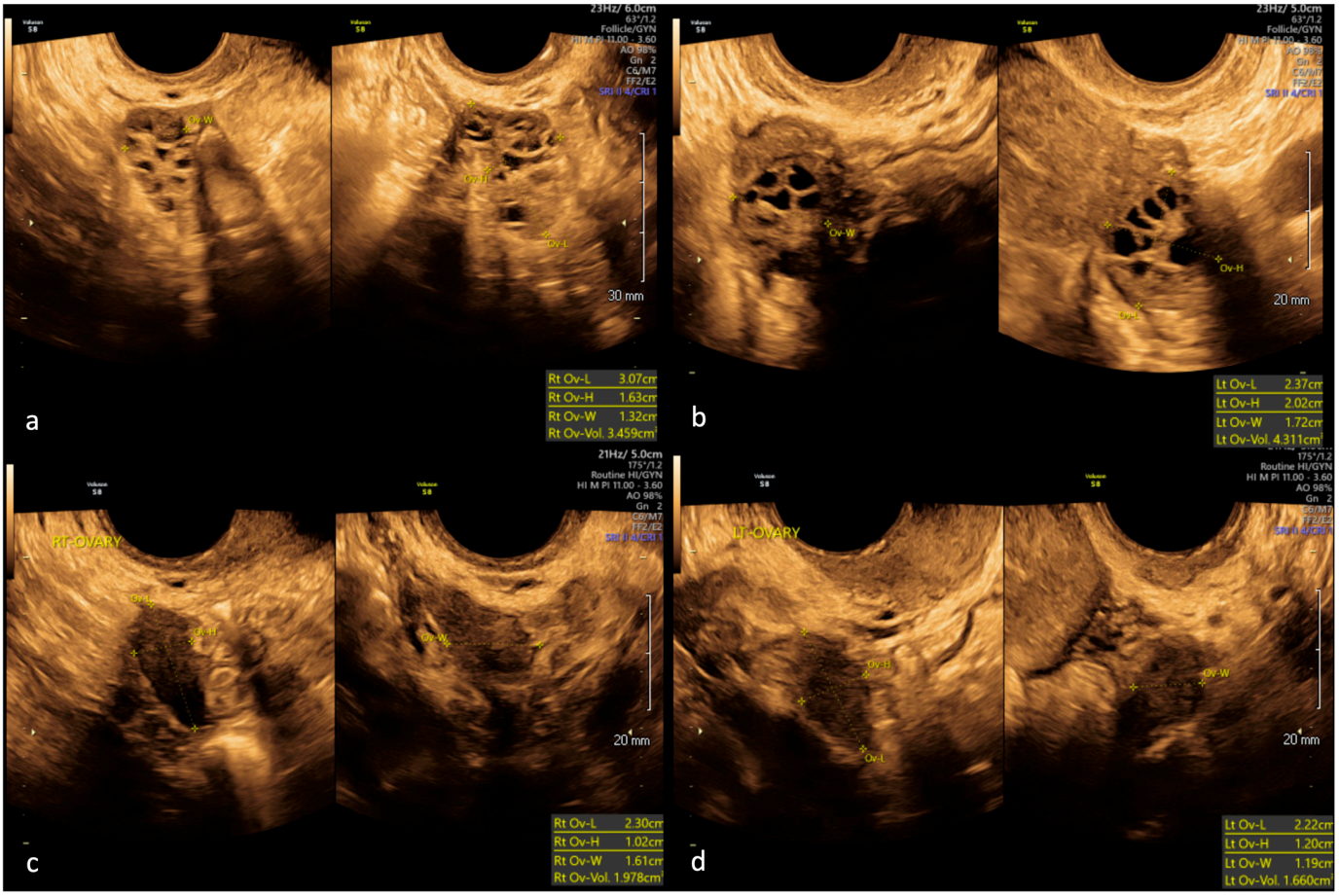

Figure 1. Transvaginal ultrasound evaluation of ovaries (**a**) Right ovary at presentation with AFC of 32 (**b**) Left ovary at presentation with AFC of 26. Total AFC count of 58 at presentation (**c**) Right ovary at follow-up with AFC of 3 (**d**) Left ovary at follow-up with AFC of 1. Total AFC count of 4 at follow-up. AFC: antral follicle count.

She underwent one IVF cycle employing antagonist protocol using 300 units of Follitropin Alpha (Gonal-F) and 150 units of Menopur. Cetrotide was started on simulation day 10 when the lead follicle was 15 mm and E2 was 211 ng/mL. On stimulation day 12, she had two dominant follicles measuring 17 and 17.5 mm with estradiol of 325 pg/mL and progesterone of 0.1 ng/mL. On stimulation day 13, her follicle growth and estradiol had plateaued (follicle sizes 16 and 17 mm, estradiol: 382 pg/mL, progesterone 0.2 ng/mL). She was triggered with 10,000 units of Chorionic Gonadotropin (hCG) and had an egg retrieval 36 h later. One oocyte was obtained. It was mature and fertilized via conventional insemination. A day 3 transfer of a seven-cell embryo was performed with no resulting pregnancy. She was offered treatment with a donor egg, but she desired instead to continue with IUIs. She became pregnant after a hybrid COS-IUI cycle of clomid 150 mg CD 3–7 with FSH 100 CD 7–10 units and luteal support with Prometrium 200 mg twice a day but was diagnosed with a chemical pregnancy. She achieved an additional pregnancy after a COH-IUI cycle with FSH 100 units daily CD 3–11 (one dominant follicle) and luteal support with Prometrium 200 mg twice a day, which unfortunately was also a chemical pregnancy. After her third chemical pregnancy, she tested for antiphospholipid syndrome which was negative. Informed consent was obtained from the patient to participate and for publication.

Per the University of Wisconsin's Health Sciences Institutional Review Board guidance, no ethical approval is required for case report studies involving less than three patients.

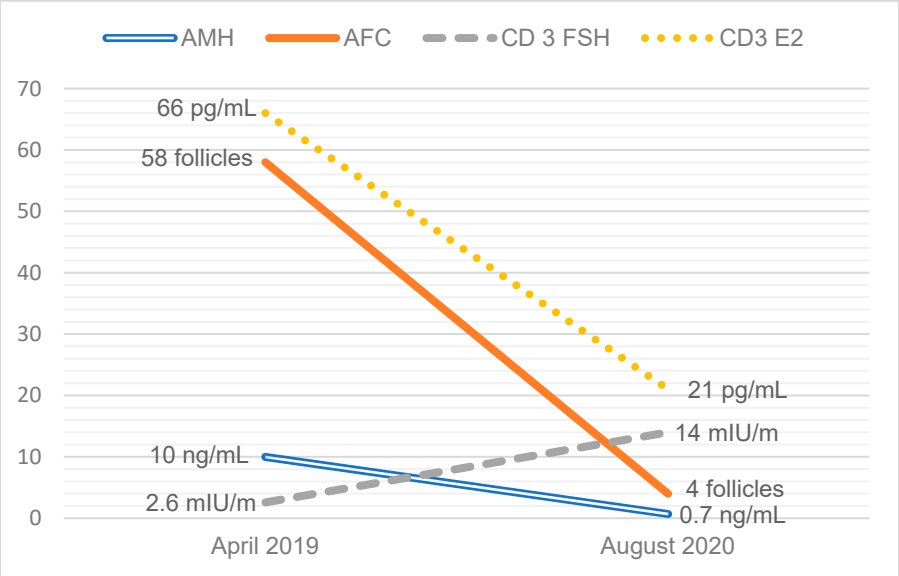

Figure 2. Comparison of AMH, AFC, CD3 FSH, and CD3 E2 after 16 months. AMH: Anti-Mullerian hormone; AFC: antral follicle count; CD3: cycle day 3; FSH: follicle-stimulating hormone; E2: estradiol.

3. Literature Review

A computerized literature search in PubMed database was performed using the following terms "inv9 (#1: pericentric inversion chromosome 9 [tiab] OR inv9 [tiab] OR Inv(9) [tiab]; #2: chromosome inversion [mesh] AND Chromosomes, Human, Pair 9 [mesh]; #3: #1 OR #2; #4: Infertility, female [mesh] OR Reproduction [tiab]; #5: Abortion, Spontaneous [mesh] OR Abortion, Habitual [mesh]; #6: #4 OR #5; #8: #3 AND #6". The total number of results was 112. Articles were included in our systematic review if they reported the prevalence of Inv(9) in women or men with infertility or recurrent pregnancy loss (RPL) or reported the prevalence of infertility or RPL in individuals with Inv(9). Only articles in English were considered. The title, abstract, and manuscript were reviewed for inclusion by two authors (L.B. and L.C.). Twelve studies met inclusion. We identified 12 additional studies while reviewing citations of the initial studies. We categorized the 24 studies into four groups: (1) studies comparing the prevalence of Inv(9) in individuals with infertility or RPL to controls, (N = 7) [7–13], (2) studies reporting the prevalence of Inv(9) in individuals with infertility or RPL, no control group (N = 12) [14–25], (3) studies comparing the prevalence of infertility or RPL in individuals with Inv(9) to controls (N= 1) [26], and (4) studies reporting the prevalence of infertility or RPL in individuals with Inv(9), no controls (N = 4) [27–30] (Table 1).

In our review, the prevalence of Inv(9) in individuals with infertility or RPL ranged from 0.01 to 3.7% with most estimates between 0.5 and 2.5% (Table 1). Of the seven studies that compared this prevalence to controls without infertility or RPL, three reported a higher rate of Inv(9) in individuals with infertility [7,9,13] and four did not find a difference [8,10–12].

The prevalence of infertility in individuals with Inv(9) varied widely from 1.3 to 45.1% with most estimates between 30 and 40% (Table 1). The only study that included a control group compared rates of "idiopathic reproductive failure" in men and women with Inv(9) compared to individuals with a normal karyotype identified from the same database using systemic sampling [26]. They did not find a difference between groups (37.1 vs. 32.4%; $p = 0.27$). Interestingly, they did report that among those with reproductive failure, women had higher rates of being Inv(9) carriers (41.9 vs. 30.9%) compared to males (29.2 vs. 34.0%) ($p = 0.004$) [26]. Two studies reported the prevalence of recurrent pregnancy loss in carriers of Inv(9). Again, this estimate ranged widely from 5.6 to 29.9% [27,28].

Table 1. The association between Inv(9) and infertility or recurrent pregnancy loss.

Author, Year	Country	Population	Control Group	Outcome	Results
Studies comparing the prevalence of Inv(9) in individuals with infertility or RPL to controls					
Cheng et al., 2017 [7]	China	Women ages 20–44 years with infertility. (N = 16,285 including N = 2175 with unexplained infertility) Women with chromosome aneuploidy were excluded.	Women in the same age group seeking preconception genetic testing for RPL or stillbirth, advanced maternal age, or history of a child with a prior genetic condition or birth defect. (N = 3665).	Prevalence of Inv(9)	Infertile cases: N = 195 (1.2%) Subset of women with unexplained infertility: N = 45 (2.1%) Fertile controls: N = 29 (0.79%) $p < 0.05$ for comparisons to controls
Dana et al., 2012 [8]	Romania	Men and women with infertility (N = 1800).	Amniocentesis from fetuses considered to be a sample of fertile population (spontaneous pregnancy) (N = 1116)	Prevalence of Inv(9) (p11q12), (p11q13)	Infertile cases: N = 41 (2.28%) Fertile controls: N = 44 (3.94%) N.S.
Kumar et al., 2012 [9]	India	Men and women with unexplained infertility (N = 1000).	Individuals of Indian origin in the general population (unpublished data) (N = 4500)	Prevalence of Inv(9)	Infertile cases: N = 26 (2.6%) General population: N = 33 (0.73) $p < 0.001$ compared to controls
Minocherhomji et al., 2009 [10]	India	Men and women with infertility (N = 760).	Age and geographically matched individuals without a history of infertility (N = 555)	Prevalence of Inv(9)	Infertile cases: N = 7 (0.9%) Fertile controls: N = 1 (0.2%) N.S.
Sahin et al., 2008 [11]	Turkey	Men and women with infertility (N = 276).	Amniocentesis from fetuses considered to be a sample of fertile population (spontaneous pregnancy) (N = 1130)	Prevalence of Inv(9)	Infertile cases: N = 4 (1.45%) Fertile controls: N = 8 (0.71%) N.S.
Xie et al., 2020 [12]	China	Men and women with infertility or RPL (N = 2816).	Adult patients without infertility were sent for karyotyping during the same time (N = 172)	Prevalence of Inv(9)	Infertile cases: N = 31 (2.1%) Fertile controls: N = 5 (2.91%) N.S.
Yamada et al., 1992 [13]	Japan	Men and women with more than two first-trimester pregnancy losses (N = 752).	Healthy volunteers (N = 1513)	Prevalence of Inv(9)	Infertile cases: N = 24 (3.2%) Fertile controls: N = 25 (1.7%) $p = 0.02$
Studies reporting the prevalence of Inv(9) in individuals with infertility or RPL, no control group					
Azim, 2003 [14]	Pakistan	Men and women with RPL (N = 600).	None	Prevalence of Inv(9)	N = 4 (0.67%)
Cozaru et al., 2012 [15]	Romania	Men and women with RPL (N = 298) or primary infertility (N = 160).	None	Prevalence of Inv(9)	RPL: N = 2 (0.67%) Primary infertility; N = 4 (2.5%)

Table 1. *Cont.*

Author, Year	Country	Population	Control Group	Outcome	Results
Dubey et al., 2005 [16]	India	Men and women with RPL (N = 1484).	None	Prevalence of Inv(9)	N = 3 (0.2%)
Dutta et al., 2011 [17]	India	Men and women with RPL (N = 2324).	None	Prevalence of Inv(9)	N = 14 (0.6%)
Elkarhart et al., 2019 [18]	Morroco	Men and women with RPL (N = 1254).	None	Prevalence of Inv(9)	N = 26 (2.1%)
Flynn et al., 2013 [19]	UK	Men and women with RPL (N = 1590).	None	Prevalence of Inv(9)	N = 1 (0.01%)
Ghazaey et al., 2015 [20]	India	Men and women with RPL (N = 1456).	None	Prevalence of Inv(9)	N = 20 (1.4%)
Makino et al., 1990 [21]	Japan	Men and women with RPL (N = 1278).	None	Prevalence of Inv(9)	N = 15 (1.2%)
Mozdarani et al., 2007 [22]	Iran	Men and women with at least 3 years of infertility (N = 601).	None	Prevalence of Inv(9)	N = 15 (2.5%)
Nonaka et al., 2019 [23]	Japan	Men and women with RPL (N = 4012).	None	Prevalence of Inv(9)	N = 52 (1.3%)
Rawal et al., 2020 [24]	India	Men and women with infertility, RPL, or IVF failure (N = 1276).	None	Prevalence of Inv(9)	N = 47 (3.7%)
Yuce et al., 2008 [25]	Turkey	Men and women with infertility (N = 2876).	None	Prevalence of Inv(9)	N = 41 (1.4%)
Studies comparing the prevalence of infertility or RPL in individuals with Inv(9) to controls					
Sipek et al., 2015 [26]	Czech Republic	Men and women with Inv(9) (N = 170) were identified from a large database of individuals referred for cytogenetic testing (N = 26,597).	Individuals with normal karyotypes were identified from the same overall cohort using the systemic sampling method (N = 661).	Prevalence of idiopathic reproductive failure	Inv(9): N = 63 (37.1%)Control: N = 214 (32.4%)$p = 0.27$
Studies comparing the prevalence of infertility or RPL in individuals with Inv(9), no control group					
Demirhan et al., 2008 [27]	Turkey	Individuals with Inv(9) (N = 157) were identified from a large database of individuals referred for cytogenetic testing (N = 15,528).	None	Prevalence of RPL, primary amenorrhea, and infertility	Infertility: N = 2 (1.3%) RPL: N = 48 (29.9%) Primary amenorrhea: N= 4 (2.5%)

Table 1. *Cont.*

Author, Year	Country	Population	Control Group	Outcome	Results
Yuksel et al., 2019 [28]	Turkey	Men and women with Inv(9) (N = 71) were identified from a large database of individuals referred for cytogenetic testing (N = 4168).	None	Prevalence of infertility and RPL	Infertility: N= 32 (45.1%) RPL: N = 4 (5.6%)
Teo et al., 1995 [29]	Singapore	Men and women with Inv(9) (N = 33) were identified from a large database of individuals referred for cytogenetic testing (N = 2448).	None	Prevalence of subfertility	Subfertility: N = 12 (36%)
Kosyakova et al., 2013 [30]	Multiple countries in Eastern + Western Europe	Individuals with Inv(9) were identified during routine diagnostic testing (N = 209).	None	Prevalence of infertility	Infertility: N = 79 (37.8%)

N.S. = not significant, RPL = Recurrent pregnancy loss. Recurrent pregnancy loss is defined as two or more pregnancy losses unless otherwise noted.

4. Discussion

This report documents a case of rapidly declining AMH in a woman with reportedly benign 46XX, Inv(9)(p11q13) karyotype. Over the course of 18 months, her clinical picture deteriorated from a diagnosis of PCOS and excellent ovarian reserve to one of IVF failure, three chemical pregnancies, and a recommendation that she cannot use her own gametes for reproduction. For patients presenting with unexplained infertility, chromosomal aberrations have been identified in 2–7% of couples [29]. To our knowledge, this is the first reported case of rapidly declining AMH in an otherwise healthy woman with Inv(9).

There are multiple reports of possible genetic factors for diminished ovarian reserve including single-nucleotide polymorphisms (SNPs), non-coding RNA molecules, and mutations in genes involved in follicle formation, germ cell formation, meiosis, or DNA repair [5]. We additionally note that chromothripsis, an extreme form of complex chromosome rearrangements (CCRs), sometimes appears as simple inversions or balanced translocations at the level of karyotype banding. Chromothripsis is characterized by simultaneous, massive chromosomal shattering and rearrangements in localized regions of the genome [31], which may result in gene disruption at the level of the primary sequence. Although this phenomenon was first described in patients with cancer [32–34], chromothripsis has been shown to occur in the germline where it forms balanced complex rearrangements, sometimes within a single chromosome, without apparent phenotypic effects [31,35]. Pericentric inversion 9 occurs within its heterochromatic region, an area with a high frequency of variants due to repetitive DNA sequences and homology between 9p12 and 9q13-21.1 regions [36]. Although the most common breakpoints involve Inv(9)(p12q13), Inv(9)(p11q13) has also been widely referenced in the literature [36]. Although these balanced complex rearrangements may appear innocuous, they can be transmitted to future generations and may increase the risk of reproductive failure [35,37]. De Pagter et al. have proposed that offspring may have inherited either a subset or full set of chromothripsis-like events from their healthy parent and then acquire de-novo rearrangements leading to copy-number changes resulting in pregnancy loss, congenital abnormalities, and congenital delays [35]. This theory has been questioned by a study of seven patients with inv9 undergoing in vitro fertilization (IVF). Using preimplantation genetic testing for aneuploidy (PGT-A) and structural rearrangement (PGT-SR) via SNP microarray analysis, they did not identify an increased risk of unbalanced chromosome products or overall aneuploidy rates in embryos (N = 52) from a parent with inv9 compared to controls [38]. However, this does take into account the possibility of multiple small inversions that would not change the absolute dosage of genes but would impact the regulatory elements.

In our literature review, we found a relatively stable prevalence of Inv(9) in individuals with infertility of 0.5–2.5% but no clear consensus on whether this is different from the general population. Moreover, the greatest limitation of the studies that reported the prevalence of Inv(9) often arose in their definition of a control group. The control group was only representative of the general population in three studies [9,10,13]. The other studies used individuals referred for karyotyping or results of amniocentesis as control groups, which introduces referral bias. Two of the three studies with appropriate control groups did show a higher rate of Inv(9) in the study population, while the third did not. The second part of our systematic review looked at rates of infertility in men and women with Inv(9) compared to controls. Similarly, there were high risks of referral biases in these studies as controls were identified from large databases of individuals referred for cytogenetic testing rather than random samples of the general population.

In this case, the initial diagnosis of PCOS adds complexity to the presentation. As PCOS is a clinical diagnosis, there is no routine genetic testing involved. In contrast, individuals with DOR or POI, and those with PCOS often have high ovarian reserve as demonstrated by high AMH and AFC. Genome-wide association studies (GWAS) studies have identified several PCOS candidate loci [5,39]; however similar to DOR, given the high heterogeneity of this disorder, there is no one gene target. Our review of the literature did

not identify any associations mentioned between Inv(9) and PCOS. Thus, we hypothesize that her PCOS diagnosis is unrelated to her rapid decline in ovarian reserve.

To our knowledge, this is the first case report in the literature of a rapid decline in ovarian reserve in an otherwise healthy reproductive-aged woman. Prior literature on Inv(9) and reproduction has focused on infertility or recurrent miscarriage, as seen in our systematic review. Unfortunately, as mentioned above, the largest limitation of this review is that the available data only look at associations, and no clear causation can be drawn. To further investigate this association between Inv(9) and rapid ovarian decline, we call for future longitudinal studies examining reproductive outcomes across a woman's fertility span in those with Inv(9).

5. Conclusions

Herein, we describe a case of a 35-year-old woman with a reportedly benign Inv(9) (p11q13) karyotype who had a rapid decline of ovarian reserve over the course of 18 months. Although data regarding the role of Inv(9) in women with reproductive failure has been conflicting, we propose that further research using higher-resolution genomic detection methods to identify Inv(9)-related chromothripsis in couples presenting with infertility might be helpful in discerning which, if any, Inv(9) carriers have clinically significant genomic alterations.

Author Contributions: Conceptualization, A.K.S. and L.G.C.; writing—original draft preparation, L.M.B.; writing—review and editing, L.M.B., A.K.S. and L.G.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Per the University of Wisconsin's Health Sciences Institutional Review Board guidance, no ethical approval is required for case report studies involving less than three patients.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing does not apply to this article.

Acknowledgments: We thank Robert Koehler, medical librarian, for his assistance with the literature review and procurement of articles.

Conflicts of Interest: The authors declare no conflict of interest.

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