Successful pregnancy after preimplantation genetic testing for structural rearrangements in a couple with complex chromosome rearrangement and recurrent in vitro fertilization failures: a case report

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Objective: To present a case of a couple with 20 years of infertility and 10 recurrent in vitro fertilization (IVF) failures, identifying a paternal complex chromosome rearrangement using high-resolution karyotype together with preimplantation genetic testing for structural rearrangements (PGT-SR) and utilizing IVF-intracytoplasmic sperm injection to achieve a successful pregnancy.
Design: Case report.
Setting: Al Ain Fertility Center, Abu Dhabi, United Arab Emirates.
Patients: A 40-year-old male patient and a 37-year-old female patient with a history of infertility and recurrent IVF failures.
Exposure: In vitro fertilization-intracytoplasmic sperm injection with high-resolution karyotype and PGT-SR.
Main Outcome Measures: Identification of chromosomal abnormalities, successful embryo development, pregnancy outcome, and newborn karyotyping.
Results: Karyotyping revealed a paternal complex chromosome rearrangement, t(3;4;12) (q21;q33;q21), and a chromosomal polymorphism in the female (1qh+). In vitro fertilization-intracytoplasmic sperm injection with PGT-SR produced one euploid/balanced female embryo from 20 embryos across 8 cycles. The patient conceived after hormone replacement therapy and frozen embryo transfer, resulting in an uneventful, full-term pregnancy and delivery of a healthy baby via C-section. Newborn karyotyping was normal (46,XX).
Conclusion: High-resolution karyotype and PGT-SR should be offered to patients undergoing IVF, especially those with severe male factors, recurrent IVF failures, implantation failures, or recurrent pregnancy losses, to enhance the chances of a successful pregnancy. (F S Rep® 2024;5:439–52. ©2024 by American Society for Reproductive Medicine.)

Key Words: Complex chromosome rearrangement (CCR), intracytoplasmic sperm injection (ICSI), preimplantation genetic testing for structural rearrangements (PGT-SR), fertility management, recurrent IVF failures

Infertility is a global health problem (1). Studies showed that approximately 30% of infertility cases around the globe were due to male factors (2, 3). Several factors such as endocrine dysfunction, inflammatory diseases, genital tract abnormalities, spermatogenesis failures, and ejaculatory problems may contribute to male infertility that could be associated with lifestyle factors, psychological issues, and genetics (4).

The genetic factors involved in male infertility may be chromosomal or monogenic disorders, mitochondrial DNA mutations, Y chromosome microdeletions, multifactorial disorders, imprinting disorders, or endocrine disorders of genetic origin (5, 6).

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Chromosomal factor alone accounts for 2%–14% of male infertility, and the prevalence increases to 15% in the population of azoospermic males (7–9).

We present a case of primary infertility and recurrent in vitro fertilization (IVF) failure in which the husband was the carrier of a complex chromosome rearrangement (CCR). She was successfully pregnant after IVF and preimplantation genetic testing for structural rearrangements (PGT-SR).

This case report is unique in presenting a couple with a 20-year history of primary infertility and 10 recurrent IVF failures, where the male partner was identified as a carrier of a CCR. Utilizing high-resolution karyotyping and PGT-SR alongside IVF-intracytoplasmic sperm injection (ICSI), the couple achieved a successful pregnancy. This case underscores the importance of advanced genetic testing and personalized fertility management in addressing complex infertility cases, adding valuable insights to the scientific literature on the effective use of PGT-SR in overcoming genetic barriers to successful conception.

CASE PRESENTATION

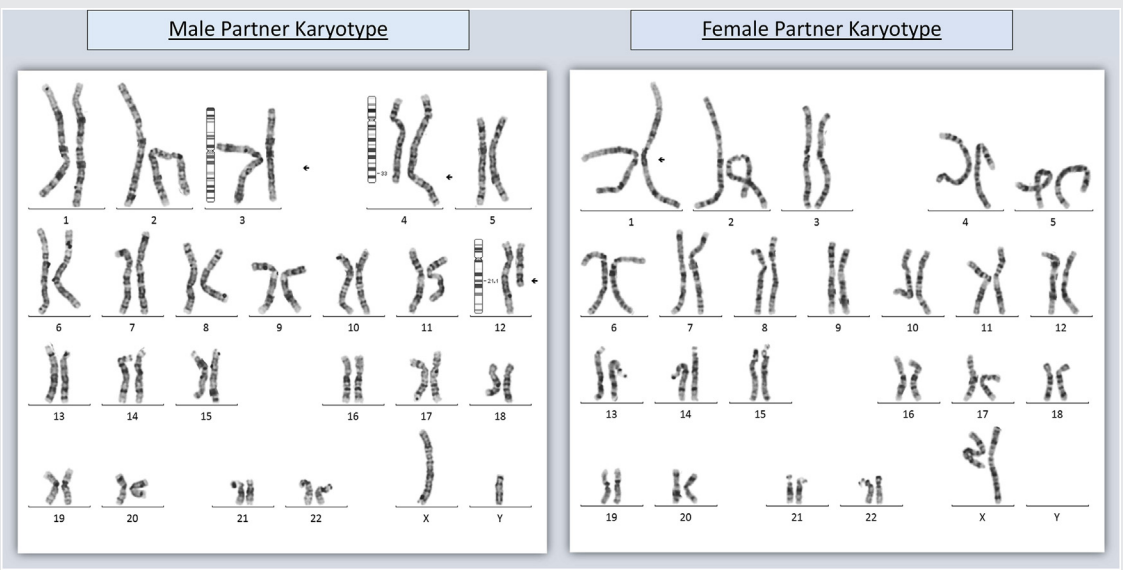
Patient Consent and Ethics Approval

Written informed consent to publish this case report was obtained from both patients. The consent process was approved and supervised by the Research Ethical Committee at Al Ain Fertility Center (Project ID: AAFC/CREC/2023/001).

A nonconsanguineous couple (a 37-year-old female and a 40-year-old male) presented to Al Ain Fertility Center, UAE, with a history of primary infertility due to male factors for 20 years. They had a history of 10 unsuccessful IVF attempts at various clinics between 2008 and 2012, when the patient was between 26 and 30 years old. During these cycles, no PGT was performed. All embryo transfers were performed on day 3, but unfortunately, none resulted in pregnancy. As a standard practice, we performed high-resolution karyotyping on both partners to identify any potential genetic factors that could impact fertility outcomes. The female partner, who never got pregnant before, had a history of uncontrolled diabetes mellitus, hypertension, bronchial asthma, anemia, and obesity (body mass index [BMI] 49.5). The male partner had a history of hypertension, chronic prostatitis, kidney stones, and varicocele. An infertility workup was recommended for the couple. The medical check-up, including the hormone profile, was within normal limits for the female partner follicle-stimulating hormone: 10.5 mIU/mL/luteinizing hormone: 40 mIU/mL/E2: 175 pg/mL/thyroid-stimulating hormone: 1.86 uIU/mL/anti-Müllerian hormone: 2.4 ng/mL. Pelvic transvaginal ultrasound showed 11 antral follicles and no abnormal findings. Her karyotype showed only a polymorphism (46XX,1qh+). For the male partner, semen analysis revealed severe oligoasthenoteratozoospermia (SOAT): one motile sperm was seen/20–30 HPF. Further cytogenetic investigations revealed that he was a carrier of a CCR involving chromosomes 3, 4, and 12 designated as t(3;4;12)(q21;q33;q21) (Figs. 1 and 2).

An IVF-ICSI treatment with PGT-SR was discussed with them. After losing weight (BMI dropped from 49.5 to 36.9), the patient went through IVF-ICSI treatment eight times under different gonadotropin-releasing hormone (GnRH) antagonist protocols with PGT-SR (10–13). The treatment methods and outcomes are summarized in Table 1. Ovarian stimulation

FIGURE 1



Couple karyotype showing chromosomes involved in CCR and heterochromatic segment. CCR = complex chromosome rearrangement.

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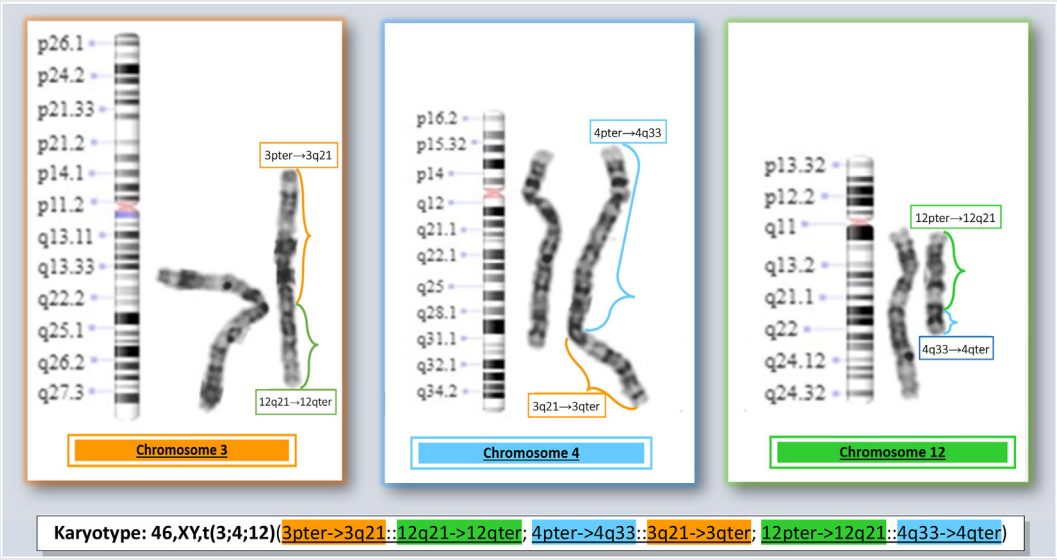
FIGURE 2



Partial karyotype showing chromosomes involved in complex chromosomal rearrangement.

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with recombinant follicle-stimulating hormone or recombinant/purified gonadotrophins was started. Because in the first IVF cycle, we got only three MII out of eight oocytes collected and four were GVs, in the next cycles we used estradiol to prolong the follicular phase in an attempt to get more mature oocytes (Table 1).

The ovarian response was evaluated by ultrasound and by estradiol level, and the dose of gonadotrophin was adjusted when necessary. The antagonist was added to the protocol when the follicles reached a diameter of 14 mm. The daily dose of 0.25 mg of GnRH antagonist was given till the day of the ovulation trigger. She was scheduled for oocyte retrieval when at least three follicles reached a mean diameter of 17 mm or more. Transvaginal oocyte retrieval was planned 36 hours after trigger injection, agonist trigger was given in the first cycle (Gonapeptyl 0.3 mg subcutaneous), whereas agonist and recombinant human chorionic gonadotropin trigger were given in the other cycles (Gonapeptyl 0.2 mg + Ovitrelle 250 mg subcutaneous). Egg collection was performed using transvaginal ultrasound-guided aspiration, according to standard protocol, under general anesthesia; ICSI was performed on all MII oocytes, and resulting fertilized oocytes were cultured in sequential media (Quinn's advantage medium, Sage Biopharma) until blastocyst stage (days 5 and 6). Twenty good-quality embryos were obtained in all eight IVF cycles, biopsied (trophectoderm), and were vitrified. After PGT-SR, only 1 out of 20 embryos was euploid (Table 1).

Cytogenetics (Karyotype) Investigation

Karyotyping was performed at our laboratory using a conventional G-banding technique by standard laboratory protocol. Phytohemagglutinin-stimulated peripheral blood lymphocytes were cultured in a Gibco PB-MAX karyotyping medium. The cell divisions were arrested in the metaphase stage using a colchicine reagent before harvesting the cultures. The cultures were treated with the hypotonic solution and fixed. The slides with G-banded metaphases were microscopically analyzed (by reading 50 or more metaphases) using Metasystem IKAROS software at 550–900 band resolution and recorded in the screening sheets according to the International System for Human Cytogenetic Nomenclature (ISCN 2016).

The male partner's karyotype has been identified with a CCR encompassing chromosomes 3, 4, and 12, labeled as t(3;4;12)(q21;q33;q21). This balanced translocation involves the following breakpoints: on chromosome 3 at band 3q21 with 122 Mbp from the p-terminal to the breakpoint and 76 Mbp to the q-terminal, yielding a chromosome length of approximately 198 Mbp; on chromosome 4 at band 4q33 with 169 Mbp from the p-terminal to the breakpoint and 21 Mbp to the q-terminal, totaling approximately 190 Mbp in length; and on chromosome 12 at band 12q21, where the distance from the p-terminal to the breakpoint is 71 Mbp, with 62 Mbp to the q-terminal, resulting in a chromosome length of approximately 133 Mbp.

These precise breakpoints and associated imbalance sizes are elaborated in Supplemental Table 1 (available online), which provide a detailed overview of the chromosomal dimensions observed in the husband's peripheral blood karyotype.

This balanced state means that there is no net gain or loss of genetic material in his somatic cells, rendering him phenotypically normal. However, during gametogenesis,

TABLE 1

PGT-SR outcome during different ART cycles.

Cycle number	Maternal age (years)	Stimulation protocol[a]	Gonadotropins	Dosage	Trigger (cycle day)	E2 pg/mL (cycle day)[b]	No. of eggs collected	M II[c]	No. of eggs fertilized	No. of blastocyst obtained	Embryo ID	Biopsy day	PGT-SR analysis number	PGT-SR findings[d,e,f,g] (Chromosome)x Ploidy	PGT-SR interpretation/ remarks
Cycle 1	37	Antagonist (Cetrotide)	Gonal F	375 IU	Cycle day 11	792 (cycle day 11)	8	3	3	2	1	Day 6	Analysis 1	CHAOTIC	Aneuploidy/not suitable for embryo transfer
											2	Day 6	Analysis 2	CHAOTIC	Aneuploidy/not suitable for embryo transfer
Cycle 2	37	E2 + Antagonist (Cetrotide)	Menopur	450 IU	Cycle day 13	1234 (cycle day 13)	16	9	7	1	5	Day 5	Analysis 3	(3p26.3p11.1) x1.65 **(LDM)** (9q33.1q34.3) x1.1 (12p13.33p11.1) x2.8	Aneuploidy/not suitable for embryo transfer
Cycle 3	38	E2 + Antagonist (Cetrotide)	Menopur	450 IU	Cycle day 15	1594 (cycle day 15)	8	7	5	4	2	Day 5	Analysis 4	(1p36.33p32.3) x1.1 (3q12.1q29)x1.3 (4q32.2q35.2) x2.85	Aneuploidy/not suitable for embryo transfer
											3	Day 5	Analysis 5	(4q32.3q35.2) x1.1 (12q13.3q24.33) x2.95	Aneuploidy/not suitable for embryo transfer
											4	**Day 5**	Analysis 6	**Euploid/Balanced Female**	**Suitable for embryo transfer**
											6	Day 5	Analysis 7	(3q13.11q29)x2.8 (4q33q35.2)x1.05 (21q11.2q22.3) x2.95	Aneuploidy/not suitable for embryo transfer

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TABLE 1

Continued.

Cycle number	Maternal age (years)	Stimulation protocol[a]	Gonadotropins	Dosage	Trigger (cycle day)	E2 pg/mL (cycle day)[b]	No. of eggs collected	M II[c]	No. of eggs fertilized	No. of blastocyst obtained	Embryo ID	Biopsy day	PGT-SR analysis number	PGT-SR findings[d,e,f,g] (Chromosome)x Ploidy	PGT-SR interpretation/ remarks
Cycle 4	39	E2 + Antagonist (Cetrotide)	Menopur and Letrozole	450 IU and 5 mg	Cycle day 16	442 (cycle day 15)	6	4	3	3	2	Day 5	Analysis 8	(3p26.3q13.11)x1.1 (12q14.1q24.33) x1.05	Aneuploidy/not suitable for embryo transfer
											3	Day 5	Analysis 9	(4q32.2q35.2)x2.85 (7p22.3q36.3)x1.3 (9p24.3q34.3)x1.25 (12q14.1q24.33) x1.0 (20p13q13.33)x1.3	Aneuploidy/not suitable for embryo transfer
											4	Day 5	Analysis 10	(3q11.1q29x1.4) x1.4 **(HDM)** Segmental trisomy of the terminal region of chromosome 4q (visually observed, not called out by ion reporter).	Aneuploidy/not suitable for embryo transfer
Cycle 5	39	E2 + Antagonist (Orgalutran)	Menopur	450 IU	Cycle day 14	1294 (cycle day 12)	10	7	5	3	3	Day 5	Analysis 11	(3p26.3q13.11)x0.9 (4p16.3q32.1)x2.7 (10p15.3q26.3)x2.7 (12p13.33q24.33) x1.1 (14q11.1q32.33) x2.75	Aneuploidy/not suitable for embryo transfer
											5	Day 5	Analysis 12	(12p13.33q24.33) x1.55 **(LDM)** (16p13.3q24.3)x1.1	Aneuploidy/not suitable for embryo transfer
											6	Day 5	Analysis 13	(3p26.3q29)x3.0 (4q32.3q35.2)x1.1 (12p13.33q14.1) x1.05 (16p13.3q24.3)x1.1 (19p13.3q13.43) x2.9 (22q11.1q13.33) x1.1	Aneuploidy/not suitable for embryo transfer

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TABLE 1

Continued.

Cycle number	Maternal age (years)	Stimulation protocol[a]	Gonadotropins	Dosage	Trigger (cycle day)	E2 pg/mL (cycle day)[b]	No. of eggs collected	M II[c]	No. of eggs fertilized	No. of blastocyst obtained	Embryo ID	Biopsy day	PGT-SR analysis number	PGT-SR findings[d,e,f,g] (Chromosome)x Ploidy	PGT-SR interpretation/ remarks
Cycle 6	40	E2 + Antagonist (Orgalutran)	Menopur	450 IU	Cycle day 23	1479 (cycle day 21)	6	5	4	3	1	Day 5	Analysis 14	(2p25.3q37.3)x1.15 (8q22.1q24.3)x1.2	Aneuploidy/not suitable for embryo transfer
											4	Day 5	Analysis 15	CHAOTIC	Aneuploidy/not suitable for embryo transfer
											5	Day 5	Analysis 16	(3p26.3q13.11) x0.95 (4q32.3q35.2)x0.95 (Xp22.33q28)x1.7	Aneuploidy/not suitable for embryo transfer
Cycle 7	40	E2 + Antagonist (Orgalutran)	Menopur	450 IU	Cycle day 15	1842 (cycle day 14)	5	5	5	2	1	Day 6	Analysis 17	CHAOTIC	Not suitable for embryo transfer
											2	Day 5	Analysis 18	(3q11.1q29)x2.95 (12q14.1q24.33) x1.05 **(13q11q34)x1.1 (Xp22.33q28)x1.0**	Not suitable for embryo transfer
Cycle 8	40	E2 + Antagonist (Orgalutran)	Menopur (6 days) then Pergoveris (4 days)	450 IU	Cycle day 18	2095 (cycle day 13)	5	4	4	2	1	Day 5	Analysis 19	(3p26.3q13.11) x1.05 (4q32.3q35.2)x1.05 (15q11.2q26.3) x2.85	Not suitable for embryo transfer
											3	Day 6	Analysis 20	(3q11.1q29)x2.7 (12p13.33p11.1) x2.85 (12q11q24.33)x2.3 **(LDM)**	Not suitable for embryo transfer

Note: **Bold** values represent the only euploid/balanced female embryo from 20 embryos across 8 cycles.
ART = assisted reproductive technology; CCR = complex chromosome rearrangement; HDM = high-degree mosaicism; LDM = low-degree mosaicism; PGT-SR = preimplantation genetic testing for structural rearrangement.
[a] Stimulation protocol: specific ovarian stimulation protocol used in each ART cycle, including estrogen (E2) and antagonist medications.
[b] E2 pg/mL (cycle day): the level of estradiol (E2), measured on a specific day of the cycle.
[c] M II: the number of eggs matured to metaphase II (M II).
[d] Euploid/balanced: embryos without any detectable aneuploidies or structural rearrangements.
[e] Low-degree mosaicism: 30%–50% aneuploidy; high-degree mosaicism: 50%–70% aneuploidy (García-Pascual et al.) (14).
[f] Chaotic pattern: more than 6 aneuploid chromosomes OR aneuploidies or those displaying chaotic patterns.
[g] PGT-SR findings (segmental/full aneuploidy, LDM/HDM mosaicism) involving chromosomes 3, 4, and 12 with CCR are highlighted in **blue**.

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particularly in the sperm cells, this translocation could lead to unbalanced chromosomal arrangements in the embryos.

Trophectoderm Biopsy and Clinical Genetics (PGT-SR) Investigation

Each embryo was incubated in a separate droplet of human embryo culture medium covered with paraffin oil in an EmbryoSlide culture dish (Vitrolife, Denmark) to allow individual assessment and documentation. All embryos were incubated in the time-lapse monitoring system (EmbryoScope; Unisense FertiliTech A/S, Aarhus, Denmark, Vitrolife) from the time of ICSI until day 6 of embryo development. Embryo biopsy was done either on day 5 or day 6 of embryo development. Only blastocysts with a well-defined inner cell mass and with a hatching trophectoderm with multiple cells were considered eligible for biopsy. For trophectoderm biopsy, embryos were biopsied using Quinn's Advantage Protein Plus Blastocyst Medium (SAGE, Cooper Surgical). Three to five laser pulses (OCTAX, Herborn, Germany) were used to cut the trophectoderm cells inside the aspiration pipette, and then trophectoderm biopsies were placed in 0.2-mL PCR tubes containing 2 μL Dulbecco's phosphate buffered saline. Blastocysts were vitrified immediately after the biopsy (Kitazato), and 8–10 cells were sent for further genetic analysis.

After retrieving trophectoderm biopsies from the IVF laboratory, we performed PGT-SR as it aims to detect smaller imbalances ($\geq$6 Mbp). The standardized protocol detects whole uniform aneuploidies, segmental ($\geq$10 Mbp), small rearrangements (deletions/duplications $\geq$6 Mbp), and degree of mosaicism with high sensitivity and specificity (14). Whole genome amplification was performed using the Ion SingleSeq Kit amplification system and further processed by next-generation sequencing using the Ion ReproSeq PGS Kit (Thermo Fisher Scientific). Analysis was conducted with Ion Reporter v5.10, Ion Chef, and Ion S5. Our PGT-SR workflow is also accredited with external quality assessment (GenQA—operated by Oxford University, NHS Foundation Trust).

In this study, we analyzed 20 embryos derived from eight IVF cycles; each embryo was subjected to biopsy, vitrification, and PGT-SR assessment. Our results indicated that 50% (10 out of 20) of the embryos displayed segmental aneuploidy involving chromosomes 3, 4, and 12, whereas an additional 20% (4 out of 20) exhibited both segmental and full chromosome aneuploidy involving these chromosomes. A further 20% (4 out of 20) of the embryos showed chaotic chromosomal configurations. Altogether, 70% (14 out of 20) of the embryos presented some form of chromosomal abnormality concerning chromosomes 3, 4, and 12. However, only 5% (1 out of 20) of the embryos did not show any segmental or full chromosome aneuploidy related to chromosomes 3, 4, and 12.

Notably, four embryos exhibited "chaotic" chromosomal patterns, characterized by the presence of more than six aneuploid chromosomes or embryos displaying ploidy that cannot be interpreted are identified.

The observed breakpoints in the embryos were as follows:

On chromosome 3 at band 3q13.11, with a distance of ~105 Mbp from the p-terminal to the breakpoint and ~93 Mbp to the q-terminal, showing a deviation of ~17 Mbp proximal to the expected 3q21; on chromosome 4 at band 4q32.3, with a distance of ~166 Mbp from the p-terminal to the breakpoint and ~24 Mbp to the q-terminal, deviating by ~3 Mbp proximal to 4q33; and on chromosome 12 at band 12q14.1, with a distance of ~60 Mbp from the p-terminal to the breakpoint and ~73 Mbp to the q-terminal, deviating by ~11 Mbp proximal to 12q21.

These observed chromosomal imbalances generally aligned with the expected breakpoints derived from the paternal karyotype, albeit with minor variations. The discrepancies noted can be partly attributed to the resolution limits of G-banding karyotyping ($\pm$5–10 Mbp) and the specificities of the PGT-SR platform utilized (ReproSeq kit by Ion Torrent Thermo Fisher), which may influence precise breakpoint localization.

We utilize the ReproSeq Mosaic PGS w1.1 workflow because it is designed to automatically identify whole-chromosome mosaicism with a sensitivity of $\geq$20%, detect and report CNVs with non-integer or decimal ploidy values, and is uniquely capable of identifying triploid conditions such as 69, XXY by recognizing mosaicism in chromosomes X and Y—scenarios where low-pass genome sequencing typically does not detect polyploidies. For PGT-SR assessments, we refer to the thresholds established by our Internal Lab Reporting Policy, which defines embryos as aneuploid if they have more than 30% aneuploidy. We do not report mosaicism in PGT-SR cases.

The detailed comparison and interpretation of expected vs. observed chromosomal imbalances are provided in Supplemental Table 1, offering a comprehensive overview of the chromosomal breakpoints and sizes (in Mbp) observed in both the husband's peripheral blood karyotype and the embryos.

Notably, previous cytogenetic investigations identified the male partner as a carrier of a CCR involving chromosomes 3, 4, and 12, specifically t(3;4;12)(q21;q33;q21). This genetic context was evident in the outcomes of the PGT-SR findings. Among the embryos with segmental abnormalities, a significant proportion, 86.7% (13 out of 15), demonstrated abnormalities in chromosomes 3, 4, and 12, aligning with the paternal CCR pattern (Table 1). These findings underscore the close correlation between the expected and observed imbalance sizes, highlighting the impact of the parental CCR on embryonic chromosomal integrity.

Despite the prevalence of chromosomal anomalies in the cohort, only one embryo was identified as euploid/balanced. After thorough counseling and obtaining informed consent, the couple agreed to proceed with the transfer of this embryo.

Embryo Transfer Protocol

Frozen embryo transfer was planned for the patient. Endometrial preparation with hormone replacement therapy for frozen embryo transfer was done under a standard protocol (13). Estradiol valerate (Progyluton, Bayer, Germany; dosage 6 mg/day), estradiol transdermal (ESTRADOT, Novartis, New

Zealand; dosage 100 mg/3 days), Aspirin (Albyl-E, Julphar, U.A.E.; dosage 75 mg/day), and prednisolone (Prednisone, Julphar, UAE; 5 mg/day) were administrated from cycle day +2. She had a transvaginal ultrasound on cycle day +10 showing a triple lining endometrium measuring 9.1 mm thickness. On the same day, she had a blood test showing 108.7 pg/mL estradiol and <0.050 ng/mL progesterone so estradiol valerate (Progyluton, Bayer, Germany) was increased to 8 mg/day. She started endometrial priming for luteal phase support with progesterone from CD12 in the form of vaginal progesterone gel (Crinone 8%, Merck Global, United Kingdom) and dydrogesterone (Duphaston, 10 mg Abbott, The Netherlands) was administered twice-daily in addition to, intramuscular natural progesterone 100 mg/mL (Prontogest, AMSA IBSA, Italy) every other day. On day 5 of progesterone priming, she had another blood test that showed 142.5 pg/mL estradiol and 13.32 ng/mL progesterone. The frozen embryo was thawed and transferred on the sixth day of progesterone priming under the usual protocol, using Echotip Soft-Pass TM Embryo Transfer Catheter (Cook Medical) without any difficulty.

After the embryo transfer (14 days), the patient had a pregnancy test that showed a positive result (serum β-hCG was 1983 mIU/mL). An ultrasound scan performed 2 weeks later (gestational age 6 weeks) showed a single gestational sac with an embryo measuring 8.8 mm (crown–rump length [CRL]), a yolk sac 2.5 mm, and a positive heartbeat of 127 bpm. The ultrasound performed at 8 gestational weeks showed a normal intrauterine gestational sac, having an embryo inside (2.1 cm CRL), positive heartbeat (167 bpm), and a 3.9 mm yolk sac. The ultrasound performed at 10 gestational weeks showed 3.9 cm CRL, and a positive heartbeat (163 bpm). Prenatal diagnostics was discussed with the patients (non-invasive prenatal test; amniocentesis), but they refused. The patient was further referred for pregnancy follow-up to an obstetric unit in a reference hospital. She had an uneventful full-term pregnancy and delivered a healthy baby girl weighing 2.4 kg via cesarean section. A high-resolution karyotype, which is our standard practice for all patients undergoing fertility management, confirmed a normal chromosomal complement (46,XX).

DISCUSSION

Chromosomal abnormalities, both numerical and structural, are identified in 5%–10% of oligozoospermia cases and 15%–25% of nonobstructive azoospermia cases (15, 16). These abnormalities, found in patients with azoospermia and oligospermia, vary in frequency from 4% to 23%. It is noteworthy that approximately 10% of genes in the genome are related to spermatogenesis. Genetic abnormalities contribute to 15%–30% of male infertility cases, often leading to partial or complete spermatogenic arrest (17). Approximately 25% of male infertility cases are reported to have a genetic origin (18).

Chromosomal abnormalities result from meiotic and post-zygotic mitotic errors of cell division and are categorized as either numerical or structural (18–25). Numerical abnormalities are due to an extra or missing chromosome, whereas structural abnormalities arise from the breakage and incorrect rejoining of chromosomal segments. Structural rearrangements are classified as balanced, where the complete chromosomal set is still present but rearranged, and unbalanced, which include deletions, duplications, or insertions of a chromosomal segment (26).

Chromosomal abnormalities such as deletions, translocations, duplications, inversions, ring chromosomes, and Y-chromosome microdeletions can predispose individuals to infertility (9, 27, 28). Males with these karyotype abnormalities are at increased risk of producing aneuploid sperms (29–31). Features of male chromosomal infertility include spermatogenic failure, characterized by azoospermia, oligospermia, and gonadal dysgenesis (9, 32). Balanced chromosomal rearrangements may go undetected because they often do not result in disease and present a normal phenotype. However, disease can arise from balanced rearrangements if breaks occur in a coding region/gene or within regulatory sequences, or if the fusion of chromosomal segments results in a damaging new protein product (33–35). Approximately 2,300 genes are involved in spermatogenesis, with 78 genes confidently linked to 92 human male infertility phenotypes (36–38). Y chromosome microdeletion on the long arm (Yq) is a frequent molecular genetic cause associated with spermatogenesis failure, prevalent in 10%–15% of nonobstructive azoospermia and 5%–10% of severe oligozoospermia cases (39, 40). AZFa, AZFb, and AZFc are defined as spermatogenesis loci, with most Y microdeletions leading to the simultaneous loss of multiple genes mapped within AZFb and AZFc loci associated with a range of infertile phenotypes. AZFa deletions are rarer and linked to Sertoli cell-only syndrome (41, 42).

Complex chromosome rearrangements involve at least three chromosomes and three or more chromosome breakpoints and can be balanced or unbalanced, de novo or familial (43–45). Balanced CCR carriers typically exhibit a normal phenotype but face higher reproductive risks (46). Complex chromosome rearrangements can cause genomic imbalances in gametes, leading to reduced fertility. Patients with CCR are at higher risk of producing unbalanced gametes due to abnormal genetic recombination during meiosis, potentially resulting in chromosomally abnormal embryos (47, 48). The occurrence of CCRs is rare in the general population (49, 50). It is hypothesized that male infertility associated with CCRs results from spermatogenic arrest/dysfunction due to complex meiotic configurations (18, 50).

In our case study, we present a male carrier of a CCR, t(3, 4, 12) (q21;q33;q21) with SOAT. Although the female partner had multiple medical comorbidities—including obesity (BMI 49.5), uncontrolled diabetes mellitus, hypertension, bronchial asthma, and anemia—that could have decreased the chance of pregnancy, we believe that the primary issue in her previous IVF attempts was the lack of PGT. Before presenting at our center, she underwent ten unsuccessful IVF cycles without PGT, likely leading to the transfer of aneuploid or genetically abnormal embryos due to the male partner's CCR. Upon

performing PGT-SR at our center, we found that only 1 out of 20 embryos was euploid, underscoring the critical role of PGT in selecting genetically normal embryos for transfer.

In our analysis, we compared the expected chromosomal imbalance sizes, based on the paternal karyotype, with the observed sizes detected in the embryos through PGT-SR. We particularly examined the breakpoints and imbalance sizes for chromosomes 3, 4, and 12 due to their involvement in the male partner's CCR. The observed breakpoints were at bands 3q13.11, 4q32.3, and 12q14.1, which differed from the expected breakpoints at 3q21, 4q33, and 12q21, respectively. Discrepancies of approximately 17 Mbp for chromosome 3, 3 Mbp for chromosome 4, and 11 Mbp for chromosome 12 can be attributed to technical limitations, human biases, and the resolution limits of both G-banding karyotyping (±5–10 Mbp) and the PGT-SR platform used. Additionally, the interpretation of karyotyping results can be subjective, leading to variability in pinpointing exact breakpoints. These factors highlight the challenges in the precise localization of chromosomal breakpoints in CCRs. Even with advanced technologies, precise localization of breakpoints remains difficult due to the complexity of CCRs, emphasizing the need for complementary techniques such as long-read whole-genome sequencing and optical genome mapping to improve accuracy (51, 52).

These findings underscore the significant impact of the parental CCR on embryonic chromosomal integrity, with a high incidence of aneuploidies involving chromosomes 3, 4, and 12. The close correlation between expected and observed imbalance sizes highlights the predictive value of the husband's karyotype in assessing embryonic chromosomal health and emphasizes the importance of precise genetic analysis in infertility treatments. Supplemental Table 1 offers an overview of the chromosomal breakpoints and sizes (in Mbp) observed in the husband's peripheral blood karyotype and in the embryos, highlighting the specific genomic alterations detected. Additionally, Supplemental Table 2 outlines the limitations of PGT-SR and karyotyping (550–900 band resolution), further clarifying the detection thresholds and the challenges faced during the study.

We discuss related studies on CCRs associated with male infertility and emphasize the importance of normal embryo selection through PGT-SR in assisted reproductive technology (ART) treatment (50, 53). This case also underlines the significance of prenatal diagnosis in subsequent pregnancies for couples with CCR. The case described involves rearrangements of chromosomes 3, 4, and 12, classified as a type I category CCR (three breakpoints involving three chromosomes with a three-way translocation) (54). The observed SOAT is likely associated with the CCR. This study contributes to the understanding of CCRs, particularly those involving chromosomes 3, 4, and 12, and highlights the importance of cytogenetic investigation and PGT for chromosome rearrangements in determining the cause of recurrent IVF failures. Moreover, this study focuses on the fact that individuals with CCR, despite significant genetic alterations, may appear normal but are susceptible to gametogenesis defects, making infertility their phenotype.

Complex Chromosome Rearrangements and Reproductive Failure (Molecular Mechanism)

Impact on meiosis and gamete formation. The CCR in the male partner, specifically t(3;4;12)(q21;q33;q21), has significant implications for meiosis and gamete formation. During meiosis, the rearranged chromosomes can form complex configurations, such as trivalents or quadrivalents, to align homologous regions. This complex pairing increases the likelihood of mis-segregation of chromosomes, leading to aneuploid gametes. Disruptions in normal chromosomal pairing and segregation can result in gametes with missing or extra chromosomal material, contributing to infertility and an increased risk of producing embryos with chromosomal abnormalities.

Correlation with embryonic aneuploidy. Our findings demonstrate a high incidence of aneuploidies involving chromosomes 3, 4, and 12 in the embryos, aligning with the chromosomes involved in the paternal CCR. The observed imbalance sizes in the embryos were generally consistent with the expected sizes based on the parental karyotype, albeit with slight variations. These variations may result from meiotic segregation errors, where the CCR increases the complexity of chromosomal pairing and segregation during meiosis, leading to variations in breakpoint positions. The close correlation between expected and observed imbalance sizes underscores the impact of the parental CCR on embryonic chromosomal integrity.

Mechanism behind full chromosome aneuploidy. The occurrence of full chromosome aneuploidies in our study may be attributed to the mis-segregation of chromosomes during meiosis due to the CCR. The structural rearrangements can interfere with spindle attachment and chromosome segregation. During meiosis, chromosomes can segregate in ways that lead to gametes with extra or missing chromosomes (e.g., adjacent-1 or adjacent-2 segregation), resulting in full aneuploidy. Additionally, the complex configurations formed during meiosis may predispose to nondisjunction events, leading to complete monosomies or trisomies in the embryos.

Meiosis, a complex process in cell division controlled by various checkpoints, responds differently in males and females to disturbances (55, 56). In males, abnormalities during spermatogenesis typically halt meiosis and trigger apoptosis, leading to azoospermia or oligozoospermia. In contrast, during oogenesis, meiosis tends to proceed, resulting in aneuploid gametes (50).

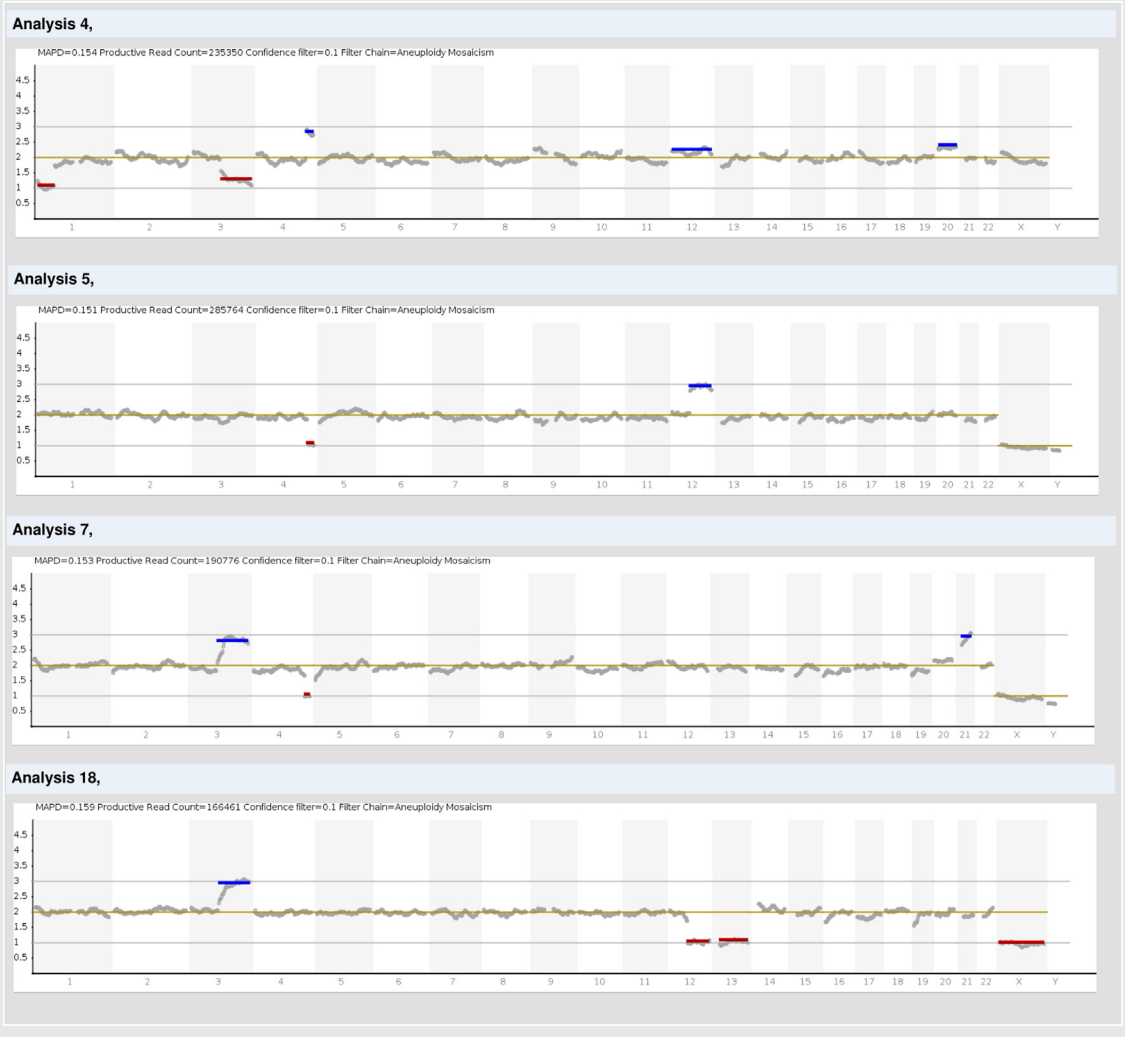
Translocations can disrupt spermatogenesis through several mechanisms, often related to the formation of quadrivalents/trivalents during meiosis. These complex structures require unique configurations to pair all homologous regions. Misalignment during this phase can lead to a variety of segregation patterns, with only a small fraction resulting in normal or balanced chromosomal complements in sperms (55, 56).

Carriers of translocations can produce chromosomally unbalanced sperm, primarily due to aberrant segregation. This results in reduced fertility, characterized by SOAT, embryonic losses, or abnormal pregnancy outcomes (57–59). The Pachytene stage of meiosis, where genetic recombination

occurs, offers insights into the mechanisms behind sterility associated with chromosomal structural rearrangements (60). Notably, the structure of CCRs influences outcomes at this stage. In three- or four-way translocations, hexavalent or octavalent configurations at meiosis I allow full synapsis of homologous segments, leading to a variety of chromosomal imbalances (50). Studies have shown that male infertility is frequently associated with CCRs, with 61.4% of males exhibiting spermatogenesis disturbances. In contrast, females with CCRs are often referred for spontaneous abortions or the birth of a malformed child (50, 61). Approximately 70%–75% of CCRs are de novo, found equally among phenotypically normal individuals and those with phenotypic abnormalities, often due to submicroscopic imbalances or other genetic defects (62, 63). These de novo CCRs seem to originate predominantly from paternal spermatogenesis and are transmitted through maternal oogenesis. Epidemiological data indicate that most prenatally ascertained balanced CCRs are maternal in origin (70% maternal vs. 30% paternal), whereas 80% of de novo structural abnormalities in newborns are of paternal origin (63). This finding aligns with the higher rate of structural chromosome aberrations observed in human male gametes. However, only a minority of CCRs are detected prenatally, with approximately 45% representing a "re-building" of the initial rearrangement through recombination, leading to simpler or more complex karyotypes (63).

In our case study, the PGT-SR results revealed abnormal embryos involving paternal balanced rearrangements. To provide a more comprehensive understanding of these results, we have included the ReproSeq (next-generation sequencing) plots for each of the 20 embryos as Supplementary Table 3. Additionally, we have included a few examples illustrating the detection of segmental aneuploidy associated with the translocation in Figure 3, of the main manuscript. This case

FIGURE 3



Examples of segmental aneuploidy detection in embryos with parental chromosomal translocation.

Upadhyay. Complex chromosomal rearrangement & IVF. F S Rep 2024.

underlines the importance of cytogenetic investigation and PGT for chromosomal rearrangements, highlighting the complexity of CCRs and their significant impact on male fertility.

This case report underscores the critical role of advanced genetic testing, particularly PGT-SR, in managing infertility associated with CCRs (50, 53). The detailed analysis highlights the importance of cytogenetic investigations in identifying genetic causes of recurrent IVF failures, contributing significantly to personalized fertility management (18, 50). However, the study's limitation lies in the small sample size, restricting broader applicability, and the inherent challenges in predicting the fertility outcomes for all CCR carriers due to the variability in chromosomal rearrangements and their effects (50, 63). Further research with larger cohorts is needed to validate these findings and optimize treatment strategies for similar cases.

Complex Chromosome Rearrangements and Male Infertility

Male carriers of CCRs are known to produce a high frequency of chromosomally abnormal spermatozoa. This is primarily due to aberrant segregation of the rearranged chromosomes during meiosis, leading to conditions such as azoospermia or oligozoospermia when meiosis is halted and apoptosis follows (50).

The chromosomally unbalanced spermatozoa resulting from this can lead to repeated spontaneous abortions and/or aneuploid liveborn children with multiple congenital abnormalities (57, 64). Factors such as the number of chromosomes and breakpoints involved in the rearrangement, the position of breakpoints, and the presence or absence of recombination within paired-rearranged segments are believed to influence the fertility of CCR carriers. Studies indicate that the risk of phenotype alterations increases with the number of chromosomes involved in CCRs and the number of breakpoints (50). In some rare cases, male carriers of CCRs can complete spermatogenesis, likely due to less robust checkpoints (65, 66).

The identification and characterization of the genetic basis of male infertility have significant implications for understanding infertility causes, determining prognosis, selecting treatment options, and managing couples. However, challenges in understanding the origin and nature of a CCR make medical genetic and reproductive counseling complex (67, 68). Proper genetic diagnosis is crucial for the success of ART techniques and, as well as for the prognosis of testicular sperm extraction in cases with azoospermia (69, 70).

Complex Chromosome Rearrangements and Infertility Case Study

In our clinical experience, one notable case that drew our attention involved a couple with a long history of infertility (20 years), severe male factor infertility, and recurrent IVF failure, including 10 failed IVF attempts, yet they had not undergone karyotyping. After PGT-SR, the impact of the CCR on the embryo's chromosomes became evident. In the three IVF attempts, although blastocysts were obtained, only one was euploid. All six embryos exhibited numerical abnormalities involving chromosomes related to the male partner's CCR. The female partner achieved pregnancy only upon the transfer of a euploid embryo.

Interestingly, a year after her successful delivery, the female partner returned to our clinic seeking further treatment. However, in the subsequent three IVF attempts, all 10 embryos were found to be abnormal. Chromosomal abnormalities were predominantly in chromosomes involved in the male partner's CCR, with other chromosomes also exhibiting abnormalities, reflecting the effect of ovarian aging.

The identification of genetic factors is crucial for appropriately managing infertile couples. Patients with certain genetic alterations often produce a higher frequency of sperm with aneuploidies, which can either be a direct result of a constitutional genetic abnormality or due to meiotic errors induced by altered testicular environments (29, 30, 71).

CONCLUSION

The prevalence of chromosomal abnormalities in infertile males underscores the necessity for routine karyotyping and counseling prior to infertility treatment (43, 50).

Advancements in the genetic study of infertility have been instrumental in integrating genetics into the daily practice of ART. There is an undeniable link between ART and genetic practices, with one facilitating the birth of children and transmission of genetic heritages, and the other ensuring the integrity of this heritage (72–74). A comprehensive understanding of genetics is vital for optimizing treatment strategies, particularly for couples facing male sterility factors such as oligozoospermia, oligoasthenoteratozoospermia, or nonobstructive azoospermia. Clinical investigations in such cases should ideally include a peripheral high-resolution blood karyotype. Techniques like Giemsa banding, fluorescence in situ hybridization, array-comparative genomic hybridization, and array painting are crucial in studying chromosomal structural changes associated with abnormal phenotypes (75).

With the advent of ICSI, the treatment of male infertility associated with oligozoospermia, oligoasthenoteratozoospermia, or nonobstructive azoospermia has become increasingly feasible. Preimplantation genetic testing for structural rearrangements is a valuable tool in assisted reproduction for patients with complex chromosomal abnormalities and infertility, aiding in risk assessment and embryo selection.

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CRediT Authorship Contribution Statement

B.P. conceived and designed the study, developed the methodology, reviewed and edited the manuscript, and supervised the study. B.P., R.A.H., and D.U. conducted the investigation. D.U. wrote the original draft of the manuscript and managed the project administration. D.U., S.A., F.A., and M.M.V. performed data curation. R.A.H. performed validation. S.A. contributed to visualization. S.A., F.A., and M.M.V. provided resources.

Declaration of Interests

D.U. has nothing to disclose. R.A.H. has nothing to disclose. S.A. has nothing to disclose. F.A. has nothing to disclose. M.M.V. has nothing to disclose. B.P., as Principal Investigator and Chair of the Research Ethical Board at Al Ain Fertility Center, acknowledges a potential conflict of interest due to his dual role. This role is fully disclosed to ensure research transparency and integrity.

WEB RESOURCES

Metasystem IKAROS Software: https://metasystems-international.com/en/products/ikaros/
Time-Lapse Monitoring System (EmbryoScope): https://www.vitrolife.com/why-vitrolife/the-patient-ivf-journey/embryoscope-time-lapse-system/
Quinn's Advantage Medium, Sage Biopharma: https://www.coopersurgical.com/brands/sage/
Progyluton, Bayer: https://www.pharma.bayer.com/
ESTRADOT Novartis: https://www.novartis.com/
Crinone 8%, Merck Global: https://www.merckgroup.com/
Duphaston, Abbott: https://www.abbott.com/ Prontogest, AMSA IBSA: https://www.ibsagroup.com/
Echotip Soft-Pass TM Embryo Transfer Catheter, Cook Medical: https://www.cookmedical.com/

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Because of the sensitive nature of the clinical information and to ensure patient confidentiality, data will not be publicly available. Requests for access to specific datasets used in this study will be considered by the authors, provided that they conform to ethical standards and regulations concerning patient data.

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